An open-label, clinical feasibility study of the efficacy of Remdesivir for Long-COVID.

ERASE-LC

Protocol Version: 2.2, 21 August 2025

IRAS Number:	1007101
ISRCTN Number:	72940450
ClinicalTrials.gov Number:	NCT05911906
SPONSORS Number:	PSL2122-0255
FUNDERS Number:	103196

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 Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) 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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: 

Date: 27AUG2025

Name (please print): Kieran Housley

Position: Sponsor Representative

Chief Investigator:

Signature: 

Date: 22AUG2025

Name: (please print): Prof Mark Faghy

Statistician:

Signature: 

Date: 09SEPT2025

Name: (please print): Victoria Allgar.

PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NA – Initial submission	1.1	30Apr2024	Kayle-Anne Sands	- Change to trial timelines (iii. Trial summary). - Wording clarification - participants may self-refer via telephone (10.1.2) - 'Anonymised' amended to '*pseudo*-anonymised' (10.2) - PET-CT scans made optional for Exeter participants (4.3.2.6, 10.2.2.2, 10.5) - Insurance and indemnity arrangements clarified (16.9) - Wording clarification – no intention to treat participants once study involvement is complete (16.11)
AM01_NA1	2.0	05Sep2024	Kayle-Anne Sands	- Wording clarifications and duplicate text removed throughout. - Update to key trial contacts. - Removal of 'use of smartphone' as inclusion criteria. - Correction – removal of eGFR and LFTs from biomarker and inflammatory profiles throughout. - Update to trial timelines (iii). - Correction to trial flowchart (ix) – enrolment is at baseline assessment. - Addition of safety information as per updated SmPC (3.1, 11.7.4, 12.4.5). Review of SmPC version changed to quarterly (11.7). - Correction – eGFR is tested at detailed screening and Day 27 (3.1.1, 4.3.2.3) - Change to numbering of subheadings (3.1) - Correction to 'Modified' Fatigue Impact Scale and addition of PROMS table and associated timepoints for assessment (4.3.2.1).

				- Correction – blood samples to be deposited within 0.5ml aliquots (4.3.2.3) - Addition of information regarding paper symptom diary throughout. - Corrections to tabulated summary of objections and outcomes (5). - References to 'digital REDCap screening log' added. - Added guidance for confirming eligibility where access to medical notes is not possible and correction to location for filing original ICF (10.2.2.2) - Subheading title updated and smoking status moved to medical history (10.2.2.3) - Correction and clarifications to CPET protocol wording (10.4). Addition of blood gas tension. - Correction to Schedule of Assessments in line with protocol updates (10.11) - Biomarker samples will be analysed at the UoD or an external vendor (10.12). - Clarifications to SAE, overdose and Serious Breach reporting process as per PenCTU SOPs and trial work instructions (12.3, 12.4, 16.6) - Correction – archiving period is 15 years (15.5). - Removal of requirement for REC annual progress report (16.1). - References added to 4.3.2.4.
AM03_NSA02	2.1	15Jan2025	Amber Lord / Kayle-Anne Sands	- Removal of PPI representative emails from key trial contacts. - Addition of inclusion criteria 'Lives within a commutable distance of the relevant centre, at the discretion of the local PI'. - Update to trial flowchart. - Clarification to masking and COVID-19 testing requirements (3.1.2). - Reference to 'LC symptom Burden' changed to 'SBQ™-

				LC' throughout - PETCT scan days changed to Days 11 and 53. - Reference to eligibility confirmation checklist added (10.2.2.2). - Tolerance windows for visit dates updated throughout. - Correction to Table 2. Progression Criteria. - Archiving period reduced to 5 years (15.5). - Reference to declaration forms removed (16.8). - Clarifications to wording made throughout.
AM05_NSA04	2.2	21Aug2025	Mark Faghy / Kayle-Anne Sands	- Update to postal address of PenCTU, named Sponsor and Funder representative at University of Derby and GILEAD Sciences, respectively. - Change to list of biomarker and inflammatory profile being analysed centrally (section 4.3.2.3 and throughout). - Respiratory compensation point (RCP) removed as key variable of interest in CPET. - Abbreviations list updated.

KEY TRIAL CONTACTS

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Funder(s):	Gilead Sciences: COVID-19 RFP Program (£1,254,076.62) Primary Contact: Nini Estevez Study Manager nini.estevez@gilead.com
Trial Steering Committee Members	Chair: Professor Michael Dewey (Emeritus Professor of Statistical Epidemiology, Kings College London). michael.dewey@kcl.ac.uk Independent members: Dr Janet Scott (Consultant in Infectious Disease & Research Medicine, NHS Highlands Long COVID service, Raigmore Hospital). Janet.scott3@nhs.scot Dr Emily Hume (Lecturer in Exercise Physiology and Rehabilitation, Department of Sport, Northumbria University). E.c.hume@northumbria.ac.uk Miss Katie Booth (Research Associate, Medical Statistics, Warwick Clinical Trials Unit, University of Warwick). K.Booth@warwick.ac.uk Dr Michelle Bull - Chartered Physiotherapist (Royal Surrey NHS Foundation Trust) mbull@nhs.net Michael Natt, Patient representative Ana Castro-Leite, Patient representative

i. Table of Contents

ii. ABBREVIATIONS

6MWT	6-minute walk test
ADL	Activities of Daily Living
AE	Adverse Event
ALCOA CCEA	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available
ALT	Alanine aminotransferase
APR	Annual Progress Report
AR	Adverse Reaction
BNF	British National Formulary
CE	European Conformity
CONSORT	Consolidated Standards of Reporting Trials
COVID 19	Coronavirus disease
CI	Chief Investigator
CRP	C-reactive Protein
CPET	Cardiopulmonary Exercise Test
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DCHS	Derbyshire Community Health Services NHS Foundation Trust
DIBD	Developmental International Birth Date
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSQ-PEM	Modified De Paul Symptom Questionnaire-Post Exertional Malaise
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EGF	Epidermal Growth Factor
eGFR	estimated Glomerular filtration rate
EMA	European Medicines Agency
Eotaxin	Eosinophil Chemotactic Protein
EQ-5D-5L	is a standardised measure of health-related quality of life developed

	by the EuroQol Group
EudraCT	European Clinical Trials Database
FAS	Fatigue Assessment Scale
FGF-basic	Basic Fibroblast Growth Factor
FDG	Fluorodeoxyglucose
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
FFP	Filtering Facepiece
GAD-7	Generalised Anxiety Disorder
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GDPR	General Data Protection Regulation
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GP	General Practitioner
HEPA	High-efficiency Particulate Absorbing
HGF	Hepatocyte Growth Factor
HLA-DP	Human Leukocyte Antigen-DP
HRA	Health Research Authority
IB	Investigator Brochure
ICF	Informed Consent Form
ICU	Intensive Care Unit
IFN- α	Interferon Alpha
IFN- γ	Interferon gamma
IL	Interleukin
IL-1β	Interleukin 1 Beta
IL1Ra	Interleukin 1 Receptor Antagonist
IL-2R	Interleukin 2 Receptor
IMP	Investigational Medicinal Product
INR	International normalised ratio
IOS	iPhone Operating System
IP-10	Interferon Gamma-Induced Protein 10
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number

IV	Intravenous
LC	Long COVID
LFT	Liver Function Test
MCP-1	Monocyte Chemoattractant Protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum Expiratory mouth Pressure
MFIS	Modified Fatigue Impact Scale
MHC	Major Histocompatibility Complex
MHRA	Medicines and Healthcare products Regulatory Agency
MIG	Monokine Induced by Gamma Interferon
MIP	Maximum Inspiratory mouth Pressure
MIP-1α	Macrophage Inflammatory Protein 1 Alpha
MIP-1β	Macrophage Inflammatory Protein 1 Beta
mmHg	Millimetres of mercury
MRC	Medical Research Council
MS	Multiple Sclerosis
NCI	National Cancer Institute
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NIHR CRN	National Institute for Health and Care Research Clinical Research Network
NIMP	Non-Investigational Medicinal Product
NLR	Neutrophil Leukocyte Ratio
ONS	Office for National Statistics
PASC	Post-acute sequelae of SARS-CoV-2 infection
PCFS	Post COVID Functional Status Scale
PCT	Procalcitonin
PDQ-5	Perceived Deficit Questionnaire
PEF	Peak Expiratory Flow
PEM	Post-Exertional Malaise
PenCTU	Peninsula Clinical Trials Unit
PET-CT	Positron Emission Tomography and Computed Tomography
PI	Principal Investigator

PIC	Participant Identification Centre
PIS	Participant Information Sheet
PLR	Polymorph Lymphocyte Ratio
PPI	Patient and Public Involvement
PPIE	Patient, Public Involvement and Engagement
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QA	Quality Assurance
QP	Qualified Person
RAG	Red/Amber/Green
RANTES	Regulated on Activation, Normal T Cell Expressed and Secreted
RCT	Randomised Control Trial
REC	Research Ethics Committee
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV2	Severe Acute Respiratory Syndrome coronavirus 2
SBQ™-LC	Symptom Burden Questionnaire for Long COVID
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised uptake value
TMF	Trial Master File
TMG	Trial Management Group
TNF-α	Tumor Necrosis Factor alpha
TSC	Trial Steering Committee
VEGF	Vascular Endothelial Growth Factor
VT	Ventilatory threshold
WHO	World Health Organisation

iii. TRIAL SUMMARY

Trial Title	An open-label, clinical feasibility study of the efficacy of Remdesivir for Long-COVID.
Acronym	ERASE-LC
Clinical Phase	IV
Trial Design	Open label, single-arm proof of concept study
Planned Sample Size	72
Planned number of sites	2
Protocol Aim	To test the feasibility of the use of a 5-day intervention of intravenous Remdesivir as a treatment for patients with Long COVID.
Primary protocol objectives	1. To ascertain screening and recruitment rates (overall and by different recruitment pathways) 2. Retention and dropout rate (due to the treatment and/or trial demands, overall and by centre) 3. Adherence to treatment regimen (attendance to 5 days of IMP) 4. Completeness of study assessments (CPET, Bloods, PET/CT if in Exeter) 5. Completeness of all data collection activities, including baseline and +28 days after treatment 6. Acceptability of outcome measurements
Secondary protocol objectives	1. To identify the most clinically relevant primary outcome for the definitive study, including: • Quality of life, functional status, and symptom burden • Tolerance to physical stimulus: exercise tolerance and reduced post-exertional symptom exacerbation following incremental exercise • Physiological function, physical function, cognitive function, and emotional status and/or capacity • Biomarker and inflammatory profiles • *Exeter patients only:* Microvascular function: whole body FDG uptake using PET/CT methods.

	2. To determine the clinical safety and tolerance parameters of the use of Remdesivir in the treatment of patients with Long COVID.
Study Population	
Trial Participants	Patients ≥18 years of age with previous confirmed SARS-CoV-2 infection and confirmed or suspected diagnosis of Long COVID.
Inclusion Criteria	• ≥18 years of age at the time of enrolment • Previously confirmed or suspected SARS-CoV-2 infection • Confirmed diagnosis of Long COVID by a Health Care Practitioner according to the *definition provided by the World Health Organisation for persistent symptoms following a confirmed SARS-CoV-2 infection. • Willing and able to provide informed consent, complete the surveys, and complete all planned clinical assessments, and return for scheduled study visits. • Evidence of persistent symptom profile relative to pre-COVID-19 status as derived from patient reported outcome measures. • Lives within commutable distance of the relevant centre, at discretion of local PI. ** WHO define Long COVID as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.*
Exclusion Criteria	• Treatment history of Remdesivir, molnupiravir, paxlovid and/or any other COVID-19 anti-viral medication (<6 months). • A diagnosis of a compromised immune system or function from a Healthcare Professional. • Currently engaged in a physical rehabilitation programme or intervention aimed to improve Long COVID symptom profile and/or functional status. • Recognised as a 'severe risk' of experiencing post-exertional malaise following engagement in physical

	tasks. Determined using the Modified De Paul Symptom Questionnaire. • Lack of mental capacity to provide informed consent. • Unable to understand verbal English/have a hearing impairment that prevents adequate communication.* • Participation in another clinical drugs trial within the last 6 months • Currently pregnant, breastfeeding or attempting to get pregnant (i.e., not using effective methods of contraception). • Currently taking medications known to have an interaction with Remdesivir (e.g., chloroquine phosphate or hydroxychloroquine) as defined by British National Formulary (BNF) information on the selection, prescribing, dispensing and administration of medicines: https://bnf.nice.org.uk/interactions/Remdesivir/ • History of serious adverse reactions to anti-viral medication and intravenous infusions • History of Hepatic or Renal Impairment (eGFR (<30ml/min) and LFTs ALT>x5 ULN). • **Exeter participants only:** No recent/long standing history of CT (within 3 months)/ ongoing radiotherapy treatment. Risks of accumulative burden to be discussed as part of study involvement but it is at the discretion of participants. ***Note:** • **English Comprehension:** Potential participants who are unable to understand verbal English will not be eligible for this study. This is due to the necessity of telephone contact which is a key aspect of this study and the unavailability of validated questionnaires in languages other than English. • **Hearing Impairment:** Unfortunately, if the participant has a hearing impairment that prevents adequate communication on the telephone, they will not be able to take part in the study. This will be clearly stated in the participant information sheet.
Summary of outcome measures	

Feasibility	***Number of patients:*** • Rates of screening (overall and by centre) • Recruitment rate (Number of patients consented (as proportion of those screened, by the different recruitment pathways) • Retention and dropout rate (due to the treatment and/or trial demands, overall and by centre) • Adherence to treatment regime (attendance to 5 days of IMP) • Attendance and completeness of study assessments (CPET, Bloods, PET/CT if in Exeter) • Completeness of all data collection activities including baseline, and +28 days after IMP • Completion of Patient-reported outcome measurements (>60% completion)
Patient reported and Clinical outcomes	***Patient-reported:*** • EQ-5D-5L • PCFS (Impact on daily life subscale of LC Symptom Burden) • DSQ-PEM • LC Symptom Burden • FAS • MFIS • MRC Dyspnoea Scale • PDQ-5 • GAD-7 ***Clinical Assessments:*** • Maximum inspiratory and expiratory mouth pressure (MIP and MEP) • Lung function • Blood pressure • Oxygen saturation • Breathing rate • Resting heart rate • Body temperature

	• 6-minute walk test (6MWT, Borg 6-20 and SPO2) ***Biomarkers and Inflammatory Profiles:*** • G-CSF • GM-CSF • IFN-α • IFN-γ • IL-1β • IL-1RA • IL-2 • IL-2R • IL-4 • IL-5 • IL-6 • IL-7 • IL-8 • IL-10 • IL-12 • IL-13 • IL-15 • IL-17 • TNF-α • Eotaxin • IP-10 • MCP-1 • MIG • MIP-1α • MIP-1β • RANTES • EGF • FGF-basic • HGF • VEGF ***Tolerance to physical stimulus using CPET:*** • First ventilatory threshold (VT1) • Peak oxygen consumption (V̇O2peak) • End-tidal CO2 ***Symptom Profiling and tracking:*** • Symptom Score Inventory • Heart rate variability ***Clinical safety and tolerance parameters:***

	• AE/SAE/AR/SAR/SUSAR ***Microvascular function using PET/CT (Exeter only):*** • Standardised uptake volume (SUV) and Ki of 18FDG uptake observed during PET/CT scans.
Timescales	
Treatment duration	5 days
Trial duration	52 days (55 in Exeter)
Planned Project Period	30 months (9 months set-up, 12 months recruitment, 3 months follow-up, 6 months analysis and report)
Planned Date to Open recruitment	16th September 2024
Planned Recruitment End Date:	16th September 2025
Planned Study End Date:	31st May 2026
Treatment	
Investigational Medicinal Product (IMP)(s)	Remdesivir (brand name: Veklury®)
Formulation, Dose, Route of Administration	Intravenous infusion. 100mg powder for concentrate for solution for infusion. Administered outside of current licensing indication for the treatment of COVID-19 in the hospitalised patient. Single loading dose of 200 mg *via* intravenous infusion over 60 minutes on day 1, then maintenance dose of 100 mg *via* intravenous infusion over 30 minutes once daily for 4 consecutive days. (Total duration of treatment is 5 days).

iv. FUNDING & SUPPORT IN KIND

Funder(s)	Financial and Non-Financial Support Given
Gilead Sciences Nini Estevez (Study Manager) nini.estevez@gilead.com	£1,254,076.62 + Study Drug (£24,060.31)

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor for this study, the University of Derby, assumes overall responsibility for the initiation and management of the trial. They are not providing funds for this trial but has taken on responsibility for ensuring finances are in place to support the research.

The Funder will not have direct involvement in trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The Sponsor will have overall responsibility for the proportionate and effective arrangements being in place to set up, run and report on the research project. The Sponsor may delegate specific tasks to any other individual or organisation that is willing and able to accept them. Any delegated tasks will be clearly recorded in a matrix of responsibilities appended to the trial agreement. Although tasks maybe delegated the overall responsibility remains with the Sponsor. The trial was designed by the Chief Investigator (CI) and co-applicants with support from Gilead Medical Affairs and Infectious Disease Committee and Peninsula Clinical Trials Unit (PenCTU). Support during the early stage of protocol development was also obtained from Derby Clinical Trials Support Unit (CTSU).

vi. ROLE OF COORDINATING CLINICAL TRIALS UNIT (CTU)

The Sponsor of the study has allocated tasks associated with overall trial management and data management to the PenCTU as outlined in the Division of Responsibilities. PenCTU's management of the trial includes the delivery of site initiation training and monitoring. A detailed breakdown of tasks undertaken by PenCTU on behalf of the CI and trial Sponsor is described in a formal written Sponsor agreement.

vii. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Trial Management Group (TMG): The trial management group will meet regularly (as detailed within the study monitoring plan) to oversee the day-to-day management of the trial, including all aspects of the conduct of the trial. Any problems with study conduct and participating centres will be raised and addressed during TMG meetings.

Trial Steering Committee (TSC): The trial steering committee will oversee and supervise the progress of the trial and ensure that it is being conducted according to ICH-GCP and the applicable regulations. The TSC is an independent body that includes mostly members who are not involved with the running of the trial. TSC meetings will be held according to the monitoring plan and will be detailed in an agreed TSC Charter.

Patient and Public Representatives (PPI): Patient, public involvement and engagement (PPIE) representatives have been involved in the design and final review of the protocol as

well as other aspects of trial design, including reviewing documentation. They will retain a pertinent role in the TMG and TSC and will attend and be involved in meetings to allow input into the ongoing management and delivery of the trial.

Protocol Contributors:

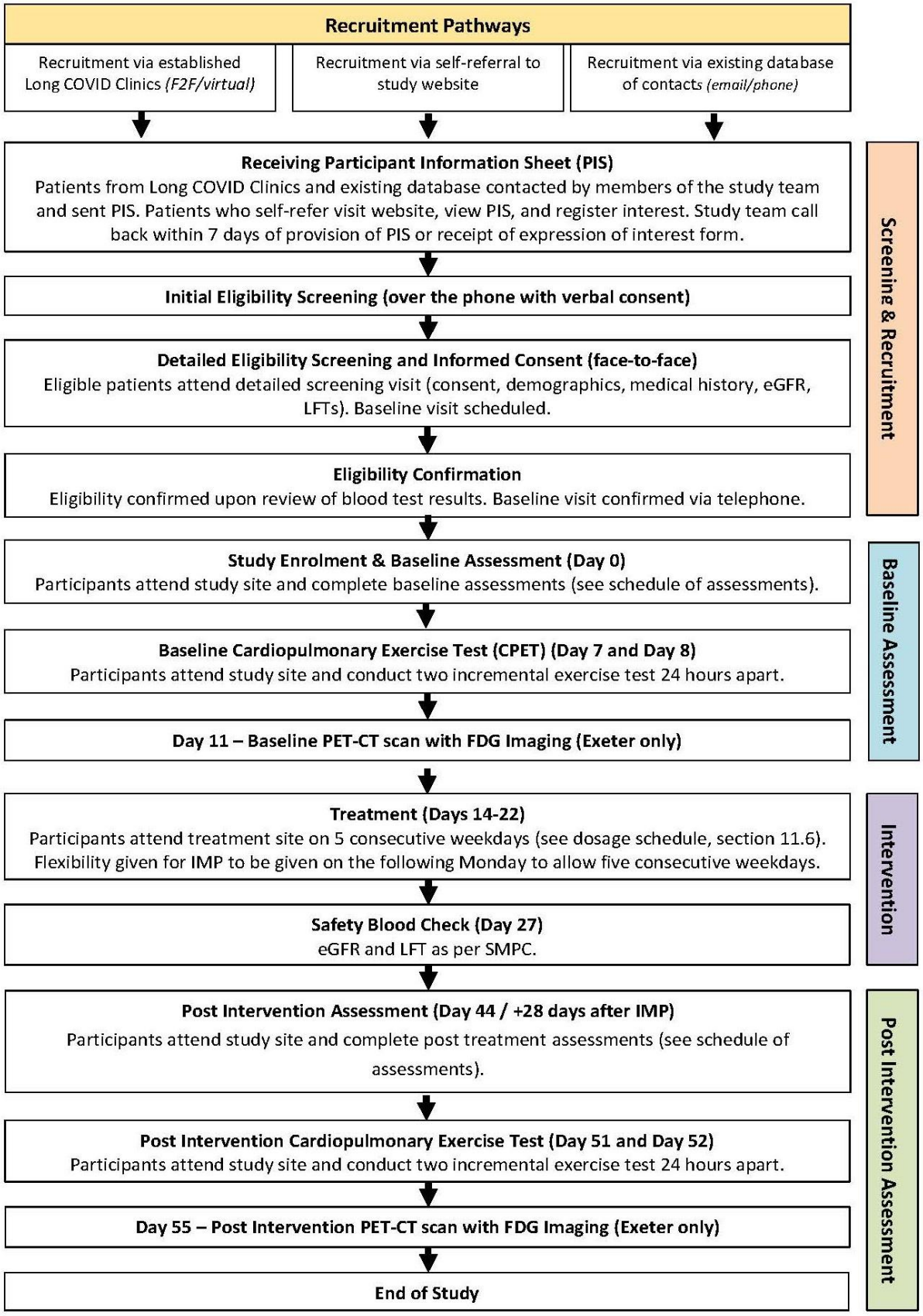
Several protocol contributors have been involved in the development of this protocol, these include the CI (Prof Mark Faghy (Academic)) and Dr Tom Bewick (Co-CI), Dr David Strain (Medical Lead), Trial Statisticians (Prof Victoria Allgar, Jade Chynoweth and Anton Barnett), Trial Pharmacist (Professor Ian Maidment), Information Systems Manager (Dr Matt Bailey) and Senior Trial Manager (Dr Helen Neilens), as well as members of the research team, Dr Ruth Ashton, Dr Karen Knapp, and Dr Hairil Razak. Protocol contributors are responsible for inputting into the design of the trial, ensuring that it is designed transparently and efficiently.

The CI would also like to recognise the early involvement and input from all colleagues at the Derby Clinical Trials Support Unit.

viii. KEYWORDS:

Covid-19, Remdesivir, Long COVID, safety, feasibility, efficacy.

ix. TRIAL FLOW CHART



1. LAY SUMMARY

Following an infection with Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV2), one in ten people will experience persisting symptoms, or develop symptoms which can last for months and even years. These symptoms affect people in different ways and have been demonstrated to broadly impact physical, mental, and cognitive health. This is called Long COVID. Currently, there are no treatments available to address the issues that patients experience but anti-viral medications have been suggested as being potentially effective. This study will recruit patients that have a confirmed long COVID diagnosis and participants will undertake a series of tests to determine their symptoms and the impact that their condition has had on their bodily systems. The total duration of each participant's involvement is approximately 8 weeks, and this will involve 13 visits (15 visits if taking part in Exeter) at the closest study location (Derby or Exeter). Initial assessments are conducted over three separate visits and then all participants will be scheduled to receive five consecutive days of a medication that has been identified as having the potential to reduce the impact of Long COVID. Following a period of 28 days, participants will be invited to repeat the same tests that were conducted before receiving the medication so that it can be determined how well the drug has worked. In this study we are specifically collecting information to understand how feasible this medication could be to help patients improve their condition and this will help us to determine how likely this drug is able to be used within the wider Long COVID community.

The medication that will be used within this study is an existing anti-viral medication (Remdesivir). If we find patients are able to tolerate the treatment and the research tasks, we will use this information to conduct a larger trial to determine how well this drug can be used to reduce the impact of Long COVID in a greater number of patients.

2. BACKGROUND

Long COVID is defined as a prolonged constellation of symptoms that people experience for at least 3 months following a probable or confirmed SARS-CoV-2 infection that cannot be explained by an alternative diagnosis[1]. Whilst vaccines are up to 95% effective at reducing mortality and Intensive Care Unit (ICU) admissions in SARS-CoV-2 patients [2], at best, they reduce Long COVID by 40% [3]. Furthermore, although the most recent Omicron variant is associated with a lower risk of hospitalisation and death, the risk of progression to long COVID remains the same as previous variants at approximately 10% of triple vaccinated people [4]. The development of Long COVID is also not associated with the severity of acute COVID-19 infection and occurs in those that were asymptomatic or with mild disease [5]. A recent scoping review by Hayes *et al* [6] reported over one hundred common patient complaints that are cyclical and prone to exacerbation. These symptoms include post-exertional malaise, cognitive dysfunction, reduced functional status and exercise capacity. They significantly impact functional status and quality of life and pose a significant burden for healthcare services and economic entities (e.g., employers). Recent data from the UK demonstrates that 668,000 patients are currently unable to complete their typical employment activities and 127,000 of

these are healthcare workers, posing additional challenges to an already stretched healthcare system[7]. Furthermore, this does not appear to be self-resolving, indeed currently there are approximately 376,000 people who have had Long COVID for more than 2 years, representing the impact of the first wave alone.

A sustained post-viral maladaptive inflammatory profile has been indicated as a contributing factor in the severity and fluctuating state of Long COVID symptoms. Hybrid imaging that uses positron emission tomography and computed tomography (PET/CT) with Fluorodeoxyglucose (FDG) can identify inflammatory responses through elevated glycolytic activity and cellular metabolism [8]. Increased uptake of FDG by inflammatory cells results from their expression of elevated levels of glucose transporters and hexokinase activity [9]. Sollini *et al* [8] explored the uptake of FDG in 13 patients >30 days post COVID recovery compared to the uptake in 26 oncology patients. Four patients with Long COVID showed lung abnormalities on CT with mild FDG uptake. Only one patient had a normal scan with no areas of increased uptake outside the expected areas of tracer accumulation but documented profound symptomology. A vascular binary pattern and diffuse bone marrow uptake of FDG in the long bones were reported in Long COVID patients. A minority had also had uptake in the lung, mediastinal lymph nodes, soft tissue, gastrointestinal tract, and muscles. Significant changes were also found in the brain with hypometabolism. The novel insight provided from PET/CT scans that use FDG could provide increased knowledge about the efficacy of pharmacological interventions.

3. RATIONALE

Data indicates that >2 million people in the United Kingdom [10] (Office for National Statistics (ONS), 2022), and >144 million globally [11] are living and suffering from Long COVID. Global restrictions and protective steps to reduce transmission have relaxed entirely and access to regular vaccines and boosters withdrawn for most of society. This coupled with the threat of sustained transmission and the evolution of future variants of concern mean that Long COVID diagnoses will create a challenge for healthcare systems for years to come [12,13]. Three aetiologies have emerged as leading candidates for instigating the manifestations of Long COVID: disordered anticoagulation, immune dysregulation, and viral persistence/reactivation [14]. In particular, prior investigators have demonstrated in preliminary data that SARS-CoV-2 can persist throughout the body for up to 230 days after acute infection [15], and that viral ribonucleic acid (RNA) has been identified within the gut mucosa and plasma of the majority of patients with post-acute sequelae of SARS-CoV-2 infection (PASC), but not within those without PASC. Direct targeting of viral persistence, coagulation, and immune dysregulation with therapeutic agents warrants further investigation.

Antiviral medications such as Remdesivir have been demonstrated to be effective in reducing the risk of progression to severe disease in high-risk patients during an acute in SARS-CoV2 infection[16], and in immunocompromised hospitalised patients with persistent viraemia. Remdesivir is licensed for use during acute admission to hospital for patients with COVID-19 and has demonstrated positive patient outcomes and reduced risk during acute illness and long-term outcomes[17], however it has yet to be tested in patients that have Long COVID that

were not hospitalised during the acute stages of infection. Remdesivir was chosen as the IMP for this trial due to the positive outcomes during the acute phase of infection (i.e., reduced likelihood of prolonged/persistent symptoms) and due to a need to assess the safety/feasibility of all anti-viral medications that might improve patient outcomes. Work is ongoing in the United States of America to determine the efficacy of alternative medications including nirmatrelvir and ritonavir (NCT0557662) [18].

Viral persistence is reported in Long COVID[19] and other infectious diseases and could be treated with candidate antiviral medications which have previously been shown to be effective in reducing the risk of progression to severe disease in high-risk patients early in SARS-CoV2 infection[16]. Remdesivir has been chosen as the IMP for this project, due to increasing data relating to the effectiveness during acute stages and due to increasing evidence demonstrating a need to address the viral reservoirs that have been identified and linked to a persistent and debilitating symptom profile. Other antiviral IMPs are available and are being studied [20] but data here is mixed, likely due to reliance on patients to consume the IMP in line with the study requirements and also due to reduced bioavailability compared with intravenous (IV) approaches[21]. The dosing strategy will follow that as licensed for patients admitted to acute settings, which has been demonstrated to reduce risk of severe acute infection and improve long term outcomes[17].

Accordingly, there is a need to assess the feasibility of using an anti-viral, administered by IV in Long COVID before commencing to a double-blind multi-centre randomised control trial to determine its effectiveness. The resulting study will inform treatment decisions that can potentially reduce Long COVID and its severity, improve patient outcomes and restore quality of life.

It is also necessary to test out all the study processes and procedures as physical and psychological demand is quite high. There is a need to ensure participants are able to follow the study protocol prior to a definitive study.

3.1 Assessment and Management of Risk

3.1.1 Treatment

The use of Remdesivir as an IMP carries no higher risk to patients than when used in standard medical care as guided by the study's CI. In addition, as per the SmPC, there is an established safety profile for Remdesivir administered at 100mg (preceded by a 200mg loading dose) *via* intravenous infusion for up to 10 days, which exceeds the treatment duration outlined by the current study (5 days total). Therefore, the risk for the current treatment protocol can be considered low.

Remdesivir is being used as part of this study outside of its current licensing arrangements to assess the feasibility of treating patients with Long COVID. Data relating to risks of using the IMP Remdesivir have been outlined in the summary of product characteristics (SmPC) which is a live document and will be reviewed routinely by the study team to check for updates that might impact participants engaged with this trial. To date, the risks outlined in the SmPC include:

Hypersensitivity including infusion-related and anaphylactic reactions.

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of Remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients for hypersensitivity reactions during and following administration of Remdesivir as appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of Remdesivir and initiate appropriate treatment.

To account for this knowledge, participants will be screened to determine previous history of adverse reaction (AR)s to infusions/medicines during the initial screening process details of which will be shared with the study's clinical team to make the final decision about suitability to be recruited to the study. During the administration period, patients will be monitored by appropriate staff members and any ARs will be reported to the sponsor immediately and the appropriate documentation completed and shared with the appropriate study/ regulatory partners. Dosing and infusion rates have been discussed and agreed in-line with the SmPC and the study's principal investigators who are medically trained and have clinical experience of using this IMP in acute settings.

Transaminase elevations (family of enzymes which may rise due to liver injury).

In healthy volunteer studies, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or both in subjects who received remdesivir were 1.25 to 2.5 times the upper limit of normal (ULN) (10%) or 2.5 to 5 times ULN (4%). In clinical studies of patients with COVID-19, the incidence of increased transaminases was similar in patients treated with remdesivir compared to placebo or standard of care.

Increased transaminase elevations are listed as a very common adverse event in the SmPC, therefore liver function will be tested prior to study enrolment (detailed screening), and monitored at the day 27 safety check, five days post the last administration of the IMP, for safety purposes.

Renal impairment

As clinically appropriate, patients should have eGFR determined prior to starting Remdesivir and while receiving it. Safety data from patients with severe renal impairment and ESRD reported during Study GS-US-540-5912 [22] were comparable to the known safety profile of Remdesivir However, there are limited safety data in this patient population. Therefore, taking the significant higher exposure of the metabolite GS-441524 into account, patients with severe renal impairment and ESRD should be closely monitored for adverse events during treatment with remdesivir (see section 5.2 of the SmPC)

All patients will have eGFR screened at the detailed screening visit and Day 27 to determine suitability for participation in the trial. Participants who return an eGFR < 30 mL/min will not be eligible for participation.

Risk of reduced antiviral activity when co-administered with chloroquine or hydroxychloroquine

Coadministration of Remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir. Patients who are taking either of these medications will be excluded from participating in the study.

3.1.2 COVID 19

The mitigation of transmission of COVID-19 at each site will be achieved via the following approaches:

- Testing and symptom reporting: Participants and research staff in direct contact with participants will be recommended to complete lateral flow tests in the event of experiencing COVID-19 symptoms. This does not follow national or local guidance but is being implemented by the study to protect those that have been identified as being at risk. Any person that reports a positive test will be prevented from direct contact with participants until a negative test is reported. For participants enrolled on the trial, adverse event protocols will be followed and reported as described in section 12.
- FFP3 masks can be provided to each site for all research/clinical staff and participants. Everyone will be asked to wear a mask unless they are medically exempt. Locally provided surgical masks may also be used in accordance with local policies. Adequate ventilation is required and should be regularly monitored in all research spaces. Where spaces do not have windows and adequate ventilation the use of a high-efficiency particulate absorbing (HEPA) filter is mandatory and will be provided by the study.
- All equipment and facilities should employ cleaning and sterilising procedures before and after each test using locally approved cleaning products. This also includes participants and research staff using hand sanitiser as they enter and leave designated research spaces.

3.1.3 Exercise testing

There is a risk of post-exertional symptom exacerbation and post-exertional malaise following completion of the CPET protocol. It has been developed with rigorous testing and piloting and has demonstrated tolerability within Long COVID patients as part of a research project (IRAS ID: 313936). This study now completed (December 2023) and there has been only one reported adverse event (AE)s in any data collection sites (2 internationally, 3 nationally) and over 175 tests. The outcome of the AE was unrelated.

To ensure safety a strict inclusion criterion will support recruitment to the study. This excludes participation from those determined (through screening) of being a serious risk of experiencing post-exertional malaise. Whilst it is acknowledged that these participants stand to achieve the largest benefit from the IMP, the insight derived from the 2-day CPET will enhance mechanistic understanding and inform the development of future non-exercise trials that are more appropriate for high-risk patients. We have also developed a strict test-termination criteria to prevent adverse outcomes for patients which includes continuous monitoring of physiological (e.g., blood pressure and O2 saturation) and functional and motor outcomes (e.g., confusion and coordination). A recent paper by Appleman *et al* (2024) demonstrated small atrophic fibres and focal necrosis in muscle tissue which was elevated in Long COVID patients following exercise via CPET [23]. It is important to note that this study used an unrestricted protocol and

participants exercised until volitional exhaustion. The approach to exercise intensities here is limited to sub-maximal intensities and is also stratified relative to current functional status. It is acknowledged that this exercise test still contains an element of risk for a small population within the intended study sample, but rigorous pilot testing and current use in clinical research have demonstrated that this adapted approach provides meaningful clinical insight and is well tolerated by patients.

3.1.4 Fatigue

Patients with Long COVID are at risk of fatigue and severe exacerbation of their symptoms if too much physical, emotional and cognitive stress is exerted. Participants must be aware of their capabilities and where possible limit exposure stress as much as possible. The following actions are in place:

- Parking adjacent to the testing and treatment rooms
- Wheelchairs available
- Minimum noise levels
- Reduced distractions
- Low level lighting in testing and treatment rooms where possible
- Rest periods provided between periods of talking

Participants will be asked to complete a series of questionnaires as part of the study. To limit fatigue these will be provided 24 hours in advance to allow for more time to complete them.

3.1.5 PET/CT scans

Participants in Exeter will be asked to consent to have two scans, pre and post treatment. These scans take approximately 75-90 minutes. Patients are not allowed to eat for 6 hours prior to the scan. They are able to drink still water. This is 4 hours for people living with insulin dependent diabetes. The actions as above will be followed to mitigate for fatigue and virus exposure. Please see PET/CT Scan Protocol for more information.

3.1.6 Postural stress

Patients may have difficulty sitting for periods of time. They may need to recline when having their IV treatment and will be offered plinths to rest their feet allowing them to lean back when seated for long periods.

Alternatively, they may have Postural Tachycardia Syndrome (PoTS) and their heart rate may increase rapidly after getting up from sitting or lying down. Research staff will be aware of this and provide time for participants to stand.

3.1.7 Incidental findings

As part of certain planned study assessments, researchers may make a finding that has potential health or reproductive importance to an individual participant, which are unrelated to the study aims. These are known as incidental findings and may be identified in this study

through the blood tests to measure biomarkers and inflammatory profiles, the cardio-respiratory assessments as part of the CPET and the PET-CT scan. In the event an incidental finding is discovered through any of the test procedures, the participant will be informed by the research team that an abnormal test result has been found and that the local PI/CI will report the finding to the participant's GP and recommend further investigation. The participant will be asked to contact their GP for further discussion about the result and if further investigations are required. Incidental findings do not warrant an immediate withdrawal from the trial and each event will be assessed on a case-by-case basis by the research team and actioned accordingly.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

In the future definitive trial, the primary research questions will be:

P: in patients with Long COVID

I: a five-day treatment of Remdesivir

C: compared to Treatment as Usual

O: will lead to better Quality of life, functional status, fewer symptoms, more tolerance to exercise, less post exertion exacerbation of symptoms, better physiological, physical, cognitive and emotional status, reduced biomarker and inflammatory profiles.

However, due to uncertainties around the ability of patients to comply with the study protocol, this study aims to conduct a feasibility study to obtain the data and experience to inform the conduct of the definitive study.

4.1 Primary objectives

To assess the feasibility of the use of Remdesivir in the treatment of patients with Long COVID. The study will provide high-quality data:

1. To ascertain screening and recruitment rates (overall and by different recruitment pathways)
2. Retention and dropout rate (due to the treatment and/or trial demands, overall and by centre)
3. Adherence to treatment regimen (attendance to 5 days of IMP)
4. Completeness of study assessments (CPET, bloods, PET/CT if in Exeter)
5. Completeness of all data collection activities, including baseline and +28 days after treatment
6. Acceptability of outcome measurements (measured by completion rates)

4.2 Secondary objectives

To identify the most clinically relevant primary outcome for the definitive study including:

1. Quality of life, functional status and symptom burden
2. Tolerance to physical stimulus: exercise tolerance and reduced post exertional symptom exacerbation following incremental exercise
3. Physiological function, physical function, cognitive function, and emotional status and/or capacity
4. Biomarker and inflammatory profiles
5. *Exeter patients only:* Microvascular function: whole body FDG uptake using PET/CT methods

To determine the clinical safety and tolerance parameters of the use of Remdesivir in the treatment of patients with Long COVID.

4.3 Outcome measures

Whilst the primary endpoints of the study are feasibility, the key secondary endpoints relate to drug efficacy, exploratory biomarkers and drug safety and tolerability.

4.3.1 Feasibility outcomes

To facilitate the design and planning of a future definitive trial, the following outcomes will be collected:

- Rates of screening (overall and by centre)
- Recruitment rate (Number of patients consented (as proportion of those screened, by the different recruitment pathways)
- Retention and dropout rate (due to the treatment and/or trial demands, overall and by centre)
- Adherence to treatment regime (attendance to 5 days of IMP)
- Attendance and completeness of study assessments (CPET, Bloods, PET/CT if in Exeter)
- Completeness of all data collection activities including baseline, and +28 days after IMP
- Completion of Patient-reported outcome measurements (>60% completion)

4.3.2 Pre- and Post-Intervention Outcome measures

Several physiological and patient-reported outcomes will be measured pre and post treatment at different time points as detailed below:

4.3.2.1 Patient-reported outcomes:

(Quality of life, functional status, symptom burden and physical, cognitive, and psychological symptoms) (Day 0 Baseline and +28 days after IMP)

- ***Quality of life:***
  Health related quality of life (EQ-5D-5L)

  - routinely used in the assessment of the quality of life in respiratory research and is available in more than 130 languages. It comprises five dimensions (previously 3): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

- ***Functional Status:***
  Post COVID Functional Status Scale (PCFS, Impact on daily life subscale of the LC Symptom Burden).

  - will be assessed to monitor direct recovery and to assess functional sequelae. The PCFS will evaluate the ultimate consequences of COVID-19 on functional status and supplement other instruments that measure the quality of life, tiredness, or dyspnoea in the acute phase. The PCFS covers the full spectrum of functional outcomes and focuses on both limitations in usual duties/activities and changes in lifestyle in six scale grades. Briefly, grade 0 reflects the absence of any functional limitation, and the death of a patient is recorded in grade D. Upward of grade 1, symptoms, pain or anxiety are present to an increasing degree. This has no effect on activities for patients in grade 1, whereas a lower intensity of the activities is required for those in grade 2. Grade 3 accounts for the inability to perform certain activities forcing patients to structurally modify these. Finally, grade 4 is reserved for those patients with severe functional limitations requiring assistance with activities of daily living (ADL).

- ***Symptom Burden:***
  *Symptom Burden Questionnaire for Long COVID (LC Symptom Burden).**

  - (SBQ™-LC) is a patient-reported outcome (PRO) measure and multi-domain item bank that has been developed to measure symptom burden in adults with “post-acute sequelae of COVID-19" (PASC). The SBQ™-LC is composed of 17 independently functioning, unidimensional scales. Sixteen scales measure symptom burden (i.e., symptom presence, severity, or frequency) across different symptom “domains” and one scale measures symptom impact on daily life.

  *Fatigue Assessment Scale (FAS).**

  - is a 10-item scale evaluating symptoms of chronic fatigue. In contrast to other similar measures (e.g., the Multidimensional Fatigue Inventory), the FAS treats fatigue

as a unidimensional construct and does not separate its measurement into different factors.

*Modified Fatigue Impact Scale (MFIS). **

- is a 20-item patient-reported scale designed to measure fatigue across five scales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue [24]. The MFI-20 has been used to assess fatigue in patients with different respiratory conditions, including COPD, pulmonary fibrosis, and lung cancer.

- ***Physical Function:***
  Medical Research Council (MRC) Dyspnoea Scale.

  - Scale to grade how breathless a patient gets doing everyday activities, the scale contains 5 response options: ranging from "I only get breathless with strenuous exercise" to "I am too breathless to leave the house".

- ***Cognitive Function:***
  Perceived Deficit Questionnaire (PDQ-5).

  - The full-length PDQ consists of 20 items and provides a self-report measure of cognitive dysfunction. This instrument provides an assessment of several domains of cognitive functioning that are frequently affected in MS: attention, retrospective memory, prospective memory, and planning and organization.

- ***Psychological:***
  Generalised Anxiety Disorder (GAD-7).

  - a seven-item diagnostic tool validated in both the primary care setting and the general population. The GAD-7 is a 7-item scale that has reporting scores from 0 to 3 on all the questions. It investigates how often the patient has been bothered by seven different symptoms of anxiety during the last two weeks with response options such as: "not at all," "several days ', "more than half the days," and "nearly daily" scored as 0, 1, 2, and 3, respectively. The scores of 5, 10, and 15 are taken as cut-off points for mild, moderate, and severe anxiety, respectively.

Please note that those with an asterisk (*) are also repeated on the day of the Cardiopulmonary exercise testing (CPET test) Pre-Intervention (Days 7&8) and Post-Intervention (Days 51 & 52).

(Symptom burden, initial screening, baseline and +28 days after IMP)

- **Modified De Paul Symptom Questionnaire-Post Exertional Malaise (DSQ-PEM)**
  Assesses symptom frequency and severity over a 6-month look back period, however, for the purposes of this study, it will be modified to assess over a 1-week look back period (in-line with Zimmerman *et al.*: Clinical Trials Identifier: 05595369). Frequency

is rated on a 5-point Likert scale: 0 = none of the time, 1 = a little of the time, 2 = about half the time, 3 = most of the time, and 4 = all the time. Severity is also rated on a 5-point Likert scale: 0 = symptom not present, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. Post-Exertional Malaise (PEM) will be deemed to be present if the participant reports having at least one moderate (rated severity ≥ 2) PEM symptom for a frequency rated ≥ 2.

Table of PROMS and associated timepoints for assessment.

Timepoint	**PROMS**
Initial screening	DSQ-PEM (total score).
Detailed screening	None.
Baseline (Day 0)	DSQ-PEM, EQ-5D-5L, SBQ™-LC, FAS, MFIS, MRC Dyspnoea, PDQ-5, GAD-7
CPET (Days 7&8, 51&52)	SBQ™-LC, FAS, MFIS
PET/CT (Days 11&55)	None.
Treatment days (Days 14-22)	None.
Safety blood check (Day 27)	None.
Post intervention (Day 44)	DSQ-PEM, EQ-5D-5L, SBQ™-LC, FAS, MFIS, MRC Dyspnoea, PDQ-5, GAD-7

4.3.2.2 Clinical assessments:

(Physiological function and physical function, Day 0 Baseline and +28 days after IMP)

- **Physical Function**

Maximum respiratory mouth pressures:

- Inspiratory and Expiratory mouth pressures and lung function testing will be measured at baseline (Day 0) and post intervention. All tests will be conducted and analysed in accordance with published and standardised test criteria from the European Respiratory Society/American Thoracic Society. Maximum inspiratory (MIP) and expiratory (MEP) mouth pressure (cmH^2O) will be assessed using a hand-held mouth pressure meter (RP Check, Medical Diagnostics, Kent, UK). Measurements will be initiated from residual volume (MIP) and total lung capacity (MEP), to determine an index of global inspiratory and expiratory muscle strength as described previously [25].

Lung Function Testing:

- Lung function testing will be assessed using a pneumotachograph (MS03, Micro Medical, Buckinghamshire, UK) to determine FEV1, FVC, PEF, FVC/FEV1 and

conducted in line with the American Thoracic society and European Respiratory Guidelines.

- **Physiological Function**
  Physiological observations will be conducted including blood pressure (mmHg), Oxygen saturation (%)*, breathing rate (breaths/minute)*, resting heart rate (bpm) and body temperature (^{O}C)*.

  6-minute walk test (6MWT).

  - a standardised and widely used measure of functional status in individuals with diseases such as chronic obstructive pulmonary disease, cystic fibrosis, congestive cardiac failure, peripheral vascular disease, and the elderly. It has been previously used to assess responses to interventions and predict morbidity and mortality. Following completion of the 6MWT, patients will provide their rating of perceived exertion (BORG 6-20 scale) and their SPO2 will be recorded. The number of times ((frequency, number) and (duration, seconds)) a patient stops, and the number of metres completed in the allotted time will be recorded.

4.3.2.3 Biomarker and inflammatory profiles

Participants will provide a venous blood sample using a standard venous collection protocol in vacutainer tubes which will be spun at 2,500 RPM for ten minutes and resulting serum and plasma will be deposited within 0.5 ml aliquots and stored in a -80^{O}C freezer for the measurement of inflammatory and metabolic biomarkers, including:

Growth Factors

- **G-CSF**: Granulocyte Colony-Stimulating Factor
- **GM-CSF**: Granulocyte-Macrophage Colony-Stimulating Factor
- **EGF**: Epidermal Growth Factor
- **FGF-basic**: Basic Fibroblast Growth Factor
- **HGF**: Hepatocyte Growth Factor
- **VEGF**: Vascular Endothelial Growth Factor

Interferons

- **IFN-α**: Interferon Alpha
- **IFN-γ**: Interferon Gamma

Interleukins

- **IL-1β**: Interleukin 1 Beta
- **IL-1RA**: Interleukin 1 Receptor Antagonist

- **IL-2**: Interleukin 2
- **IL-2R**: Interleukin 2 Receptor
- **IL-4**: Interleukin 4
- **IL-5**: Interleukin 5
- **IL-6**: Interleukin 6
- **IL-7**: Interleukin 7
- **IL-8**: Interleukin 8
- **IL-10**: Interleukin 10
- **IL-12**: Interleukin 12
- **IL-13**: Interleukin 13
- **IL-15**: Interleukin 15
- **IL-17**: Interleukin 17

Tumor Necrosis Factor

- **TNF-α**: Tumor Necrosis Factor Alpha

Chemokines

- **Eotaxin**: Eosinophil Chemotactic Protein (also known as CCL11)
- **IP-10**: Interferon Gamma-Induced Protein 10 (also known as CXCL10)
- **MCP-1**: Monocyte Chemoattractant Protein 1 (also known as CCL2)
- **MIG**: Monokine Induced by Gamma Interferon (also known as CXCL9)
- **MIP-1α**: Macrophage Inflammatory Protein 1 Alpha (also known as CCL3)
- **MIP-1β**: Macrophage Inflammatory Protein 1 Beta (also known as CCL4)
- **RANTES**: Regulated on Activation, Normal T Cell Expressed and Secreted (also known as CCL5)

These biomarkers have been selected because current research in Long COVID has demonstrated the importance and relevance of a biomarker profile that includes cytokines, chemokines, and growth factors that are associated with Long COVID severity, symptoms and a persistent reduction in quality-of-life [26,27]. Blood samples will be collected during baseline (Day 0) and follow up assessment (Day 44 (+28)) as well as cardiopulmonary exercise test days (Day 7, Day 8, Day 51, and Day 52).

A safety monitoring blood test will also be collected at detailed screening and +/- 7 days following the last intravenous infusion to determine any changes in eGFR and LFT as per details provided in the SmPC.

4.3.2.4 Tolerance to physical stimulus:

Exercise tolerance and post exertional symptom exacerbation following incremental exercise (Cardiopulmonary Exercise Test – Days 7, 8, 51 and 52)

The 2-day CPET protocol has been specifically designed to determine impaired cardio-respiratory and muscular physiology in patients that are at risk of post-exertional malaise/post-exertional symptom exacerbation. The test uses a non-maximal design which allows for the detection of key ventilatory, cardiovascular and perfusion parameters to be observed whilst also imposing a strict inclusion/test termination criterion. The protocol also consists of different strata and the chosen protocol is determined relative to a patient's current ability to undertake functional tasks:

- **Strata 1:** Starting intensity of 10 watts with a five watt per minute increase for 12 minutes (max intensity 70 watts). This protocol is used for participants who achieve <350 meters on the 6MWT.
- **Strata 2:** Starting intensity of 20 watts with a five watt per minute increase for 12 minutes (max intensity 80 watts). This protocol is used for participants who achieve 350-400 meters on the 6MWT.
- **Strata 3:** Starting intensity of 30 watts with a five watt per minute increase for 12 minutes (max intensity 90 watts). This protocol is used for participants who achieve >400 meters on the 6MWT.

Cardiopulmonary exercise testing will be performed/overseen by experienced and accredited clinical exercise physiologists. Tests will be used to determine VO_2 peak and parameters representative of cardiovascular reserve [28]. CPETs will include continuous/regular monitoring of standard measurements including inspired/expired air, ventilation profile, 12 lead ECG, blood pressure, blood lactate and blood gas tensions (where possible). The two latter measures have relevance to Long COVID populations due to the established hypothesis of impaired mitochondrial function and abnormal aerobic contribution to exercise [29]. Blood samples will be obtained via capillary sampling (finger-prick). These measures are standard protocol as outlined by the British Association of Sport and Exercise Sciences [30] and the American College of Sports Medicine [31]. Tests will be conducted using a standard bicycle ramp protocol in accordance with American Thoracic Society guidelines [32].

Key variables of interest include:

- the first ventilatory threshold (VT1)
- peak oxygen consumption ($\dot{V}O_2$peak)
- end-tidal CO_2.

See Section 10.4 for more details.

4.3.2.5 Continuous Symptom profiling and tracking (Baseline to Day 52)

All patients will undertake continuous symptom monitoring Participants who have access to a smartphone will do this using an iPhone Operating System (IOS) and android compatible application that has been specifically developed for Long COVID. '**Visible**' is free to access and is GDPR compliant with data being stored within a cloud-based server in Europe. Patients will be asked to create an account and as part of the Visible App, they will have to complete a

personalised eighteen item Symptom Score Inventory which tracks the daily impact of different physical and cognitive Long COVID symptoms. Participants will be provided with instructions.

The application also has features that allow continuous monitoring of heart rate variability. To enable this feature patients will be provided with a CE marked wearable sensor (Polar Verity Sensor, Polar, Kempele, Finland) that is worn on the upper arm and uses optical technology to record heart rate and heart rate variability.

Upon completion of their participation of the study, data will be exported by the host company from their server (GDPR compliant) using the participant's unique ID code (see section 16.7). Data will then be transferred to the study team for processing and analysis.

Participants who do not have access to a smartphone will complete a daily paper symptom diary. The diary should be returned on the Day 52 visit and the data will be uploaded to the eCRF by the local research team. Heart rate variability data will not be collected for these participants.

4.3.2.6 *Exeter patients only:* Microvascular function: Whole body FDG uptake using PET/CT methods

Imaging and multi-organ metabolic changes

Participants will be asked to consent to two whole-body FDG PET/CT scans at the University of Exeter using the Siemens Biograph Vision (Siemens Healthiness, Germany). Participants will fast for six hours, and blood glucose will be analysed *via* capillary sampling techniques before F-18 FDG is intravenously injected. The activity of FDG administered for each instance of PET/CT imaging will be based on the participant weight (3MBq/kg) up to a maximum of 400MBq. The maximum effective dose from one of these administrations would be 7.6mSv. A parametric (dynamic) protocol will be used for PET/CT imaging and will commence at the time of injection, with the first 6 minutes positioned over the heart and lungs, then using the Siemens motion flow protocol up to one hour post FDG injection. Standard attenuation correction CT scan at 120kV with mAs modulation and PET emission scan using a 3D acquisition mode will be performed immediately. Fusion PET/CT images will be used for accurate anatomical localisation of the avid FDG uptake of Long COVID lesions. Standardised uptake values (SUVs) and K_i will be calculated for major organs and bone marrow. To reduce FDG being taken up by the muscles after physical exertion, both pre and post intervention PET/CT scans will be scheduled at least 3 days post CPET2/CPET4. Upon completion of the baseline PET/CT scan (day 11), patients will be administered Remdesivir in line with details highlighted in the treatment regime section and repeat scans will be conducted on day 55. Specific Scan Arrangements/Details:

- Image from top of skull to mid-femur (PET scan from Inferior to Superior)
- CTAC: kVp: 120; CareDose4d with a quality reference of 60mAs. Rotation time 0.5s; Colimate 128 x 0.6mm; Reconstructed slice thickness 5mm.
- Conduct the baseline CT scan prior to injecting the patient.
- FDG administered at the same time as the PET acquisition is commenced.
- Image from top of skull to mid-femur (PET scan from Inferior to Superior)
- Use the motion-flow facility and shuttle bed mode.

- Start the image over the heart for the first 6 minutes using list mode. Ensure the heart is in the centre of the field of view. 1 bed position for the 6 minutes.
- Perform PET whole body dynamic with shuttle mode sweeps following the 6-minute initial scan up to a minimum of 75 minutes. The following protocols: 7 passes x 2 mins = 14 mins, and 14 passes x 5 mins = 70 mins (the last 6 frames are summed for SUV image).
- You will be prompted to enter the glucose levels and FDG dose.
- A second ultra-low dose CT scan may be required at the end of the PET acquisition if the patient is considered to have moved (as per Long_Covid_Protocol_Patlak protocol on scanner).
- Normal breathing throughout.
- Reconstruction: 2.5mm slices and 1mm slices for the lungs.
- Patlak calculation and SUV for PET data.

4.3.2.7 Long term assessments

Long term follow-up assessments are not planned within the entire study cohort. All participants' General Practitioner (GP)s will receive notification of their involvement in the trial which will be recorded in their medical notes.

5. TABULATED SUMMARY OF OBJECTIVES AND OUTCOMES

	Outcome Measures	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Feasibility Objectives		
Rates of screening	Number of patients screened overall and by centre	Initial and detailed screening
Recruitment	Number of patients consented (as a proportion of patients screened. Overall and by centre)	Consented measured at Initial Screening, Detailed screening and Baseline visit
Retention to the study	1. Number of recruited patients completing outcome measures 2. Number of patients attending each appointment 3. Number of participants completing the intervention 4. Number of participants that withdraw at different stages of the trial	1 and 2. At Baseline, CPET tests and post-Intervention visit (Days 0, 7&8, 44, 51&52 (11 & 55 in Exeter)) 3. Number of patients completing each day of treatment 4. At Baseline, CPET test, treatment and post-Intervention visits (Days 0,

		7&8, 14 – 22, 44, 51&52 (11 & 55 in Exeter))
Adherence to the treatment regime of Remdesivir	Attend clinic appointments and complete each treatment session.	Measure Days 14 -22 during treatment phase
Completeness of study assessments	Attend appointments and complete assessments	CPET, Bloods (and PET/CT if in Exeter)
Completeness of data collection activities	1. Participants complete all patient - reported measures 2. Number of participants that complete physical and physiological tests	At Baseline, CPET test and post-Intervention visits (Days 0, 7&8, 44, 51&52).
Secondary objectives		
Pre and Post Intervention Patient-reported Outcome measures		Day 0 and +28 days after IMP (Day 44) *Days 7, 8, 51, 52
Quality of life	EQ-5D-5L	
Functional status	PCFS Impact on daily life subscale (SBQ™-LC)	
Physical Symptoms	MRC Dyspnoea Scale	
Cognitive symptoms	PDQ-5	
Emotional symptoms	GAD-7	
Symptom Burden	DSQ-PEM	
	SBQ™-LC *	
	FAS*	
	MFIS*	
Clinical Assessments		Day 0 and +28 days after IMP (Day 44) *Days 7, 8, 51, 52
Physiological function and physical function	Maximum inspiratory and expiratory mouth pressure (MIP and MEP) Lung function Blood pressure* Oxygen saturation *	

	Breathing rate* Resting heart rate Body temperature* 6-minute walk test (6MWT, Borg 6-20 and SPO^2)	
Biomarker and inflammatory profiles	See section 4.3.2.3 for full list	Days 0, 7, 8, 44, 51, 52
Tolerance to physical stimulus (CPET)	First ventilatory threshold (VT1) Peak oxygen consumption (V̇O2peak) End-tidal CO_2	Days 7, 8, 51 and 52
Daily Symptoms and heart rate variability (VISIBLE)	Symptom Score Inventory Heart rate variability	Day 0 to day 52
Clinical Safety and tolerance parameters of the use of Remdesivir	AE/SAE/AR/SAR/SUSAR	Consent to day 52 (55 if Exeter)
(Exeter patients only) Microvascular function: whole body FDG uptake using PET/CT methods	Standardised uptake volume (SUV) and Ki of 18FDG uptake observed during PET/CT scans.	Days 11 and 55

5.1 Clinical safety and tolerance parameters

Frequency, seriousness, and intensity of Adverse Events (AE), Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) will be assessed throughout the study by patient reporting and testing/observation/questioning by medical personnel or investigators (See Section 12).

6. TRIAL INTERVENTION

All participants will receive the antiviral medication Remdesivir via intravenous infusion over 5 consecutive days. It is licenced for use in patients with COVID-19 who have been admitted to hospital with acute illness. Remdesivir was chosen as the IMP for this trial due to the positive outcomes during the acute phase of infection (i.e., reduced likelihood of prolonged/persistent symptoms).

For further information on the dosing schedule see Section 11.6.

7. TRIAL DESIGN

This is a Phase IV, multi-site open label, single-arm proof of concept study of patients with Long COVID, where the primary endpoints are related to feasibility of administering IV Remdesivir over a 5-day treatment period. The trial design and schedule of events are summarised in the trial flow chart and Table 1. Participating units are supported by a Medical Principal Investigator and research nurses.

8. TRIAL SETTING

The study will be conducted in NHS and non-NHS sites. Additional sites will be activated where required to achieve the total recruitment target.

University of Derby: Testing site. Participants recruited to the study in and around the Derby/Derbyshire area will conduct all testing and assessment sessions outlined in the schedule of assessments (section 10.11) at a dedicated Long COVID research laboratory at the University of Derby (Kedleston Road, Derby). Participants will have access to free onsite parking located less than 200 metres away from the research space where testing will occur. Participants will also have access to private changing and showering facilities and a resting space should they wish to use them. Participants that are accompanied by a chaperone will be able to make use of a small waiting area. Everyone will have access to complimentary light refreshments.

University Hospitals of Derby and Burton NHS Foundation Trust: Treatment site. Participants entered into the study that have completed all baseline assessments, will attend a suitable clinical research space at the Royal Derby Hospital (Uttoxeter Road, Derby) to receive their treatment course (see section 11.6, for full details).

University of Exeter: Testing site. Participants recruited to the study in and around Exeter will have PET/CT scans conducted at the Mireille Gillings Neuroimaging Centre (MGNC), University of Exeter. Participants will have access to free onsite parking from the rooms in which testing will occur. Participants will also have access to private changing and showering facilities should they wish to use them and participants that are accompanied by a chaperone will be able to make use of a small waiting area. Everyone will have access to light refreshments.

Derbyshire Community Health Services NHS Foundation Trust (DCHS) and Royal Devon University Healthcare NHS Foundation Trust (RDUH): Patient Identification Centres *via* established Long COVID services that makes use of existing routes to access and contact patients. Participant Identification Centre (PIC) agreements will be used in coordination with clinical staff to assist with recruitment. RDUH will also act as the treatment site for participants enrolled onto the study at the University of Exeter.

9. PARTICIPANT ELIGIBILITY CRITERIA

Eligibility criteria have been established in conjunction with the guidance set out by the National Institute for Health and Care Excellence (NICE), British National Formulary (BNF) for selecting and the product summary of product characteristic documentation:

9.1 Inclusion criteria

Patients must satisfy all the following criteria to be enrolled on the study:

Initial Screening Criteria: Phone call	• ≥18 years of age at the time of enrolment • Previously confirmed or suspected SARS-CoV-2 infection. • Confirmed diagnosis of Long COVID by a Health Care Practitioner according to the definition provided by the World Health Organisation* for persistent symptoms following a confirmed SARS-CoV-2 infection. • Willing and able to provide informed consent, complete the surveys, and complete all planned clinical assessments, and return for scheduled study visits. • Lives within commutable distance of the relevant site, at discretion of local PI.
Detailed Screening Criteria (Patient Reported Outcomes): In clinic	• Evidence of persistent symptom profile relative to pre-COVID-19 status as derived from patient reported outcome measures.

** WHO define Long COVID as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.*

9.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from study participation:

Initial Screening criteria: Phone call	• Treatment history of Remdesivir, molnupiravir, paxlovid and/or any other COVID-19 anti-viral medication (<6 months). • Confirmed compromised immune system/function. • Currently engaged in a physical rehabilitation programme or intervention aimed to improve Long COVID symptom profile and/or functional status.

	• Recognised as a 'severe risk' of experiencing post-exertional malaise following engagement in physical tasks. Determined using the De Paul symptom questionnaire (total score). • Lack of mental capacity to provide informed consent. • Unable to understand verbal English/have a hearing impairment that prevents adequate communication.* • Participation in another clinical drugs trial within the last 6 months • Currently pregnant, breastfeeding or attempting to get pregnant (i.e., not using effective methods of contraception). • Currently taking medications known to have an interaction with Remdesivir (e.g., chloroquine phosphate or hydroxychloroquine) as defined by British National Formulary (BNF) information on the selection, prescribing, dispensing and administration of medicines: https://bnf.nice.org.uk/interactions/remdesivir/ • History of serious adverse reactions to medication/infusions
Detailed Screening Criteria (diagnostic testing):	• History of Hepatic or Renal Impairment (eGFR (<30ml/min) and LFTs ALT>x5 ULN). • Currently pregnant. • **Exeter participants only:** Recent/long-standing history of CT (within 3 months)/ ongoing radiotherapy treatment. Risks of accumulative burden to be discussed as part of study involvement, but it is at the discretion of participants.

***Note:**

- **English Comprehension:** Potential participants who are unable to understand verbal English will not be eligible for this study. This is due to the necessity of telephone contact which is a key aspect of this study and the unavailability of validated questionnaires in languages other than English.
- **Hearing Impairment:** Unfortunately, if the participant has a hearing impairment that prevents adequate communication on the telephone, they will not be able to take part in the study. This will be clearly stated in the participant information sheet.

10. TRIAL PROCEDURES

10.1 Participant identification

There are multiple routes in which potential participants may be identified and recruited onto the study to facilitate target recruitment rates. These routes are detailed in the following sections.

Section 10.1.1 describes the identification and recruitment from clinics.

Sections 10.1.2 refers to self-referral routes.

10.1.1 Participant identification through established Long COVID Centres clinics

Clinical teams at Long COVID centres in Derbyshire (Derbyshire Community Health Services NHS Trust) and Exeter (Royal Devon University Healthcare NHS Foundation Trust) will screen existing and new referrals to the service to determine eligibility. This will be supported by the local clinical research network nurses. Patient identifiable information provided by the referring clinical team will be used to identify potential participants. Patient identifiable information will not be used by anyone other than the clinical team. Members of the research team will not require access to identifiable patient data for the purpose of identifying potential participants.

Site Principal Investigators (PIs) / lead local collaborators (LCCs) will be responsible for promoting the study amongst relevant staff at the centres to optimise participant identification. Performance at each site will be closely monitored by the Trial Management Group (TMG). Participants identified in centres that appear to fulfil inclusion/exclusion criteria will be potentially eligible for the study. The clinician may discuss the study with potential participants in clinic at their regular appointment. This may be a face-to-face appointment or virtual/telephone appointment, depending on the site's local arrangements.

If the potential participant is interested, they will be provided with a Participant Information Sheet (PIS) describing the study and including contact details of the local ERASE-LC research team, who they can contact if they have any questions. If the potential participant attends for a face-to-face appointment, the PIS will be handed to them during the visit. If their appointment occurs virtually or over the telephone, the PIS will be emailed or posted to the potential participant, depending on their preference.

Potential participants will also be asked if they wish to be contacted by the research team in a few days to discuss the study further, and if so the best time of day to contact them. If yes, the PIC will forward the contact details to the local research team. If they do not wish to be contacted, they will not be contacted again about the study unless they are the ones to initiate this. To do so they will be advised to use the contact details on the PIS to inform the research team should they wish to participate/discuss the study further. They may also be referred to the study website to complete an Expression of Interest.

Details of potential participants who have been identified *via* this route will be documented on the digital REDCap Community screening log and will include the date the PIS has been provided, whether it was handed to the patient, e-mailed or posted and whether they wish to be contacted by a researcher. If the participant wishes to be contacted, a member of the research team will call them after 48-hours. If the PIS has been posted to the patient, the research team will call the participant after 72-hours, to allow time for the PIS to be delivered.

If a potential participant does not wish to be contacted by the research team, and they have not contacted the team themselves using the details on the PIS after 4-weeks, it should be documented on the screening log that they are no longer interested.

If the potential participant is not being seen face to face, then an introductory letter/email with the PIS attached will be sent to the patient and if the patient is interested, they are asked to contact the research team for further information. Alternatively, they will be able to access the ERASE-LC Website and read the PIS. If interested, they may complete the Expression of Interest form.

10.1.2 Self-referral

Database

Following previous involvement in Long COVID research undertaken by the University of Derby on social media, patients have given consent to be contacted about involvement in future research trials. This database is hosted by the University of Derby and contains approximately 1000 potential participants who have contacted directly *via* e-mail and/or telephone to enquire about interest in participating in the study. Once the study is approved, the database will be made available to the study team at the University of Derby and the University of Exeter to contact potential participants.

Data will be filtered for geographic location and age. Only potential participants in proximity to attend either Derby or Exeter centres will be eligible for the feasibility study. However, those that live further away will be asked whether their information may be stored for a future national study.

Participants on the database will be contacted about participation and sent a Patient Information Sheet. If they are interested in taking part, they will be asked to complete an Expression of Interest form.

ERASE-LC Website, social media, posters and leaflets

Social media will be used to promote the study and patients guided to the ERASE-LC Website which will be hosted on the University of Plymouth website. Leaflets containing a lay summary of the study and key eligibility criteria and posters will also be provided for sites to place in the clinical areas where patients with Long COVID attend for their appointments. These will direct people with Long COVID to the ERASE-LC website. QR codes will be used on documents so potential participants can access the information digitally immediately. On the website will be information about the study, and the PIS. Patients that are interested may complete the

Expression of Interest form or contact the local research team directly using the contact details provided on the localised Participant Information Sheet.

The poster and leaflets will also be available in a digital format, and sites will be encouraged to disseminate it *via* their communication routes, such as newsletters, and share on their social media accounts.

10.2 Screening and Eligibility

Once participants have been identified and given consent to be contacted, either through clinics or having completed Expressions of Interest, members of the research team will undertake initial screening, conduct eligibility checks and if appropriate arrange a Detailed Screening appointment. Data relating to eligibility and screening will be collated within the trial master file (TMF) to ensure reporting is collated and reported in line with the consolidated standards of reporting trials (CONSORT) guidelines. Data will be pseudo-anonymised and include reference to the following non-identifiable information: Age, Sex at birth, Ethnicity, registered to the trial or not.

10.2.1 Initial Screening (approx. 20 mins)

All potentially eligible patients

Once completed, Expression of Interest forms will be sent to the study teams at their local site. Potential participants must indicate that they are happy to be contacted to submit the form. Other patients may contact the study team directly or have consented to be contacted if recruited through PIC sites. The research team must log details from their emails and contact information on their local site screening log to keep a record of potential participants who need to be contacted. Sites are responsible for ensuring this information is maintained and up to date. De-identified data only may be entered on the electronic study screening log on REDCap.

Potential participants will be contacted *via* telephone by one of the ERASE-LC research team, who is delegated the roles of screening and confirming eligibility. Attempt to contact will be made three times, after which a person will be documented as ‘not contactable’ on the screening log, and no further attempts at contact will be made. Patients with Long COVID may screen calls due to fatigue. They will be able to provide consent for messages to be left on the Expression of Interest.

During this telephone call, participants will be asked if they have read and understood the PIS and encouraged to ask any questions that they have about the study. The researcher should then provide an overview of the study requirements. If the participant requires more time to consider the study, then a further telephone call should be scheduled for a later date. If the patient is happy to progress, then the research team may proceed with the Initial eligibility check, referring to Work Instruction for Screening and Eligibility.

The researcher will also ascertain if the patient has any particular communication needs that can be met. According to the Accessible Information Standards (NHS Publications Gateway, 2016), participants should be asked to self-define their communication support needs (and not their disability). The participant may inform the study team voluntarily or be asked about any such communication difficulties (e.g., if the participant finds it difficult to read small, printed text or if the participant struggles to read and would appreciate the documents being read aloud by the study team).

If the participant meets the inclusion/exclusion criteria, as far as can be determined during the phone call, the researcher will then schedule a face-to-face visit for a detailed screening assessment. The patient should be informed that this assessment will last approximately 60 minutes and will involve providing informed consent if willing to participate, re-confirming eligibility criteria and several more invasive screening tests; Pregnancy (if female), and blood tests. Information obtained from this call will be logged on the REDCap database with consent from the patient.

Patients will receive a reminder 24 hours prior to the appointment.

10.2.2 Detailed Screening Visit

The participant will attend an appointment at the University located nearest to them at the allocated time to be seen by the Research team. A total of 60 minutes should be allowed for the face-to-face screening visit. This will consist of confirming initial eligibility (20 minutes), receiving informed consent (10 minutes) and clinical tests (30 minutes).

10.2.2.1 Eligibility Confirmation

This will take approximately 20 minutes and conducted by a member of the research team. Inclusion criteria from the initial screening will be confirmed. A combination of discussion with the participant and use of medical notes may be used to confirm eligibility. Paper CRFs will be provided as a data collection aid for the member of the research team to record data on these initially and transfer them to the database later after consent.

10.2.2.2 Informed Consent

Approximately 10 minutes should be allowed for this process at the local study site. Informed consent must be obtained by the site PI, or an authorised delegate prior to collecting any study data. Authorised delegates (recorded on the study delegation log) must be suitably trained in the relevant principles of Good Clinical Practice and the requirements of the trial protocol. Doctors, registered nurses, Allied Health Professionals (band 5 or higher) and trained researchers may be authorised to receive consent for this study. Consent should only be provided after potential participants have had enough time to consider and discuss the study with their clinicians, family or friends. If they agree to take part, written formal consent will be taken from the potential participant by the PI or delegated individual using a study specific informed consent form (ICF).

The PI retains overall responsibility for the conduct of research at their site, this includes receiving informed consent from participants at their site. They must ensure that any person

delegated the responsibility to participate in the informed consent process is duly authorised, trained and competent. If delegation of consent is acceptable, then details should be provided in the site delegation log. A medically trained Doctor will confirm that the patient is eligible and able to progress in the trial. Where possible, this will be done by referring to the medical notes. If the medical notes cannot be accessed (e.g., the patient is not registered at the linked Trust), the patient must provide evidence of a Long-COVID diagnosis from a Healthcare Professional to proceed. Medically trained staff will need to countersign all eligibility criteria via a trial-specific eligibility checklist. A copy of the checklist should be filed in the medical notes. this will be monitored by PenCTU.

Informed consent will be received prior to the potential participant undergoing procedures that are specifically for the purposes of the trial and are outside standard routine care at the participating centre.

The informed consent form will include optional consent for storage of blood samples for use in future ethically approved research and to being contacted about future research opportunities. Participants at Exeter will also be given the option to opt-out of the PET-CT scans.

The participant will be informed they have a right to withdraw from the study, without giving a reason, at any time and without prejudicing their further treatment. Data collected up to the point of withdrawal will still be retained and used in analysis. This data will remain pseudonymised and any intention to utilise such data is outlined in the consent literature. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure that this is carried out in a timely manner.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily, in an environment free from coercion or undue influence. Where a participant can consent for the trial but later becomes incapacitated, the participant will be withdrawn from the trial as following the trial instructions and procedures will not be possible.

Original versions of completed ICFs should be stored in the Investigator Site File, and copies should be provided to the GP, the participant and filed in the medical notes.

10.2.2.3 Demographics and Medical History

Once consent is provided, the following data, tests and measures will be taken as part of the Detailed Screening.

Demographics:

- Age
- Sex at birth
- Height
- Weight
- Ethnicity

Medical History:

- Endocrine/diabetes

- Renal
- Cardiovascular
- Neurological/cerebrovascular
- Gastrointestinal
- Liver
- Malignancy (including haematological)
- Infarction
- Smoking status (previous/current/how many years/typical daily amount).

Concomitant Medications:

Patients taking medications that are known to interact with the IMP will be excluded from the study. These are documented within the SmPC and established libraries (BNF/EMA) which will be reviewed on a monthly basis during screening and recruitment to ensure current safety practices for patients.

This includes the following medications:

- Apalutamide
- Carbamazepine
- Chloroquine
- Enzalutamide
- Fosphenytoin
- Hydroxychloroquine
- Mitotane/Phenobarbital
- Phenytoin
- Primidone
- Rifampicin

Long COVID Symptoms

Data on symptoms consistent with Long COVID will be collected to include the most common listed below. This list is not exhaustive as there are over 250 documented symptoms recorded.

To include:

- Extreme tiredness (fatigue)
- Feeling short of breath
- Loss of smell
- Muscle aches
- Problems with your memory and concentration ("brain fog")
- Chest pain or tightness
- Difficulty sleeping (insomnia)
- Heart palpitations
- Dizziness
- Pins and needles
- Joint pain

- Depression and anxiety
- Tinnitus
- Earaches
- Feeling sick
- Diarrhoea
- Stomach aches
- Loss of appetite
- High temperature
- Cough
- Headaches
- Sore throat
- Changes to sense of smell or taste
- Rashes
- Any other

10.2.2.4 Clinical tests for eligibility

At this visit several clinical tests have to be conducted to confirm eligibility which will take approximately 10 minutes. Patients will be informed that they still may not be eligible dependent on the outcome of the following tests.

To test for the following:

- Current pregnancy status – a pregnancy urine dip test will be requested where appropriate.
- History of Hepatic or Renal Impairment - Venepuncture samples will also be tested to determine kidney function (glomerular filtration rate, eGFR), and liver function tests (LFTs). Any value returned outside of clinical reference ranges (eGFR >30 and LFTs ALT>x5 ULN) will be excluded.

Results will be available in approximately five days. A date for the Baseline assessment visit will be arranged before they leave the clinic. Patients who are found not to be eligible due to any of the results will receive a phone call from the research team to discuss the results and provide further advice if required. Patients who are eligible will be notified and will receive a phone call or email (as arranged) from the research team to confirm the baseline assessment visit.

Participants will be sent their Patient Reported Questionnaires by email 24 hours prior to their baseline appointment to allow more time for them to complete them: EQ-5D-5L, MRC Dyspnoea Scale, PDQ-5, GAD-7, DSQ-PEM, SBQ™-LC, FAS and MFIS as described in Section 4.3.2.1. For those requiring paper questionnaire booklets, these will be handed to the participant at the preceding visit with instructions not to complete the questionnaires until 24 hours prior to baseline visit. A text will be sent to all participants to remind them about their baseline visit and to complete the required questionnaires 24 hours beforehand.

10.3 Baseline Assessment (Day 0)

All participants will be provided with an appointment for the baseline assessment within a month of their detailed screening visit. Participants will attend the Universities of Derby or Exeter for their baseline assessment which will take approximately 90 minutes. To support the assessment patients will be asked to bring details/records of their COVID-19 infections and vaccinations with them.

At the assessment participants will be given time to complete their questionnaires if not already done so. Pregnancy status will be ascertained via urine dip test and confirmation that the participant is still eligible and willing to take part will be recorded.

Participants will be reviewed for adverse events at every study visit from the point of informed consent.

Clinical assessments will also be undertaken;

Physiological function and physical function.

- Maximum inspiratory and expiratory mouth pressure (MIP and MEP)
- Lung function
- Blood pressure
- Breathing rate
- Resting heart rate
- Body temperature
- 6-minute walk test (6MWT, Borg 6-20 and SPO^2)

Biomarker and inflammatory profiles

See section 4.3.2.3.

The following information will then be collected.

COVID-19 History:

- Overall health prior to first Covid-19 infection (Very good/good/moderate/bad/very bad)
- Health rating today (Very good/good/moderate/bad/very bad)
- Number of confirmed positive COVID-19 infections by LFT/PCR
- Number of suspected COVID-19 infections
- Date of last known COVID-19 Infection
- Details of last COVID-19 infection (severity mild/moderate/severe)
- Details of last COVID-19 infection (duration 0-5 days/6-10 days/11-15 days/16+ days)
- Symptoms experienced with COVID-19 infection:
    - high temperature or shivering (chills),
    - new, continuous cough,
    - loss or change to your sense of smell or taste,

    - shortness of breath,
    - feeling tired or exhausted,
    - aching body,
    - headache,
    - sore throat,
    - blocked or runny nose,
    - loss of appetite,
    - diarrhoea,
    - feeling sick or being sick
- Known variants of Known COVID-19 (Alpha/Epsilon/Omicron/Theta/Kappa/Ioata/Zeta/Mu/Lambda/Beta/Gamma/Delta/Not sure)
- Admissions to hospital in previous 6 months (0/1/2/3/4/5/6/7+)
- Previous GP visits in previous 6 months (0/1/2/3/4/5/6/7+)
- Admission to hospital due to COVID-19
- Date of last admission
- Route of admission (A&E / GP admission to acute medical area / Other)
- Length of stay
- Details of stay (Admitted to a level 2 or 3 area? Mechanical ventilation/NIV/Re-admitted to hospital within 30 days)
- Referred to LC Clinic (Yes/no/date)
- Route to LC Clinic (A&E / GP admission to acute medical area/self-referral/other)
- Current engagement with LC Clinic (Waiting for referral/waiting for assessment/under an established clinic/discharged)
- Vaccine status (number had/0/1/2/3/4/5+)
- Dates of all vaccines
- Manufacturers of vaccines had (Moderna/Pfizer/Sanofi and GSK/unknown)

Once all the data has been collected, participants will be provided with a CE marked wearable sensor in order to track Daily symptoms and heart rate variability, see Section 4.3.2.5 for more information on the Visible App. Instructions and training will be given. For patients without a smartphone, they will be provided with a paper symptom diary to track these daily symptoms.

The dates for the CPETs will be confirmed with the participant before they leave (9 days after baseline / post intervention assessment, + / - 2 days).

10.4 Cardiopulmonary Exercise Test (Days 7, 8, 51 and 52)

Participants will receive an email with a reminder 24 hours before each CPET day. This will also include the Symptom Burden questionnaires; SBQ™-LC, FAS and MFIS as described in Section 4.3.2.1 to complete in advance if participants would like to have more time. A text reminder of the appointments will also be sent.

On arrival at each session pregnancy status will be confirmed.

Bloods will be taken as described in Section 4.3.2.3 to be tested for biomarkers and inflammatory profiles. Once patients are ready, they will progress with the CPET test.

Equipment and setup:

Participants will complete a maximal graded exercise test on a magnetically braked ergometer (Lode, Excalibur Sport Groningen, Netherlands). The cycle ergometer wheel will be calibrated according to manufacturer recommendations before the study. The cycle ergometer will be set up according to each participant's body size and personal preference which will be recorded in the CRF and used for all follow-up assessments. The knee angle at the bottom of the pedal stroke will be ~25°, which is optimal for movement economy and injury prevention. Knee angle will be measured using a universal goniometer. The cycle ergometer handlebars will be positioned so that the participant can comfortably maintain an upright posture. The cycle ergometer set-up will be identical for each visit.

Exercise Protocol:

A stepwise incremental exercise test will be performed at a cadence of 60 revolutions per minute (rpm) (±10%). The exercise protocol will begin with a 3-minute rest period, followed by a stepwise incremental protocol and last no longer than 12 minutes. The exercise protocol will be individualised based on participants' predicted exercise capacity, as described above. Heart rate and pulmonary gas exchange data will be measured continuously. Blood pressure and rating of perceived exertion (RPE; 6 to 20 scale) will be measured during the final 15 second period of each minute. Participants will be asked to relax their arm and shoulder muscles whilst their forearm is rested on the researcher's shoulder (padded with a folded towel). This will ensure that the participant's arm is positioned near the heart level to reduce measurement error. At the end of the exercise test, participants will complete a cooldown consisting of unloaded pedalling at 20 rpm for 5-10 minutes. All data will be recorded in the device software (MetaSoft Studio) and raw breath by breath data exported for offline analysis using Microsoft Excel (Washington, USA) for analysis and data at specific timepoints (baseline and post-exercise) included within the CRF.

In accordance with our pilot data and use within unpublished work (clintrials.gov: NCT04649957) , we will stratify individuals starting load based on their 6MWT distance, Strata I: 6MWD < 350 (starting load of 10 watts; with subsequent increments of 5 watts), Strata II: 6MWD 350 – 400 (starting load of 20w with subsequent increments of 5w and Strata III: 6MWD > 400 (starting load of 30w with subsequent increments of 5W).

In test measurements:

Breath-by-breath pulmonary gas exchange data will be smoothed using a middle five of seven breath average. Key variables of interest include the first ventilatory threshold (VT1), peak oxygen consumption ($\dot{V}O_2$peak) and end-tidal CO_2. $\dot{V}O_2$peak is defined as the mean $\dot{V}O_2$ over the last 30 seconds of the exercise test, adjusted for body mass (ml·kg−1·min−1). VT1 will be determined by using the V-slope method to identify the deflection point in the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ – indicating a disproportionate rise in CO_2 production due to increasing anaerobic glycolytic activity. VT1 will be confirmed using the nadir of the ventilatory equivalent (VE) for $\dot{V}O_2$ (VE/$\dot{V}O_2$). The VT1 will be confirmed by two researchers at each site. Where agreement is not reached, a third researcher will adjudicate. End-tidal CO_2 is the partial

pressure of CO_2 measured at the end of each breath. Blood lactate and blood gas tensions (where possible) will be collected pre and post CPET via capillary sampling techniques (100 µl) and analysed at the point of collection.

Exercise termination criteria:

- Chest pain suggestive of ischaemia
- Fall in systolic blood pressure >20 mmHg from the highest value during exercise.
- >225 mmHg systolic blood pressure
- >130 mmHg diastolic blood pressure
- Hypotension (<100 mmHg systolic)
- Severe desaturation: $SpO_2 \leqslant 80\%$ when accompanied by symptoms of severe hypoxaemia.
- Sudden pallor
- Loss of coordination
- Mental confusion
- Dizziness or faintness

Safety note:

Trained first aiders will be present during the delivery of all tests and if required access to a defibrillator and telephone to contact emergency services will be in proximity (e.g., in the same building) to the laboratory used for testing, should they be required.

Maximum effort determination and criteria:

Criteria for the assessment of a good participant effort will include peak respiratory exchange ratio (RER) >1.10, peak HR≥85% predicted and RPE ≥18.31 (Balady *et al*., 2010). Prior to the test, participants will be monitored for 5 minutes to allow passive data collection and for a total of 10 minutes after completion. We will analyse over 30s averages to allow for differences in Gas analysis systems and monitor heart rate throughout the test and 10 minutes of seated recovery. Blood Pressure monitoring continuously (every 30s). Blood lactate concentration and blood gas tensions will be monitored through via capillary sampling at the start and end of the exercise component of the test.

Test Interpretation:

Each test will be interpreted following published guidelines provided by the American College of Sports Medicine. Upon the conclusion of each test, the key descriptive characteristics and findings will be recorded to facilitate the use of cohort analyses. Data will be stratified according to the demographic (age, sex at birth, ethnicity, pre-COVID-19 functional status and important physiological parameters for a given workload (absolute and relative oxygen consumption or VO_2 peak, O_2 pulse, alveolar-arterial O_2 gradient, arterial to end-tidal CO_2 difference and the relationship between carbon dioxide output and ventilation (VE/VCO_2 slope)). These approaches will be used to identify differences, trends and patterns in key defining variables that might lead to longstanding impairment/morbidity. CPET 1 will be at least 7 days post baseline measures to ensure no symptoms of post exertional malaise and/or

excessive fatigue from baseline assessments. Patients will wear accelerometers during this period to compare baseline and follow up.

Key variables of interest include:

- the first ventilatory threshold (VT1)
- peak oxygen consumption ($\dot{V}O_2$peak)
- end-tidal CO_2.

Once the exercise test is complete participants will have time to recuperate and will be provided with refreshments.

For patients in Derby after they have completed the two CPET days (7&8) they will not be required to attend hospital until the Treatment phase (approximate days 14 – 22 to allow for range in days to allow for consecutive administration on weekdays),

Exeter participants will be booked in for their pre-treatment PET/CT scan on Day 11 (see Section 4.3.2.6 for details) prior to commencement of treatment on Day 14.

10.5 Exeter participants only pre-Intervention PET/CT (Days 11)

Participants recruited in Exeter will be asked to attend the Mireille Gillings Neuroimaging Centre (MGNC) at the University of Exeter Medical School for a PET/CT scan on day 11 (+ 2 days), see Section 4.3.2.6 for details. Participants will be able to opt out of the PET/CT scans if they wish (see Section 10.2.2.2).

Prior to the scan a pregnancy test (urine dip) will be performed by those participants of childbearing potential.

10.6 Treatment phase (Days 14 to 22)

Participants will attend their local site (Exeter or Derby) for five consecutive days. They will need to attend for approximately 2 hours which includes time for details of any adverse responses, preparation and delivery of the infusion plus monitoring post IV intervention. Refer to Intervention Flow Chart (Figure 1) for further information.

The participant will arrive at the allocated time. Once comfortable the research team will establish any changes in details or circumstances and ensure that they are happy to progress. Participants able to conceive will have a pregnancy test at the start of each session to ensure that they are still eligible.

They will check whether there have been any adverse responses since their last treatment if they have had one. This will take approximately 10 minutes.

Once satisfied the IV infusion will be prepared (approximately 15 minutes).

Participants will receive a single loading dose of 200 milligrams of Remdesivir in 250ml sodium chloride 0.9% bag *via* IV over 60 minutes on day 1, followed by, on days 2 – 5, a dose of 100

milligrams of Remdesivir in 250ml sodium chloride 0.9% bag *via* IV once daily over 30 minutes. Please see Section 11 for further details of study drug.

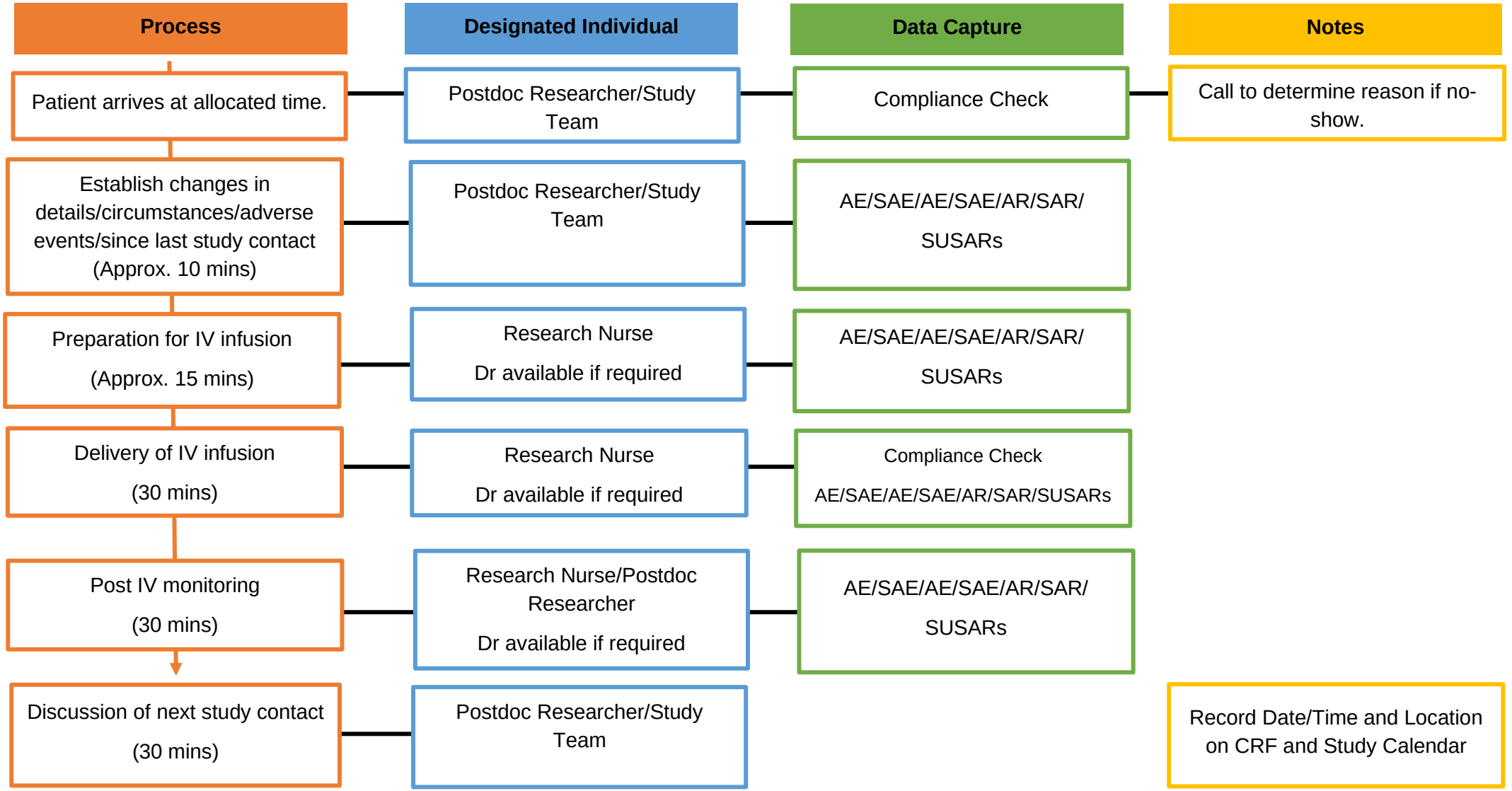
Once the IV Treatment is completed the participant will be monitored for a further 30 minutes. A Doctor will be available at all of the treatment sessions.

Time will be allocated to discuss the next study contact and answer any questions (approximately 30 minutes).

All clinical and research staff will have had training on the needs of the patient group and will be ensuring their safety and comfort as set out in Section 3.

If for any reason (e.g., participant is unable to attend clinic, or PI decides to cease IMP) a participant misses a dose of study drug after treatment has commenced, the participant will be withdrawn from treatment. In instances of treatment withdrawal, if willing, the participant will continue with all other scheduled assessments as planned, but no further study drug will be administered.

Figure 1. Intervention Flow Chart



10.7 Safety Blood Check (Day 27)

Post intervention all participants will attend their respective site for a safety blood check 5-7 days after their final dose of IMP, see Section 10.7 for details. Pregnancy tests and AE assessments will again be conducted.

10.8 Post Intervention Assessment (Day 44 (+28 days after treatment phase))

All participants will attend their respective site for a post intervention assessment 28 days after their final dose of IMP (+ 5 days). 24 hours prior to this appointment patients will be sent all the patient reported outcome measures to complete as before; EQ-5D-5L, MRC Dyspnoea Scale, PDQ-5, GAD-7, SBQ™-LC FAS and MFIS as described in Section 4.3.2.1. They will also be provided with the Modified De Paul Symptom Questionnaire-Post Exertional Malaise (DSQ-PEM).

On arrival at clinic pregnancy and AE assessments will be conducted in addition to taking blood for testing biomarkers and inflammatory profiles.

Physiological and functional status conducted in the baseline will be repeated.

- Maximum inspiratory and expiratory mouth pressure (MIP and MEP)
- Lung function
- Blood pressure
- Breathing rate
- Resting heart rate
- Body temperature
- 6-minute walk test (6MWT, Borg 6-20 and SPO^2)

10.9 Post Intervention CPET (Days 51 & 52)

Repeat as days 7 and 8. The participant should return the VISIBLE sensor and, where applicable, the paper symptom diary to the research team at the end of the visit.

For participants at the Derby site the study is now over, and all visits concluded.

10.10 Exeter Only PET/CT scan (Day 55)

Participants in Exeter will attend the Imaging Centre for their post-treatment scan on day 55 (+ 2 days). The procedure including pregnancy test and AE assessments will be a repeat of Day 11 after which they have completed all study visits.

10.11 Trial assessments

Table 1: Schedule of Assessments

	Screening		Pre-Intervention			Treatment Phase	Post-Intervention			
	Initial Screening	Detailed Screening	Enrolment & Baseline Assessment	CPET Test	PET/CT scan*		Safety Blood Check	Post Intervention Assessment	CPET Test	PET/CT scan*
Day			Day 0	Days 7 & 8	Day 11	Days 14-22#	Day 27	Day 44 (+28 days after IMP)	Days 51 & 52	Day 55
Informed consent	X	X	X							
Demographics		X								
Medical history		X	X							
Compliance			X	X	X	X	X	X	X	X
AE assessments			X	X	X	X	X	X	X	X
IMP Administration						X				
Pregnancy Testing+		X	X	X	X	X	X	X	X	X
PROMS			X					X		
Symptom Burden				X					X	
DSQ-PEM	X		X					X		
Physiological and Functional Status			X					X		

Exercise Markers				X					X	
Safety Bloods		X					X			
Blood Markers			X	X				X	X	
Symptom Tracking			X	X	X	X	X	X	X	

* Denotes sub-group of participants that will undergo PET/CT scans at the University of Exeter. #Denotes range in days to allow for consecutive administration on weekdays. +denotes pregnancy tests that will be administered to women of childbearing potential. **PROMS:** EQ-5D-5L, LC Symptom Burden, FAS, MFIS, MRC Dyspnoea, PDQ-5, GAD-7. **Symptom Burden:** SBQ™-LC, FAS, MFIS. **Physiological and Functional Status:** MIP, MEP, Lung Function, Blood Pressure, O2 Sats, HR, Breathing rate, Temperature, RPE, 6MWT. **Exercise Markers:** VO2 Peak, VCO2, RER, Blood Lactate, Blood Gas Tension, VT1, VT2, VE, VE/VCO2, ET-CO2. **Safety bloods:** eGFR, LFTs **Blood markers:** G-CSF, GM-CSF, IFN-α, IFN-γ, IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-α, Eotaxin, IP-10, MCP-1, MIG, MIP-1α, MIP-1β, RANTES, EGF, FGF-basic, HGF, VEGF.

10.12 Storage and analysis of clinical samples

Venous blood samples will be taken from the arm of participants by trained and competent research staff at each research site (conducted according to each site's standard operating procedures). In line with the outlined biomarkers in section 4.3.2.3, participants will have a plasma or serum sample taken for the measurement of inflammatory and metabolic biomarkers on days 0, 7, 8, 44, 51 and 52.

Biomarker samples will be stored on ice at their local site. Once mixed with anticoagulant solution and after 30 minutes, samples will be spun at 2,500g for 10mins (RT) with slow deceleration at the end. Processed samples will be aliquoted into 0.5mL Eppendorf at –80ºC and stored locally before being transferred to the University of Derby at the end of recruitment. Batch testing will be performed either in Laboratories at the University of Derby or a contracted external vendor.

Participants will be asked to consent to the storage and retention of all samples for use in future COVID-19 research studies which will be stored in accordance with the Human Tissue Act (2004).

Safety blood samples will be taken from participants on detailed screening and day 27 and will be assessed to monitor changes in eGFR and LFT measures. Following collection, samples will be transported to the local accredited laboratory for processing and analysis at University Hospitals of Derby and Burton NHS Foundation Trust or Royal Devon University Healthcare NHS Foundation Trust in accordance with the Laboratory Manual and local procedures.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

10.13 Withdrawal Criteria

Each participant has the right to withdraw from the study at any time. Participants will be made aware (*via* the Participant Information Sheet/study team) that if they withdraw from the study all study data collected until that point will be kept for the analysis.

The PIs may withdraw a participant from the study or withdraw aspects of the study (i.e., medication, exercise, or specific scans) if it is determined that the participant's health is compromised by remaining in the study. All data collected from withdrawn participants will be included in the study report.

A PI may decide to withdraw a participant from the study or reduce their participation at any time for any reason including but not limited to:

- Ineligibility (arising during study or retrospective having been overlooked at screening)
- An AE/SAE/AR/SUSAR which results in an inability to continue to complete study procedures.
- Consent is withdrawn.
- A participant reports a confirmed pregnancy as guided by the SmPC.

The reason for withdrawal will be clearly stated (wherever possible) and recorded in the Case Report Form (CRF). If the participant is withdrawn due to an AE related to the study medication or trial assessments, the PI will arrange for a follow-up telephone call until the AE has resolved or stabilised.

If the participant is withdrawn from treatment only, all scheduled assessments will be carried out as planned, but no further study drug will be administered.

If the participant is fully withdrawn from the trial, any required safety checks will still need to be undertaken as planned (e.g., safety bloods at Day 27). This will be explained to the participant fully by the research team member documenting the withdrawal.

10.14 Payment

Payments to the participants will not be made to compensate for their time during the study. Any travel (including parking) costs incurred during participation can be reimbursed to a UK registered bank account for participants. This will be documented on a claim form that will be given to participants at their baseline visit which will be processed at the end of their study involvement. Participants that use private (taxis) or public transport (buses or trains) will be asked to provide tickets/receipts. Those using their personal cars can be reimbursed for mileage paid at a rate of 0.45pence/mile from their home address to the study site.

11. TRIAL TREATMENT

11.1 Name and description of investigational medicinal product(s)

There is one Investigational Medical Product (IMP), Remdesivir which is also sold under the brand name Veklury.

IMP: Remdesivir (Veklury)

Agency product number: EMEA/H/C/005622

Active substance: Remdesivir

International non-proprietary name (INN) or common name: Remdesivir

Marketing Authorisation Number: PLGB 11972/0036

Marketing Authorisation Holder: Gilead Sciences Ltd, 280 High Holborn, London, WC1V 7EE, United Kingdom

11.2 Regulatory status of the drug

Remdesivir (marketed as Veklury) is an antiviral medicine with a Marketing Authorisation to treat COVID-19.

11.3 Product Characteristics

The Summary of Product Characteristics (SmPC) for Remdesivir (Veklury) infusion can be accessed *via* https://www.medicines.org.uk/emc/product/11597.

11.4 Drug storage and supply

The IMP for this trial is being provided by the funder of the trial as an in-kind contribution (£24,060.31) and being shipped to the UK. All IMP will be allocated and distributed to each site following labelling and final batch release activities by the Qualified Person (SHARP QP Services, Cardiff, UK).

There are no special precautions for storage. Storage conditions after reconstitution and dilution of the medicinal product are as follows: Store diluted Remdesivir solution for infusion for up to 24 hours at below 25°C or 48 hours in a refrigerator (2°C – 8°C).

Detailed information regarding drug storage, shipment, receipt, distribution, preparation of infusion, return and destruction of IMP is detailed in the Pharmacy Manual.

Trial medication will be provided by the manufacturer (Gilead Sciences) and requested by members of the study team in accordance with the Pharmacy Manual

Accurate records for medication dispensed and returned must be maintained and a record available for inspection.

11.5 Preparation and labelling of Investigational Medicinal Product

Allocated treatment will be drawn up for intravenous infusion by appropriately trained members of the study team at each study site. Once prepared, trial medication will be provided to the trial team for administration by intravenous infusion. Details relating to preparation and labelling of the IMP is detailed below (briefly) and in the Pharmacy Manual.

11.6 Dosage schedules

Patients will receive five intravenous infusions. The first loading dose will be infused over 60 minutes. Subsequent maintenance doses will be infused over a 30-minute period. Dosing schedules are guided by the SmPC and will be consistent for each participant.

- Day 1: Loading dose of 200 milligrams of Remdesivir in 250ml sodium chloride 0.9% bag *via* intravenous infusion over 60 minutes.
- Day 2 - 5: Dose of 100 milligrams of Remdesivir in 250ml sodium chloride 0.9% bag via intravenous infusion over 30 minutes.

Dosage modification: No dosage modifications are permitted.

Individual stopping criteria: If a participant develops clinical evidence of a significant adverse reaction during treatment administration, then the administration can be stopped at the direction of the treating clinician.

If a product recall should occur, the medication will be quarantined, and the trial will temporarily halt recruitment until the matter is resolved.

11.7 Known drug reactions and interaction with other therapies

The IMP will be administered in an out-patient setting and will be monitored according to local medical practice. It must be used under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis, is possible. The most common adverse reaction in healthy volunteers as reported via the MHRA is increased transaminases (14%) and in patients is nausea (4%). The SmPC (section 4.8) will be reviewed throughout the trial to ensure that new reactions and learning is incorporated into the trial design and recruitment of patients to the study. The SmPC is a live document that is updated to share new learning and updated knowledge, and this will be reviewed frequently (quarterly) to ensure that the study team are working with the most up-to date information. Any changes that result from updates to the SmPC will be raised with the study CIs, TMG and TSC (where appropriate). Any changes to the study design, recruitment procedures will be reported to the research ethics committee (REC) that approved the study, using the standard amendments template.

Coadministration of Remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir (see sections 4.5 and 5.1 of the SmPC). Consequently, participants receiving this medication will be excluded from the trial.

Additional Information Provided by the Electronic Medicines Compendium (https://www.medicines.org.uk/emc)

11.7.1 Hypersensitivity including infusion-related and anaphylactic reactions

Participants should be monitored for hypersensitivity reactions during and following the administration of Remdesivir as appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, the administration of Remdesivir should be immediately discontinued and appropriate treatment initiated.

11.7.2 Transaminase elevations

Transaminase elevations have been observed in the Remdesivir clinical trials, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all participants before starting Remdesivir and should be monitored while receiving it as clinically appropriate.

11.7.3 Renal impairment

All participants should have eGFR determined before starting Remdesivir and while receiving it as clinically appropriate.

11.7.4 Excipients

Remdesivir contains 212 mg sodium per 100 mg dose, equivalent to 10.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

11.8 Concomitant medication

All concomitant medication, including over the counter or prescription medication, vitamins, and/or herbal supplements taken by the participant during their time in the study will be recorded. All medications that are disclosed by patients in the screening visit will be checked against details provided in the BNF(https://bnf.nice.org.uk/interactions/remdesivir/) and/or the COVID-19 Drug interactions database (https://www.covid19-druginteractions.org/checker).

Any associated adverse events should be recorded as directed in Section 12.

11.9 Trial restrictions

There are no restrictions related to involvement in the trial other than those covered by the exclusion criteria.

11.10 Assessment of compliance with treatment

Participants are administered medication by slow intravenous infusion. A record of administration must be kept in the medical notes, and available for inspection on request; it will also be recorded in the eCRF.

11.11 Labelling of IMP

Medication issued for use in the trial will be supplied in the original manufacturer's packaging (primary label). QP services will be provided by SHARP Clinical Services who will provide the relevant certification and trial labelling. This will be conducted in accordance with Annex 13 of the Rules and Guidance for Pharmaceutical Manufacturers 2007 to indicate use in this trial.

12. PHARMACOVIGILANCE

12.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening. • requires inpatient hospitalisation admission for treatment or prolongation of existing hospitalisation. • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

12.2 Operational Definitions for (S)AEs

Remdesivir will be used outside of its licensed indication. For this trial, it is expected that all AEs that show a potential causal relationship with the IMP (known as ARs) are recorded. Other AEs of unexpected severity (in the opinion of and in discussion with the principal investigator), or which meet the criteria for an SAE should also be reported. Investigators must seek further information on such adverse events, and record details in the patient's medical notes and on the eCRF. They should be recorded using the Common Terminology Criteria for Adverse Events (CTCAE term) provided in the National Cancer Institute (NCI) CTCAE v5.0. Severity should be assessed using the NCI CTCAE v5.0 grading as per Section 12.4.1. The clinical course of each event should be followed until resolution or stabilisation.

12.3 Recording and Reporting SAEs and SUSARs

All AEs and SAEs from the time of written informed consent until the last study visit must be recorded in the patient's medical notes. Any AEs of unexpected severity or ARs must be reported by the investigator via the eCRF as per the work instruction for reporting safety events. The PI is responsible for checking for AEs and ARs when participants attend treatment and follow-up visits. All SAEs must be reported by the investigator using the digital PenCTU AE reporting form **within 24 hours of the research team first becoming aware of the event;** even if not all information is available at the time. Any change of condition or other follow-up information should be recorded within the eCRF using the PenCTU SAE Resolution form as soon as it is available, and within 24 hours of first awareness. Events will be followed until the event has been resolved, stabilised or to Sponsor satisfaction.

CTU contact information	
Email	erase.penctu@plymouth.ac.uk
Telephone	01752 439831

For each SAE/ SUSAR the following information will be collected:

- Full details of the event, including a diagnosis
- MedDRA coding (system organ class and preferred term)

- Duration (start and end dates)
- Seriousness criteria
- Outcome
- Action taken
- Causality (i.e., related to IMP)
- Expectedness

Each SAE that is assigned as both suspected to be related to IMP treatment and unexpected as per the Reference Safety Information will be classified as a SUSAR and will be subject to expedited reporting to the MHRA. The Sponsor will report SUSARs to the MHRA (who will liaise with the REC if necessary). Fatal or life-threatening SUSARS will be reported within 7 calendar days of first awareness of the reaction. Any additional relevant information will be sent within the following 8 calendar days. All other SUSARs will be reported within 15 calendar days of first awareness. Once a report has been made to the MHRA, PenCTU in collaboration with the CI will inform all sites.

Safety information will be reviewed for ongoing assessment during TMG and TSC meetings as per the trial monitoring plan.

12.4 Assessment of AEs and SAEs

12.4.1 Severity

The Principal Investigator or authorised delegate should determine the severity of the AE.

- Mild: no interference with daily activities.
- Moderate: moderate interference with daily activities.
- Severe: considerable interference with daily activities (e.g., inability to work).

NOTE: to avoid confusion or misunderstanding the term “severe” is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as “serious” which is described in the safety definitions.

12.4.2 Causality

Clinical judgement should be used to determine the relationship between the IMP and the occurrence of each AE.

- Not related: There is no evidence of a causal relationship between the event and IMP.
- Related: There is evidence of a causal relationship between the event and IMP i.e., a relationship to the IMP cannot be completely ruled out.

A medically qualified doctor (usually the principal investigator) must assess causality. If a doctor is unavailable, initial reports should be submitted to PenCTU without the causality assessment, but they must be followed up with a medical assessment as soon as possible (and within 3 working days).

12.4.3 Expectedness

The assessment of expectedness is only required if the event is deemed to be related to the IMP.

- Expected: Reaction previously identified and described in the reference safety information (RSI) and/or protocol.
- Unexpected: Reaction not previously described in the protocol or RSI.

The expectedness assessment is delegated to the Clinical CI who will perform a clinical review. The RSI for this trial is in Section 4.8 of the Remdesivir SmPC.

12.4.4 Notification of Deaths

All deaths will be reported to the PenCTU within the CRF. 'Death' is not an SAE, but the outcome of an SAE, and should be reported as such.

12.4.5 Pregnancy reporting

Remdesivir should not be used during the first trimester in pregnancy and women of childbearing potential must use effective contraception during treatment. Females that are of childbearing age will be asked to conduct a pregnancy test at each study visit. There is limited data on pregnancy outcomes (< 300) following exposure to Remdesivir in the second and third trimester, and clinical experience on the effect of Remdesivir on breastfeeding is limited, therefore women who are pregnant or breastfeeding will be excluded from participating in the trial.

If a participant becomes pregnant or is suspected to be pregnant during trial participation, the investigator must notify the PenCTU within 24 hours of first becoming aware of the pregnancy using the PenCTU electronic pregnancy notification form. If a confirmed pregnancy occurs during study participation, the participant will be withdrawn from the trial as guided by the SmPC. The Sponsor and Funder will be informed of any reported pregnancies by PenCTU within 1 working day of being notified. Follow up information will be transmitted within the same timelines.

Pregnancy occurring in a participant in a Clinical Trial of Investigational Medicinal Product (CTIMP), whilst not considered a Serious Adverse Event (SAE), requires monitoring and follow up by the investigator. The pregnancy must be followed-up no less than 10 months after completion of the trial and the investigator must complete the PenCTU electronic pregnancy outcome form. The CI or Principal investigator (PI) must collect all information to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of birth defects, congenital abnormalities, or maternal and/or new-born complications. Any negative or consequential outcomes in pregnancy for the mother and/or child/foetus, should be reported as an SAE as per section 12.3, if the event meets the serious criteria.

An exposed pregnancy will be reported by PenCTU by telephone to UK Teratology Information Service (UKTIS) which is operating the UK COVID-19 Antivirals Pregnancy Registry to collect information about and enable follow-up of reported exposures to COVID-19 antivirals in pregnancy. For more information, see the UKTIS Registry website (available at: *https://www.medicinesinpregnancy.org/bumps/COVID-19-Antivirals-Pregnancy-Registry/*

12.4.6 Overdose

Any instance of an overdose regardless of whether this results in an adverse event must be reported to PenCTU **within 24 hours of first becoming aware of the overdose** using the digital deviation form in REDCap. The overdose should also be recorded in the medical notes. If the overdose results in an AE or SAE, this must also be reported according to the PenCTU procedure described above. In the instance of an overdose all responsible parties will review and rectify systems and processes to prevent reoccurrence and all details/findings will be reported to the PenCTU, Sponsor and regulatory bodies as appropriate.

12.4.7 Reporting Urgent Safety Measures

If any urgent safety measures are required, the CI/Sponsor will telephone the MHRA's Clinical Trial Unit immediately (i.e., within 24 hours of measures being taken) to discuss the issue with a medical assessor. The Sponsor will submit a written notice of the USM(s) to the MHRA and the relevant REC via the IRAS, within 3 days of the measures being implemented. A substantial amendment covering the changes made as part of the USM will also be submitted within 2 weeks of the written notification to the MHRA.

If an USM is implemented at site, PenCTU should be notified **immediately** by telephone or emailing erase.penctu@plymouth.ac.uk. The PenCTU will notify all participating sites within 24 hours of USM(s) being implemented and acknowledgement of receipt from each site PI will be recorded.

12.4.8 Development Safety Update Reports

PenCTU will provide (in collaboration with the CI) Development Safety Update Reports (DSURs) once a year throughout the clinical trial, or on request, for submission to the Competent Authority (MHRA in the UK). The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

All safety reports will be presented and discussed within the TSC and resulting data will be considered when establishing the final conclusions about the appropriateness of progressing to a definitive trial.

12.4.9 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement to assess the severity, seriousness and relatedness of the event to the IMP using the SmPC approved for the trial.
2. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement to assess the seriousness, causality and expectedness of the event in accordance with the approved RSI for the trial.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the DSUR.

Sponsor: (NB where relevant these can be delegated to CI or PenCTU)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial TSC according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for and notifying PIs of updates to the RSI for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA.

Trial Steering Committee (TSC):

Periodically review safety data in accordance with the TSC Charter.

13. END OF TRIAL

The end of the trial is defined as the last visit of the last participant or upon completion of any follow-up and data collection process and all queries resolved. The Clinical Trials Manager will notify the participating sites, MHRA and REC within 90 days of the end the of trial. The clinical trial report will be written within 12 months of the end of the trial.

14. STATISTICS AND DATA ANALYSIS

14.1 Sample size calculation

A key aspect of this study is to inform progression to the main trial. The sample size is based on the feasibility outcomes of process assessments (e.g. recruitment, follow-up) focused on the RAG system (Table 2) that tests against being in the RED zone (unacceptable outcome) based on an expectation of being in the GREEN zone (acceptable outcome) and the sample size to give high power to reject being in the RED zone if the GREEN zone holds true, using the sample sizes provided in Table 1 in Lewis *et al* [33].

The three key feasibility objectives, to assess (i) recruitment uptake (percent of screened patients recruited), (ii) treatment fidelity and (iii) participant retention (follow up).

i. Based on recruitment rate, if we assume the upper boundary of the RED zone is 25% and the lower boundary of the GREEN zone is 50% (designating unacceptable and acceptable recruitment, respectively), the sample size required for analysis given 90% power and one-sided 5% alpha would be at least n = 33 (total screened patients).

ii. Based on treatment fidelity (defined at completion of all 5 sessions), if we assume the upper boundary of the RED zone is 70% and the lower boundary of the GREEN zone is 85%, the sample size required for analysis given 90% power and one-sided 5% alpha would be at least n = 72

iii. Based on follow-up at 28 days post IMP, if we assume the upper boundary of the RED zone is 65% and the lower boundary of the GREEN zone is 85%, the sample size required for analysis given 90% power and one-sided 5% alpha would be at least n = 44.

The sample sizes across criteria (i)-(iii) are at different levels—(i) is at the level of screened patients, whereas (ii)–(iii) are at the level of recruited patients. To meet criteria (i), we need $n_s \geq 33$ (although we will screen $n_s \geq 144$ (i.e. (1/0.50) × n_r (72) where 0.50 is the expected proportion uptake of the total number screened), and for (ii)–(iii), **we need n_r = 72 based on (ii)).**

14.2 Planned recruitment rate

In the two UK based centres that will take part in this study (Exeter and Derby), we expect a total of at least 120 patients that will be potentially eligible for the study from established Long COVID clinics and a further 100 from an existing database of patients who have engaged in non-interventional research and have consented to contacted about relevant research opportunities. Based on 220 potentially eligible participants, if at least 50% agree to participate ((i). GREEN zone), this is an indication that enough patients could be approached to participate in this study**.** 72 patient-participants will be recruited over 12 months (5-6 per month).

14.3 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be drafted by the trial statisticians and approved by an independent statistician prior to database lock. The study will be reported following the relevant Consolidated Standards Of Reporting Trials (CONSORT) 2010 statement extension to pilot and feasibility trials.

14.3.1 Summary of baseline data and flow of patients

Baseline characteristics of participants will be summarised descriptively. Loss to follow-up after baseline will be summarised visually *via* a CONSORT style flow diagram. Baseline characteristics will be subjectively examined to assess potential differences between participants who withdraw, discontinue, and those who complete the trial.

14.3.2 Primary outcome analysis

Study process will be descriptively summarised (with 95% confidence intervals). This will include recruitment and retention rates. The proportion of patients who did not meet eligibility criteria will be looked at. Adherence and compliance rates will be examined.

14.3.3 Secondary outcome analysis

Safety outcome measures with reporting as per CTIMP protocol (MHRA guidelines) will be descriptively summarised.

In general, the use of hypothesis tests is not appropriate for a feasibility study, as the study has not been powered to address these and use of estimates with confidence intervals is preferred to obtain signals of efficacy. Secondary outcome analyses should be considered as hypothesis generating rather than providing firm conclusions. Key continuous secondary outcomes will be descriptively summarised and analysed using paired-sample t-test approach to calculate the unadjusted change in scores and 95% confidence interval and (ii) using normal linear mixed effects repeated measures models. The changes between baseline and each of the follow- up time points will be modelled on time point, with adjustment for baseline and recruitment site (stratification factor). Key binary secondary outcomes will be analysed using logistic regression models, with adjustment for recruiting site.

14.4 Subgroup analyses

Not applicable.

14.5 Adjusted analysis

Not applicable.

14.6 Interim analysis and criteria for the premature termination of the trial

There will be no formal interim analysis. The TSC will meet at pre-specified intervals. Analysis will be undertaken at end of study. The integrity of the trial will be protected by regular site visits and conferences (telephone, online and face-to-face meetings) with PIs. The authority to stop or modify the trial lies with the CI, TSC, or sponsor. Although there is no formal DMC due to the small size of the study, some of the responsibilities of a DMC will be undertaken by the TSC as there is a pharmacovigilance aspect to this study.

The Sponsor may suspend or prematurely terminate either the entire study, or the study at an individual site, for significant reasons that must be documented (e.g., an unacceptable risk to participants or serious repeated deviations from the protocol/ regulations). If this occurs the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e., participants, investigators, participating sites, REC, regulatory bodies).

14.7 Participant population

- All-treated population: Any participant consented into the trial that received at least one dose of trial drug.
- Protocol-compliant population: Any participant who was consented and received the protocol required trial drug exposure and required protocol processing.

14.8 Procedure(s) to account for missing or spurious data

Data from all eligible consented population will be subjected to the study analysis, regardless of whether they received study drug and protocol adherence. This will be an intention to treat analysis.

Reasons for being unable to collect data during an assessment will be recorded on the electronic case report form (eCRF), where appropriate. eCRFs will be assessed for missing data by PenCTU and sites will be regularly chased for missing data. PenCTU will maintain a record of site compliance with eCRF completion. If data completion is poor, a monitoring visit may be scheduled (See Section 15.6 Trial Monitoring).

The eCRFs will include mandatory fields, which must be filled in before the eCRF can be saved to reduce the risk of missing data. Where questions may need to be left blank, options such as ‘Not applicable’ or ‘Prefer not to say’ will be available, to differentiate these from missing data. Validations will be written into the REDCap database, to raise queries with particular data field, such as flagging if the date of a visit does not correspond to the correct timepoint.

PenCTU data manager will write a series of R scripts to perform the following data tasks to aid data completeness, including checking overall completeness by field of all CRFs, checking all visits have been recorded in a logical order and checking SAE forms have been completed within the timeframe stipulated in Section 12, Pharmacovigilance. The scripts will be run on a regular basis and any concerns will be raised individually with sites.

To reduce the risk of missing data for patient-reported outcome measures (PROMs), participants will complete these during their assessment visits (PROMS will be finalised during the visit if completed at home by the participant). The assessor will check for missing data once PROM is completed.

14.9 Other statistical considerations

Any changes made to the SAP will be documented, including details of when the change was made (e.g., prior to data export).

14.10 Progression Criteria

The research team will review progression criteria:

Red/Amber/Green (RAG) stop-go criteria will be used to assess whether study design requires modification. Process data will identify "fixable", "manageable", and "insurmountable" challenges to data collection and intervention fidelity.

We shall progress to a definitive RCT if minimum success criteria for key feasibility aims/objectives are achieved.

Table 2. Progression Criteria:

Feasibility Outcome	Do not proceed to definitive trial (Red)	Proceed to definitive trial with protocol amendments (Amber)	Proceed to definitive trial (Green)
Each site is able to run the study	No sites able	1/2 sites able	2/2 sites able
Recruitment uptake (proportion recruited once marked eligible from screening)	<25%	25-50%	>50%
Treatment fidelity (defined at completion of all 5 sessions)	<70%	70-85%	>85%
Follow-up at 28 days post IMP	<65%	65-85%	>85%
Completion of key outcome measures	<60%	60-80%	>80%
Completion of CPETs at 7, 8, 51 and 52 days.	<60%	60-80%	>80%

15. DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate Data Management Plan (DMP).

15.1 Data collection tools and source document identification

A REDCap database, developed by PenCTU, will be used for data management and recording participant data. Data capture will be via a web-based, fully validated system, compliant with MHRA guidance. PenCTU will be responsible for database build and system validation. Data will be hosted externally in compliance with current regulatory requirements. The system uses validation and verification features to monitor study data quality and completeness.

15.2 Source Data

Source data will include participants' medical records (e.g., for certain eligibility criteria and medical history), participant-completed documents (e.g. informed consent forms), worksheets provided by PenCTU and eCRFs. In the context of clinical care, investigator site staff must ensure that details of a patient's participation in the trial are recorded in the participant's health record. As a minimum, the participant's health record should be updated to include:

• Consent and eligibility for study

• Dates of all study visits and follow ups

• IMP related adverse events

• Completion or discontinuation of study

Source data should be compliant with ALCOA CCEA guidance (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available). The CTU will verify source data and source documents as stipulated in the study monitoring plan (see Section 15.6 Trial Monitoring). Study data will be recorded on eCRFs.

Where applicable, Patient Reported Questionnaires (PROMS) will be uploaded to the eCRF by site staff once complete.

The investigator should keep a record of all participating patients and all original signed informed consent forms.

The investigator and trial team will ensure that the participant's identity is protected at every stage of their participation in the trial, according to the Caldicott principles. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

The trial database will be designed to capture the clinical data in accordance with the best principles of clinical data management and relevant SOPs on Clinical Data Management System Specification and Validation, Data Capture, Instrument Design and Database Development developed by the PenCTU.

15.3 Data handling and record keeping

All eCRF data is stored in PenCTU's REDCap Community production infrastructure, hosted by AIMES on MS Azure datacentres located in the European Union. AIMES are NHS DSP Toolkit compliant and hold ISO27001 and Cyber Essentials Plus certifications. Microsoft Azure datacentres are Service Organization Control (SOC) type 1 and type 2 compliant. Data will be stored on hardware dedicated to PenCTU's instance of REDCap Community. All electronic data are backed up and stored with a full audit trail.

15.4 Access to Data

Direct access to investigator site records will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections – in line with participant consent.

15.5 Archiving

Following completion of trial data analysis, the Sponsor will be responsible for archiving the study data and TMF in a secure location for 5 years after the end of the trial. PenCTU will prepare the TMF for archiving in accordance with the requirements of the Sponsor's SOP. PenCTU will prepare a copy of the final dataset for archiving according to the requirements of their SOP.

Principal Investigators at sites will be responsible for archiving Investigator Site File (ISF)s and trial data generated at the site according to local policy. No trial-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other trial related information should be labelled, physically or electronically, so as to ensure retention until the Sponsor gives authorisation to destroy. e.g., "Keep until dd/mm/yyyy" (where the date given is five years after the last participant's final visit).

15.6 Monitoring, Audit & Inspection

In accordance with PenCTU standard operating procedures for risk assessment and monitoring, a specific trial monitoring plan will be generated by the PenCTU, based on the PenCTU's risk assessment,

with input from the TMG. The monitoring plan will be signed off by the CI and Sponsor before implementation.

PenCTU will perform ongoing central monitoring, outputs from which will be discussed by the TMG. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance, calendar checks (to identify deviations from participants' visit schedules), consent process checks (through collection of completed de-identified consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation logs). Central monitoring will be used to identify areas of potential poor performance at individual investigator sites. Poor performance at sites may trigger on-site monitoring visits (subject to any COVID-restrictions), hosted by the investigator site PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by PenCTU staff according to established PenCTU SOPs. The Investigator(s) must ensure that source documents and other documentation for this study are made available to study monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor and competent authority may visit the participating sites to conduct audits/ inspections.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Research Ethics Committee (REC) Review & Reports

The CI will obtain approval from the UK Health Research Authority (HRA), REC and MHRA for the trial protocol, informed consent forms and other study documentation (e.g., Patient Information Sheet, Informed Consent Form, GP letters, study advertisements). The Chief Investigator will ensure that this study is conducted in conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

Substantial amendments will not be implemented before review and acceptance by the MHRA, REC and finally the HRA. NHS R&D departments have up to 35 days after HRA approval to decide whether they can implement the substantial amendment in practice at sites. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

All correspondence with the REC will be retained in the TMF/ISF. The CI / delegate will notify the REC of the end of the trial. If the trial is ended prematurely, the CI / delegate will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

16.2 Peer review

This study has been peer reviewed and approved as part of the Gilead Science Research Funding application process. Independent peer reviews of this protocol have been provided by the following people:

- **Dr Mel Chiang, Dr Eun Young, Dr Gina Brown and Ms Priya Siddhanathi (**Gilead Sciences (Funder) medical affairs research team).

16.3 Public and Patient Involvement

The protocol and supporting documentation have been reviewed by members of the research teams established Patient and Public Involvement group. Their feedback has shaped the design of the study processes. Ms. Lindsay Skipper will function as the trial's public and patient involvement representative, and she is a Long COVID patient and a former Physiotherapist. Ms. Skipper has worked alongside the study team to ensure all the documentation and study processes are appropriate for patients with Long COVID. She has been extremely involved in ensuring that the study risks are identified and mitigated as much as possible. Ms. Skipper will be an active member of the TMG to ensure that the project maintains a patient and translatable approach.

Study progress will be discussed at the Patient and Public Involvement Group monthly meetings. Their input will have significant impact on the future trial also.

16.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA (along with Favourable REC opinion and HRA approval). The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Before any site can enrol patients into the trial, PenCTU will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the trial, the PenCTU, in agreement with the sponsor will submit an amendment for submission to review bodies. PenCTU will work with sites (R&D departments at NHS sites as well as the trial delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the trial as amended.

16.5 Protocol compliance

Non-compliance with protocol will be captured on specific non-compliance report forms according to instructions provided by PenCTU and in accordance with PenCTU SOPs. Protocol non-compliance will be reviewed periodically by the TMG as part of central monitoring (see 'Section 15.6 Monitoring, audit

and inspection'), with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance is reviewed by the PenCTU trial manager. PenCTU staff must immediately inform the PenCTU Quality Assurance (QA) Manager if they believe that a serious breach has occurred (see below). Where the trial manager and/or PenCTU QA Manger believes that a non-compliance might constitute a serious breach, the trial manager should ensure that a completed non-compliance report form is provided to the Sponsor immediately (i.e., within 1 working day of first awareness).

16.6 Notification of Serious Breaches to GCP and/or the protocol

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

(1.a) the safety, rights or physical or mental integrity of the participants of the trial; or

(1.b) the scientific value of the trial

Where a non-compliance meets the above criteria, PenCTU will immediately notify (i.e., within 1 working day of first awareness) the CI and Sponsor. The Sponsor will email a serious breach report to the REC and HRA directly and to the MHRA (using the GCP SeriousBreaches@mhra.gov.uk email address) within seven calendar days of becoming aware of the event. If the PI (or delegate) is unsure if non-compliance meets these criteria, they should consult the Sponsor for further guidance.

Complete investigations of breaches will be fully documented, filed in the TMF and a copy provided to the Sponsor.

16.7 Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR). The trial Sponsor is the Data Controller for the trial data. PenCTU is a data processor, centrally managing trial data generated at investigator sites. The University of Plymouth is the data custodian since data are stored on databases managed by the University of Plymouth.

Data including the number of patients screened, approached and interested in taking part will be collected *via* a log completed by staff conducting screening. Investigator site staff will ensure that the participants' anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval.

Any paper-based data collection tools (e.g., worksheets and questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purpose designed data capture systems. Access to the system for all users (including PenCTU staff) is *via* a secure password-protected web-interface. Each participant will be allocated a unique system-generated study number which will be related to site and recruitment number e.g., 01001. Participants will be identified in all study-related documentation by their study number. Data collected and analysed during the study will be pseudonymised by the use of this unique identifier. A record of trial participants' names and

contact details, hospital numbers and assigned trial numbers will be stored securely in a locked room at the trial site and is the responsibility of the site PI.

In order to facilitate central coordination of the study participants' contact details will be entered into the data capture system by investigator site staff (after consent only). Only limited staff at PenCTU will have access to these details and these details will not be made available in any form to any persons unless needed for study conduct. Datasets prepared for transmission to statisticians (for analysis), co-applicants or Sponsor will be pseudonymised and will not contain any direct identifiers or participant contact details.

16.8 Financial and other competing interests

The Chief Investigator, PIs at each site and TSC committee members will be asked to disclose any financial or other competing interests including, but not limited to:

- any ownership interests that may be related to products, services or interventions considered for use in the trial or that may be significantly affected by the trial.
- commercial ties including, but not restricted to, any pharmaceutical, behaviour modification, and/or technology company.
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

At the time of protocol writing, there are no known financial or other competing interests of the Chief Investigators or their team.

16.9 Indemnity

University of Derby is the Sponsor for this trial and clinical trials insurance and indemnity is provided by U.M. Association Limited (UMAL) to cover this trial. The provision of insurance provides cover for legal liabilities. Non-negligent harm is not covered by the insurance/indemnity scheme, and it cannot be agreed in advance to pay compensation in these circumstances. In exceptional circumstances, an *ex-gratia* payment may be offered.

The participating site will be liable for clinical negligence and other negligent harm to participants taking part in the study and covered by the duty of care owed to them by the site concerned. For participating sites that are part of the NHS, the NHS indemnity scheme will also apply.

16.10 Amendments

If changes to the study are requested, these must be discussed with the Sponsor, who is responsible for deciding if an amendment is required and if it should be deemed substantial or non-substantial.

Substantial amendments will be submitted to the relevant regulatory bodies (MHRA, REC, HRA) for review and approval. The amendments will only be implemented after approval from the HRA, once they have received MHRA approval and a favourable opinion from REC. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgements will not be implemented until all relevant approvals are in place.

16.11 Post trial care

All participants will undertake safety blood tests 5-7 days following the administration of the IMP, these tests (eGFR and LFT) are in accordance with known renal and hepatic side effects. Samples will be analysed at the nearest accredited pathology laboratory at each testing site for immediate analysis and reporting. Participants will have no further access to the study drug once their treatment is complete (maximum 5 days). All participants will continue to receive the standard care for their condition and participation in this study will not affect or delay this care.

16.12 Access to Final Trial Dataset

During the study, the PenCTU data team will have access to the trial dataset, including identifiable participant data. Other members of the CTU and the wider study team will have restricted access to pseudo-anonymised study data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit study-related monitoring, audits and inspections. Access will be overseen by the CTU data manager and trial manager. Access to the final dataset will be provided to the trial statisticians for analysis.

After the trial has been reported, the anonymised individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g., data dictionaries, blank data collection forms, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requestors whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

17. DISSEMINATION POLICY

The data arising from the trial will be owned by the Sponsor. On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared. This report will be submitted to the Trial Sponsor and Funder and will be publicly available. Participating investigators will not have rights to publish any of the trial data without the permission of the CI and Sponsor.

The trial will be reported in a manuscript that will be submitted to a peer-reviewed medical journal as open access. The trial will be reported in accordance with relevant Consort Guidelines. All publications

arising from this trial will acknowledge the Funder and a copy of all manuscripts will be provided to the Funder for review at the time of submission to a journal. However, the Funder does not have the right to revise any submission prior to publication. The trial protocol will also be submitted for open access publication to a peer-reviewed journal. A lay summary of the trial results will be produced and published on the PenCTU / University of Plymouth website, trial participants will receive a notification via email (if provided) or post when available. An anonymised participant level dataset will be produced and held within PenCTU.

Upon completion of the trial, an End of Trial report will be generated and submitted to REC within 12 months. As the funder for the trial, Gilead will also be provided with a report of the trial, per their requirements.

The results of this trial will be submitted to peer-reviewed journals for publication as soon as data analysis is completed. Participants will not be identified in any publications. PPIE representatives involved in the trial will support the dissemination of the information into the public domain and to the participants involved in the trial, in an appropriate manner. The findings will be presented at national and international conferences.

Social media: findings will be disseminated and publicised through links with organisations with a large social media presence.

17.1 Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts and papers relating to this trial will be determined according to the International Committee of Medical Journal Editors criteria. All members of the TMG who have contributed to trial design, management, analysis and interpretation will be granted authorship of the Final Trial Report. The CI will retain lead author status on the Final Trial Report. There is no intention to use professional writers.

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