STATISTICAL ANALYSIS PLAN

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

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Contents

ADMINISTRATIVE INFORMATION

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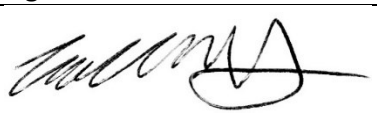
	Name	Signature	Date
Statistical Analysis Plan authored by	Trial Statistician: Jade Chynoweth		22SEP2025
	Trial Statistician: Anton Barnett		22SEP2025
	Senior Trial Statistician: Prof Victoria Allgar		10OCT2025
Approved by	Chief Investigator: Prof Mark Faghy		23SEP2025
	Independent Statistician: Katie Booth		15OCT2025

LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-minute Walk Test
AE	Adverse Event
ALT	Alanine aminotransferase
AR	Adverse Reaction
BNF	British National Formulary
CFS	Chronic Fatigue Syndrome
CO2	Carbon Dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID	Coronavirus disease
CPET	Cardiopulmonary Exercise Test
CT	Computed Tomography
DSQ-PEM	Modified De Paul Symptom Questionnaire-Post Exertional Malaise
EGF	Epidermal Growth Factor
eGFR	Estimated Glomerular Filtration Rate
Eotaxin	Eosinophil Chemotactic Protein
EQ-5D-5L	Standardised measure of health-related quality of life developed by the EuroQol Group
F2F	Face-to-Face
FAS	Fatigue Assessment Scale
FGF-basic	Basic Fibroblast Growth Factor
FDG	Fluorodeoxyglucose
GAD-7	Generalised Anxiety Disorder
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HGF	Hepatocyte Growth Factor
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
IP-10	Interferon Gamma-Induced Protein 10
IV	Intravenous
LC	Long COVID
LFT	Liver Function Test
MCP-1	Monocyte Chemoattractant Protein 1
ME	Myalgic Encephalomyelitis
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximum Expiratory mouth Pressure
MFIS	Modified Fatigue Impact Scale
MIG	Monokine Induced by Gamma Interferon
MIP	Maximum Inspiratory mouth Pressure

Abbreviation	Definition
MIP-1α	Macrophage Inflammatory Protein 1 Alpha
MIP-1β	Macrophage Inflammatory Protein 1 Beta
MRC	Medical Research Council
ONS	Office for National Statistics
PCFS	Post COVID Functional Status Scale
PDQ-5	Perceived Deficit Questionnaire
PenCTU	Peninsula Clinical Trials Unit
PET	Positron Emission Tomography
PI	Principal Investigator
PIS	Participant Information Sheet
PT	Preferred Term
RAG	Red/Amber/Green
RANTES	Regulated on Activation, Normal T Cell Expressed and Secreted
RCT	Randomised Controlled Trial
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
SMPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPO2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised Uptake Volume
TMG	Trial Management Group
TNF-α	Tumor Necrosis Factor alpha
VEGF	Vascular Endothelial Growth Factor
VO2	Volume of Oxygen
VT	Ventilatory threshold
WHO	World Health Organisation

1 INTRODUCTION

1.1 Background and rationale for the trial

Long coronavirus disease (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 Severe Acute Respiratory Syndrome coronavirus 2 (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]. 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 [5]. 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.

Data indicates that >2 million people in the United Kingdom [6] (Office for National Statistics (ONS), 2022), and >144 million globally [7] 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 [8,9].

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 SARS-CoV2 infection [10], 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 [11], 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 Investigational Medicinal Product (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.

Accordingly, there is a need to assess the feasibility of using an anti-viral, administered by intravenous (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.

1.2 Purpose of Statistical Analysis Plan

This statistical analysis plan (SAP) sets out the methods to be used to analyse the data from the ERASE-LC feasibility trial. This plan is based on the updated study protocol (Version 2.2, dated 21/08/2025) and follows the recently published "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" [12] the consolidated standards of reporting trials (CONSORT) extension for pilot and feasibility studies [13] and CONSORT extension for reporting patient-reported outcomes [14]. However, it is worth noting that, as this is a feasibility trial, formal or inferential statistical analysis and hypothesis testing of the outcome measures is not appropriate and thus will not be undertaken.

2 Feasibility trial objectives

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

Population: in patients with Long COVID

Intervention: a five-day treatment of Remdesivir

Comparison: compared to Treatment as Usual

Outcome: 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.

2.1 Primary objective

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)

2.2 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

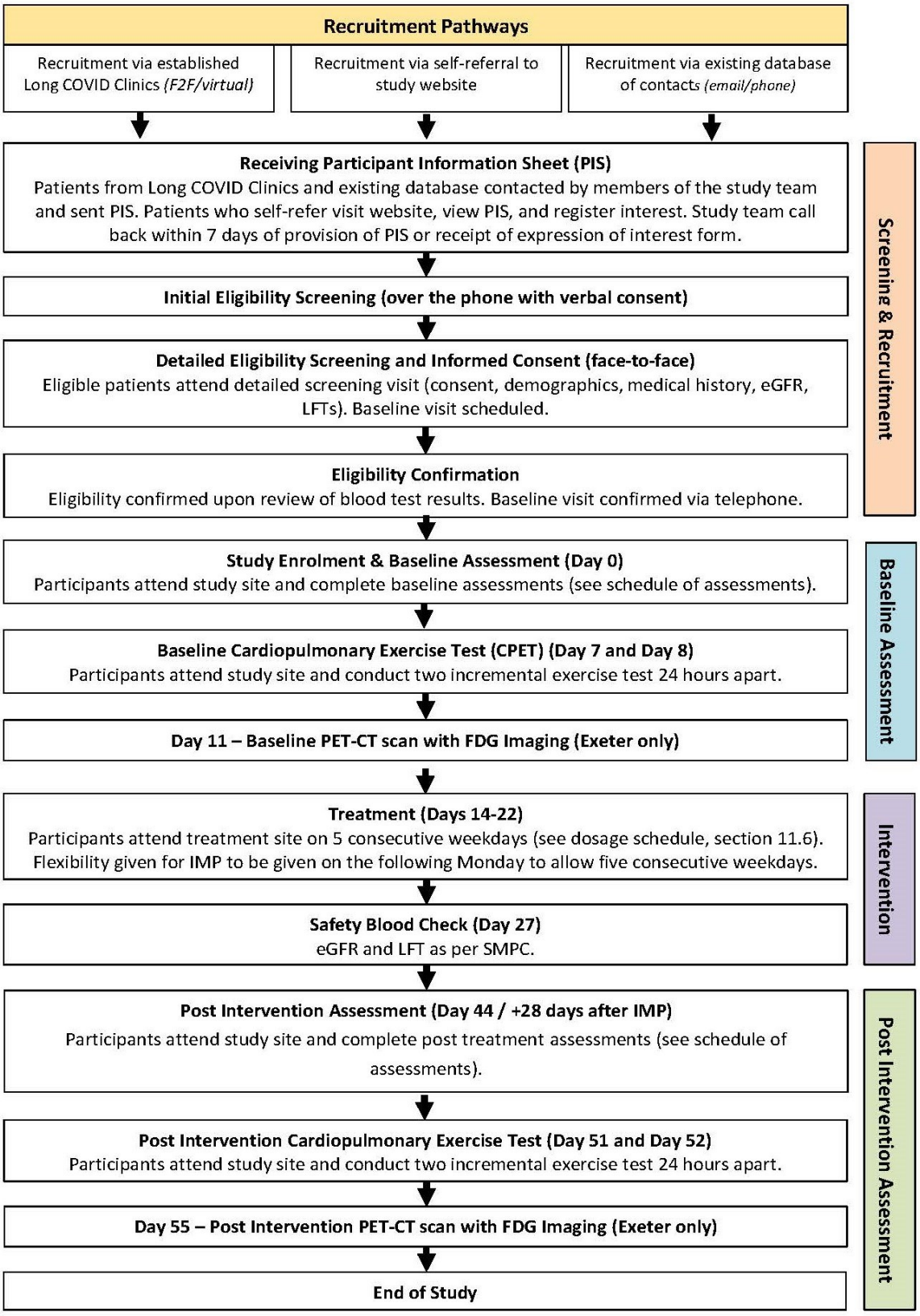
To determine the clinical safety and tolerance parameters of the use of Remdesivir in the treatment of patients with Long COVID.

3 Trial design

3.1 General 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 will be conducted in the University Hospitals of Derby and Burton NHS Foundation Trust and Royal Devon University Healthcare NHS Foundation Trust and two non-NHS sites, the University of Derby and University of Exeter. Patients will be assessed pre-intervention at day 0 (enrolment and baseline assessment), days 7 & 8 (CPET) and day 11 (PET/CT scan – *Exeter only*). The treatment phase will occur on five consecutive weekdays between days 14 & 22. Post intervention assessment will occur on day 27 (safety blood check), day 44 (i.e. +28 days after IMP, post intervention assessment), days 51 & 52 (CPET) and day 55 (PET/CT scan – *Exeter only*). Figure 1 shows the participants timeline through the ERASE-LC feasibility study.

Figure 1: Participant flowchart through the ERASE-LC feasibility study



3.2 Randomisation

Since this is a single-arm study, there is no need for randomisation or blinding of participants.

3.3 Sample size

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 red/amber/green (RAG) system (Section 6.5) 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* [15].

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)).**

3.4 Statistical interim analyses and stopping guidance

No formal statistical interim analyses are planned for this feasibility trial. Analysis will be undertaken at the 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 Principal Investigators (PIs).

3.5 Timing of final analysis

All analysis will be undertaken once the database is locked after the final participant has completed the final assessment at day 52 for Derby and day 55 for Exeter.

3.6 Timing of outcome assessments

3.6.1 Feasibility trial outcome measures

	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, CPETs and post-Intervention visit (Days 0, 7&8, 44, 51&52 (11 and 55 in Exeter)) 3. Number of patients completing each day of treatment 4. At Baseline, CPET, treatment and post-Intervention visits (Days 0, 7&8, 14 – 22, 44, 51&52 (11 and 55 in Exeter))
Adherence to the treatment regime of Remdesivir	Number of clinic appointments attended and number that complete each treatment session.	Measure Days 14 -22 during treatment phase
Completeness of study assessments	Number of appointments attended and number of complete assessments	CPET, Bloods (and PET/CT if in Exeter)
Completeness of data collection activities	1. Number of participants that complete all patient -reported measures (both in full and partially) 2. Number of participants that complete physical and physiological tests	At Baseline, CPET and post-Intervention visits (Days 0, 7&8, 44, 51&52).

3.6.2 Pre and Post Intervention Patient-reported Outcome measures

	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Quality of life	EQ-5D-5L [16]	Day 0 and +28 days after IMP (Day 44) *Days 7, 8, 51, 52
Functional status	PCFS (Impact on daily life subscale of LC Symptom Burden) [17]	
Physical Symptoms	mMRC Dyspnoea Scale [18]	
Cognitive symptoms	PDQ-5 [19]	
Emotional symptoms	GAD-7 [20]	
Symptom Burden	DSQ-PEM [21]	
	SBQ™-LC* [22]	
	FAS* [23]	
	MFIS* [19]	

3.6.3 Clinical Assessments

	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
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 SPO2)	Day 0 and +28 days after IMP (Day 44) *Days 7, 8, 51, 52

	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Biomarker 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	Days 0, 7, 8, 44, 51, 52
Tolerance to physical stimulus (CPET)	• First ventilatory threshold (VT1) • Peak oxygen consumption ($\dot{V}O_2$ peak) • End-tidal CO_2 (at VT1 and $\dot{V}O_2$ peak)	Days 7, 8, 51 and 52

	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
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

4 Statistical principles

4.1 Statistical significance levels

As this is a feasibility study, no formal hypothesis testing will be undertaken. Feasibility outcomes, such as recruitment and retention rates, will be summarised descriptively and presented with two-tailed 95% confidence intervals.

Change between pre- and post- intervention for the key patient-reported outcomes (EQ-5D-5L utility index score, SBQ™-LC impact on daily life subtotal), key biomarkers (IL-1β, IL-4, IL-8, IL-12, IP-10 and RANTES) and key CPET outcomes (VT1 and V̇O2 peak) will be summarised and presented with two-sided 75%, 85% and 95% confidence intervals, as recommended by [24].

Estimates such as standard deviation for the change between baseline and each follow-up for the proposed primary outcomes, that may be used to aid future sample-size calculations (listed in section 6.6), will be presented with two-sided 80% and 90% confidence intervals [25,26].

4.2 Intervention adherence and protocol compliance

4.2.1 Intervention adherence

All study participants will receive the antiviral medication Remdesivir via intravenous infusion over 5 consecutive days. Intervention adherence will be defined as completing the full 5-day treatment. The number and percentage of participants for each number of treatment days received (up to 5 days) will be presented. In addition, the number and percentage of days where participants attended but the treatment was not administered will be presented. No formal statistical testing will be undertaken.

4.2.2 Protocol compliance

Non-compliance with protocol will be captured on specific non-compliance report forms according to instructions provided by Peninsula Clinical Trials Unit (PenCTU) and in accordance with PenCTU standard operating procedures (SOPs). Protocol non-compliance (e.g. overdose of remdesivir, blood samples retaken) will be reviewed periodically by the Trial Management Group (TMG) as part of central monitoring, with the aim of identifying and addressing recurrent episodes of non-compliance. The proportion of participants with any protocol deviations will be summarised.

4.3 Analysis population

Data from all eligible consented population will be subjected to the study analysis, regardless of whether they received study drug and protocol adherence (provided their outcome data are not missing, as no imputation is planned). This will be an intention to treat analysis, assuming each participant has been given remdesivir via intravenous infusion over 5 consecutive days. The safety population will be defined as any participant consented into the trial that received at least one dose of trial drug.

5 Trial population

5.1 Participant eligibility criteria

5.1.1 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 (WHO)* 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 from 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.*

5.1.2 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.

5.2 Recruitment

Details of participants from the screening process to the completion of the trial will be recorded and presented in the CONSORT-style flow chart (Figure 2 and 3 in Appendix).

In particular, the following data will be collected and provided, where applicable:

- Number of people identified to participate in the trial
- Number of people screened for eligibility
- Number of people (percentage of screened) ineligible (with reasons where available)
- Number of people (percentage of screened) declined to participate (with reasons where available)
- Number of people (percentage of screened) consented to participate
- Number of participants (percentage of consented) who completed baseline assessment (day 0)
- Number of participants (percentage of consented) who completed baseline CPET assessments (day 7 and day 8)
- Number of participants (percentage of consented from Exeter site) who completed baseline PET/CT assessment (day 11)
- Number of participants (percentage of consented) who did not receive any doses of remdesivir
- Number of participants (percentage of consented) who did not receive all five doses of remdesivir
- Number of participants (percentage of consented) who received post-intervention safety blood checks (day 27)
- Number of participants (percentage of consented) who completed post-intervention assessment (day 44)
- Number of participants (percentage of consented) who completed post-intervention CPET assessments (day 51 and day 52)

- Number of participants (percentage of consented from Exeter site) who completed post-intervention PET/CT assessment (day 55)
- Number of participants (percentage of consented) lost to follow-up
- Number of participants (percentage of consented) that fully withdraw from the trial
- Number of participants (percentage of consented) included in final analysis.

5.3 Withdrawal/follow-up

There is a potential of participant withdrawal from the trial due to lack of tolerance of the remdesivir via intravenous infusion and baseline assessments (including CPET and PET/CT assessments). Participants may request to withdraw at any time during the study. These participants may continue to consent for follow-up and data collection (discontinuation of treatment only) or withdraw from future follow-up and data collection, allowing study use of only pre-collected data.

In line with CONSORT Guidelines, reasons for withdrawal (where provided) will be summarised during each stage of the trial (participants who did not receive treatment, non-completion of treatment, lost to follow-up). Participants that withdraw will not be replaced. The level of discontinuation, withdrawal and loss to follow-up will be used to inform the future sample size calculation of the definitive trial to allow for a sufficiently powered analysis.

5.4 Baseline patient characteristics

Baseline characteristics, collected during screening after consent, will be summarised descriptively to provide an overview of the trial population. Continuous data will be summarised by means, standard deviations and ranges, unless data are at least moderately skewed, in which case medians, interquartile ranges and ranges will be used. Categorical variables will be summarised by frequencies and percentages.

Demographics:

- Age (years)
- Sex at birth
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Medical History:

- Endocrine/diabetes
- Renal
- Cardiovascular

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

6 Statistical analyses

6.1 Outcomes

6.1.1 Feasibility trial outcome measures

To facilitate the design and planning of a future definitive trial, the feasibility outcomes described in section 3.6.1 will be collected.

6.1.2 Pre and Post Intervention Patient-reported Outcome measures

Patient-reported outcomes (quality of life, functional status, symptom burden and physical, cognitive, and psychological symptoms) will be measured pre and post treatment at different time points as detailed in section 3.6.2.

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

  - EQ-5D-5L consists of five dimensions (previously 3): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [16]. 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)

  - PCFS has six scale grades [17]. 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**

  - The SBQ™-LC is composed of 17 independently functioning, unidimensional scales [22]. 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.

  Modified De Paul Symptom Questionnaire-Post Exertional Malaise (DSQ-PEM)

  - DSQ-PEM is a 10-item questionnaire used to measure post-exertional malaise (PEM) [21]. The first 5 questions have answers split into frequency and severity, where both are scored from 0 to 4. For frequency; 0 = none of the time, 1 = a little of the time, 2 = about half of the time, 3 = most of the time and 4 = all of the time. For severity; 0 = symptom not present, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe. Items 6, 7, 8 and 10 are questions with yes/no answers. Item 9 has a time duration response, with options; <1h, 2-3h, 4-10h, 11-13h, 14-23h, and >24h.

  *Fatigue Assessment Scale (FAS)**

  - is a 10-item scale evaluating symptoms of chronic fatigue [23]. Each item has five response options ranging from 1 to 5, where values are assigned as 1 = Never, 2 = Sometimes, 3 = Regularly, 4 = Often and 5 = Always. Items 4, 'I have enough energy for everyday life' and 10, 'When I am doing something, I can concentrate quite well' are reverse scored. The scale score is calculated by summing all items (score can range from 10 to 50).

  *Modified Fatigue Impact Scale (MFIS) **

  - is a 21-item patient-reported scale designed to measure fatigue across five scales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue). Each item has five response options ranging from 0 to 4 [19]. Values are assigned as 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often and 4 = Almost always. Items are aggregated into three subscales (physical, cognitive and psychological), as well as a total MFIS score. The Physical scale can range from 0 to 36. It is computed by adding raw scores of items 4, 6, 7, 10, 13, 14, 17, 20 and 21. The cognitive scale can range from 0 to 40. It is computed by adding raw scores of items 1, 2, 3, 5, 11, 12, 15, 16, 18 and 19. The Psychological scale can range from 0 to 8. It is computed by adding raw scores of items 8 and 9. The Total MFIS score can range from 0 to 84. It is computed by adding raw scores of all 21 items.

- ***Physical Function:***

  Modified Medical Research Council (mMRC) Dyspnoea Scale

  - The mMRC Dyspnoea Scale grades how breathless a patient gets doing everyday activities [18], 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)

  - This instrument provides an assessment of five domains of cognitive functioning that are frequently affected: attention, retrospective memory, prospective memory, and planning and organization [19]. Each item is scored from 0 to 4, where 0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often and 4 = Almost always. Calculate the total PDQ-5 score by summing the raw scores across all items (scores can range from 0 to 20).

- ***Psychological:***

  Generalised Anxiety Disorder (GAD-7)

  - The GAD-7 is a 7-item scale that has reporting scores from 0 to 3 on all the questions [20]. 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. The scale score is calculated by summing the raw scores of each item (scores range from 0 to 21).

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

6.1.3 Clinical assessments

Physiological outcomes (physical, physiological, cognitive function and emotional status and/or capacity), biomarker and inflammatory profiles, tolerance to physical stimulus (CPET), daily symptoms and heart rate variability and microvascular function will be measured pre and post treatment at different time points as detailed in section 3.6.3.

For the *6-minute walk test (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.

6.1.4 Derived outcome measures and other derived variables

- Age at baseline (years) calculated by: (date of baseline minus date of birth in days)/365.25
- BMI at baseline (kg/m^2) calculated by: weight in kilograms divided by (height in metres)^2
- EQ-5D-5L utility index scores using guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit [27] . R package: *eq5d* [28]. If a UK value set is not available for 5L, a 3L value set will be used by mapping the 5L to 3L.
- DSQ-PEM: A frequency and severity score of 2,2 or greater on any items 1-5 is indicative of Post-Exertional Malaise (PEM). A response of 14-23h or >24h on item 9 and a yes for either items 7 or 8 are required to indicate myalgic encephalomyelitis (ME) and/or chronic fatigue syndrome (CFS). Items 6 and 10 are not used to indicate ME/CFS, but to provide a description of patient PEM for clinical evaluations.
- SBQ™-LC: Convert scale raw scores of the 17 scales to the transformed scores as described in the Appendix B: Conversion Tables to transform the scale raw score to the Rasch 0-100 linear score of the Symptom Burden Questionnaire™ for Long COVID User Manual Version 1.1 and shown in the Appendices as Figure 4 of this statistical analysis plan.

6.2 Analysis

As this is a feasibility study, it is not powered to support any conclusion regarding the efficacy of the intervention. Analyses will be descriptive, informing the design of the fully powered definitive trial. Appropriate plots will be used to illustrate key data; however, no formal hypothesis tests will be undertaken.

Continuous measures will be summarised as means, standard deviations, and ranges where the distribution appears approximately normally distributed, and as medians, inter-quartile ranges and ranges otherwise. Categorical data will be summarised using frequencies and percentages. No subgroup analyses are planned.

6.2.1 Feasibility outcome measures

Summary statistics of the feasibility outcomes described in Section 3.6.1 will be provided. The number and percentage of blood samples retaken at each time point will also be presented.

6.2.2 Pre- and Post-Intervention Outcome measures

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. Pre- and post-intervention outcome analyses should be considered as hypothesis generating rather than providing firm conclusions.

Continuous key patient-reported outcomes (EQ-5D-5L utility index score, SBQ™-LC impact on daily life subtotal), key biomarkers (IL-1β, IL-4, IL-8, IL-12, IP-10 and RANTES) and key CPET outcomes (VT1, V̇O2 peak) will be descriptively summarised and analysed using paired-sample t-test approach to calculate the unadjusted change in scores between baseline and follow-up with confidence intervals and using multivariable linear mixed effects models for the adjusted change in scores. For key CPET outcomes, pre-intervention change (difference between day 7 and day 8) and post-intervention change (difference between day 51 and day 52) will be used. The changes between baseline (day 0 or pre-intervention change in CPET) and follow-up (day 44 or post-intervention change in CPET) will be modelled on time point, with adjustment for recruitment site in the multivariable linear mixed effect models.

Box or violin plots will be produced, and the mean and corresponding confidence interval calculated for the continuous key patient-reported outcomes, key biomarkers and change in key CPET outcomes by pre- and post-intervention.

As this is a feasibility study, summary statistics are focused on completeness of symptom tracking and heart rate variability. Symptom tracking will be completed using the Visible app. Participants who do not have access to a smartphone will complete a daily paper symptom diary. Summary statistics of the number of days participants complete symptom tracking will be produced. Heart rate variability will be measured using a Polar Verity wearable sensor, which participants with smartphone access will wear on their upper arm. Summary statistics of the number of days participants wore the device and the mean wear time on the days the device was worn will be produced. Plots of wear time will be produced to track changes in wear time (by week) for each participant.

6.2.3 Planned sensitivity analysis

A per-protocol sensitivity analysis will also be done to account for participants who: i) did not receive all of the study drug and ii) did not receive any of the study drug for each of the key patient-reported outcomes, key biomarkers and key CPET outcome measures. This will involve only including participants who: i) adhered to the treatment regimen (protocol-compliant population) and ii) participants who received at least one dose of remdesivir (all-treated population) in the analysis.

6.3 Missing data

A feasibility outcome of the ERASE-LC feasibility trial is to assess the completeness of patient-reported outcome measures. Completeness of data will be reported for each patient-reported outcome measure at each relevant time point. The summary of missing data may help inform the decision of the choice of primary outcome measure and may highlight areas to improve data collection in the main trial. There will be no imputation of outcome measures.

6.4 Safety data

Clinical safety and tolerance parameters such as frequency, seriousness, and severity of Adverse Events (AE), Serious Adverse Events (SAE), Adverse Reactions (AR), Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reactions (SUSAR) will be assessed throughout the study. AEs

(including ARs) and SAEs (including SARs and SUSARs) will be recorded from the time of written consent until the last study visit.

AEs (AEs of unexpected severity or ARs) and SAEs (including SARs and SUSARs) will be summarised as part of the safety data. Safety data will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), the seriousness, the severity and the relatedness to treatment, with the number of AEs and SAEs per participant presented.

If more than 10 AEs or SAEs are reported overall (regardless of number of participants), graphical representations of the safety data will be produced. These visualisations will include a bar chart presenting the number of AEs or SAEs per participant, a dot plot to display the absolute and relative risks within each MedDRA organ system class, and a stacked bar chart displaying the percentage of participants with each event within each organ system class and severity, using the maximum severity for each participant within each category of event (see Figures A1-A3 in Phillips et al. [29]).

6.5 Progression to definitive trial

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 randomised controlled trial (RCT) if minimum success criteria for key feasibility aims/objectives are achieved.

Table 1: 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* at 0 and 44 days	<60%	60-80%	>80%

Completion of CPETs at 7, 8, 51 and 52 days.	<60%	60-80%	>80%

*EQ-5D-5L, SBQ™-LC and all biomarkers and inflammatory profiles (yes/no)

6.6 Sample size for a definitive trial

We aim to present data resulting from the ERASE-LC feasibility trial to aid in the formal sample size calculation for the main trial.

Potential primary outcomes for the definitive trial include key patient-reported outcomes (EQ-5D-5L index utility score, SBQ™-LC impact on daily life subtotal) and key biomarkers (IL-1β, IL-4, IL-8, IL-12, IP-10 and RANTES). To assist with the potential sample size calculations, for each of the proposed primary outcome we will calculate the standard deviation at baseline and each follow-up. Point estimates of the mean of each potential primary outcome will be presented alongside two-sided 80% and 90% CIs.

6.7 Statistical software

Statistical analysis will be undertaken using StataSE version 17 [30] or later and R version 4.2.1 [31] or later.

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Appendices

A - Template CONSORT diagram

Figure 2: CONSORT diagram of participant flow through the ERASE-LC feasibility study (part 1)

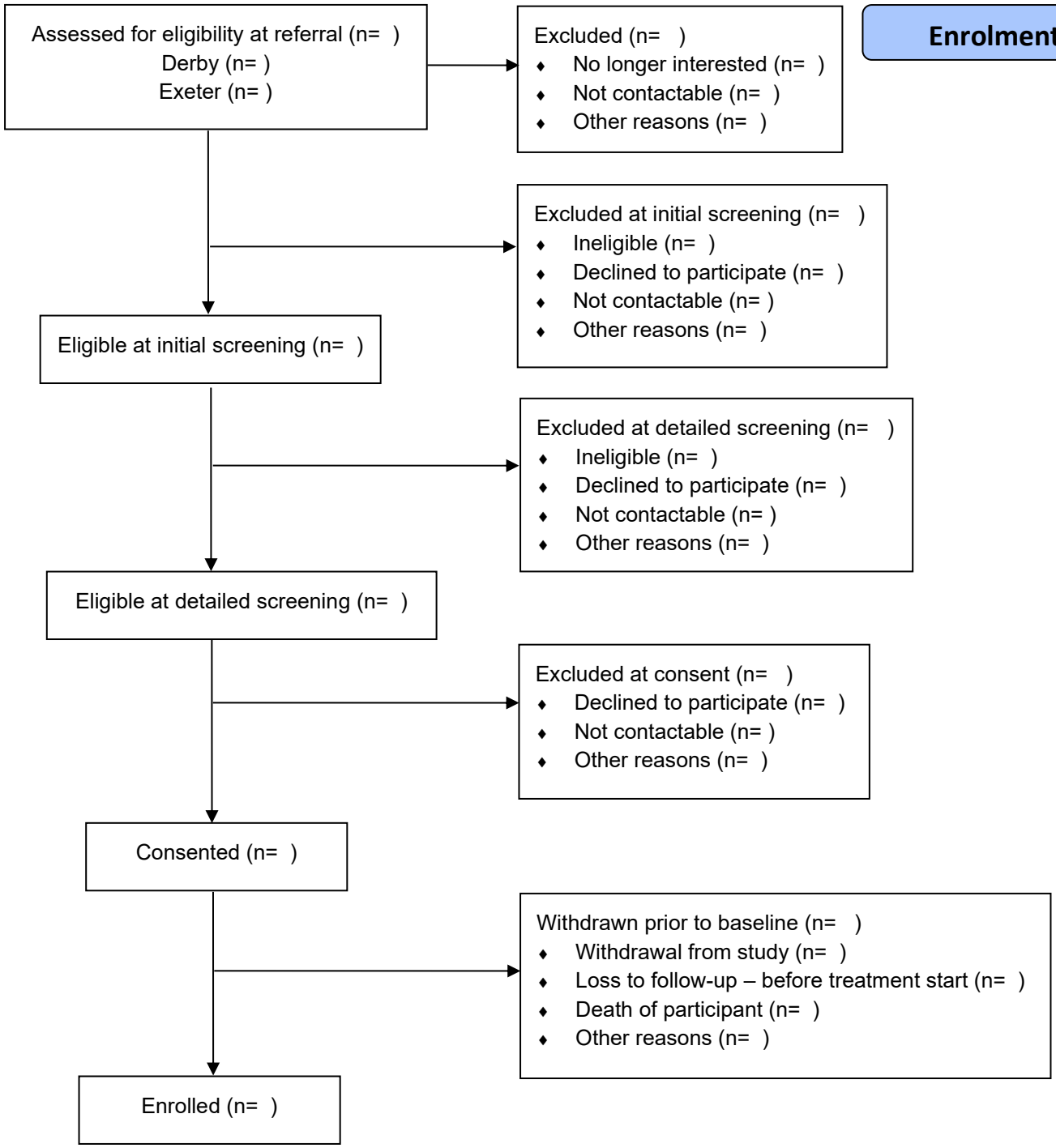
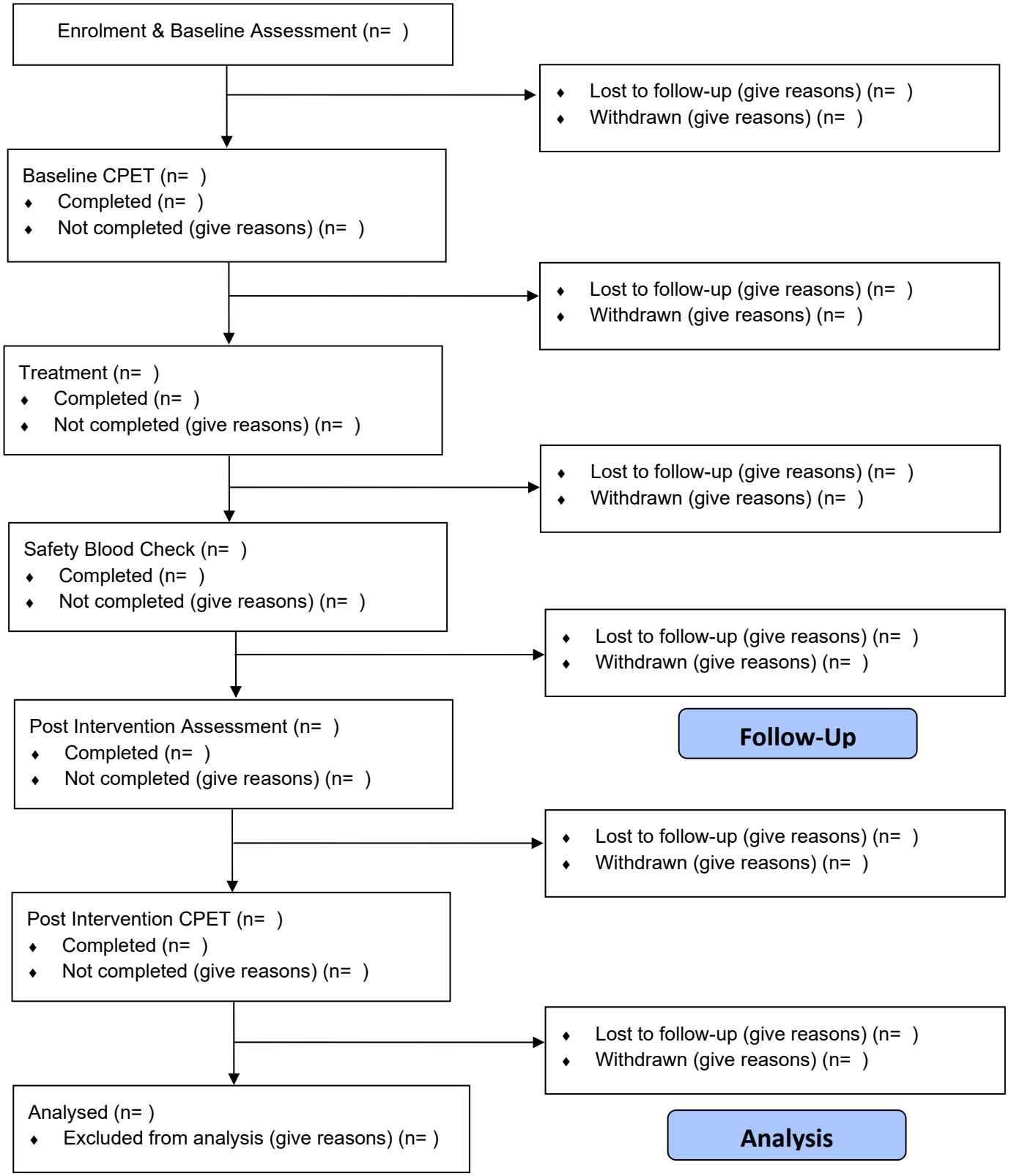


Figure 3: CONSORT diagram of participant flow through the ERASE-LC feasibility study (part 2)



B- Conversion Tables for Symptom Burden Questionnaire™ for Long COVID

Figure 4: Conversion Tables to transform the scale raw score to the Rasch 0-100 linear score from the Symptom Burden Questionnaire™ for Long COVID User Manual Version 1.1

Breathing

Scale Raw Score	Transformed Score
0	0
1	12
2	20
3	26
4	31
5	35
6	39
7	42
8	46
9	49

Scale Raw Score	Transformed Score
10	53
11	58
12	62
13	67
14	72
15	79
16	88
17	100

Pain

Scale Raw Score	Transformed Score
0	0
1	12
2	20
3	26
4	31
5	37
6	43

Scale Raw Score	Transformed Score
7	50
8	58
9	66
10	74
11	85
12	100

Circulation

Scale Raw Score	Transformed Score
0	0
1	16
2	25
3	32
4	38
5	44

Scale Raw Score	Transformed Score
6	51
7	59
8	69
9	82
10	100
11	100

Fatigue

Scale Raw Score	Transformed Score
0	0
1	11
2	18
3	22
4	26
5	30
6	34

Scale Raw Score	Transformed Score
7	40
8	53
9	69
10	78
11	88
12	100

Memory, Thinking and Communication

Scale Raw Score	Transformed Score
0	0
1	11
2	18
3	23
4	26
5	29
6	32
7	34
8	36
9	38
10	40
11	42
12	44
13	46
14	48
15	50
16	51

Scale Raw Score	Transformed Score
17	53
18	55
19	57
20	59
21	61
22	63
23	65
24	67
25	70
26	73
27	78
28	81
29	88
30	100

Movement

Scale Raw Score	Transformed Score
0	0
1	11
2	42
3	70
4	75

Scale Raw Score	Transformed Score
5	80
6	83
7	87
8	92
9	100

Sleep

Scale Raw Score	Transformed Score
0	0
1	20
2	39
3	51
4	57
5	62
6	65

Scale Raw Score	Transformed Score
7	68
8	72
9	75
10	80
11	87
12	100

Ears, Nose and Throat

Scale Raw Score	Transformed Score
0	0
1	14
2	22
3	26
4	29
5	32
6	33
7	35
8	36
9	38
10	39
11	40
12	41
13	42
14	43
15	44
16	45
17	46
18	47
19	48

Scale Raw Score	Transformed Score
20	49
21	50
22	51
23	52
24	53
25	54
26	55
27	56
28	57
29	58
30	59
31	61
32	63
33	65
34	68
35	71
36	76
37	85
38	100

Stomach and Digestion

Scale Raw Score	Transformed Score
0	0
1	14
2	22
3	26
4	30
5	32
6	35
7	37
8	39
9	41
10	43

Scale Raw Score	Transformed Score
11	45
12	46
13	49
14	51
15	53
16	57
17	61
18	67
19	80
20	100

Muscles and Joints

Scale Raw Score	Transformed Score
0	0
1	14
2	22
3	26
4	30
5	32
6	35
7	37
8	39
9	40
10	42
11	44
12	45
13	47
14	49

Scale Raw Score	Transformed Score
15	50
16	52
17	54
18	56
19	58
20	60
21	62
22	64
23	67
24	71
25	76
26	85
27	100

Mental Health and Wellbeing

Scale Raw Score	Transformed Score
0	0
1	10
2	19
3	24
4	28
5	30
6	33
7	35
8	37
9	39
10	40
11	42

Scale Raw Score	Transformed Score
12	44
13	46
14	48
15	50
16	52
17	55
18	58
19	62
20	67
21	74
22	85
23	100

Skin and Hair

Scale Raw Score	Transformed Score
0	0
1	14
2	22
3	27
4	30
5	33
6	36
7	39
8	42
9	44

Scale Raw Score	Transformed Score
10	47
11	50
12	53
13	57
14	62
15	67
16	74
17	84
18	100

Eyes

Scale Raw Score	Transformed Score
0	0
1	16
2	25
3	30
4	34
5	37
6	39
7	42
8	44
9	46
10	48

Scale Raw Score	Transformed Score
11	50
12	52
13	55
14	57
15	60
16	63
17	67
18	73
19	83
20	100

Female

Scale Raw Score	Transformed Score
0	0
1	12
2	20
3	27
4	35
5	42
6	49

Scale Raw Score	Transformed Score
7	54
8	60
9	65
10	72
11	83
12	100
13	100

Male

Scale Raw Score	Transformed Score
0	0
1	35
2	64
3	81
4	100
5	100

Other Symptoms

Scale Raw Score	Transformed Score
0	0
1	12
2	18
3	22
4	25
5	28
6	29
7	31
8	33
9	35
10	36
11	37
12	38
13	39
14	40
15	41
16	42
17	43
18	44
19	45

Scale Raw Score	Transformed Score
20	46
21	47
22	48
23	49
24	50
25	51
26	53
27	54
28	56
29	57
30	59
31	61
32	64
33	67
34	70
35	74
36	80
37	89
38	100

Impact on Daily Life

Scale Raw Score	Transformed Score
0	0
1	0
2	10
3	17
4	22
5	25
6	28
7	30
8	33
9	35
10	37
11	39
12	41

Scale Raw Score	Transformed Score
13	43
14	45
15	48
16	50
17	53
18	56
19	59
20	63
21	68
22	75
23	86
24	100

C - Template tables

Table 2: Recruitment by site – n (%)

	Derby				Exeter				Total
	LC clinic referral (PIC)	Self referral (database)	Self-referral (Other_	Total	LC clinic referral (PIC)	Self-referral (database)	Self-referral (Other)	Total	
Number from each pathway									
Approached									
Eligible									
Informed consent									

Table 3: Reasons for non-participation

Time point	Reason		n (%)
Initial screening	Uncontactable		
	Ineligible		
	Declined	Not interested	
		Too busy	
		General health reasons	
		Did not want treatment	
		Other	
	Other		
Detailed screening	Uncontactable		
	Ineligible		
	Declined	Not interested	
		Too busy	
		General health reasons	
		Did not want treatment	
		Other	
	Other		
Pre-consent	Ineligible		
	Declined	Not interested	
		Too busy	
		General health reasons	
		Did not want treatment	
		Other	
	Other		

Table 4: Discontinuation and withdrawal

Time point	Reason	n (%)
	Treatment withdrawal	
Baseline CPET	Protocol non-compliance	
	Withdrawal of consent	
	Ineligible	
	AE/SAE/AR/SUSAR	
	Pregnancy	
	Other	
Post intervention assessment	Protocol non-compliance	
	Withdrawal of consent	
	Ineligible	
	AE/SAE/AR/SUSAR	
	Pregnancy	
	Other	
Post intervention CPET	Protocol non-compliance	
	Withdrawal of consent	
	Ineligible	
	AE/SAE/AR/SUSAR	
	Pregnancy	
	Other	
PET/CT (Exeter only)	Protocol non-compliance	
	Withdrawal of consent	
	Ineligible	
	AE/SAE/AR/SUSAR	
	Pregnancy	
	Other	

Table 5: Completeness of clinical assessments – n (%)

Measure	Time-point	**Derby** (n=)	**Exeter** (n=)	**All** (n=)
MIP	Baseline			
	Post-intervention			
MEP	Baseline			
	Post-intervention			
Lung function	Baseline			
	Post-intervention			
Systolic pressure	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
Diastolic pressure	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			

Measure	Time-point	**Derby** (n=)	**Exeter** (n=)	**All** (n=)
Oxygen saturation	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
Breathing rate	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
Resting heart rate	Baseline			
	Post-intervention			
Body temperature	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
All biomarkers and inflammatory profiles	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
Blood sample retaken	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
6-minute walk test	Baseline			
	Post-intervention			

Table 6: Completeness of tolerance to physical stimulus (CPET) and PET/CT outcome measures – n (%)

Measure		**Time-point**	**Derby** (n=)	**Exeter** (n=)	**All** (n=)
CPET day 1	VT1	Baseline			
		Post-intervention			
	VO2 peak	Baseline			
		Post-intervention			
	End-tidal CO2 at VT1	Baseline			
		Post-intervention			
	End-tidal CO2 at VO2 peak	Baseline			
		Post-intervention			
CPET day 2	VT1	Baseline			
		Post-intervention			
	VO2 peak	Baseline			
		Post-intervention			
	End-tidal CO2 at VT1	Baseline			
		Post-intervention			
	End-tidal CO2 at VO2 peak	Baseline			
		Post-intervention			
PET/CT scan		Baseline			
		Post-intervention			

Table 7: Completeness of patient reported outcome measures – n (%)

	Time-point	**Derby** (n=)	**Exeter** (n=)	**All** (n=)
SBQ™-LC	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
EQ-5D-5L	Baseline			
	Post-intervention			
Fatigue Assessment Scale	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
Modified Fatigue Impact Scale	Baseline			
	Day 7			
	Day 8			
	Post-intervention			
	Day 51			
	Day 52			
PDQ-5	Baseline			
	Post-intervention			
GAD-7	Baseline			
	Post-intervention			
	Baseline			

	Time-point	**Derby** (n=)	**Exeter** (n=)	**All** (n=)
DePaul Symptom Questionnaire	Post-intervention			
Post-COVID-19 Functional Status	Baseline			
	Post-intervention			
mMRC Dyspnoea Scale	Baseline			
	Post-intervention			

Table 8: Intervention adherence – n (%) for each session

Session		**Number (%) attending at each site**		**Cumulative total n (%)**
		Derby	Exeter	
Treatment day	1			
	2			
	3			
	4			
	5			
Safety blood check				

Table 9: Completeness of daily symptoms and heart rate variability (VISIBLE)

Measure	Symptom tracking	Heart rate variability
Participants with data n (%)		
Number of days with data n, mean (SD) [min,max] median (Q1,Q3)		
Mean wear time on days worn n, mean (SD) [min,max] median (Q1,Q3)		

Table 10: Summary statistics for baseline characteristics and demographics – n (%) unless otherwise stated

		Derby (n=)	**Exeter** (n=)	**All** (n=)
Age (years) n, mean (SD) [min,max] median (Q1,Q3)				
Sex	Male			
	Female			
Ethnicity	White			
	Mixed/Multiple			
	Asian/Asian British			
	Black/African/Caribbean/Black British			
	Other			
Height (cm) n, mean (SD) [min,max] median (Q1,Q3)				
Weight (kg) n, mean (SD) [min,max] median (Q1,Q3)				
BMI (kg/m^2) n, mean (SD) [min,max] median (Q1,Q3)				

Table 11: Summary statistics for COVID-19 history – n (%) unless otherwise stated

		Derby (n=)	**Exeter** (n=)	**Overall** (n=)
Rate health prior to COVID-19	Very good			
	Good			
	Moderate			
	Bad			
	Very bad			
Rate health today	Very good			
	Good			
	Moderate			
	Bad			
	Very bad			
Number of confirmed COVID infections n, mean (SD) [min,max] median (Q1,Q3)				
Number of suspected COVID infections n, mean (SD) [min,max] median (Q1,Q3)				
Severity of last COVID-19 infection	Mild			
	Moderate			
	Severe			
Duration of last COVID-19 infection	0-5 days			
	6-10 days			
	11-15 days			

		Derby (n=)	**Exeter** (n=)	**Overall** (n=)
	16+ days			
Admission to hospital due to COVID-19, yes				
Referred to long COVID clinic, yes				
Number of COVID vaccines received n, mean (SD) [min,max] median (Q1,Q3)				
Long COVID symptoms affecting daily life (0 – No effect, 10 - Big effect) n, mean (SD) [min,max] median (Q1,Q3)				

Table 12: Summary statistics for medical history – n (%)

		Derby (n=)	**Exeter** (n=)	**Overall** (n=)
Smoking status	Current smoker			
	Ex-smoker			
	Never smoked			
Co-morbidities	Endocrine/diabetes			
	Renal			
	Cardiovascular			
	Neurological/cerebrovascular			
	Malignancy/haematological			
	Gastrointestinal			
	Liver			
	Infarction			
	Other			

Table 13: Summary statistics for clinical assessments

Measure			**Baseline**	**Post-intervention**
Physiological function n, mean (SD) [min,max] median (Q1,Q3)		MIP		
		MEP		
		Lung function		
		Diastolic pressure		
		Systolic pressure		
		Oxygen saturation		
		Breathing rate		
		Resting heart rate		
Blood markers n, mean (SD) [min,max] median (Q1,Q3)	CytoKines	G-CSF		
		GM-CSF		
		IFN-α		
		IFN-γ		
		IL-1β		

Measure			Baseline	Post-intervention
		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		
	Chemokines	Eotaxin		
		IP-10		
		MCP-1		
		MIG		
		MIP-1α		
		MIP-1β		
		RANTES		
	Growth factors	EGF		
		FGF-basic		
		HGF		
		VEGF		
6-minute walk test n, mean (SD) [min,max] median (Q1,Q3)		6MWT		
		Borg 6-20		
		SPO2		

Table 14: Summary statistics of CPET and PET/CT outcome measures

Measure		Time-point	Baseline	Post-intervention
CPET n, mean (SD) [min,max] median (Q1,Q3)	VT1	Day 1		
		Day 2		
		Change		
	VO2 peak	Day 1		
		Day 2		
		Change		
	End-tidal CO2 at VT1	Day 1		
		Day 2		
		Change		
	End-tidal CO2 at VO2 peak	Day 1		
		Day 2		
		Change		
PET/CT scan (Exeter site only)				

Table 15: Summary statistics for Symptom Burden PROMS

Measure		**Baseline**	**Post-intervention**
SBQ™-LC n, mean (SD) [min,max] median (Q1,Q3)	Breathing		
	Pain		
	Circulation		
	Fatigue		
	Memory, thinking and communication		
	Movement		
	Sleep		
	Ears, nose and throat		
	Stomach and digestion		
	Muscles and joints		
	Mental health and wellbeing		
	Skin and hair		
	Eyes		
	Female reproductive health		
	Male reproductive health		
	Other symptoms		
	Impact on daily life		
Fatigue Assessment Scale (total) n, mean (SD) [min,max] median (Q1,Q3)			
Modified Fatigue Impact Scale n, mean (SD) [min,max] median (Q1,Q3)	Physical		
	Cognitive		
	Psychological		
	Total		

Table 16: Summary statistics for other patient reported outcome measures

Measure		**Baseline**	**Post-intervention**
EQ-5D-5L n, mean (SD) [min,max] Median (Q1,Q3)	Mobility		
	Self-care		
	Usual activities		
	Pain/discomfort		
	Anxiety/depression		
	Index score		
PDQ-5 n, mean (SD) [min,max] Median (Q1,Q3)			
GAD-7	Raw score n, mean (SD) [min,max] median (Q1,Q3)		
	Mild anxiety – n (%)		
	Moderate anxiety – n (%)		
	Severe anxiety – n (%)		
DePaul Symptom Questionnaire total score n, mean (SD) [min,max] Median (Q1,Q3)			
Post-COVID-19 Functional Status. Severity of functional limitations – n (%)	None		
	Negligible		
	Slight		
	Moderate		
	Severe		
mMRC Dyspnoea Scale – n (%)	Grade 0		
	Grade 1		
	Grade 2		
	Grade 3		
	Grade 4		

Table 17: Pre/post intervention differences (unadjusted) and confidence intervals in key continuous outcome measures

Measure		Pre/post intervention change	75% confidence interval	85% confidence interval	95% confidence interval
EQ-5D-5L utility index score					
SBQ™-LC – impact on daily life subtotal					
Biomarkers and inflammatory profiles	IL-1β				
	IL-4				
	IL-8				
	IL-12				
	IP-10				
	RANTES				
CPET	VT1				
	Peak V̇O2				

Table 18: Pre/post intervention differences (adjusted) and confidence intervals in key continuous outcome measures

Measure		Pre/post intervention change	75% confidence interval	85% confidence interval	95% confidence interval
EQ-5D-5L utility index score					
SBQ™-LC – impact on daily life subtotal					
Biomarkers and inflammatory profiles	IL-1β				
	IL-4				
	IL-8				
	IL-12				
	IP-10				
	RANTES				
CPET	VT1				
	Peak V̇O2				

Table 19: Pre/post intervention differences (unadjusted) and confidence intervals in key continuous outcome measures – per-protocol analysis (protocol compliant population)

Measure		**Pre/post intervention change**	**75% confidence interval**	**85% confidence interval**	**95% confidence interval**
EQ-5D-5L utility index score					
SBQ™-LC – impact on daily life subtotal					
Biomarkers and inflammatory profiles	IL-1β				
	IL-4				
	IL-8				
	IL-12				
	IP-10				
	RANTES				
CPET	VT1				
	Peak V̇O2				

Table 20: Pre/post intervention differences (adjusted) and confidence intervals in key continuous outcome measures – per-protocol analysis (protocol compliant population)

Measure		**Pre/post intervention change**	**75% confidence interval**	**85% confidence interval**	**95% confidence interval**
EQ-5D-5L utility index score					
SBQ™-LC – impact on daily life subtotal					
Biomarkers and inflammatory profiles	IL-1β				
	IL-4				
	IL-8				
	IL-12				
	IP-10				
	RANTES				
CPET	VT1				
	Peak V̇O2				

Table 21: Pre/post intervention differences (unadjusted) and confidence intervals in key continuous outcome measures – per-protocol analysis (all-treated population)

Measure		**Pre/post intervention change**	**75% confidence interval**	**85% confidence interval**	**95% confidence interval**
EQ-5D-5L utility index score					
SBQ™-LC – impact on daily life subtotal					
Biomarkers and inflammatory profiles	IL-1β				
	IL-4				
	IL-8				
	IL-12				
	IP-10				
	RANTES				
CPET	VT1				
	Peak V̇O2				

Table 22: Pre/post intervention differences (adjusted) and confidence intervals in key continuous outcome measures – per-protocol analysis (all-treated population)

Measure		**Pre/post intervention change**	**75% confidence interval**	**85% confidence interval**	**95% confidence interval**
EQ-5D-5L utility index score					
SBQ™-LC – impact on daily life subtotal					
Biomarkers and inflammatory profiles	IL-1β				
	IL-4				
	IL-8				
	IL-12				
	IP-10				
	RANTES				
CPET	VT1				
	Peak V̇O2				

Table 23: Summary statistics of safety data

Type		
SAEs[1]	**Relatedness, yes** - n (%)	
	Severity n, mean (SD) [min,max] median (Q1,Q3)	
	Number per participant n, mean (SD) [min,max] median (Q1,Q3)	
AEs[2]	**Relatedness, yes** - n (%)	
	Severity n, mean (SD) [min,max] median (Q1,Q3)	
	Number per participant n, mean (SD) [min,max] median (Q1,Q3)	

[1]including SARs and SUSARs; [2]including ARs

Table 24: Summary statistics for concomitant medication

Measure	
Number of participants taking medication, yes – n (%)	
Number of medications if taking medication n, mean (SD) [min,max] median (Q1,Q3)	

Table 25: Estimates of standard deviations and confidence intervals for proposed primary outcome measures for the definitive trial

Measure		Time point	Estimate	80% confidence interval	90% confidence interval
EQ-5D-5L utility index score		Baseline			
		Post-intervention			
		Both			
SBQ™-LC – impact on daily life subtotal		Baseline			
		Post-intervention			
		Both			
Biomarkers and inflammatory profiles	IL-1β	Baseline			
		Post-intervention			
		Both			
	IL-4	Baseline			
		Post-intervention			
		Both			
	IL-8	Baseline			
		Post-intervention			
		Both			
	IL-12	Baseline			
		Post-intervention			
		Both			
	IP-10	Baseline			
		Post-intervention			
		Both			
	RANTES	Baseline			
		Post-intervention			
		Both			