EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original Research Article

Post-Hospitalisation COVID-19 Rehabilitation (PHOSP-R): A randomised controlled trial of exercise-based rehabilitation

Enya Daynes, Rachael A Evans, Neil J Greening, Nicolette C Bishop, Thomas Yates, Daniel Lozano-Rojas, Kimon Ntotsis, Matthew Richardson, Molly M Baldwin, Malik Hamrouni, Emily Hume, Hamish McAuley, George Mills, Dimitrios Megaritis, Matthew Roberts, Charlotte E Bolton, James D Chalmers, Trudie Chalder, Annemarie B Docherty, Omer Elneima, Ewen M Harrison, Victoria C Harris, Ling p Ho, Alex Horsley, Linzy Houchen-Wolloff, Olivia C Leavy, Michael Marks, Krishna Poinasamy, Jennifer K Quint, Betty Raman, Ruth M Saunders, Aarti Shikotra, Amisha Singapuri, Marco Sereno, Sarah Terry, Louise V Wain, William D-C Man2, Carlos Echevarria, Ioannis Vogiatzis, Christopher Brightling, Sally J Singh, , on behalf of the PHOSP-COVID Study Collaborative Group

Please cite this article as: Daynes E, Evans RA, Greening NJ, *et al*. Post-Hospitalisation COVID-19 Rehabilitation (PHOSP-R): A randomised controlled trial of exercise-based rehabilitation. *Eur Respir J* 2025; in press (https://doi.org/10.1183/13993003.02152-2024).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©The authors 2025. This version is distributed under the terms of the Creative Commons Attribution Licence 4.0.

Post-Hospitalisation COVID-19 Rehabilitation (PHOSP-R): A randomised controlled trial of exercise-based rehabilitation.

Enya Daynes[1,2] PhD enya.daynes@uhl-tr.nhs.uk corresponding author https://orcid.org/0000-0003-0127-1649

Rachael A Evans[1,2] PhD

Neil J Greening[1,2] PhD

Nicolette C Bishop[3] PhD

Thomas Yates[4,5] PhD

Daniel Lozano-Rojas[1,2] PhD

Kimon Ntotsis[1,2] PhD

Matthew Richardson[1,2] PhD

Molly M Baldwin[1,2] PhD

Malik Hamrouni[5] PhD

Emily Hume[6] PhD

Hamish McAuley[1,2] PhD

George Mills[1,2] PGCert

Dimitrios Megaritis[6] PhD

Matthew Roberts[5] PhD

Charlotte E Bolton[7,8] MD

James D Chalmers[9]PhD

Trudie Chalder[10] PhD

Annemarie B Docherty[11] PhD

Omer Elneima[1,2] MD

Ewen M Harrison[12] PhD

Victoria C Harris[1] BSc

Ling P Ho[12, 13] PhD

Alex Horsley[14] PhD

Linzy Houchen-Wolloff[1,2] PhD

Olivia C Leavy[1,15] PhD

Michael Marks[16, 17] PhD

Krishna Poinasamy[18]

Jennifer K Quint[19] PhD

Betty Raman[20,21] PhD

Ruth M Saunders[1]

Aarti Shikotra[1]

Amisha Singapuri[1]

Marco Sereno[1]

Sarah Terry[1]

Louise V Wain[1,15] PhD

William D-C Man[22. 23,24] PhD

Carlos Echevarria[25] PhD

Ioannis Vogiatzis[6] PhD

Christopher Brightling[1,2] PhD

Sally J Singh[1,2] PhD

on behalf of the PHOSP-COVID Study Collaborative Group

1. The institute for Lung Health, NIHR Leicester Biomedical Research Centre, University Hospitals of Leicester, Leicester, UK. 2. Department of Respiratory Sciences, University of Leicester, Leicester, UK. 3. National Centre for Sport and Exercise Medicine, School of Sport, Exercise and Health Sciences, Loughborough University, UK. 4. NIHR Leicester Biomedical Research Centre- Diabetes, Leicester, UK. 5. Diabetes Research Centre, College of Life Sciences, University of Leicester. 6. Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University Newcastle, UK. 7. Centre for Respiratory Research, Translational Medical Sciences, School of Medicine, University of Nottingham, Nottingham UK. 8. NIHR Nottingham Biomedical Research Centre, Nottingham. UK. 9. University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. 10. Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK. 11. Centre for Medical Informatics, The Usher Institute, University of Edinburgh, Edinburgh, UK. 12. MRC Human Immunology Unit, University of Oxford, Oxford, UK. 13. NIHR Oxford Biomedical Research Centre, Oxford, UK. 14. Manchester University NHS Foundation Trust, Manchester, UK. 15. Department of Population Health Sciences, University of Leicester, Leicester, UK. 16. Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK. 17. Hospital for Tropical Diseases, University College London Hospital, London, UK. 18. Asthma and Lung UK, London, UK. 19. SPH, Imperial College London, London, UK. 20. Radcliffe Department of Medicine, University of Oxford, Oxford, UK. 21. Oxford University Hospitals NHS Foundation Trust, Oxford, UK. 22. Harefield Respiratory Research Group, Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, UK. 23. National Heart and Lung Institute, Imperial College, London, UK.24. King's Centre for Lung Health, Faculty of Life Sciences & Medicine, King's College London. 25. The Newcastle upon Tyne

Hospitals NHS Foundation Trust, Translational and Clinical Research Institute, Newcastle University.

Short running title PHOSP-R

Contributors

The manuscript was initially drafted by ED, RAE, NG, SJS, CEB, and further developed by the writing committee. ED, SJS, NG, RAE, TY, NCB, DLR, KN and MR made substantial contributions to the conception and design of the work. ED, MB, GM, DM, EH, IV, CE, SJS, NG, RAE, MH, MR, and NCB made substantial contributions to the acquisition of data. ED, DLR, KN, MR, SJS, NG, CEB, NCB, MR, MH, TY, and RAE made contributions to the analysis or interpretation of data for the work. DLR, ED, KN, NCB, MH, MR, and verified the underlying data. All authors contributed to data interpretation and critical review and revision of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Funding

This research was jointly funded by a grant from the MRC-UK Research and Innovation and the Department of Health and Social Care through the National Institute for Health Research (NIHR) rapid response panel to tackle COVID-19 (grant references: MR/V027859/1 and COV0319). This is a summary of independent research that was carried out at the National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the funder, the NIHR or the Department of Health and Social Care.

Declaration of interest

ED reports honoraria from ClinicalPhysio, Neuroscience and Mental Health Institute (funding committee 2023) and leadership roles with the BTS as chair of the Pulmonary

Rehabilitation Specialist Advisory Group (unpaid) and The Royal College of Physicians (paid). RAE reports funding from UKRI/MRC/NIHR, consulting fees for Astrazenica/Evidera for Long COVID, speaker fee for Boeringher and Moderna on the topic of Long COVID. NJG reports consultancy fees for Genetech/Roche, and honoraria from Chiesa, GSK, Astrazeneca and pulmonx. JQ reports consulting fees for Evidera for advice on COVID-19 studies. AH reports finding from UKRI, NIHR and NIHR Manchester BRC for unrelated grants. AD reports funding from Wellcome in an unrelated fellowship. LVW reports grants UKRI, GSK/Asthma and Lung UK, NIHR, Orion Pharma, GSK, Genetech, and AstraZeneca. She reports consulting fees for Galapagos and Boehringer Ingelheim. CEB reports grants from NIHR, UKRI, Nottingham Hospitals Charity, UoN charitably gifts and Nottingham University Hospitals Trust. TC is on the Expert Advisory Panel for Covid-19 Rapid Guidelines and is the author of several self-help books on chronic fatigue for which she has received royalties. WM Honorary President, Association for Respiratory Technology and Physiology. AH Chair NIHR Translational Research Collaboration (unpaid). AD reports Wellcome Fellowship 216606/Z/19/Z. CB has received grants and consultancy fees from 4D Pharma, Areteia, AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, Mologic, Novartis, Regeneron Pharmaceuticals, Roche and Sanofi. CB has received grants and consultancy fees from 4D Pharma, Areteia, AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, Mologic, Novartis, Regeneron Pharmaceuticals, Roche and Sanofi. JDC reports grants and personal fees from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, and Insmed, personal fees from Chiesi, Zambon, Janssen, and Grifols, and grants from Gilead Sciences, outside the submitted work. The remaining authors report no conflicts of interest.

Word count: 3000

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Objective

Post-COVID syndrome involves prolonged symptoms with multi-system and functional impairment lasting at least 12 weeks after acute COVID-19. We aimed to determine the efficacy of exercise-based rehabilitation interventions, either face-to-face or remote, compared to usual care in individuals experiencing Post-COVID syndrome following a hospitalisation of acute COVID-19.

Design

This single-blind randomised controlled trial compared two COVID exercise-based rehabilitation interventions (face-to-face or remote) to usual care in participants with Post-COVID syndrome following a hospitalisation. The interventions were either a face-to-face or remote eight-week program of individually prescribed exercise and education. The primary outcome was the change in Incremental Shuttle Walking Test (ISWT) following eight weeks of intervention (either face-to-face or remote) compared to usual care. Other secondary outcomes were measured including health related quality of life (HRQoL), and exploratory outcomes included lymphocyte immunotyping.

Results

181 participants (55% male, mean [SD] age 59 [12] years, length of hospital stay 12 [19] days) were randomised. There was an improvement in the ISWT distance following face-to-face rehabilitation (mean 52 [95% CI 19 to 85]m, p=0·002) and remote rehabilitation (mean 34 [95% CI 1 to 66]m, p=0·047) compared to usual care alone. There were no differences between groups for HRQoL of self-reported symptoms. Analysis of immune markers revealed significant increases in naïve and memory CD8+ T cells following face-to-face rehabilitation versus usual care alone (p<0·001, n=31).

Conclusion

Exercise-based rehabilitation improved short-term exercise capacity in Post-COVID syndrome following an acute hospitalisation and showed potential for beneficial immunomodulatory effects.

Introduction

Coronavirus Disease-19 (COVID-19) is a complex, multisystem condition caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 resulted in >1 million hospital admissions in UK which was approximately 5-10% of all individuals infected with COVID-19. Symptoms lasting >12 weeks are termed 'post-COVID-syndrome' or 'Long COVID'[1,2]. The World Health Organisation (WHO) estimates that 10-20% of people infected with COVID will experience post-COVID syndrome, however true estimates are unknown[3]. Up to 70% of individuals in the PHOSP-COVID study reported an incomplete recovery at 1 year following hospitalisation, though this continues to improve as reported by the Global Burden of Disease with approximately 1 in 3 of those infected self-report symptoms of post-COVID syndrome at three months and 15.1% at 12 months[4,5]. [1]Individuals with post-COVID syndrome experience a range of symptoms (e.g., breathlessness, fatigue) leading to functional impairment, reduced exercise capacity, and difficulty performing activities[4]. The exact mechanisms of these impairments are not entirely understood, but it is likely an interaction of ongoing pathology including acute treatment complications, immune system dysregulation and ongoing inflammation, compounded by the impacts of a hospitalisation[6-8].

In chronic respiratory diseases, comprehensive rehabilitation programmes comprising of individually prescribed and progressed exercise and education, significantly improve symptoms (e.g. breathlessness and fatigue), exercise intolerance and health-related quality of life[6]. These benefits have been demonstrated in other post-hospitalisation cohorts[9]. Given the overlap between some symptoms of post-COVID syndrome and those with other chronic diseases, it is plausible that similar rehabilitation programmes may convey comparable benefits[6]. This is supported by the WHO recommendation to consider rehabilitation for those with post-COVID syndrome and specifically to provide a programme of education and support for self-management of breathlessness, resumption of activities and a gradual increase of exercise based on symptoms[10].

Previous studies have demonstrated maladaptation in the immune system following COVID-19 with decreases in T and Natural Killer (NK) immune cell populations and a reduced frequency and number of naïve CD4 and CD8 T cells in those with severe symptoms compared to healthy controls [11]. Evidence in other respiratory diseases has highlighted that exercise rehabilitation can improve CD4+T cells and reduce hospitalisations. It is therefore plausible that exercise-based rehabilitation may impact the immune system in post-COVID syndrome [12].

Several systematic reviews demonstrated improvements in symptoms following rehabilitation interventions, though the evidence is heterogeneous, with a high risk of bias and consists predominantly of uncontrolled trials and poorly defined interventions[13-15]. Early evidence supports this hypothesis demonstrating increased exercise tolerance, improved respiratory symptoms, fatigue, and cognition in individuals with post-COVID syndrome[16]. Remote programmes performed synchronously as a group (REGAIN trial) have been shown to

improve quality of life for individuals with post-COVID syndrome[17] though, did not include prescribed exercise training following exercise testing.

Despite the promise of existing evidence many patients describe symptoms that present a challenge and could impact engagement[18,19,20]. Therefore, there is a need to investigate exercise-based rehabilitation programmes by different modes of delivery: supervised, face-to-face rehabilitation programmes for those who can attend and where a digital solution is not acceptable; and asynchronous remotely monitored digital methods that are flexible to cater for the needs of individuals with post-COVID syndrome.

In this randomised controlled trial (RCT), we hypothesised that face-to-face and remote interventions added to usual care will improve exercise capacity compared to usual care alone in individuals with Post-COVID syndrome, following a hospitalisation. A sub-group analysis explored the response of immune biomarkers to face-to-face rehabilitation.

Methods

This study consisted of a single-blind, three-arm, RCT conducted at the University of Leicester and Northumbria University. The trial was approved by Yorkshire & the Humber-Leeds West Research Ethics Committee (Reference Number: 20/YH/0225) and registered on the ISRCTN trial registry (ISRCTN10980107/ISRCTN13293865). Full details of the methodology are available and described in detail[21].

Participants

Participants were eligible if they were adults ≥18 years of age, admitted to hospital during a confirmed acute episode of COVID-19 (PCR positive or clinician diagnosed) and had

ongoing symptoms lasting more than 12 weeks resulting in self-described functional impairment. Participants had a clinician determined diagnosis of post-COVID syndrome in the specialist COVIDclinic prior to referral.

Individuals were excluded if they: had any contraindication to exercise[22]; experienced symptoms indicative of another medical condition that required further investigation/management (i.e. clinical diagnosis or self-reported severe post-exertional malaise (PEM)/ symptom exacerbation (PESE) rendering the individual bedbound or postural orthostatic tachycardia syndrome); unstable comorbidities; or completion of a rehabilitation programme in the preceding six months.

Randomisation and masking

Block randomisation (blocks size 6) was performed on sealedenvelope.com with allocation concealment by unblinded members of the study team who arranged the intervention. A randomisation log was maintained by the unblinded study team. A participant's ability to undertake each intervention was determined through discussion with a healthcare professional (e.g., low digital literacy preventing remote rehabilitation). Participants able to access any intervention were randomised in a 1:1:1 ratio. Those unable to access one of the interventions (either face-to-face or remote) were randomised in a 2:1 ratio in favour of the remaining intervention. This was based on ability to access, rather than preference. Outcome assessors and data analysts were blinded to intervention allocation. There were no incidences of unblinding throughout the trial.

Procedures

The interventions have been fully described elsewhere[21]. The intervention phase was eight weeks in duration. The exercise component was individually prescribed using the Incremental Shuttle Walking Test (ISWT) which calculates a predicted VO_2 max, and intensity is prescribed aiming for moderate-high intensity training where able (approx. 80-85% of maximum) and tailored in response to symptoms. Usual care was offered to all three groups.

Face-to-face rehabilitation

The programme comprised of twice weekly face-to-face sessions (approx. 90-120 minutes per session) involving symptom-titrated exercise training (aerobic (walking and cycling) and resistance), a package of education (16 topics in total, table S1), self-management strategies including individualised pacing, prioritising, and planning advice, 1:1 management and symptom advice and vocational advice where relevant. This was delivered by a multidisciplinary team including physiotherapists, occupational therapists, nurses, exercise physiologists, and support assistants. Educational sessions followed an interactive discussion-based approach (rather than didactic lectures). Exercise was individually tailored following a comprehensive assessment and supplemented by an individualised home exercise programme recorded in a symptom and activity diary. The home exercise programme consisted of an additional three sessions, typically two aerobic only and one both strength and aerobic, as indicated All symptoms in response to exercise were monitored by a healthcare professional at sessions and the programme was individually tailored accordingly. Adjustments to frequency, intensity, or exercise adaptations (for example changing exercise components due to pain) were made. This was a group programme and therefore participants also received informal peer support.

Remote rehabilitation

The intervention used the YourCOVIDRecovery© (www.yourcovidrecovery.nhs.uk) platform which was a password protected site comprised of four phases, allocating two weeks per phase. This was a remotely monitored programme where participants completed symptom-titrated exercise training (aerobic (walking) and resistance) and self-directed symptom management advice supported by a healthcare professional. Equipment was not provided for home use. Participants were supported by a healthcare professional through fortnightly phone calls and the website messaging service as required, this included a 1:1 discussion to monitor progression and support implementation of self-management strategies, offer individual symptom advice and vocational advice where relevant. Symptoms and exercises were monitored on the platform and the education was tailored accordingly. High scoring/worsening of symptoms triggered a notification to a healthcare professional and support/follow-up was offered as required either through direct messaging or telephone contact.

Usual care

Usual care was offered to all groups and ensured participants could access any treatment that was offered in the management of their post-COVID syndrome. All participants were seen in a specialist outpatient COVID clinic hosted within secondary care, led by a multidisciplinary team of consultants (respiratory, cardiology, neurology, diabetologist, renal and general practitioner), nurses and physiotherapists. Participants had their care optimised prior to enrolment in the trial through the COVID clinic, frequency of appointments is tailored to the individual's needs. At the time of this trial conduct, treatment was not standardised but was offered based on an individual and thorough assessment, this could include, but is not limited to, psychological interventions, medical treatment, symptom self-management or breathing

pattern retraining. As rehabilitation was not considered usual care at trial set up, participants were excluded from engaging in exercised-based rehabilitation during the trial period. The control group for this study was usual care alone.

Outcome measures

Primary outcome

The primary outcome was the change in the Incremental Shuttle Walking Test (ISWT)[23] reported in distance walked (metres) pre- and post- intervention. The comparison focused on one intervention (either face-to-face rehabilitation or remote rehabilitation) compared to usual care alone from pre- to post- intervention. The ISWT was completed in line with European Respiratory Society (ERS)/American Thoracic Society (ATS) technical standards, on a 10m track and included a familiarisation test [23].

Secondary outcomes

Physical measurements included: Short Physical Performance Battery (SPPB), handgrip strength and quadriceps strength using quadriceps maximum isometric voluntary contraction (QMVC). Symptoms and health related quality of life were assessed by self-reported questionnaires as follows: EuroQol five-dimension five-level questionnaire (EQ5D), Patient Health Questionnaire (PHQ9), the Generalised Anxiety Disorder (GAD7) 7-item scale, Dyspnoea-12, the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT), the DePaul Symptom Questionnaire, and the Brief Pain Inventory (BPI). Cognition was assessed by the Montreal Cognitive Assessment (MoCA). These measures were completed pre- and post- intervention.

The modified MRC Dyspnoea scale, SARC-F, General Practice Physical Activity Questionnaire (GPPAQ), and Nijmegen Questionnaire were used to describe participant characteristics at baseline. Participants were categorised by WHO severity index as: non-severe requiring hospitalisation but no ventilatory support; severe requiring oxygen therapy (including high flow); critical requiring mechanical ventilation (invasive or non-invasive).

Exploratory outcomes

Immune outcomes

Venous immune outcomes were collected on a subset of participants in the face-to-face rehabilitation and usual care group (n=40), including T cells (naïve, central memory, effector memory, and terminally differentiated effector memory), and NK cells (further details in online supplement, and figure S1) pre- and post- intervention. Flow cytometry was performed to analyse immune cell subsets using fluorescently conjugated antibodies.

A subgroup of participants received optional muscle biopsies (as described in the trial protocol) however the results are not available at present.

Statistical analysis

The sample size was based on a mean difference between groups of 50m in the primary outcome (ISWT), with a SD of 72m taken from previous cohort studies[16]. The study was powered at 90% with a type I error of two sided alpha 0.05 and required 44 participants per group, 132 participants in total. The sample size was inflated by 20% to account for attrition to give a final target sample size of 159 participants[21].

Statistical analysis was performed in R version 4.2.0 and the analysis compared the interventions separately (face-to-face or remote) to usual care alone. The primary analysis utilised Generalized Linear Mixed Models (GLMM) with an intention-to-treat approach. Assumptions were assessed (online supplement). The GLMM predicts the ISWT accounting random variability of participants to be excluded from the correlations between covariates and model's output variable. GLMM considers the baseline of participants that did not complete the post ISWT. The GLMM compared changes from baseline following eight weeks of either face-to-face rehabilitation to usual care or remote rehabilitation to usual care. and within group changes were calculated by the estimation of marginal mean differences. Independent variables included the interaction between time point and treatment group (face-to-face vs. usual care and remote vs. usual care), with age, sex, BMI, time since hospitalization, number of comorbidities, WHO severity index, and recruiting site included as fixed independent variables in the model. An interaction term, time point x group to measure a difference between treatments and a random intercept per individual (random effect) were included in the model. Further information on statistical analysis, including per-protocol analysis and immune subgroup analysis can be found in the online supplement (figure S2-S4, table S2).

Results

181 participants were randomised (mean [SD] age 59 [12] years, n=99 (55%) male, n=142(78%) white British, n=54 (30%) critical WHO Severity Index, requiring ventilatory support, at the time of admission) between March 2022 to May 2023. The median [IQR] length of stay was 6 [1, 12] days and mean [SD] time since initial infection was 545 [211] days. 123 (68%) participants were recruited at the University of Leicester and 58 (32%) were recruited from Northumbria University, Newcastle. 86 (48%) participants were able to attend

either face-to-face or remote interventions, 53 (29%) were unable to attend a face-to-face programme, primarily due to other commitments and 42 (23%) were unable to access a remote intervention, primarily due to limited access to digital technologies. 149 (82%) participants completed the trial, providing primary outcome data at follow up (Figure 1). Full baseline characteristics are shown in table 1.

Figure 1 consort diagram

Table 1 Baseline characteristics

The primary adjusted analysis demonstrated a statistically significant improvement in ISWT between the face-to-face rehabilitation and usual care group with a mean [95% CI] difference of 52 [19 to 85] m in favour of the intervention (p=0.002) (Figure 2). The face-to-face rehabilitation group improved from 285 [219 to 351] m to 312 [244 to 380] m (p<0·001). The unadjusted analysis demonstrated a statistically significant difference of 55 [19 to 92] m in favour of the intervention (p<0·001).

The primary adjusted analysis demonstrated a statistically significant difference between the remote rehabilitation and usual care group with a mean [95% CI] difference of 34 [1 to 66] m in favour of the intervention (p=0.047) (figure 2). The remote rehabilitation group improved from 353 [296-411] m to 388 [334 to 442] m (p<0·01). The unadjusted analysis demonstrated a statistically significant difference with a mean [CI] difference of 49 [13 to 86] m in favour of the intervention (p<0.001).

140/181 participants were included in the per-protocol analysis, 40/56 (71%) face-to-face, 38/62 (61%) remote, 60/62 (98%) usual care completing 75% of the intervention and the follow-up measures. The difference between the face-to-face rehabilitation and usual care

group was 66 [32 to 100] m in favour of the intervention (p<0.001). The difference between the remote rehabilitation and usual care group was 42 [7 to 78] m in favour of the intervention (p=0.021) (Table S3). The number (%) of participants achieving more than a 35m improvement was 25(56%), 22(50%) and 11(19%) for the face-to-face, remote, and usual care groups respectively.

Figure 2. Mean [95% CI] change from baseline for face-to-face, usual care and remote groups. Comparisons are made from face-to-face to usual care and remote to usual care.

Secondary outcomes are detailed in Table 2. There were clinical improvements in the SPPB compared to usual care for both the face-to-face and remote interventions (mean [CI] 1·2 [-0·01 to 2·38], 1·5 [0·27 to 2·66] respectively). There were clinical improvements in the 4mGait Speed compared to usual care for both the face-to-face and remote interventions (mean [95% CI] 0·12 [-0·01 to 0·21] m/s, 1.5 [-0·05 to 0·14] m/s, respectively). There were clinical important improvements in the QMVC compared to usual care for the face-to-face and remote interventions (3·33 [-0·55 to 7·10] kg, 3·35 [0·43 to 7·10] kg, respectively). There were clinically important improvements in handgrip strength in the face-to-face rehabilitation programme compared to usual care (2·06 [0·07 to 4·18] kg). There were no differences between groups for HRQoL or self-reported symptoms measured by the EQ5D, Dyspnoea-12, PHQ-9, GAD-7, FACIT-FS, MoCA and DSQ. There were clinically important improvements in fatigue for the face-to-face rehabilitation group within group (table 2). The per-protocol analysis demonstrated similar changes (supplement table S3, S4).

Table 2 Secondary outcomes

Example flow cytometry dot plots for lymphocyte immunotyping are as shown in online supplement figure 1 (n=31). There was no significant group*time point interaction for total lymphocytes. However, significant interactions were found for central memory $CD4^+$T cell counts, total $CD8^+$T cell counts, naïve, central and effector memory $CD8^+$T cell counts, and NK cell counts. These cell counts increased from pre- to post-intervention in the exercise group but decreased in the control group. There were no other significant group*time point interactions (table 3, Figure S5).

Safety

There were two reported serious adverse events during the study period, one of which was resolved on the same day (details redacted to protect anonymity) and the other was a reported death during the study period. All were adjudged to be unrelated to the intervention.

Discussion

In this fully powered randomised controlled trial, we demonstrated that both face-to-face and remote exercise-based rehabilitation significantly improve exercise capacity compared to usual care alone in those previously hospitalised with COVID-19. These between group improvements exceed the established MCID (35m)[24], highlighting improvements of clinical relevance in those with post-COVID syndrome.

We deliberately assessed two different models of delivering rehabilitation, avoiding direct comparison, recognising the need for models of care delivery appropriate to different segments of the population. The value of this strategy was demonstrated by the number of participants unable to uptake either intervention (n=94/181 52%). Traditional comparator

trials would require participants to be able to access both interventions, which would have resulted in excluding 94 participants, typically those that were working age so unable to attend face-to-face or those that have low digitally literacy (often compounded by health inequalities). Therefore, this randomisation procedure offered a solution to be inclusive providing a more representative sample but did result in some baseline differences (notable age, and time since hospitalisation) which were adjusted for in the analysis.

Consistent with our primary outcome we found potential improvements in several other physical outcomes above the established MCID when compared to usual care[25,26]. Despite this, we did not detect improvements in self-reported health-related quality of life above the usual care group. This study did not demonstrate improvements in the EQ5D utility index between groups. Given the broad range of symptoms in post-COVID syndrome, it is plausible that many participants meet the floor or ceiling of the symptom specific outcome measures, and that generic health-related quality of life tools are insensitive, and therefore specific Post-COVID syndrome health-related quality of life outcome measures maybe more sensitive and are now available[27,28]. The REGAIN trial has demonstrated improvements in quality of life, measured by PROMIS-PROPr score, through a synchronised remote intervention in the absence of a measure of exercise capacity/physical function[17].

Immune dysregulation is common in Post-COVID syndrome, characterised by persistent decreases in T and NK immune cell populations, central to viral defence[11,29]. Research has demonstrated reduced frequency and number of naïve CD4 and CD8 T cells, increased frequency and number of memory CD4 and CD8 T cells and higher frequency and absolute numbers of senescent CD4 and CD8 T cells in those with severe symptoms compared to healthy controls[11]. While changes in senescent phenotypes were unchanged, numbers of

naïve and memory CD4 and CD8 T cell subsets increased in this study, which adds to the increasing body of evidence that exercise-based rehabilitation promotes restoration of some anti-viral aspects of post-COVID syndrome-related immune dysfunction, potentially protecting against new infections. This was a sub-study within the RCT, and therefore has a small sample size. Further exploration of immune dysregulation and recovery through rehabilitation would be valuable. It is encouraging that there is no signal of a negative influence on the immune system by an exercise-based rehabilitation programme.

Some patients with post-COVID syndrome experience PEM/PESE which can present a challenge. We excluded those under active investigation for, or a diagnosis of severe and debilitating PEM (n=1) resulting in inability to leave the house as this intervention was not deemed appropriate for this patient group. We used extensive PESE monitoring and screening in those included in the trial to ensure symptoms were not worsened by the intervention in any participants[6]. Measures of fatigue and symptoms improved across all three groups suggesting that the rehabilitation exercise was not harmful in appropriately selected patients The presence of severe PEM/PESE is likely higher in patients under the care of COVID clinics than reported in this trial, which is potentially the result of careful participant selection and identification.

The trial has limitations in that it included only hospitalised patients with COVID-19. Participants were randomised based on their ability to access each intervention, this led to some differences between groups with those unable to attend remote programmes being older, but we controlled for these variables in our predefined analysis plan and this was not considered a fault of the randomisation. We found improvement in the usual care group, particularly in relation to the EQ5D utility index, with an increase in the summary score

greater than what has been previously reported [4]. The EQ5D utility index is determined by five domains, which includes anxiety and depression. It is therefore possible that these improvements are related to improvements in anxiety and depression supported by similar changes in the PHQ-9,

Our population included 55% males, comparable to the overall hospitalised populations who were at higher risk of severe COVID-19[30]. This is consistent to the gender reported in the REGAIN trial whereby participants were 45% males[17,30]. Whilst females are more at risk of post-COVID syndrome, post hospitalised populations are biased towards males[16]. The age of our population is comparable to that described in the REGAIN trial. The population appears to be reflective of those that require rehabilitation, and this may be a result of those of younger age requiring less support and therefore not being referred. The results of this trial demonstrate that two modes of delivery are efficacious at improving exercise capacity in those with post-COVID syndrome following hospitalisation. Therefore, it is recommended that adult's post-hospitalisation from COVID-19 with ongoing symptoms, and functional/exercise impairment should be referred to an appropriate rehabilitation programme, with symptom-titrated exercise prescribed to individual patient needs.

Our study demonstrates the efficacy of exercise-based rehabilitation programmes when provided by two delivery methods, for adults living with post-COVID syndrome following a hospitalisation. Improving exercise capacity may have important secondary beneficial effects on the immune system in post-COVID syndrome.

Characteristics		Face-to-face (n=56)	Remote (n=63)	Usual Care (n=62)	Total (n=181)
Age (years) mean (SD)		61(13)	55(11)	62(11)	59(12)
Male sex, n (%)		31(55)	29(46)	39(63)	99(55)
Ethnicity , n (%)					
	White	44(79)	50(79)	48(77)	142(78)
	Asian	9(16)	12(19)	10(16)	31(17)
	Other	3(5)	1(2)	4(6)	8(4)
BMI (kg/m^2), mean (SD)		32·0(3·6)	31·5(3·5)	31·3(3·2)	31·6(3·4)
Index of Multiple Deprivation, median [IQR]		6[3-9]	5[5-8]	6[4-8]	6[3-8]
Comorbidities, n (%)					
	0 comorbidities	11(20)	20(32)	11(18)	42(23)
	1 comorbidity	11(20)	9(14)	15(24)	35(19)
	≥2 comorbidities	34(61)	34(54)	36(58)	104(57)
WHO severity classification, n (%) during hospital admission					
	Non-severe	14(25)	22(35)	27(44)	63(35)
	Severe	23(41)	17(27)	20(32)	60(33)
	Critical	19(34)	22(35)	13(21)	54(30)
Length of hospital stay (days), median [IQR]		7[4, 14]	5[1, 13]	4[0, 10]	6[1, 12]
Time since hospitalisation (days), mean (SD)		578(176)	542(219)	519(232)	545(211)
MRC dyspnoea scale, median [IQR]		3[2-4]	2[2-3]	3[2-3]	3[2-4]
SARC-F, median [IQR]		2[1-4]	2[0-4]	2[1-4]	2[1-4]
Nijmegen, mean (SD)		20(12)	23(13)	21(12)	21(13)
GP Physical Activity Questionnaire, n(%)					
	Inactive	31(55)	33(53)	35(56)	99(55)
	Moderately inactive	14(25)	6(10)	4(6)	24(13)
	Moderately active	5(9)	12(19)	10(16)	27(15)
	Active	6(11)	12(19)	11(18)	29(16)

Table 1 Baseline characteristics of study participants to the group they were randomised (regardless of randomisation procedure). Measures are at first study visit unless indicated otherwise.

	Face-to-face n=56			Remote n=62			Usual care n=63			Face-to-face vs Usual care	Remote vs Usual care
	Pre-	Post-	Change	Pre-	Post-	Change	Pre-	Post-	Change	Difference	Difference
SPPB (median)†	9[7 to 11]	10 [8 to 12]	1·5 [0·56 to 2·39]	10[8 to 11]	11[9 to 12]	1·8[0·84 to 2·67]	10[8 to 11]	10[8 to 12]	0·4[-0·48 to 1·06]	1·2 [-0·01 to 2·38]	1·5 [0·27 to 2·66]
4MGS (m/s)†	0.92 [0.84 to 1.01]	0.98 [0.9 to 1.07]	0.11 [0.037 to 0.18]	1.04 [0.95 to 1.12]	1.06 [0.99 to 1.12]	0.33 [0.04 to 0.11]	1.03 [0.96 to 1.09]	1.04 [0.98 to 1.10]	0.01 [0.07 to 0.05]	0.12 [0.02 to 0.21]	0.04 [-0.05 to 0.14]
Handgrip (kg)†	27·64 [23·67 to 31·62]	31·76 [28·1 to 35·43]	3·91 [2·29 to 5·52]	31·96[28·98 to 34·95]	34·11[30·84 to 37·38]	1·23[-0·35 to 2·83]	31·75[28·65 to 34·85]	34·21[31 to 37·41]	1·85[0·43 to 3·28]	2·06 [0·07 to 4·18]	-0·62 [-2·72 to 1·50]
QMVC (kg)†	29·14 [24·4 to 33·89]	30·75 [25·78 to 35·72]	3·22 [0·22 to 6·23]	31·35[27·69 to 35·01]	36·01[32·42 to 39·59]	3·24[0·31 to 6·18]	31·77[28·09 to 35·44]	32·37[28·96 to 35·75]	0·11[-2·57 to 2·35]	3·33 [-0·55 to 7·10]	3·35 [0·43 to 7·10]
EQ5D 5L											
Utility Index†	0·58 [0·53 to 0·63]	0·61 [0·56 to 0·66]	0·03 [-0·04 to 0·10]	0·65[0·6 to 0·69]	0·65[0·62 to 0·69]	0·00[-0·07 to 0·07]	0·59[0·52 to 0·66]	0·64[0·59 to 0·69]	0·05[-0·01 to 0·11]	-0·02 [-0·11 to 0·07]	-0·05 [-0·14 to 0·04]
Thermo-meter†	57·75 [52·44 to 63·05]	62·4 [57·14 to 67·65]	4·48 [-0·42 to 9·38]	59·7[54·20 to 65·20]	68·37[16·70]	4·59[-0·27 to 9·46]	60·84[55·59 to 66·09]	65·61[60·75 to 70·48]	5·56[1·09 to 10·36]	-1·08 [-7·65 to 5·46]	0·97 [-7·38 to 5·73]
PHQ9	9·73 [8·13 to 11·34]	7·78 [6·19 to 9·37]	1·88 [-2·99 to -0·77]	8·97[7·47 to 10·47]	4·50[4·87 to 7·13]	1·77[-2·91 to -0·63]	10·29[8·58 to 12·00]	8[6·48to 9·52	2·29[-3·33 to -1·27]	-0·41 [-1·08 to 1·91]	-0·52 [-1·02 to 2·02]
GAD7											
Severity score	7·54 [6·02 to 9·05]	6·27 [4·76 to 7·78]	1·37 [-2·51 to -0·24]	7·11[5·65 to 8·58]	4·81[3·67 to 5·95]	-1·33[-2·51 to -0·15]	6·5[5·04 to 7·96]	6·00[4·54 to 7·46]	-0·81[-1·86 to 0·22]	-0·56 [-2·07 to 0·96]	-0·52 [-2·09 to 1·02]
MoCA†	24·19 [23·18-25·19]	24·30 [23·19 to 25·40]	0·41 [-0·32 to 1·14]	25·16[24·28 to 26·03]	26·6[26·09 to 27·10]	1·07 [0·32 to 1·82]	24·77[23·85 to 25·69]	25·05[24·02 to 26·09]	0·26[-0·39 to 0·91]	0·15 [-0·82 to 1·10]	0·81 [-0·16 to 1·79]
FACIT-FS†	26·23 [22·77 to 29·69]	32·27 [29·22 to 25·31]	6·36 [3·95 to 8·79]	29·71[26·60 to 32·81]	33·73[30·58 to 36·87]	1·68 [-0·78 to 4·15]	27·44[24·04 to 30·84]	30·67[27·50 to 33·84]	3·43[1·24 to 5·64]	2·93 [-0·31 to 6·16]	-1·75 [-4·97 to 1·57]
Dyspnoea-12	11·35 [9·02 to 13·67]	8·60 [6·55 to 10·65]	-3·09 [-4·77 to -1·42]	11·76[9·28 to 14·24]	6·64[4·97 to 8·32]	-2·66 [-4·39 to 0·94]	10·15[7·78 to 12·52]	8·79[6·67 to 10·91]	-0·98[-2·50 to 0·54]	-2·11 [-4·33 to 0·13]	1·68 [-4·00 to 0·55]
DSQ											
Frequency	37·92 [30·22 to 45·63]	37·56 [28·74 to 46·38]	0·04 [-6·15 to 6·24]	38·71 [31·18 to 46·24]	28·49 [21·44 to 35·53]	-6·73 [-12·76 to -0·71]	39·00[31·35 to 46·65]	37·23[30·08 to 44·38]	-1·01[-6·33 to 4·31]	1·05 [-7·00 to 7·11]	-5·72 [-13·73 to 2·13]
Severity	32·36 [25·63 to 39·08]	32·38 [24·59 to 40·16]	-0·02 [-1·31 to 1·27]	32·42 [25·87 to 38·96]	26·40 [19·63 to 33·16]	-0·84 [-2·09 to 0·41]	36·67[29 to 44·33]	35·18[28·02 to 42·33]	-0·24[-1·33 to 0·85]	0·22 [-1·43 to 1·88]	-0·6 [-2·24 to 1·02]

Table 2 Secondary outcomes for face-to-face rehabilitation vs usual care, and remote rehabilitation vs usual care. *SPPB Short Physical Performance Battery, QMVC Quadriceps Maximal Voluntary Contraction, EQ5D-5L EuroQol 5 Domain- 5 Level, PHQ9 Patient Health Questionnaire 9, GAD7 Generalised Anxiety and Depression 7, MoCA Montreal Cognitive Assessment FACIT-FS Functional Assessment of Chronic Illness Therapy Fatigue Scale, DSQ DePauls Symptom Questionnaire.* †*Outcomes where a higher score is an improvement.*

Table 3. The effect of exercise intervention vs control on immune cell subset changes from pre- to post-trial

Cell concentration	Face-to-face Rehabilitation		Usual Care		p-value for interaction
	Pre	Post	Pre	Post	
†Total lymphocytes (10^9/L)	2.03 (1.86 – 2.22) (n=13)	2.22 (2.03 – 2.43) (n=13)	1.92 (1.77 – 2.08) (n=18)	1.93 (1.78 – 2.09) (n=18)	0.19
$CD4^+$ (cells/µL)	636 (442 - 914) (n=8)	684 (476 – 983) (n= 8)	568 (429 - 752) (n=15)	394 (298 - 522) (n=15)	0.12
$CD8^+$ (cells/µL)	373 (304 - 441) (n=10)	491 (423 - 560) (n=10)	399 (343 - 454) (n=16)	324 (266 - 382) (n=16)	0.003
NK cells (cells/µL)	271 (198 - 345) (n =10)	378 (298 - 459) (n=10)	302 (236 - 367) (n=16)	265 (200 - 331) (n=16)	0.04

Analyses were adjusted for sex and the baseline value of the dependent variable and are presented as means (95% CI) for each group.

Data sharing

Data can be shared to scientists upon reasonable request to the corresponding author, ensuring relevant research training evidence is provided (i.e GCP, IG).

Acknowledgements

This is a summary of independent research funded by UKRI/NIHR and carried out at the National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of UKRI/NIHR, the NIHR or the Department of Health and Social Care.

We would like to acknowledge the contribution of the late Professor Gavin Donaldson in the study set up period. The study team would like to acknowledge the contributions of the Pulmonary Rehabilitation teams at the University Hospitals of Leicester and Newcastle upon Tyne NHS Foundation Trust for their support in delivering COVID rehabilitation.

This study would not be possible without all the participants who have given their time and support. We thank all the participants and their families. We thank the many research administrators, health-care and social-care professionals who contributed to setting up and delivering the study at all of the 65 NHS trusts/Health boards and 25 research institutions across the UK, as well as all the supporting staff at the NIHR Clinical Research Network, Health Research Authority, Research Ethics Committee, Department of Health and Social Care, Public Health Scotland, and Public Health England, and support from the ISARIC Coronavirus Clinical Characterisation Consortium. We thank Kate Holmes at the NIHR Office for Clinical Research Infrastructure (NOCRI) for her support in coordinating the charities group. The PHOSP-COVID industry framework was formed to provide advice and

support in commercial discussions, and we thank the Association of the British Pharmaceutical Industry as well NOCRI for coordinating this. We are very grateful to all the charities that have provided insight to the study: Action Pulmonary Fibrosis, Alzheimer's Research UK, Asthma + Lung UK, British Heart Foundation, Diabetes UK, Cystic Fibrosis Trust, Kidney Research UK, MQ Mental Health, Muscular Dystrophy UK, Stroke Association Blood Cancer UK, McPin Foundations, and Versus Arthritis. We thank the NIHR Leicester Biomedical Research Centre patient and public involvement group and Long Covid Support.

References

1. NHSE. Post-COVID syndrome (long COVID). 2022; Available at: https://www.england.nhs.uk/coronavirus/post-covid-syndrome-long-covid/. Accessed 20/04, 2024.

2. Ely EW, Brown LM, Fineberg HV; National Academies of Sciences, Engineering, and Medicine Committee on Examining the Working Definition for Long Covid. Long Covid Defined. N Engl J Med. 2024 Nov 7;391(18):1746-1753. doi: 10.1056/NEJMsb2408466. Epub 2024 Jul 31.

3. World Health Organisation. Post COVID-19 condition (Long COVID). Available at: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition#:~:text=Definition,months%20with%20no%20other%20explanation. Accessed 20/04, 2024.

4. Evans RA, Mcauley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *The Lancet Respiratory Medicine* 2021 -10-07**;9**(11):1275.

5. Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. JAMA 2022 -10-10;328(16).

6. Daynes E, Mills G, Hull JH, Bishop NC, Bakali M, Burtin C, et al. Pulmonary Rehabilitation for People With Persistent Symptoms After COVID-19. *CHEST* 2024 -01.

7. Singh SJ, Daynes E, Mcauley HJC, Raman B, Greening NJ, Chalder T, et al. Balancing the value and risk of exercise-based therapy post-COVID-19: a narrative review. *Eur Respir Rev* 2023 -12-20**;32**(170).

8. Appelman B, Charlton BT, Goulding RP, Kerkhoff TJ, Breedveld EA, Noort W, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nat Commun* 2024 -01-04**;15**(1).

9. Man W, Chaplin E, Daynes E, Drummond A, Evans RA, Greening NJ, et al. British Thoracic Society Clinical Statement on pulmonary rehabilitation. *Thorax* 2023 -10**;78**(Suppl 5):s2.

10. World Health Organisaton Clinical management of COVID-19: living guideline. WHO Reference Number: WHO/2019-nCoV/clinical/2021.2 https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2

11. Lord JM, Veenith T, Sullivan J, Sharma-Oates A, Richter AG, Greening NJ, et al. Accelerated immune ageing is associated with COVID-19 disease severity. *Immun Ageing* 2024 -01-11**;21**(1).

12. Xiong T, Bai X, Wei X, Wang L, Li F, Shi H, et al. Exercise Rehabilitation and Chronic Respiratory Diseases: Effects, Mechanisms, and Therapeutic Benefits. *COPD* 2023 -06-19**;Volume18**:1251.

13. Meléndez-Oliva E, Martínez-Pozas O, Cuenca-Zaldívar JN, Villafañe JH, Jiménez-Ortega L, Sánchez-Romero EA. Efficacy of Pulmonary Rehabilitation in Post-COVID-19: A Systematic Review and Meta-Analysis. *Biomedicines* 2023 -08-07**;11**(8).

14. Pouliopoulou DV, Macdermid JC, Saunders E, Peters S, Brunton L, Miller E, et al. Rehabilitation Interventions for Physical Capacity and Quality of Life in Adults With Post–COVID-19 Condition. *JAMA Netw Open* 2023 -09-19**;6**(9).

15. Li J, Xia W, Zhan C, Liu S, Yin Z, Wang J, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. *Thorax* 2021 -07-26**;77**(7):697.

16. Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition – A cohort study. *Chron Respir Dis* 2021 -01-01**;18**.

17. Mcgregor G, Sandhu H, Bruce J, Sheehan B, Mcwilliams D, Yeung J, et al. Clinical effectiveness of an online supervised group physical and mental health rehabilitation programme for adults with post-covid-19 condition (REGAIN study): multicentre randomised controlled trial. *BMJ* 2024 -02-07.

18. Isaac RO, Corrado J, Sivan M. Detecting Orthostatic Intolerance in Long COVID in a Clinic Setting. *IJERPH* 2023 -05-12**;20**(10).

19. Burton C, Dawes H, Goodwill S, Thelwell M, Dalton C. Within and between-day variation and associations of symptoms in Long Covid: Intensive longitudinal study. *PLoS ONE* 2023 -01-19**;18**(1).

20. Shepherd Charles, Harding Rachel. When rest may be best for post-viral fatigue. *The Guardian* 2021 14/03.

21. Daynes E, Baldwin M, Greening NJ, Yates T, Bishop NC, Mills G, et al. The effect of COVID rehabilitation for ongoing symptoms Post HOSPitalisation with COVID-19 (PHOSP-R): protocol for a randomised parallel group controlled trial on behalf of the PHOSP consortium. *Trials* 2023 -01-26**;24**(1).

22. American College of Sports Medicine, Gary Liguori, Yuri Feito, Charles Fountaine, Brad A. Roy. ACSM's guidelines for exercise testing and prescription. 11th ed.: Wolters Kluwer; 2022.

23. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014 De;44(6):1428–1446.

24. Evans RA, Singh SJ. Minimum important difference of the incremental shuttle walk test distance in patients with COPD. *Thorax* 2019 -05-30**;74**(10):994.

25. Edwards George, Patel Suhani, Jenkins Timothy, Ingram Karen, Man William D, Nolan Claire M. Estimation of the minimal important difference (MID) of quadriceps maximum voluntary contraction (QMVC) in response to pulmonary rehabilitation (PR) in COPD. European Respiratory Journal 2023 Se:PA508.

26. Kon SSC, Canavan JL, Nolan CM, Clark AL, Jones SE, Cullinan P, et al. The 4-metre gait speed in COPD: responsiveness and minimal clinically important difference. *European Respiratory Journal* 2013 -10-31**;43**(5):1298.

27. O'connor RJ, Preston N, Parkin A, Makower S, Ross D, Gee J, et al. The COVID-19 Yorkshire Rehabilitation Scale (C19-YRS): Application and psychometric analysis in a post-COVID-19 syndrome cohort. *Journal of Medical Virology* 2021 -11-05**;94**(3):1027.

28. Hughes SE, Haroon S, Subramanian A, Mcmullan C, Aiyegbusi OL, Turner GM, et al. Development and validation of the symptom burden questionnaire for long covid (SBQ-LC): Rasch analysis. *BMJ* 2022 -04-27.

29. Shuwa HA, Shaw TN, Knight SB, Wemyss K, Mcclure FA, Pearmain L, et al. Alterations in T and B cell function persist in convalescent COVID-19 patients. *Med* 2021 -06-11**;2**(6):720.

30. Drake TM, Riad AM, Fairfield CJ, Egan C, Knight SR, Pius R, et al. Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol UK: a prospective, multicentre cohort study. 2021 -07-29.

31. Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SSC, et al. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax* 2016 -03-30**;71**(6):493.

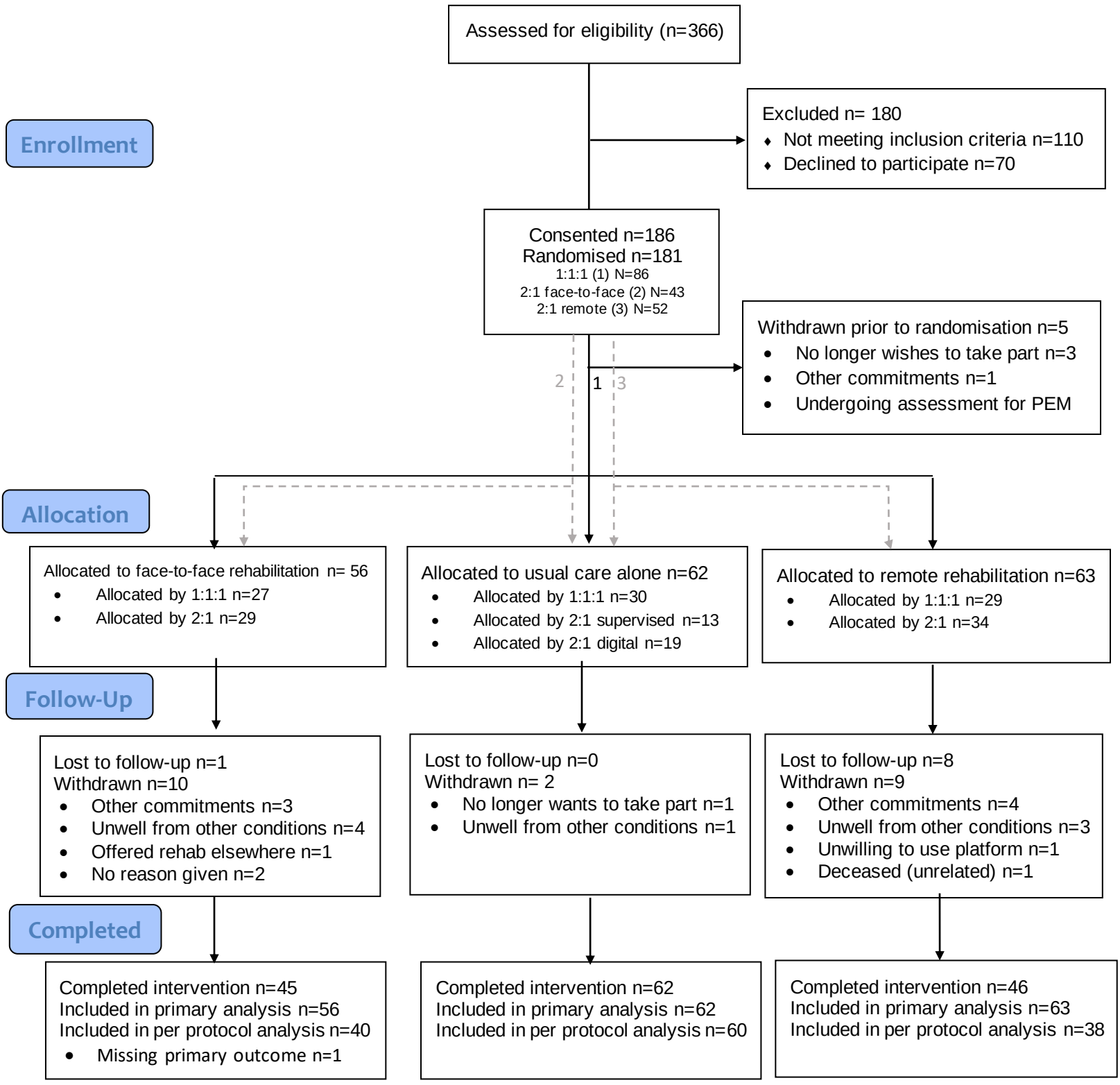


Figure 1 Consort Diagram for PHOSP-R study. Randomisation procedure indicated as (1) following a 1:1:1 ratio, (2) following a 2:1 ratio in favour of face-to-face rehabilitation and (3) following a 2:1 ratio in favour of digital rehabilitation.

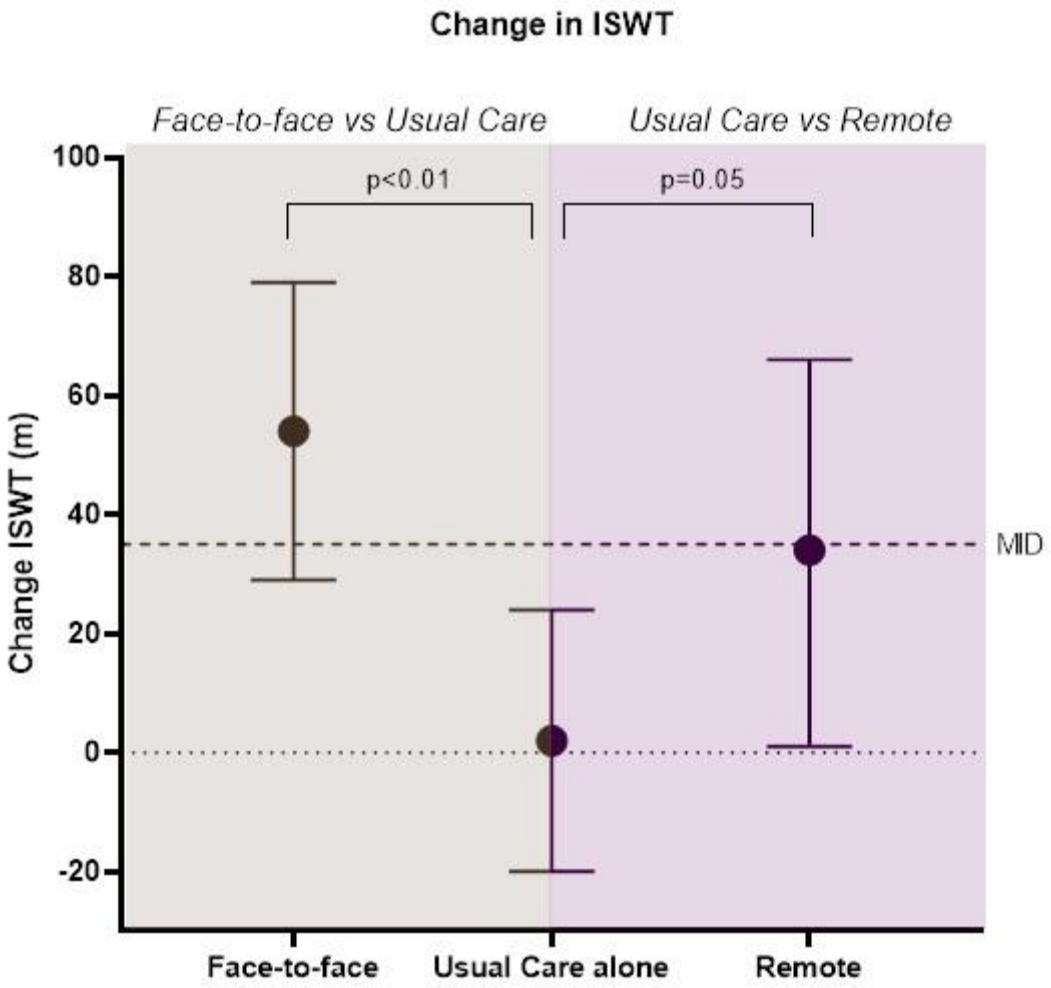
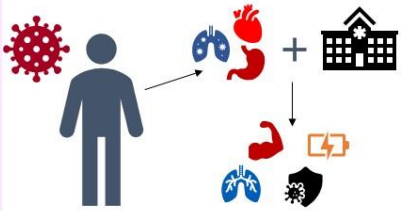

Change in ISWT
Face-to-face vs Usual Care
Usual Care vs Remote
p<0.01
p=0.05
100
80
60
40
20
0
-20
Change ISWT (m)
MID
Face-to-face
Usual Care alone
Remote

Figure 2

Background

COVID-19 can result in post-COVID syndrome



COVID-19 results in multi-organ impairment leading to hospitalisation

The effects of COVID-19 compounded by hospitalisation can result in symptoms such as breathlessness, fatigue, functional impairment, and immune dysfunction.

Aim: We aimed to determine the efficacy of exercise-based rehabilitation interventions in individuals experiencing post-COVID syndrome.

Methods

Face-to-face rehabilitation

vs

Usual care alone

vs

Remote rehabilitation

PHOSP-COVID
Improving long-term health outcomes

Results

Sub study

The face-to-face group showed an increase in central memory CD4+T, CD8+T, naïve, central and effector memory CD8+T, and NK cells (compared to a reduction in the Usual Care alone group).

Face-to-face rehabilitation vs Usual care alone on exercise capacity (Incremental Shuttle Walking Test)

Remote rehabilitation vs Usual care alone on exercise capacity (Incremental Shuttle Walking Test)

Online supplement

Educational topics included in the face-to-face rehabilitation programme are listed below, at the time of the study, handouts were available on a public facing website (www.yourcovidrecovery.nhs.uk). Education was delivered in a group setting, with facilitated discussion. This was delivered on a rolling programme.

Getting moving again	Fear & Anxiety	Eating well	Headaches
Breathlessness	Mood and coping	Sleeping well	Post-exertional symptom exacerbation
Cough	Memory/concentration	Managing ADLs	Next steps - active lifestyle
Fatigue	Goal setting	Return to work	Q&A

Table S1 Educational topics for face-to-face rehabilitation.

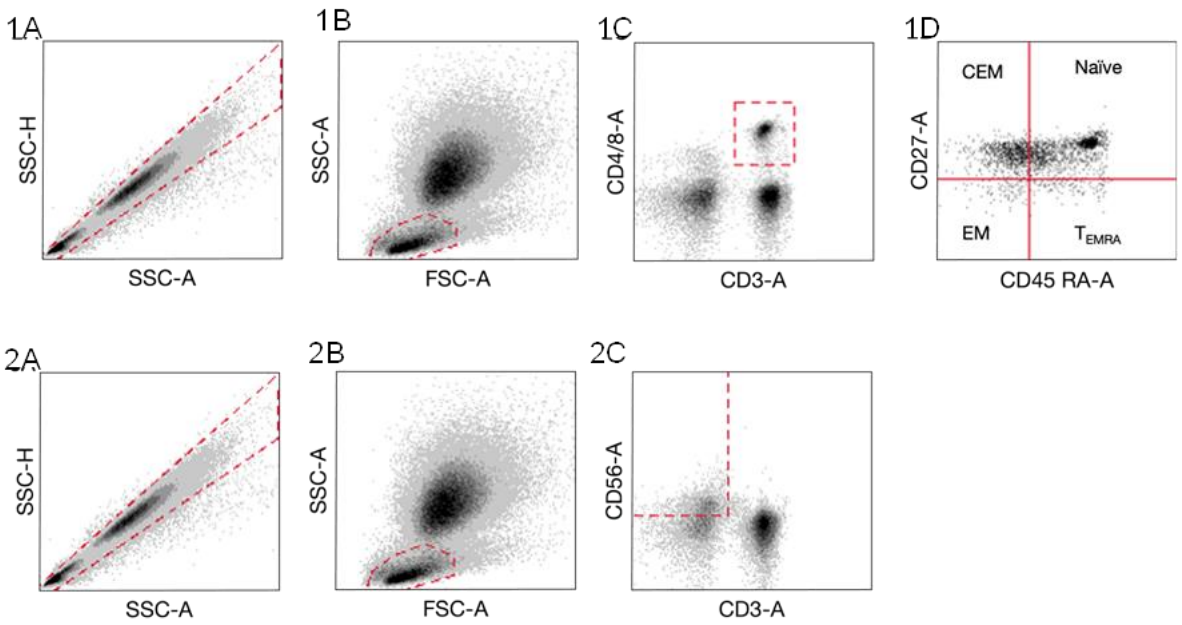
Immune biomarkers methods

Prior to and following the intervention period, venous blood samples were collected via venepuncture into EDTA- and sodium heparin-coated monovettes. Heparinised blood (12ml) was used for flow cytometric determination of immune cell subsets. EDTA blood was used for analysis of total lymphocyte counts with an automated haematology analyser.

Fluorescently conjugated antibodies were used to identify the following subsets: T cells ($CD3^+$ $CD4/CD8^+$) – naïve ($CD27^+$ $CD45RA^+$), central memory ($CD27^+$ $CD45RA^-$), effector memory ($CD27^-$ $CD45RA^-$), and terminally differentiated effector memory ($CD27^-$ $CD45RA^+$); NK cells ($CD3^-$ $CD56^+$) – (Figure 1). Fluorescence minus one controls were used to gate the aforementioned subsets. The proportions of the different subsets were used with total lymphocyte count (obtained from the haematology analyser) to calculate the circulating numbers for each subset.

To prepare samples for flow cytometry, heparinised blood was mixed with the appropriate antibodies and incubated for a total of 20min at room temperature, with BD FACS™ lysing solution added at the 10-minute mark. The samples were then centrifuged at 3500rpm for 6min at 4°C. The resulting pellet from each sample was resuspended in wash buffer (Dulbecco's phosphate buffered saline (D-PBS) supplemented with 0.5% bovine serum albumin and 2 mM EDTA), before undergoing another centrifuge spin with the same configuration. Lastly, the pellet from each sample was resuspended in D-PBS before data acquisition using a 4-colour flow cytometer (Accuri C6, BD, Oxford, UK).

Figure S1 *Example gating protocol for T cells and NK cells. T cells:* ***1A*** *Selection of singlets;* ***1B*** *Selection of lymphocytes;* ***1C*** *Selection of T cells;* ***1D****; Identification of T cell subsets (Naïve, CM, EM, T_{EMRA}).NK cells:* ***2A*** *Selection of singlets;* ***2B*** *Selection of lymphocytes;* ***2C*** *Selection of NK cells SSC, side scatter; FSC, forward scatter; -H suffix denotes height; -A suffix denotes area; CEM, central memory; EM, effector memory; T_{EMRA}, terminally differentiated.*



Secondary outcomes

The per protocol analysis is available in table S2. 40 participants were eligible for the face-to-face rehabilitation group, meeting 75% of class sessions attended (12/16) and attended a follow up appointment. 38 participants were eligible for the remote rehabilitation group, reaching at last phase three of four on the website platform and attending a follow up appointment.

Statistical analysis

The GLMM allows for adjustments of random effects (within-subject variability), baseline differences and accounts for missing data, assuming missing at random, providing a more accurate calculation of effects compared to other models. The final model reported the difference between and within groups. Appropriate assumptions were checked, including linearity assumption distribution and homoscedasticity of the residuals, distribution of the random effects and multicollinearity. A pre-planned additional analysis was conducted without adjusting for independent variables. A per-protocol analysis was performed on individuals with complete data on the primary outcome (attended baseline and follow-up assessment) and adherence to the intervention, defined as attending ≥75% of face-to-face sessions (12/16) or reaching phase three of the remote intervention. Data were presented as mean [95% Confidence Interval (CI), calculated using function confint method in R] unless stated otherwise. Adverse events were reported for each group and trial uptake and intervention compliance were reported as frequency data.

Linear mixed models were employed to assess the changes in immune cell counts across the study duration among different groups. Fixed effects in the linear mixed models included: group (exercise intervention vs control), time point (pre vs post), group*time, the baseline value of the dependent variable and any potential confounders with significant differences between groups at baseline. The participant identifier was treated as a random effect.

Assumptions of GLMM

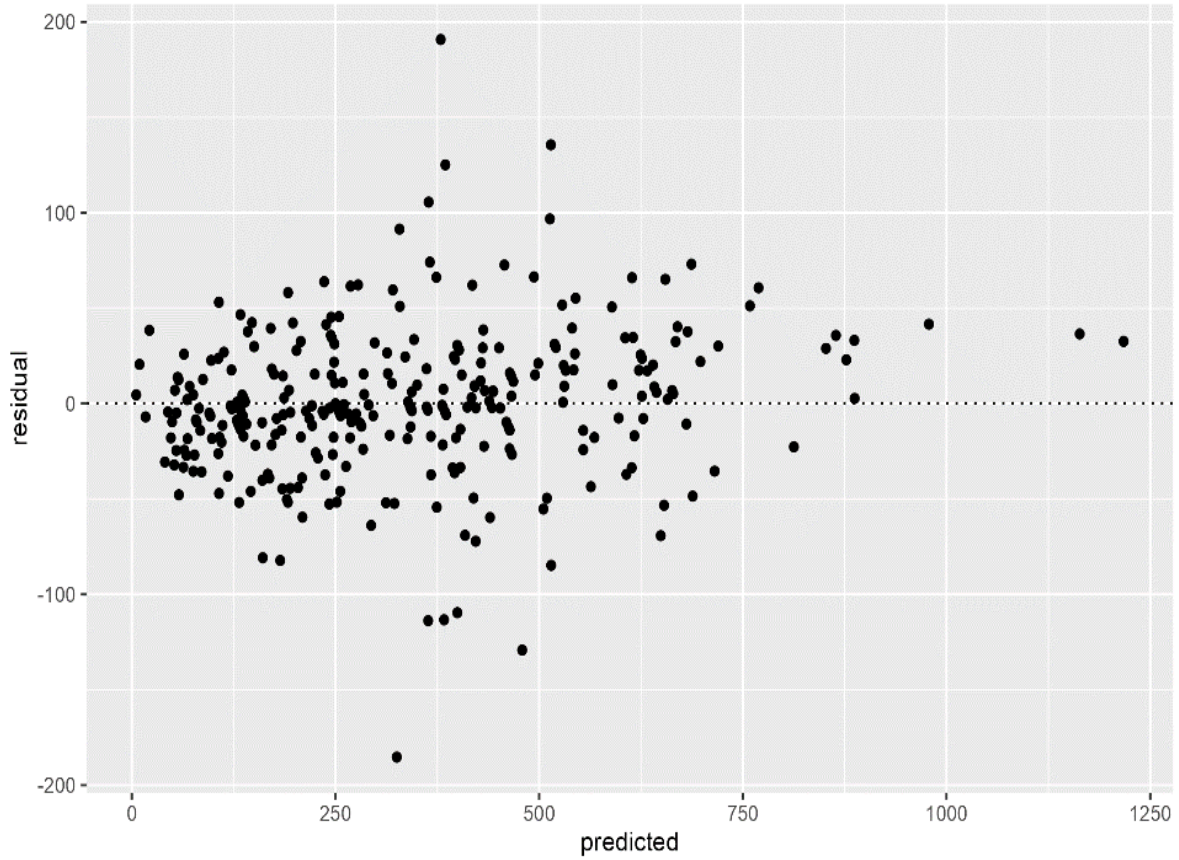
The assumptions assessed for the GLMM with Gaussian function link are:

- Linear behavior of the covariates and the target variable (scatter plot)
- Residuals follow a normal distribution around the zero (QQ plot and Shapiro-Wilk test)
- Random effects follow a normal distribution (Q-Q plot)
- Homoscedasticity (Levene's Test)
- Collinearity

ITT Model

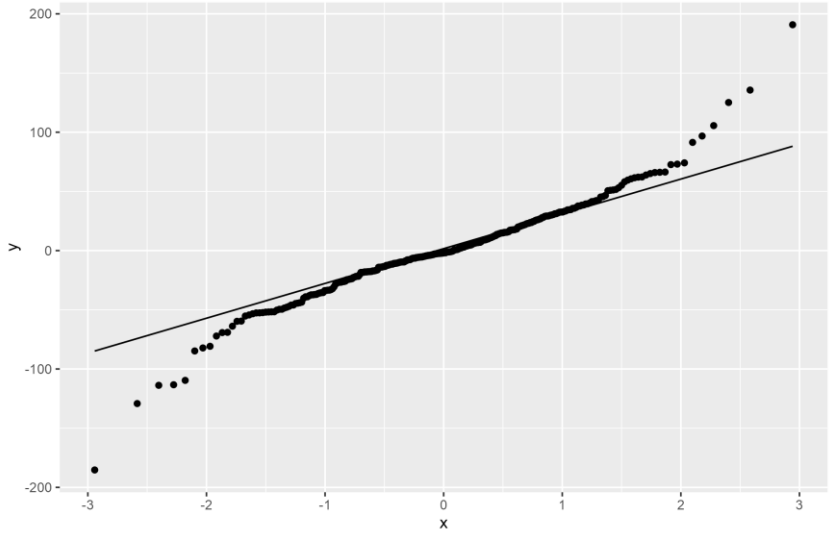
Linearity covariates and output

Figure S2. Residuals plot of the model showing that residuals are randomly distributed around zero, linearity assumption check.



Normality of the residuals

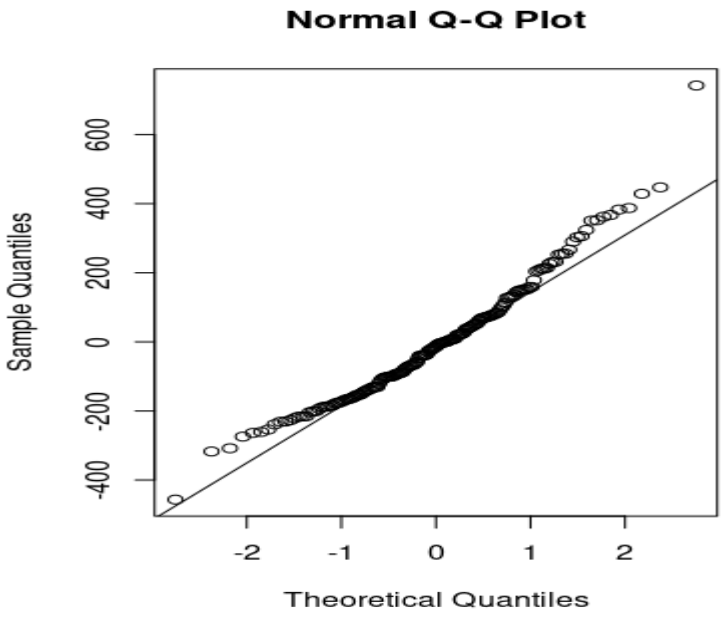
Figure S3. Q-Q Plot of the ITT model assessing the assumption of distribution of normality of the residuals with Shapiro-Wilk test



Shapiro-Wilk Test: W = 0.95389, p-value = 3.028e-08

Normality of Random Effects

Figure S4 Q-Q Plot of the ITT model assessing the assumption of distribution of normality of the random effects with Shapiro-Wilk test



Shapiro-Wil Test : W = 0.96722, p-value = 0.0004828

Homoscedasticity (homogeneity of the variance)

Table S2 Levene's Test to test Homogeneity of Variance

	Df	F Value	P-Value
Group	5	0.0635	0.9973

Multicollinearity

Covariate	**VIF [95%IC]**
age_treatment	1.24 [1.13 – 1.46]
crf1a_Sex	1.72 [1.51 – 2.04]
BMI	1.76 [1.54 – 2.08]
Time Since Hosp	1.09 [1.02 – 1.57]
Resp_support_3levels	1.33 [1.20 – 1.57]
Site	1.38 [1.23 – 1.62]
Period_point	2.55 [2.17 – 3/06]
treatment_group	1.33 [1.19 – 1.56]

	Face-to-face n=40			Remote n=38			Usual care n=62			Face-to-face vs Usual care	Remote vs Usual care
	Pre-	Post-	Change	Pre-	Post-	Change	Pre-	Post-	Change	Difference	Difference
ISWT	252[179 to 324]	319[238 to 400]	67[41 to 94]	363[289 to 437]	409[341 to 476]	44[15 to 73]	328[277 to 380]	331[280 to 381]	2[-20 to 23]	66[32 to 99]	42[7 to 78]
SPPB	9(7 to 11)	11(9 to 12)	1.47(0.56 to 2.39)	10(9 to 11)	11(10 to 12)	1.75(0.84 to 2.67)	10(8 to 11)	10(8 to 12)	0.29(-0.47 to 1.06)	1.18(-0.01 to 2.38)	1.46(0.27 to 2.66)
4MGS	0.88[0.79 to 0.96]	1.01[0.91 to 1.11]	0.14[-0.06 to 0.22]	1.08[0.98 to 1.18]	1.09[1 to 1.18]	0.01[-0.07 to 0.1]	1.03[0.96 to 1.09]	1.04[0.98 to 1.1]	-.01[-0.07 to 0.05]	0.15[0.05 to 0.24]	-0.02[-0.08 to 0.12]
Handgrip	26.92[22.18 to 31.67]	31.93[27.54 to 36.31]	3.93[2.11 to 5.76]	33.52[29.88 to 37.15]	36.72[32.75 to 40.69]	1.63[-0.33 to 3.60]	31.75[28.65 to 34.85]	24.21[31.00 to 37.41]	1.83[0.36 to 3.31]	2.10[-0.196 to 4.42]	-0.20[-2.59 to 2.24]
QMVC	27.33[21.57 to 33.10]	31.79[25.95 to 37.62]	4.16[0.89 to 7.43]	31.67[27.03 to 36.91]	36.15[31.09 to 41.20]	3.64[0.16 to 7.12]	31.77[28.09 to 35.44]	32.37[28.96 to 35.78]	-0.12[-2.63 to 2.38]	4.28[0.22 to 8.30]	3.76[-0.46 to 7.96]
EQ5D 5L											
Utility Index	0.60[0.54 to 0.66]	0.62[0.56 to 0.68]	0.02[-0.06 to 0.10]	0.66[0.61 to 0.72]	0.67[0.61 to 0.72]	0.00[-0.09 to 0.08]	0.59[0.52 to 0.66]	0.64[0.59 to 0.69]	0.04 [-0.02 to 0.011]	-0.02 [-0.13 to 0.08]	-0.04 [-0.15 to 0.05]
Thermo-meter	56.95[50.86 to 63.04]	62.84[56.87 to 68.81]	4.96 [-0.70 to 10.62]	63.53[53.89 to 71.17]	67.52[61.53 to 73.50]	1.96[-4.16 to 8.09]	60.84 [55.59 to 66.09]	65.61 [60.75 to 70.48]	5.58[0.93 to 10.24]	-0.62[-7.87 to 6.58]	-3.62 [-11.07 to 4.13]
PHQ9	9.63[7.64 to 11.61]	7.50[5.63 to 9.37]	-1.78[-2.98 to -0.59	6.95[5.23 to 8.66]	5.1[3.82 to 6.38]	-1.44[-2.76 to 0.12]	10.29 [8.58 to 12.00]	8.00[6.48 to 9.52]	-2.29[-3.31 to 1.29]	0.51[-1.04 to 2.04]	0.85[-0.79 to 2.48]
GAD7											
Severity score	7.40[5.59 to 9.21]	6.08 [4.24 to 7.91]	-1.07 [-2.29 to 0.15]	5.38[3.85 to 6.91]	3.93[2.72 to 5.15]	-1.38[-2.75 to 0.02]	6.50[5.04 to 7.96]	6.00[4.54 to 7.46]	-0.82[-1.84 to 0.19]	-0.25[-1.81 to 1.31]	-0.56[-2.23 to 1.11]
Inference score	2 [2 to 3]	2 [1 to 2]	-0.44 [-1.25 to 0.46]	2 [2 to 2]	2 [1 to 2]	-0.59 [-1.56 to 0.38]	2 [1 to 3]	12 [2 to 3]	-.13 [-0.66 to 0.86]	-0.57 [-1.74 to 0.6]	-0.72 [-1.94 to 0.5]
MoCA	MoCA	24.05[22.87 to 25.23]	24.00[22.68 to 25.32]	0.06[-0.74 to 0.86]	25.71[24.84 to 26.58]	27.07[26.47 to 27.68]	1.02[0.135 to 1.92]	24.77[23.85 to 25.69]	25.05[24.02 to 26.09]	0.26[-0.38 to 0.90]	-0.20[-1.21 to 0.80]
FACIT-FS	FACIT-FS	26.43[22.26 to 30.59]	32.86[29.31 to 36.48]	6.06[3.34 to 8.78]	33.09[29.36 to 36.82]	35.23[31.24 to 39.21]	1.21[-1.74 to 4.17]	27.44[24.04 to 30.84]	30.67[27.50 to 33.84]	3.44[1.21 to 5.68]	2.62[-0.85 to 6.09]
Dyspnoea-12	Dyspnoea-12	10.85[8.11 to 13.58]	8.08[5.68 to 10.48]	-2.68[-4.40 to -0.96]	9.68[6.95 to 12.42]	6.52[4.44 to 8.60]	-1.73[-3.64 to 0.18]	10.15[7.78 to 12.52]	8.79[6.67 to 10.91]	-0.97[-2.38 to 0.44]	-1.71[-3.89 to 0.49]
DSQ											
Frequency	39.05[30.03 to 48.08]	34.71[24.49 to 44.92]	-1.71 [-16.17 to -2.01]	35.00[25.26 to 44.74]	24.50[15.39 to 33.61]	-9.08 [-6.28 to 4.23]	39.00[31.35 to 46.65]	37.23[30.08 to 44.38]	-1.02[-8.57 to 5.15]	-0.69[-9.21 to 7.79]	-8.06 [-16.77 to 0.56]
Severity	32.97[25.3 to 40.65]	29.09[20.41 to 37.77]	-0.36[-1.83 to 1.09]	30.41[21.21 to 39.60]	21.00[12.67 to 29.33]	-1.70[-3.18 to -0.22]	36.67[29.00 to 44.33]	35.18[28.02 to 42.33]	-0.24[-1.34 to 0.85]	-0.12[-1.92 to 1.66]	-1.46[-3.28 to 0.34]

Table S3 Per protocol analysis for all outcomes for face-to-face rehabilitation vs usual care, and remote rehabilitation vs usual care presented as mean[95% CI] or median (25^{th} – 75^{th} quartile). *SPPB Short Physical Performance Battery, QMVC Quadriceps Maximal Voluntary Contraction, EQ5D-5L EuroQol 5*

Domain- 5 Level, PHQ9 Patient Health Questionnaire 9, GAD7 Generalised Anxiety and Depression 7, MoCA Montreal Cognitive Assessment FACIT-FS Functional Assessment of Chronic Illness Therapy Fatigue Scale, DSQ DePauls Symptom Questionnaire.

Brief pain inventory

The Brief Pain Inventory is completed in full if participants indicate they are experiencing any pain. Therefore there are data available on 118 participants for the primary analysis and 92 participants for the per protocol analysis. The results of the Brief Pain Inventory is presented in table SX.

	Face-to-face n=36			Remote n=42			Usual Care n=40			Face-to-face vs Usual care	Remote vs Usual care
	Pre-	Post-	Change	Pre-	Post-	Change	Pre-	Post-	Change	Difference	Difference
BPI severity	16.44 [14.07 to 18.81]	16.37 [13.57 to 19.17]	1.34 [-2.12 to 4.81]	12.25 [10.17 to 14.33]	11.09 [8.64 to 13.54]	-1.99 [-5.89 to 1.91]	13.90[11.82 to 15.97]	13.48[11.34 to 15.63]	0.23[-2.84 to 3.31]	1.11 [-3.57 to 5.49]	-2.22 [-0.71 to 2.58]
BPI interference	36.22 [30.43 to 42.01]	23.14 [17.88 to 28.40]	-8.91 [-14.89 to -2.94]	26.17 [21.14 to 31.19]	22.42 [18.26 to 26.59]	-5.1 [-11.15 to 0.94]	27.40[22.63 to 32.17]	24.43[19.71 to 29.14]	-4.87[-10.05 to 0.30]	-4.04 [-12.03 to 3.48]	-0.23 [-8.33 to 7.33]
Per protocol analysis											
	Face-to-face n=26			Remote n=27			Usual Care n=39			Face-to-face vs Usual care	Remote vs Usual care
BPI severity	16.54[13.49 to 19.59]	17.36[13.96 to 2.77]	3.11[-0.59 to 6.81]	11.39[8.40 to 14.38]	8.86[5.67 to 12.04]	-3.97[-8.74 to 0.80]	13.90[11.82 to 15.97]	13.48[11.34 to 15.63]	0.21[-2.67 to 3.10]	2.90[-1.86 to 7.26]	-4.18[-9.55 to 1.22]
BPI interference	35.81[29.15 to 42.46]	20.04[14.05 to 26.46]	-9.83[-16.70 to 2.97]	22.89[16.69 to 29.09]	20.53[14.78 to 26.28]	-6.35[-13.66 to 0.96]	27.40[22.63 to 32.17]	24.43[19.71 to 29.14]	-4.84[-10.01 to 0.33]	-4.99[-13.73 to 3.06]	-1.51[-10.26 to 7.09]

Table S4 Primary and per protocol analysis for the Brief Pain Inventory (BPI) for face-to-face rehabilitation vs usual care, and remote rehabilitation vs usual care presented as mean[95% CI].

*Figure S5 The effect of face-to-face rehabilitation (Ex) vs Usual Care (Con) on CD4+ (A-D) and CD8+ (E-H) subset changes from pre- to post-trial. Data are mean (95% CI) and adjusted for sex and baseline value of the dependent variable. * Sig difference from pre, within trial. CD4+ subsets; n=7 for Ex, N=15 for Con. CD8+ subsets; n=10 for Ex, n=16 for Con. CM, central memory; EM, Effector Memory; TEMRA, terminally differentiated effector memory.*