Study Title: **Reducing fatigue in Long COVID-19: A feasibility study of a self-help intervention to reduce fatigue-related symptoms among patients in general practice**

Short Title: Reducing fatigue after Long COVID-19

Sponsored by:

Northern Care Alliance
NHS Foundation Trust

Salford I Oldham I Bury I Rochdale

Study Protocol

Version 0.2
Date 10/12/2021

IRAS ID: **291940**

Sponsor ID: **21OTHER01-S**

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 investigation without the prior written consent of the Sponsor

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

For and on behalf of the Study Sponsor:

Signature:

Date:

Name (please print):

Beverley Greenhalgh

Position:

Sponsorship Support & Compliance Manager

Chief Investigator:

Signature:

Date:
1 October 2021

.....
Name: (please print):

AH Heald / AH Heald

.....

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

Contents

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

1 Study summary

Background

We know from previous worldwide pandemics of Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS), caused by viruses similar to that causing COVID-19, that whilst many people had a severe acute respiratory infection, many of those surviving, went on to develop long-term effects (Moldofsky & Patcai, 2011). Follow-up studies showed post-viral fatigue was still present up to five years later, impacting on peoples long-term functioning.

As hospitals learn how best to improve outcomes there are an increasing number of COVID-19 survivors. Many are now reporting persistent ongoing fatigue related symptoms (Huang et al., 2020). Both laboratory (Lu et al., 2020) and observational studies (Sun et al., 2020) suggest that this fatigue is a result of cytokine storm activity, centred largely in the brain and spinal cord (Paterson et al., 2020).

The fatigue related symptoms observed are similar to those seen in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), a condition characterised by unremitting depletion of energy, lack of refreshing sleep, brain fog and profound fatigue after any significant mental or physical exertion (Perrin et al., 2020; Shepherd, 2019; MEA Association, 2020).

We propose trialling an adaptation of a brain and spinal lymphatic drainage technique for use by patients at-home. Self-massage of the head, neck and chest and alternating warm and cool gel packs on the upper spine encourages lymph drainage of the brain and spine along with gentle mobility exercises that improve spinal mobility. This technique is already widely used by patients with CFS/ME as a maintenance programme in-between receiving lymphatic drainage treatment in clinical settings. Whilst this intervention does not attempt to replicate what is delivered by physiotherapist and osteopathic practitioners, it offers a relatively low-cost self-help programme which can be delivered without the need for face to face intervention, important in the COVID-19 and post-COVID-19 landscape and for patients with persistent fatigue.

Purpose

The purpose of the feasibility study is to address the following questions:

1. Can we use an online screening questionnaire to determine the prevalence of physical and mental fatigue associated with ‘Long COVID-19’?

2. Can we recruit and retain participants into a Randomised Controlled Trial (RCT) which tests a lymphatic self-massage intervention, spinal mobility exercises and alternating warm and cool gel packs on the upper spine over 3 months to alleviate fatigue related symptoms for those affected by the longer-term sequelae of COVID-19?

*Sponsor’s representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

2 Study Team Roles and Responsibilities

2.1 Contributorship

Dr Adrian Heald	Consultant / Clinician Salford Care Organisation Fatigue Service & Senior Clinical Research Fellow, School of Medicine, Faculty of Biology, Medicine and Health, The University of Manchester.
Dr Lisa Riste	Research Fellow, NIHR Greater Manchester Patient Safety Translational Research Centre & Department of Pharmacy & Optometry, The University of Manchester.
Dr Ray Perrin	Osteopath & Hon Clinical Research Fellow, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester.
Mr Mark Hann	Research Fellow & Statistician, Division of Population Health, Health Services Research & Primary Care, The University of Manchester.
Mrs Bev McDonald	Chair of Funding for Osteopathic Research into ME (FORME)

The study design was conceived by Dr Lisa Riste and Dr Adrian Heald and Dr Ray Perrin. The study protocol was written by Dr Adrian Heald, Dr Lisa Riste, Dr Ray Perrin and Mr Mark Hann. Dr Ray Perrin developed the lymphatic massage technique used in clinic and adapted the self-care protocol that is being trialled in this intervention. Mr Mark Hann has provided statistical advice during the development of the study. Mrs Bev McDonald has provided PPI advice and insight during the development of this bid along with patient insight.

2.2 Sponsor contact information

Northern Care Alliance NHS Foundation Trust has accepted the responsibilities of Sponsorship for the study. The sponsor's representative is Professor Steve Woby

Study Sponsor:	Northern Care Alliance NHS Foundation Trust
Sponsor Reference:	21OTHER01-S
Contact Details:	Professor Steve Woby, Managing Director of R&I
Address:	Research and Innovation Salford Care Organisation Northern Care Alliance NHS Foundation Trust Summerfield House 544 Eccles New Road Salford M5 5AP
Telephone:	0161 206 5235
Email:	Steve.Woby@nca.nhs.uk

2.3 Funding

£49,623.00 from the Fund for Osteopathic Research into ME (FORME) charity

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

2.4 Organisational Structure and Responsibilities

Chief Investigator: Dr AH Heald
Design and conduct of study
Preparation of protocol and revisions
Recruitment of participants
Reviewing progress of the study and agreeing to changes in the protocol if necessary
Publication of study reports
Study budget holder
Responsible for data management plan
Lead clinician: respond to clinical queries

Study Coordinator: Dr Lisa Riste
Design and conduct of study
Preparation of protocol and revisions
Recruitment of participants
Reviewing progress of the study and agreeing to changes in the protocol if necessary
Publication of study reports
Liaison and support for the PPI contributors
Study co-ordinator: liaise with GPs and patients
Supervision of Research Practitioner

Study Management Team: Dr. Lisa Riste, Dr Adrian Heald, & Mr Mark Hann
Reviewing progress of the study and agreeing to changes in the protocol if necessary
Publication of study reports
Study budget holder
Responsible for data management plan

Public & Patient Involvement & Engagement group: Mrs Bev McDonald, Ms Olivia McDonald, Dr Lisa Riste (support role)
Ensure patient voice is embedded throughout the project
Provide insight during qualitative analysis phase
Help plan dissemination activities to ensure their appropriateness

Collaborator 1: Dr Raymond Perrin (Osteopath & Director, The Perrin Clinic)
NB: Funded via Perrin Clinic – Advisor for intervention queries

Collaborator 2: Ms Olivia McDonald (Patient Liaison Advisor & Public relations at Perrin Clinic)
NB: Funded via the Perrin Clinic – Her contact details will be provided for patients to check their technique for the self-massage and exercises are correct.

Name	Employed	% funded by grant	Hours/ month
AH	Northern Care Alliance NHS Foundation Trust	2.5	8

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

SB	**Northern Care Alliance NHS Foundation Trust**	**2.5**	**8**
RA	**Northern Care Alliance NHS Foundation Trust**	**40**	**60**
LR	**UOM**	**15**	**21**
MH	**UOM**	**5**	**7**
RP	**Perrin**	**0**	**8**
BM		**0**	**2**
OM	**Perrin**	**0**	**8**

3 Contact Details

Chief Investigator:

Dr. Adrian Heald
Dept of Endocrinology and Diabetes
Salford Royal Hospital
Northern Care Alliance NHS Foundation Trust
Telephone: 0161 206 5157

Email: adrian.heald@nca.nhs.uk

Study Coordinator:

Dr. Lisa Riste
Research Fellow Patient Safety Translational Research Centre
Room 1.134 Stopford Building
Oxford Road
University of Manchester
Manchester
Telephone: 0161 275 8357

Email: lisa.riste@manchester.ac.uk

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

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4 Background Information and Rationale

The recent SARS-CoV-2 (COVID-19) pandemic has seen over 460,000 patients hospitalised in the UK, with almost a quarter dying, largely from acute respiratory syndrome. We have seen from previous pandemics caused by similar viruses, that survivors of the acute phase of illness often go on to develop longstanding fatigue related symptoms. Follow-ups among those with post SARS syndrome showed this fatigue was still present three years later and caused substantial functional impairment (Moldolsky & Patcai, 2011).

Post-mortem research in SARS patients indicated that the virus had crossed the blood-brain barrier into the hypothalamus via the olfactory pathway (Moldofsky & Patcai 2011). This same route was proposed in Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) where disturbance of the lymphatic drainage from the brain occurs. One of the main routes for lymphatic draining is via perivascular spaces along the olfactory nerves and into the nasal mucosa, which might explain the anosmia experienced in some COVID-19 patients which has recently been included as a screening symptom (https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/#symptoms). Disturbance of this lymphatic drainage causes a build-up of pro-inflammation agents in the brain and spine, especially cytokines which lead to autonomic dysfunction typified by high fever, disrupted sleep/wake cycles and cognitive problems, all now starting to be reported among COVID-19 survivors (Fauci, 2020; Perrin et al., 2020). Lymphatic self-massage supports lymph drainage from the brain.

Our study seeks to understand this persistent fatigue that follows on from such a pandemic and its effect on physical functioning and patients' quality of life to determine the prevalence of Post COVID-19 Syndrome which for ease, and as a term used in the media and understood by patients, we will refer to as 'Long COVID'.

We propose to follow-up a sample of patients identified using the FARSITE database for the study that will be utilise data held by and run from Northern Care Alliance NHS Foundation Trust. We will invite GPs initially in Salford, but potentially extending into Greater Manchester to screen all adults (aged 18 years or over) registered with their practice using the FARSITE database (held by Northern Care Alliance NHS Foundation Trust in conjunction with NW e-Health). This process will identify patients with a positive SARS-CoV2 test since 20th July 2020 (when these data were routinely incorporated into GP records) and ensure study inclusion criteria are met and no exclusion criteria are present.

The study will be registered with ISRCTN and we will request Portfolio adoption by GM CRN.

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We will conduct a wait-list RCT of an intervention which aims to help reduce fatigue using lymphatic self-massage alongside head and spinal mobility exercises and alternate warming and cooling of the upper spine. Together these intervention components will improve lymphatic drainage from the brain and spine to help alleviate the symptoms of fatigue. Progress over time will be determined by following up RCT participants at 3 and 6 months.

5 Aims of the proposed research

- To estimate the prevalence of physical and mental fatigue, its' effect on physical functioning and quality of life in people who tested positive to COVID-19 previously in a primary care sample.

- To determine whether patients reporting fatigue associated with post COVID-19 post viral syndrome (long COVID) will participate in a 2-arm randomised control trial offering a lymphatic self-massage technique or a wait-list control group who will receive the intervention after 3 months.

- To determine the recruitment and retention rate of participants in such a trial and to assess follow-up rates at 3 and 6 months in both groups

- To understand the acceptability of the lymphatic self-massage technique to participants (via qualitative semi-structured interview) and to assess compliance with the regime suggested (via tick sheet to measure intervention adherence at follow-up).

- To determine possible effects of using the intervention vs not by comparing data from the intervention group and wait-list control group at 3 months.

- To determine possible effects of delaying the use of the intervention by comparing data from the intervention group and wait-list control group.

6 Study Design

This study comprises two-phases:

Phase 1: Survey to determine prevalence of 'Long COVID' in primary care

Patients will be recruited from general practice and provided a link to complete an online survey to determine levels of fatigue (physical and mental) using the Chalder fatigue Questionnaire – CFQ), physical functioning using SF-12 and quality of life using EQ5D at least 12 weeks after previously testing positive (SARS CoV-2) for COVID-19.

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The results of CFQ will be used to screen respondents for 'Long COVID' with those scoring >= 4 on CFQ scored bimodally, being invited to participate in Phase 2 RCT. This will be advised on screen explaining that the symptoms they reported mean they are suitable to join the second phase of the study. A tick box on screen will allow those interested in participating to view a copy of the Participation Information Sheet (PIS) and Consent Form (CF) on screen and also receive a copy by email or post. Interested participants will be asked to provide their telephone number so the research practitioner can call them back to answer any questions they might have about the study and to take informed consent over the telephone for those who agree to participate. The data collected in the Phase 1 Survey will be used as the proxy baseline data for Phase 2 to reduce the need for participant to repeat measures unnecessarily.

Phase 2: Wait-list RCT Intervention Study

Those eligible will receive a PIS and CF explaining the Phase 2 RCT study either by email or by post. After 5 days, participants will be telephoned by a research practitioner based in Northern Care Alliance NHS Foundation Trust's Research delivery team.

100 participants providing informed consent will be allocated 1:1 into a two-arm wait-list randomised control trial (RCT) comparing lymphatic self-massage technique (the intervention) plus any usual care (UC) from their healthcare professionals vs. UC alone. This means any treatment received by participants will not be constrained. Those in the intervention group will receive instructions and equipment required via post as soon as they are randomised, with the UC wait-list group receiving their equipment 3 months later (after completion of their 3m follow-up), meaning all Phase 2 participants will be given access to the intervention. Both groups will be asked to complete follow-up measures at 3m and 6m.

Qualitative interviews will be conducted with 10 participants in the intervention arm at 3 months and a further 10 in each of the intervention arm and UC arms at 6 months to assess acceptability of the intervention, adherence to the intervention (over time for intervention group) and to explore potential barriers and drivers to its use.

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7 Detailed Plan of Investigation

Research Activity		Done	Year and Month 1												Year and Month 2			Responsible
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Pre-work: On run up to research becoming active																		
PPIE	Consultation and patient input	✓																LR/RP
FARSITE	Agree FARSITE search criteria with NW e-Health/CRN	✓																LR/AH/CRN
	Run FARSITE search - indicative numbers																	CRN
Qualtrics Survey	Set up Phase 1 survey	✓																SB/LR/AH/RP/MH
	Set up & test Phase 2 eligibility checks	✓																SB/LR/AH
	Set up Phase 2 surveys at 3m and 6m																	SB/LR/AH
Approvals	Sponsorship																	AH/LR
	Ethical application (IRAS)																	AH/LR
	Capacity & Capability checks: Salford & GM																	AH/LR
Phase 1: Online Survey																		SB
Engagement with GP practices			4															LR / RA (CRN)
Survey launch	Eligible patients receive invite from their GP		5															SB
	Implied consent by completing survey - 0m data																	GP Staff (CRN)
	Automatic screening for Phase 2 eligibility																	Participant
Quantitative	Data analysis: Survey data																	MH/SB
	Data linkage to eligible Phase 2 participants																	SB
Phase 2: Wait-list Intervention RCT																		
NB: Intervention ONLY offered to Phase 1 participants																		
	Participant receives Phase 2 PIS & CF online																	QUALTRICS
	Participant provides contact details																	Participant
	Explain Phase 2 & consent by phone																	RA / LR
Recruitment	Participant consents		6															RA / LR
	RDZ allocation																	MH
Intervention phase	Particpant receives intervention immediately or in 3m		I	I	I	I	I											RA / LR
	Intervention phase (3m)																	Participant & OM
Fup 3m	Data collection 3m using same online qsts																	
	Wait-list group receive intervention						W	W	W	W								RA / LR
	Intervention phase (3m)																	Participant & OM
Fup 6m	Data collection 6m using same online qsts																	RA/LR
Qualitative interview	Interviews with participants both arms																	RA/LR
	Interviews transcribed & analysed																	RA/LR/OM
Quantitative	Data analysis: feasibility & intervention														7			MH/LR/AH/RP/RA/OM
Outputs & Dissemination activities																		
Outputs	Preparation Research paper / conference abstracts															8		ALL
	Feedback to participants & GPs																9	ALL
	Preparation and submission larger funding bid																10	ALL
Final Reporting & return unspent funds to funder																		LR/AH
Management																		
Ethics Approval Submission / Annual & End of study reporting		PRE															11	LR/AH
PPIE Advisory Panel meetings		PRE	1															LR/OM
Fortnightly Research meetings		PRE	2															LR/AH/RP
Recruitment Review - decision to expand recruitment area					3													ALL

Milestones

1 PPIE Advisory Panel
2 Fortnightly Research Steering Meetings
3 Recruitment Reviews
4 Promote study to GPs
5 First participant in Phase 1 Survey
6 First participant in Phase 2 RCT
7 Fieldwork and analysis complete
8 Research Paper submitted
9 Participant feedback
10 Further funding bid
11 End of study reporting

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
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7.1 Recruitment procedure

We will invite Salford GPs to screen their adult patients (aged 18 or over) whose notes indicate a previous positive SARS CoV-2 test for COVID-19 and reported in the last 12 weeks or more to participate in a prevalence study of fatigue-related symptoms. Screening will be facilitated using the FARSITE system (Hosted by Northern Care Alliance NHS Foundation Trust & NW e-Health). FARSITE when used as anonymised intelligence tool indicated 14,083 patients with a previous positive COVID-19 test. We plan to invite up to 32 GP practices whose number of patients is greater than 100 per practice to participate in order to generate the n=2,000 survey responses expected to recruit the 100 patients required into our Phase 2 study.

GPs will send a letter inviting patients who meet the study inclusion criteria to participate in a survey to look at Long COVID symptoms and their impact with some people being asked to participate in an intervention study to try to help reduce fatigue levels. This will be funded by Dr Heald's PI fund at the Northern Care Alliance NHS Foundation Trust.

Survey respondents in Phase 1 will be allocated a survey Participant ID number. Survey completion will predominantly be online, although paper copies will also be available for patients without internet / computer access. To facilitate this, a Research Practitioner (RA) based in the Research Delivery Team at Northern Care Alliance NHS Foundation Trust will assign a number manually on the recruitment log and enter it on the paper survey form that will be sent by post for completion along with a reply-paid envelope. Pseudonymised participant ID number will allow the RA will enter and link data to its respective participant but without compromising the confidentiality of clinical responses received. ID numbers will allow linkage to GP practice to monitor recruitment rates and to permit accrual data to be collected for the Local Care Research Network (LCRN).

Prior to FARSITE data being available, we had used recruitment trajectories based on a 'Recruitment Estimate' of 28,720 potentially eligible participants in Greater Manchester, equating to 2.9% with positive SARS-CoV-2 test recorded in their GP notes (FARSITE Data provided by Greater Manchester Comprehensive Research Network using data at April 2021). Applying this same rate to Salford's 226,000 adult population we anticipate identification of approximately 6,554 COVID-19 positive patients, although June data now suggest 14,083 eligible adults within Salford GP practices alone.

We anticipate that around 50% of those eligible to take part in the Phase 1 study will be willing to take part in the study, this number is based on 51% households in England participating in ONS Coronavirus Infection Survey (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionsurveypilot/previousReleases) although we expect uptake to an invitation via the patients GP may be higher.

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

Whilst work on infection rates has been the focus, there is much less work around the prevalence of Long COVID and individual symptoms, so we do not have confirmed percentages of those likely to meet CFQ cut-off scores. Data modelling by Northern Care Alliance NHS Foundation Trust surveillance unit however adopts a 'Long COVID' rate of 10% having symptoms at 4 weeks or longer, with fatigue being the major symptom (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/datasets/prevalenceoflongcovidsymptomsandcovid19complications).

Assuming an uptake rate of 50% into the Phase 2 Intervention for those who meet the screening criteria based on CFQ agreeing to participate in the Phase 2 intervention, we should be able to recruit our proposed sample size of 100 by 4 months. This is based on invitation letters being sent out to 4000 patients, 2000 of whom we hope will participate in the survey, 200 of which may have Long COVID fatigue related symptoms, with 100 agreeing to participate in the intervention study.

Phase 1: Post COVID Survey

Patients meeting study inclusion criteria will be invited to take part in a survey of the long-term effects of COVID-19. Participants will be sent an invitation letter by their GP and a participant information sheet. The letter will include an online link and when patients log onto the website, they will be asked to confirm their participation in the survey which will be by implied consent, used in lieu of patients having to sign and return paper consent forms. Participants will be allocated a survey participant ID number and once the box is ticked indicating they give consent, they will be prompted to complete measures on the following:

- fatigue using the Chalder Fatigue Questionnaire (CFQ) (Chalder et al. 1993),
- physical functioning using the Short Form SF-12 (Gandek,et al.1998) and
- quality of life EQ5D5L (Rabin & Charro. 2001)

plus demographic information (age, sex, start date of COVID-19 symptoms, date of positive COVID-19 test, tick box of symptoms, whether they were hospitalised with COVID-19 and if so dates and whether they received breathing support and what type (Oxygen, CPAP, Ventilation).

Patients scoring 4 or more on the CFQ (when scored binomially) will be invited to participate in Phase 2. A screen pop-up will inform those meeting screening criteria that their reported symptoms make them eligible to take part in the next phase of the study to try to help reduce fatigue associated with Long COVID.

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

Phase 2: Long COVID Intervention Study

A Participant Information Sheet for Phase 2 and a consent form will then be displayed with an option to download a copy or request a copy by email or post. Participants will be provided with a contact number for the study co-ordinator in case participants have any questions before deciding if they wish to join the study. Since Phase 2 requires an additional and ongoing commitment, all potential participants will be asked to provide their name and a contact telephone number and/or email address.

Prior to joining the Phase 2 study, a Research Practitioner (costed at 40%) who is part of the Research Delivery Team based at No, will telephone patients complete the telephone-based consent form with them. Prospective participants will be asked if they have a nut allergy and if so, will be sent apricot kernel massage oil as an alternative to the almond oil which is routinely provided for participants.

Should recruitment fall below 80% of the number planned each month (20/25), we will recruit further GP practices and should we exhaust practices in Salford can extend recruitment into an adjacent area (Central Manchester CCG). Recruitment will be closely monitored at fortnightly research meetings and if across a 4-week period the recruitment falls below the trigger level stated, the additional recruitment areas will be added. Portfolio adoption has been sought for this study (for inclusion on Primary Care workstream). If successful, recruitment data will be submitted on a monthly basis to CRN.

Patients responding to the Phase 1 survey who meet Phase 2 entry criteria will receive an on-screen message telling them they are invited to participate. They will be able to access the Phase 2 PIS on screen to read and can complete their email, name and contact number if they would like to rake part.

They will then receive a copy of the Phase 2 PIS and Phase 2 consent form to the email address supplied. The research practitioner from NCA will telephone potential participants and will read through the consent form over the telephone and answer any queries participants might have.

Once patients have agreed to participate they will receive a copy of their telephone completed consent alongside their randomisation letter and/or intervention kit if selected to take part in the initial group.

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Randomisation for Phase 2 Intervention RCT

Randomisation will be carried out using an internal STATA routine (Chaimani et al. 2013) by an independent member of the University of Manchester Biostatistics Group who will be responsible for this, along with conveying the allocation to the RA in order for the intervention pack to be sent to participants. This method ensures the statistician carrying out the analyses (MH) remains masked to treatment allocation.

Eligible participants will be allocated at random (1:1) in blocks of size 4, 6 or 8 (chosen at random and in equal numbers) to either the immediate lymphatic self-massage intervention plus UC or UC alone plus the intervention from 3 months. Due to the known gender differences between women and men both in terms of CFS/ME and also Long COVID itself, we will stratify for gender within the randomisation. We will set up the randomisation so that should extra sites outside of Salford be required to achieve recruitment targets, we will ensure a balance between the two trial arms.

All Phase 2 participants will receive a letter thanking them for completing the Phase 1 survey and letting them know which group they have been allocated to. The letter will explain how RCTs work and the importance of follow-up data irrespective of which group participants are allocated to, and that all participants will receive the intervention described but at different times, and that they will be followed up for 6 months in total (at 3m and 6m) using the same survey measures they have already completed in the baseline survey. One additional tick sheet will be used to capture participants' use of the intervention which will be sent to the intervention participants at 3m and 6m and to the control – wait-list group at 6 m only.

The group randomised to receive the intervention will receive this immediately after randomisation along with this letter. The UC wait-list control group will be sent the intervention pack after submission of their 3m follow-up data. We will not tell patients when to stop using the intervention but will monitor its use in the two study arms over time.

Intervention components

There are three components to this intervention:

1. Lymphatic self-massage: The instructions for lymphatic self-massage technique will be available to those in the intervention arm in both leaflet and online and DVD format (this will be password protected to reduce risk of those in the UC arm accessing the information before the 3 months when they are eligible to receive the intervention after the waiting-list period has elapsed).

2. Gentle spinal mobility & breathing exercises: again, these instructions will be provided online and in a DVD format.

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3. Contrast bathing: Participants will be recommended to place alternating warm and cool packs placed on the upper spine for a total of 10 minutes, once a day to stimulate circulation, following the this process; COLD - 3 minutes, WARM - 1 minute, COLD - 1 minute, WARM - 1 minute, COLD - 1 minute, WARM - 3 minutes, so 10 Minutes total.

The hot water bottle and gel pack required, along with a long handled back massager will be sourced and supplied by the research team to ensure participants have access to suitable equipment. Gel packs are currently sourced for CFS/ME patients receiving lymphatic drainage in clinic. We have been advised that this constitutes general equipment so does not require specific approval by Northern Care Alliance NHS Foundation Trust's Medical Equipment Management team (personal communication Dr S. Watson) and that a safety evaluation will suffice.

Participants in addition to receiving the equipment required will also receive the contact details for our Patient Liaison Advisor (OM) in case they wish to check any of the techniques with her this can be carried out using encrypted Zoom, MS Teams or WhatsApp video conferencing features.

Participants will be informed of the potential side effect of nausea and headache.

The usual care (UC) participants will receive the same equipment and access to the intervention instructions after their 3m follow-up has been completed.

Follow-ups

Survey data collected in Phase 1 will be treated as baseline or 0-month data. Table 1 shows the schedule for subsequent study assessments. The CFQ, SF-12 and EQ5D-5D will be completed by the patient online or via a paper form returned to the research office. The 3m follow-up allows us to see any changes between those receiving the intervention and those not. The 6-month (6m) follow-up enables us to see if any benefits observed at 3m are maintained beyond the intervention period, and to compare this between the two groups.

	0m (baseline)	3m	6m
CFQ	X	X	X
SF-12	X	X	X
EQ-5D-5L	X	X	X
Intervention diary		X (intervention group only)	X
Qualitative interview		X	X

Table 1: Assessments and timescales for the feasibility study

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

***Proposed Primary outcome measures*:** These will be the logistical findings arising from the feasibility study (i.e. related to the conduct of the trial)

Secondary 'Clinical' Outcome measures;

Chalder Fatigue Questionnaire (CFQ) (Chalder et al., 1993): Our data analysis of CFQ scores at 3m will compare those who have used the intervention (on an intention to treat ITT basis – i.e. assuming those randomised to receive the intervention use it as intended) vs those who have not.

SF-12 (https://www.rand.org/health-care/surveys_tools/mos/12-item-short-form.html): This self-reported outcome measure developed from the Medical Outcomes Study assesses the impact of health on an individual's everyday life. It is often used as a quality-of-life measure and will be used to see if differences exist in quality of life between the two groups.

Euroquol EQ-5D-5L (htpps://euroquol.org): This will permit us to calculate change in quality of life and determine Quality Adjusted Life Years scores (QALYs) for the intervention and wait-list control comparison group over 9m.

Qualitative Interviews

Semi-structured qualitative interviews will be conducted by RA and/or LR over the telephone with a sample of those who at the end of the intervention period agree to participate in a 1:1 interview. We will conduct interviews at two timepoints; 3m and 6m for the intervention group and 6m only for the wait-list control group. Sampling will aim to include 20 participants from the intervention group (10 different patients selected at each time point 3 months and 6 months– this will allow us to see if people continue to use the intervention beyond the 3 month period – patients will only be interviewed once) and 10 people from the wait-list control group (after completing 6m in the study) = Total of 30 interviews. Audio-recorded interviews will be transcribed by an approved supplier who has signed a confidentiality agreement. We will seek to determine drivers for and barriers to the use of this self-help intervention by interviewing those who are allocated to receive the intervention treatment who do not start or drop out prior to the end of the intervention period and facilitators to the treatment among those who use the lymphatic self-massage technique to all or some extent, and to the feasibility study in general also sampling those in the control arm. A thematic approach will be adopted for the analysis and Public and Patient Involvement (PPI) team will be involved in discussions around the emergent themes and to ensure correct meanings are attributed to participant comments. Findings will also then be used to inform potential future larger studies using this intervention.

Audio recordings will be destroyed after transcription.

7.2 Inclusion / Exclusion Criteria

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

This will be achieved by eligibility screening conducted using FARSITE prior to Phase 1 invitation by patients GPs. At Phase 2 consent process, participants eligible from Phase 1 will be asked to confirm that they meet eligibility criteria and none of the exclusion criteria.

Inclusion Criteria:

Participants aged 18 or over

COVID positive result recorded since July 2020

For the Phase 2 intervention a CFQ score >4 when scored binomially.

Exclusion Criteria:

Currently living in a Care Home setting

Pregnant and lactating women.

End stage heart failure, cancer, major mental illness and primary sleep disorders (alternative causes of fatigue).

Dementia

7.3 Study duration

Participants are enrolled in the study for a maximum of 6 months.

The project will run for Fifteen months (1 month lead in time, 4 months recruitment phase plus 6 months follow-up for intervention study and an optional qualitative interview for n=30 participants) plus 4 months analysis and write up time and submission of final reporting.

7.4 Consent procedure

Because this is a two-stage study there are two separate consent points:

Phase 1: Survey
Patients with a previous positive SARS-CoV-2 test for COVID 19 who received a letter from their GP and opened a link to complete the survey will before starting to provide their survey responses be directed to our consent statement. Participants will be asked to tick the relevant consent clauses and by virtue of completing the survey participants are providing implied consent to take part in this survey.

Only participants who meet screening criteria for 'Long COVID' within the survey will be invited to participate in Phase 2.

Phase 2: Intervention RCT

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

Potential participants will be shown a message that they are eligible for the next phase of the study and potential participants will see the Phase 2 participant information sheet (PIS) and consent form (CF) after completing the survey. They will have the option to receive copies of these by email or by post.

Participants who wish to join the Phase 2 study will be asked to enter their name and contact telephone number and an email. A Research Practitioner will then telephone the potential participant and go through the consent form with them over the telephone. At this point they will be able to ask any questions they might have about participating ahead of providing informed consent.

A copy of the telephone consent will be retained by the Research Practitioner at Salford Care Organisation and a copy sent to participants along with details of their randomisation.

7.5 Outcome measurement

1. To determine the participation rate for an online survey of Long COVID within general practice.
2. To determine the prevalence of Long COVID using a case cut-off of 4 or above on the CFQ (binomially scored)
3. To determine recruitment and retention of participants into an RCT which tests a lymphatic self-massage intervention over 6 months to alleviate fatigue related symptoms for those affected by the longer-term sequelae of COVID-19.

7.6 Withdrawal criteria

Participants will be allowed to withdraw from the study at any point. We will not collect any further data from this participant however will use data available during their time in the study for the final study analysis. If it is in the participant's best interest the clinician in charge of the study (AH) may also choose to withdraw the participant in the interests of their own health.

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

8 Regulatory and Ethical Considerations

8.1 Study conduct

- The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and other applicable guidance.
- The study will not commence until all regulatory approvals are in place, which will include HRA Approval, REC Approval and confirmation from local R&I that the Trust has capacity and capability to carry out the research.

8.2 Monitoring and audit

- The study will be subject to the standard procedures for monitoring and auditing of studies by the sponsor.
- Any changes to the protocol will be agreed with the sponsor prior to submission to NHS research ethics committee for review with the exception of where urgent safety measures apply.
- All staff working in the study will have completed appropriate training to undertake the duties delegated to them by the Principal investigator such an ICH-GCP.

8.3 Protocol deviations

- Any deviations to the protocol will be reported to the sponsor within 24 hours of the occurrence to allow an impact assessment to be completed.
- Consideration will be given to the nature of the deviation, its causes and the potential impact on the study.
- Where necessary, a deviation from the protocol may lead to an amendment to the protocol

8.4 Study progress reports

The PI and research team will submit progress reports to the Sponsor as requested and prior to submission to NHS REC, in accordance with the terms and condition of the study approval.

8.5 Stopping rules

It is not anticipated that the study will be stopped prior to its intended end-date. However, the study will be halted if:

- New information comes to light which means that the aims of the study are futile.
- Safety issues come to light regarding the intervention.
- Resources to conduct the study are no longer available.

9 Record keeping and data management

As the sponsor, Northern Care Alliance NHS Foundation Trust will be responsible for secure data storage on an encrypted Northern Care Alliance NHS Foundation Trust computer. The use of participant ID numbers on study documentation will allow analysis of pseudonymised data by our statistician at The University of Manchester who will remain blind to the randomisation group that participants were assigned to.

*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

The electronic database will be kept at Northern Care Alliance NHS Foundation Trust and will be completely anonymised, password protected and only accessible to members of the study team.

10 Statistical analyses and data handling

Analysis

This is a feasibility study, so we will not be carrying out formal hypothesis testing to determine if the intervention is effective. Data analysis will follow an Intention-To-Treat (ITT) protocol and will be used to inform power calculations for a definitive trial in addition to other published sources. Attrition and reasons for drop-out will be recorded where possible. We will assess rates of missing data (and which elements in particular) and proportions of dropouts at different trial stages. We will also assess whether any of the measures display floor and/ or ceiling effects.

We will calculate and present in a CONSORT (Eldridge et al, 2010) flow chart: the proportion of people with CFQ scores greater than or equal to 4, consenting to the study; those entering the randomised phase; the proportion completing 50% and 100% intervention (using patient reported compliance sheet); the proportion completing follow-up assessments at 3 and 6 months post-randomisation.

We will summarise, as appropriate (e.g. mean/ standard deviation; median/ inter-quartile range; proportion/ 95% confidence interval; data range) data for all potential outcome measures, overall and by group. Outcome data and changes (mean differences) in patient-reported measures between baseline (initial clinical assessment) and 3 and 6 month follow-up will be plotted with 95% confidence intervals by randomisation group on an intention to treat basis.

Adherence with the intervention will be measured and used to calculate an estimate of dose response. Where participants adhere to all 3 stages of the intervention fully – using the intervention as intended daily this will be deemed full intervention, with non-use of any stages of the intervention as a zero dose.

The SD of the (potential) Primary Outcome, along with the estimated attrition rate and the average number recruited per PCT/CCG (plus the range of this data) will be used to help inform the sample size calculation for the large-scale RCT.

The Primary feasibility outcomes will be recruitment and retention rates, and we will gain an estimate of likely effect sizes of the self-help intervention for a range of outcome measures and based on this determine the appropriate sample size for a larger trial to evaluate its effectiveness and cost-effectiveness versus standard treatments delivered within an NHS CFS/ME Service.

Adverse events, including serious adverse reactions (SARS) to trial interventions will be reported to the Sponsor and recorded and reported within the CONSORT diagram.

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Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

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Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

11 Dissemination of Results and Publication Policy

We will aim to have research outputs in the form of original research articles published in Open Access peer review journals and will seek to raise the profile of our work at conference presentations. All the study team will be invited to participate in the writing, reviewing and editing of papers and will conform to guidance issues by IJCME.

Results of the study will be disseminated by the Northern Care Alliance NHS Foundation Trust via their website: Https://www.reserchforthefutureorg, newsletters and social media. This will ensure that volunteers who have participated in this research have access to the study findings

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*Sponsor's representative: Professor Steve Woby, Managing Director of Research & Innovation
Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk

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Norther Care Alliance NHS Foundation Trust, Summerfield House, 544 Eccles New Road, Salford, M5 5AP
Tel: 0161 206 5235; email: Steve.Woby@nca.nhs.uk