HEART rate variability biofeedback for long COVID symptoms (HEARTLOC): protocol for a feasibility study

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ABSTRACT

Introduction Long COVID (LC), also known as post-COVID-19 syndrome, refers to symptoms persisting 12 weeks after COVID-19 infection. It affects up to one in seven people contracting the illness and causes a wide range of symptoms, including fatigue, breathlessness, palpitations, dizziness, pain and brain fog. Many of these symptoms can be linked to dysautonomia or dysregulation of the autonomic nervous system after SARS-CoV2 infection. This study aims to test the feasibility and estimate the efficacy, of the heart rate variability biofeedback (HRV-B) technique via a standardised slow diaphragmatic breathing programme in individuals with LC.

Methods and analysis 30 adult LC patients with symptoms of palpitations or dizziness and an abnormal NASA Lean Test will be selected from a specialist Long COVID rehabilitation service. They will undergo a 4-week HRV-B intervention using a Polar chest strap device linked to the Elite HRV phone application while undertaking the breathing exercise technique for two 10 min periods everyday for at least 5 days a week. Quantitative data will be gathered during the study period using: HRV data from the chest strap and wrist-worn Filbit, the modified COVID-19 Yorkshire Rehabilitation Scale, Composite Autonomic Symptom Score, WHO Disability Assessment Schedule and EQ-5D-5L health-related quality of life measures. Qualitative feedback on user experience and feasibility of using the technology in a home setting will also be gathered. Standard statistical tests for correlation and significant difference will be used to analyse the quantitative data.

Ethics and dissemination The study has received ethical approval from Health Research Authority (HRA) Leicester South Research Ethics Committee (21/EM/0271). Dissemination plans include academic and lay publications.

Trial registration number NCT05228665.

INTRODUCTION

Post-COVID-19 syndrome or Long COVID (LC) refers to persistent symptoms 12 weeks after SARS-CoV2 infection and can include symptoms of physical fatigue, cognitive fatigue or ‘brain fog’, breathlessness, pain and psychological distress.1-5 An estimated 1.4 million people are reported to be affected by LC in the UK alone.4 The condition can be highly debilitating for some, particularly middle-aged individuals who were previously functioning at a high level and in demanding vocational roles.3 Many will experience significant disruption to employment, social and caregiving roles and participation in society.

Many LC symptoms such as palpitations, dizziness, fatigue, pain and breathlessness can be explained by the theory of dysautonomia.6,7 This is a state of episodic dysregulation in the autonomic nervous system (ANS) with sympathetic overdrive and reduced parasympathetic activity. Dysautonomia plays a significant role in the symptomology of many long-term conditions including multiple sclerosis, Parkinson’s disease, diabetes mellitus, fibromyalgia, chronic fatigue syndrome and migraine.8

One way of estimating and measuring autonomic function is through heart rate variability (HRV), as cardiac rate and rhythm are controlled largely by the ANS. The parasympathetic nervous system chiefly activates
a slowing of heart rate through the vagus nerve, and
the sympathetic response acts through the activation of
β-adrenergic receptors.1 HRV can be measured either in
the time domain or frequency domain. HRV represents
a measure of the variation in time between heartbeats
(captured on an Electrocardiogram (ECG) strip as a time
interval between the R waves of the QRS complexes). A
low HRV is associated with sympathetic nervous system
activation, also described as a state of ‘fight or flight’. Higher
HRV correspond with parasympathetic nervous system
activation and is believed to reflect a state of
rest and recovery. Lower HRV has been observed to be
associated with fatigue and pain symptoms of chronic
fatigue syndrome/myalgic encephalomyelitis and fibromyalgia10–12 as well as other chronic physical and mental
health pathologies including asthma, anxiety and stress.10–14

HRV biofeedback
When physiological parameters such as HRV are moni-
tored in real time with self-regulation techniques such as
breathing exercises applied to influence the parameters,
this is known as biofeedback.15,16 In this study, for moni-
toring and modulating the HRV, we are using breathing
techniques to encourage the predominance of parasympa-
thetic nervous activity through vagus nerve activation.
To the best of our knowledge, there have not yet been
any studies of HRV biofeedback (HRV-B) in LC. However,
HRV-B using breathing techniques has been tested in
other clinical conditions such as asthma,17 depression17
and fibromyalgia.12 A normal respiratory rate is between
12 bpm and 20 bpm.18 The optimal breathing frequency
to produce maximal increase in HRV varies for each
individual but on average is between 5.5 bpm and 6 bpm
and is known as resonant breathing.13,18,19 Resonant breathing
helps to restore autonomic balance due to baroreflex
gain and vagal activation.13,18–20

There are several means of assessing HRV but most
commonly these include the use of either wearable
devices such as smartwatches or chest straps, or through
small attachable Holter ECG units. These are non-invasive
and readily available, although reliability differs between
devices and platforms. Many commercial HRV devices
are associated with smartphone app technology, which
have Effect on LC symptoms.

The inclusion criteria are
► Age ≥18 years.
► Confirmed LC diagnosis as per the National Institute
for Health and Care Excellence (NICE) criteria for
post-COVID syndrome.1
► Self-rating of at least ‘moderate’ or ‘severe’ on
dysautonomia questions of palpitations or dizziness
on the COVID-19 Yorkshire Rehabilitation Scale
(C19-YSm).23
► Abnormal NASA Lean Test (NLT).24–26
HR increase in 30 bpm or ≥120 bpm.
Blood pressure (BP) decrease in 20 mm Hg systolic or
10 mm Hg diastolic in the first 3 min of standing.

The aim of this study is to determine the feasibility
and impact of a structured HRV-B regime incorporating
diaphragmatic breathing exercise, on LC symptoms.
We wish to test the acceptability and compliance of the
intervention and estimate effect on symptoms using stan-
dardised validated measures of LC and dysautonomia.

Aims and objectives
The aim of this study is: to assess the feasibility of a 4-week
HRV-B-structured breathing programme in individuals
with LC.

The objectives include:
1. Does regular HRV-B have any effect on LC symptoms?
2. Are consumer-grade monitors appropriate technology

METHODS
Study design
This is a phase 2 uncontrolled open-label feasibility study
of a home technology-based HRV-B in 30 individuals with
LC. Potential participants will be identified through the
Leeds COVID-19 Rehabilitation Service, based at Leeds
Community Healthcare NHS Trust. The study period will
be 6 weeks for each participant. The study start date is 24
January 2022, and the anticipated end date is 31 March
2024.

Eligibility criteria
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Blood pressure (BP) decrease in 20 mm Hg systolic or
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NL T is an accepted measure of cardiovascular insta-
Bility and is conducted at initial assessment clinic for all
LC service users in the Leeds COVID-19 rehabilitation
service. The patient lies down for 2–5 min prior to the test
with HR and BP taken each minute to calculate average
supine values. They then stand with heels 6 inches from a
wall and lean back against it with HR and BP taken each
minute for 10 min. Abnormal results (as described above)
are demonstrated through orthostatic hypotension or
tachycardia on standing which are hallmarks of dysau-
tonomia and, therefore, objectively quantifiable. The
participants who have dysautonomia symptoms but do
not meet the mentioned thresholds will not be included
in this feasibility study but will be potential recruits for
future larger scale studies using the same intervention.
The exclusion criteria are

- Unable to use the wearable or smartphone app technology.
- Cognitive difficulties or mental health disorders causing inability to consent.
- Any cardiac arrhythmias that are being planned for further investigations and specialist management in the Cardiology service.
- Any unstable cardiorespiratory disease that needs further medical interventions (except asthma management).

**Equipment and technology**

To collect medium-term HRV data, participants will wear a Fitbit Charge 5 smartwatch for a total of 6 weeks. The HRV-B itself will be conducted using a Polar H10 chest strap for 10 min two times per day. This connects via Bluetooth to the Elite HRV smartphone app, which is downloaded to participants’ phones. Participants will aim to increase their HRV score as displayed in Elite HRV in real time using a diaphragmatic breathing technique (figure 1). Omron M2 blood pressure monitor (endorsed by the British Hypertension Society) will be used to conduct NLT in clinic and the adapted Autonomic Profile (aAP).

**Study phases**

The study will be carried out in the following three phases:

- Pre-HRV-B phase.
- HRV-B phase.
- Post-HRV-B phase.

**Pre-HRV-B phase**

The participant will either be invited to a research clinic or visited at their home by a member of the research team (first appointment A1). They would have already received the participant information sheet (PIS) at screening and would have had more than 24 hours to read and understand the content of the PIS. Written consent will be signed by the participant and the researcher during this first visit. Devices and baseline outcome measures used in this stage are:

- Fitbit charge five device and the Fitbit smartphone application: The participant will be requested to have the Fitbit device on most of the time during the 6-week period. The application records HRV at night along with other measures of sleep (sleep stages, HR) and daytime activity (such as step count).

- C19YRSm: the COVID-19 Yorkshire Rehabilitation Scale (C19YRS) is the literature’s first condition-specific patient recorded outcome measure, which has been validated in the LC population. The modified scale provides a symptom severity score (out of 30), functional disability score (out of 15), other symptoms score (out of 25) and overall health score (out of 10). The participant will complete C19YRSm (online supplemental file 1) at weekly intervals to monitor the impact of the intervention on LC symptoms. They will also have weekly telephone reviews with study researchers for troubleshooting and to ensure maximal compliance with the study.

- Composite Autonomic Symptom Score (COMPASS): the COMPASS 31 will be completed by the participant at the initial visit and again 6 weeks later at the end of the study. Autonomic symptoms are scored for different domains including orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor. Total scores for each domain are multiplied by a set weighting and then added together.
to provide a score out of 100 representing severity of autonomic symptoms. A higher score represents greater severity.30

- aAP: this is an autonomic profile test developed by St Mary’s Hospital and the National Hospital for Neurology and Neurosurgery and later adapted for domiciliary use during the COVID-19 pandemic.²⁷ Participants are asked to monitor their heart rate and BP on lying, and at 3 min of standing at various intervals over 24 hours, including after waking, after eating breakfast/lunch/dinner, before and after 5 min of exercise, and before bed (online supplemental file 2). Abnormal results are calculated using the same criteria for heart rate and BP differences as the NLT (HR increase >30/min or BP drop >20 mm Hg).

- WHO Disability Assessment Schedule (WHODAS): this is a validated generic measure of functioning and disability. The 36-item scale captures six domains of life (cognition, mobility, self-care, getting along, life activities and participation) with a summary score ranging from 0 (no disability) to 100 (full disability).³¹ ³²

- EQ-5D-5L: The EQ-5D-5L instrument, provided by the EuroQol Group, is one of widely used quality of life measures, consists of five items covering: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.³³ The item scores can be converted into a total index score by applying health preference weights elicited from a general population. This index score can also be used in economic evaluations to assess the cost-effectiveness of health interventions.³⁴

The A1 appointment will last approximately 2 hours and may be longer for those with cognitive fatigue or ‘brain fog’. If felt necessary, it will be divided into two 1-hour visits to reduce cognitive fatigue.

HRV-B phase

One week after the A1 appointment, the participant will be either invited to attend a research clinic or visited at home by a researcher (second appointment A2) to commence the HRV-B study phase. This involves:

- Polar H10 chest strap and Elite HRVB application: The participant will be familiarised with the technology and introduced to a paced breathing regimen via a one-to-one demonstration. They will be instructed to perform the breathing technique using the application at least twice a day, 10 min per session, for a period of 4 weeks. The chest strap device will record HRV for the duration of the session, and the data get recorded in the application. While this phase is ongoing, participants will continue to wear the Fitbit Charge 5 device for the duration of this phase.

- Fitbit charge 5 device and the Fitbit smartphone application.

- C19 YRSm.

Post-HRV-B phase

The participant will be asked to stop the HRV-B intervention after completing 4 weeks of the treatment. They will be asked to continue using the Fitbit device for another week when not doing the intervention. They will then either be invited to a research clinic or be visited at home by a study researcher. At this appointment (A3), the participant will complete:

- C19 YRSm: the C19-YRSm will be completed by the patient every week for a total of 6 weeks. There will be a total of 7 C19-YRS documents completed.

- Fitbit charge 5 device and the Fitbit smartphone application.

- NLT and aAP.

- COMPASS 31.

- WHODAS.

- EQ-5D-5L.

During the A3 appointment, the Polar H10 strap and the Fitbit device will be retrieved.

The participants will be invited to complete a further C19-YRS, by email or postal 4 weeks after completion aAP for 24 hours and to email or post the results to the study researcher.

Outcome measures

The primary outcome measure is the C19 YRSm, a self-reported patient-reported outcome measure to assess LC symptom severity, functional disability and overall health status.

Secondary outcome measures include:

- Heart rate measures from chest strap:
  - 7-day average HRV score out of 100—quantified by the Elite HRV app via the root mean square of successive differences between normal heartbeats (rMSSD).
  - A natural log (ln) is applied to this figure and then expanded to generate a 1 to 100 score.
  - Mean R–R interval.
  - Heart rate.
  - rMSSD.
  - SDNN (SD of Normal to Normal intervals).
  - Total power.
  - Low-frequency power (LF).
  - High-frequency power (HF).
  - LF:HF ratio.

Fitbit data:

- Sleep staging data.
- Resting heart rate.
- Daily activity levels, for example, step count and exercise type and duration.

Patient-reported outcome measures:

- NLT and aAP.
- COMPASS 31.
- WHODAS.
- EQ-5D-5L.

During our final interaction with participants in the study, we will ask them the following questions to assess the feasibility of the study:

1. ‘How did you find using the technology?’
2. ‘How did you find the breathing intervention?’
3. ‘Have you noticed any change in your symptoms?’

Their opinions and suggestions will be recorded as quotes in their participant files. However, we are not planning to
undertake a formal qualitative analysis of responses as it is not
one of the main objectives of this study.

A summary of the schedule for the completion of outcome
measures is shown in table 1.

**SAMPLE SIZE**

A formal sample size calculation is not required for a feasi-
bility study as it does not mimic a definitive randomised
trial and aim is not to measure effect size.35 A sample size
of 30 is the average sample size across feasibility studies
and is accepted as reasonable size to assess the accept-
ability and suitability of the intervention.36

**STATISTICAL ANALYSIS**

Quantitative data from standardised questionnaires will
be scored as per standard procedures. Data downloaded
from the wearable devices will be extracted, cleaned and
summarised using specific software packages, including
Matlab and Python. Quantitative data will be analysed
with simple descriptive statistics. The presence and
magnitude of pre and postintervention differences will
be examined using repeated paired sample t tests (with
Bonferroni adjustment for multiple comparisons), and
the effect size will be explored using both Analysis of
Variance (ANOVA) partial $\eta^2$, and Cohen’s d. Additional
exploratory analyses may also be performed to fully
analyse the data set produced, guided by the findings of
the descriptive statistics.

**Patient and public involvement**

Members of the Patient Advisory Group (PAG) with lived
experience of LC have been involved in the design, de-
velopment and delivery of the project. Members of the PAG
attended proposal research planning meetings and shared
their experiences on symptoms of dysautonomia, which
helped shaped the research question, design and outcome
measures of this study. Members of this group have contacts
with wider patient community groups and helped dissemi-
nate information about the study. The PAG meets quan-
terly with the research team to review progress, ensure the
research continues to answer relevant issues and that findings
can inform LC care. The group will be involved in the dissem-
nation of research findings and writing lay summary reports
that will be shared with the participants.

**Ethics and dissemination**

The study has received ethical approval from Health
Research Authority (HRA) Leicester South Research
Ethics Committee (21/EM/0271). Informed consent will
be obtained from all participants. Potential participants
will have a minimum of 24 hours to review the PIS and
discuss queries with the researcher prior to signing the
written consent. General Data Protection Regulation
(GDPR) rules will be strictly followed for all data gath-
ered during the study. All data will be fully anonymised
as soon as practical. All devices used are (Conformité
Européenne (CE) marked and are being used for their
intended purposes. There is potential for minor skin irri-
tation from wearing the Fitbit and Polar H10 devices. This
will be enquired about at each weekly telephone review.

For participants with cognitive fatigue or ‘brain fog’ relating
to LC, the length of the appointments with the researcher
(A1, A2 and A3) may be longer than normal. Supplemen-
tary written information will be provided, and if necessary,
each of these appointments may be conducted in two shorter
sessions to reduce information overload and possible impact
on LC symptoms. Participants will be advised that they do not
need to proceed with the appointments or the study if they
do not want to. All appointments other than the initial NLT
can occur at the participants’ homes to reduce travel and
inconvenience. Participants are free to withdraw at any point
in the study. They will be encouraged to give reasons for the
withdrawal, but it will not be compulsory to give a reason for
withdrawal.

Dissemination will include both academic publications
and lay summaries in various formats. Academic outputs
will include both medical and engineering literature. Policy
impact will be aided by our strong existing links to NHS
England and the UK Long COVID National Task
Force. Dr Sivan, who leads the NIHR project Long COVID
Multidisciplinary consortium for Optimising Treatments
and Services across the NHS (LOCOMOTION),37 is
also an advisor for the WHO—Europe on COVID-19


<table>
<thead>
<tr>
<th>Table 1</th>
<th>Outcome measures summary schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial assessment Clinic</td>
</tr>
<tr>
<td>Autonomic screening (NLT)</td>
<td>✓</td>
</tr>
<tr>
<td>Autonomic function (COMPASS 31)</td>
<td>✓</td>
</tr>
<tr>
<td>Home autonomic test (aAP)</td>
<td>✓</td>
</tr>
<tr>
<td>Fitbit wrist strap HRV, sleep data</td>
<td>✓</td>
</tr>
<tr>
<td>Polar H10 chest strap HRV data</td>
<td>✓</td>
</tr>
<tr>
<td>LC-specific PROM C19-YRSm</td>
<td>✓</td>
</tr>
<tr>
<td>Daily function (WHODAS)</td>
<td>✓</td>
</tr>
<tr>
<td>Quality of life (EQ5D-5L)</td>
<td>✓</td>
</tr>
</tbody>
</table>

aAP: adapted Autonomic Profile; COMPASS 31, Composite Autonomic Symptom Score; C19-YRSm, modified COVID-19 Yorkshire Rehabilitation Scale; EQ-5D-5L, EuroQol
5-Dimension 5-Level; HRV-B, heart rate variability biofeedback; LC, long COVID; NLT, NASA Lean Test; WHODAS, WHO Disability Assessment Schedule.
rehabilitation and is also involved in the WHO working party developing a core set of outcome measures for LC.

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**Contributors** MS and AC conceptualised the study. MS, AC and RJ0°C were awarded EPSRC IAA pump-priming grant for the feasibility study with MS as the Principal Investigator. JC, SH, NP, D, DW, RT, JD, ADS, RJ0°C, AC and MS contributed to the study design and obtained ethical approval. JC and MS wrote an initial draft of the paper by adapting the grant proposal and the ethics protocol. All authors approved the final manuscript. All authors will contribute to recruitment, data acquisition and analysis of the study findings. MS is the corresponding author and guarantor.

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**Competing interests** Manoj Sivan is an advisor to the WHO for the Long COVID policy in Europe.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Not applicable as this is the protocol paper with no patient data included.

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