Effectiveness of a Personalised Self-management Intervention for People Living with Long Covid: the LISTEN randomised controlled trial.

Monica Busse[a]*∞, Philip Pallmann[a], Muhammad Riaz[a], Claire Potter[a], Fiona Leggat[b], Shaun Harris[c,d], Andrea Longman[a], Rachel Lowe[a], Adrian Edwards[e], Aloysius Niroshan Siriwardena[f], Nick Sevdalis[g], Jackie McRae[b], Jessica Fish[h,i], Bernadette Sewell[c], Fiona Jones[bj]∞

a. Cardiff University, School of Medicine, Centre for Trials Research, Cardiff, Cardiff UK.
b. St George's University of London, Population Health Research Institute, London, London, UK.
c. Swansea University, Swansea Centre for Health Economics, Swansea, Swansea, UK.
d. Swansea University, Swansea, West Glamorgan, UK.
e. Cardiff University School of Medicine, Primary Care and Public Health, Cardiff, Cardiff, UK.
f. University of Lincoln, Community and Health Research Unit, School of Health and Social Care Brayford Campus, Lincoln, UK LN6 7TS.
g. National University of Singapore Yong Loo Lin School of Medicine, Centre for Behavioural and Implementation Science Interventions, Singapore, SG.
h. University of Glasgow, School of Health and Wellbeing, Glasgow, UK.
i. St George's University Hospitals NHS Foundation Trust, Department of Clinical Neuropsychology & Clinical Health Psychology, London, UK.
j. Bridges Self-Management, London, England, UK.

∞Joint first author
*Correspondence to:
Monica Busse.
Centre for Trials Research, Cardiff University, Heath Park, Cardiff, CF14 4XN.
busseme@cardiff.ac.uk
(ORCID 0000-0002-5331-5909)

Keywords: Long Covid, self-management, rehabilitation, participation, process evaluation, implementation, co-design, personalised care.

Abstract.

Objective. To evaluate the effectiveness of LISTEN, a self-management support intervention, for non-hospitalised people living with Long Covid.
Design. Pragmatic, multi-centre, parallel group, superiority randomised controlled trial.
Setting. Twenty-four sites in England and Wales.
Participants. Five hundred and fifty-four adults with Long Covid, identified from long covid clinic waiting lists, word of mouth and adverts/social media self-referred to the trial and were randomised to receive either the LISTEN trial intervention or NHS usual care.
Interventions. The LISTEN intervention involved up to six one-to-one personalised sessions with trained healthcare practitioners and an accompanying co-designed handbook. Usual NHS care was variable ranging from no access, to access to mobile applications and resources, to specialist Long Covid clinics.
Main outcome measures. The primary outcome was the Oxford Participation and Activities Questionnaire (Ox-PAQ) routine activities scale score (RASS) at three months. Secondary outcomes included Ox-PAQ emotional wellbeing (EWSS) and social engagement (SESS) scale scores, the Short Form-12 (SF-12) Health Survey, the Fatigue Impact Scale (FIS), and the Generalised Self-Efficacy Scale (GSES). Serious adverse events were recorded. The EuroQol five-dimension five-level (EQ-5D-5L) assessed health utility.
Results. Between June 2022 and November 2023, 554 people with Long Covid (mean (SD) age 50 (12.3) years; 394 (72.4%) female) were randomised. At three months, LISTEN intervention arm participants reported small non-significant improvements in capacity for daily activities as assessed by Ox-PAQ RASS (adjusted mean difference (95% confidence interval) -2.68 (-5.38, 0.02), p=0.052) compared to usual NHS care. Those receiving the intervention also reported significant improvements in mental health (Ox-PAQ EWSS -5.29 (-8.37, -2.20), p=0.001; SF-12 2.36 (0.77, 3.96), p=0.004), reductions in fatigue impact (FIS -7.93 (-11.97, -3.88), p<0.001), and increases in self-efficacy (GSES 2.63 (1.50, 3.75), p<0.001). No differences were found in social engagement (SESS -2.07 (-5.36, 1.22), p=0.218) or SF-12 physical health 0.32 (-0.93, 1.57), p=0.612). There were no intervention-related serious adverse events.
Conclusions. The LISTEN personalised self-management support intervention resulted in non-significant short-term improvements in routine activities when compared to usual care. Improvements in emotional wellbeing, fatigue, quality of life and self-efficacy for people living with Long Covid were also reported. Physical health and social engagement were not impacted on by the trial intervention. The limited understanding of how much change is clinically meaningful in this population along with the unblinded design, the use of self-referral as a recruitment method and variable usual care may have introduced unintended bias and thus limits robust conclusions about this intervention. Further research is required to fully establish the impact of the intervention.
Trial registration: ISRCTN36407216, registered 27/01/2022.

What is already known about this subject?

- The physical symptoms of Long Covid such as extreme fatigue, breathlessness, cognitive difficulties and joint pains can be fluctuating and episodic and have a major impact on everyday activities, emotional wellbeing and social participation.
- Rehabilitation for people with Long Covid is variable with National Institute for Health and Care Excellence (NICE) policy guidance advocating supported self-management depending on need.
- Supported self-management interventions that rely on signposting and generic advice and information, rather than personalised treatment approaches, have limited evidence of effectiveness.

What are the new findings?

- LISTEN is a relatively brief, personalised self-management support intervention that integrates theoretical evidenced-based outputs and real-world lived experiences and contexts of non-hospitalised people with Long Covid. There was a non-significant effect on our primary outcome of everyday activities; secondary outcome data suggested a modest benefit in fatigue management, emotional wellbeing and confidence to self-manage but no impact on physical health or social engagement.

How might these results change the focus of research or clinical practice?

- Personalised support sessions using core principles such as those evaluated in the LISTEN intervention show promise, and training healthcare practitioners to listen, validate symptoms, and facilitate problem-solving to support other self-management strategies are worth considering when planning health services that accommodate the varied needs of people living with long Covid. Further research to explore clinical outcomes of the intervention with a longer follow-up, and implementation across different healthcare settings are warranted.

Background.

Long Covid, the name agreed by a community of people living with long-lasting symptoms following a Covid-19 illness, now encompasses the UK definitions of ongoing symptomatic Covid-19 (symptoms from 4 weeks up to 12 weeks), post Covid-19 syndrome (symptoms beyond 12 weeks), and the World Health Organization's post Covid-19 condition (symptoms beyond 3 months and persisting for at least 2 months).[1-3] In the UK, at least 1.9 million people are estimated to meet the criteria for Long Covid. Of these, 1.3 million have symptoms lasting for more than a year and 762,000 people live with symptoms for more than two years.[3] A comprehensive study in 2021 reported a total of 203 symptoms across 10 organ systems[4], which are both diverse and fluctuating, and may include fatigue, joint or muscle pain, altered smell and/or taste, cognitive impairment, anxiety, and sleep disorders. Fatigue is by far the most common symptom (72%), followed by difficulties with cognitive function (51%), muscle aches (49%) and shortness of breath (48%). [1] The potential legacy of Long Covid is serious, with a high incidence of individuals not returning to work by six months and continuing to experience limitations in their day-to-day activities[4-6], which could result in macroeconomic costs of £1.5bn each year. [7]

The uncertainty and confusion surrounding Long Covid, with its varied, relapsing and remitting symptoms, has also been heightened by a heavy sense of loss and stigma experienced by those living with the condition.[8] Furthermore, the lack of clear diagnosis in Long Covid increases the risk of individuals with the condition feeling overlooked and misunderstood by healthcare practitioners (HCPs) and services.[9] Published reports of individuals being dismissed as 'anxious' while presenting with wide-ranging and serious symptoms are concerning, and there is an ongoing need to broaden the medical community's knowledge and understanding of the long-term consequences of Covid-19 and access to timely and adequate care.[1]

The Long Covid Personalised Self-managemenT support co-design and EvaluatioN (LISTEN) trial was a randomised pragmatic effectiveness and cost-effectiveness trial of the co-designed LISTEN intervention[10], one of 15 research projects funded by the UK's National Institute for Health and Care Research (NIHR) Long Covid research programme in July 2021. The LISTEN trial intervention integrated evidence that relatively short self-management interventions can facilitate positive outcomes, contrary to the principles underpinning many rehabilitation interventions that advocate 'more is better'.[11, 12] It also addressed the emerging view that interventions that rely on signposting and information-giving, which can be the case for long-term conditions including Long Covid (e.g.,[13]), have limited evidence of effect.[14 15] There was also growing awareness that approaches such as a graded exercise programme were ineffective or possibly harmful[16] and a focus on recommendations to personalise treatment approaches through recognition and validation of patient experiences was needed.[17]

The complexity of Long Covid, with the uniqueness and variability of symptoms impacting on everyday life, presents challenges for interventions or services that do not provide scope or space for personalised support. A personalised intervention that integrates theoretical evidenced-based outputs as well as the real-world lived experiences and context of people with Long Covid, is likely to be more impactful.[18] The LISTEN intervention was co-designed to ensure that it was contextualised and relevant to the specific challenges and complexity of living with Long Covid.[19] The LISTEN intervention was also informed by national surveys which showed exclusion of seldom-heard groups and individuals who had neither received a positive Covid test nor presented to NHS services.[20] The extent to which current understanding of Long Covid, and specifically its impacts and strategies to

manage the condition, have included the experiences of people of diverse abilities and people of Black, Asian and Minority Ethnic backgrounds, were unclear. These groups have also been among the most impacted by Covid[20] and therefore strategies to engage and involve them in developing interventions were critical to address marginalisation.

We evaluated the effectiveness of the co-designed LISTEN personalised self-management support intervention for non-hospitalised people living with Long Covid in a randomised controlled trial. Recognising the highly diverse and fluctuating symptoms impacting on multiple aspects of everyday life, we selected participation in routine activities as our primary measure of interest. We also gathered information on social participation, emotional wellbeing, quality of life, fatigue and self-efficacy and compared these outcomes for those who received the LISTEN intervention in the trial to the outcomes of those who received usual NHS care. Healthcare Professionals (HCPs) delivering the LISTEN intervention were provided with targeted training to ensure they had the knowledge and skills to deliver a personalised approach to supporting self-management.[21-23] They were also provided with ongoing support to enable sustained utilisation of core co-designed intervention principles including specific language and techniques to support key self-management skills such as problem-solving, reflection and personalised goal setting.[22] These were also integrated into a fidelity checklist to ensure the intervention was delivered as intended.

Methods.

Trial design and setting. The LISTEN trial was a pragmatic, multi-centre, two-arm, parallel group, superiority, individually randomised controlled trial with both primary and secondary care sites (Supplementary Table S1) recruiting in England and Wales. The trial methods were developed, and protocol written, in line with the SPIRIT reporting guidelines[24, 25] and are published elsewhere.[10]We also conducted an integrated health economic evaluation which assessed the cost-effectiveness of the LISTEN intervention from both an NHS and Personal Social Services (PSS) perspective and a societal perspective. The health economic analyses will be reported elsewhere (manuscript in submission).

Participants. Eligible participants were aged 18 years or older and had experienced at least one Long Covid symptom for 12 weeks or longer and additionally met at least one of the following criteria:

i) positive SARS-CoV-2 PCR or antigen test (positive Covid-19 test) during the acute phase of illness,
ii) positive SARS-CoV-2 antibody test (positive Covid-19 antibody test) at any time point in the absence of SARS-CoV-2 (Covid-19) vaccination history,
iii) loss of sense of smell or taste during the acute phase in the absence of any other identified cause,
iv) symptoms consistent with SARS-CoV-2 (Covid-19) infection during the acute phase and high prevalence of Covid-19 at time and location of onset,
v) at least one symptom consistent with SARS-CoV-2 (Covid-19) infection during the acute phase and close contact of a confirmed case of Covid-19 around the time of onset.

Participants had to have consulted with their GP to rule out serious complications or the need for further investigation in relation to persistent symptoms following Covid-19 infection. Individuals with a palliative condition, or receiving end-of-life care, or those who were hospitalised during the acute phase of Covid-19 or actively participating in another Long Covid intervention trial were not eligible. Potential participants were sent study information by post, email and/or text messages. Self-referrals were also enabled through broad reaching publicity.

Public and Patient Involvement and Engagement (PPIE). The NIHR's six standards for PPIE (UK Standards for Public Involvement) underpinned decision-making with regards to all research processes in the LISTEN trial, including participant-facing communications, recruitment strategies, interpretation of study results, and knowledge dissemination. See Supplementary Table S2 for detailed description of activities as per Guidance for Reporting Involvement of Patients and the Public version 2 (GRIPP2).[26]

Recruitment, expression of interest, consent and demographic data collection.
Our primary method of recruitment was self-referral. People who were on waiting lists for the Long Covid clinics were sent invitation letters in the post. The trial was further promoted via social media and advertisement (posters) within primary and secondary care sites. We also opened 30 primary care (GP practices) Participant Identification Centres (PICs) in England and Wales. Participants identified via a medical record search at a PIC were sent text messages if on screening of records there was indication that they attended for a GP consultation having had a positive Covid test and had ongoing post Covid symptoms which meant that they may have been eligible for the LISTEN

trial. The text message introduced the LISTEN trial and included a link to the LISTEN website for more information.

All potential participants identified from waiting lists for Long Covid services at LISTEN trial sites or responding to public advertisements or text messages were required to complete an expression of interest form on the trial website and were then assessed for eligibility. We asked those (n=1026) who completed the online expression of interest forms (who were thus assessed for eligibility) to indicate how they heard about the trial. Responses were as follows: Advertisement in Press (n=32); recruited by trial site either via letter/ referral from healthcare practitioner (n=287); social media (353) and other (n=354)). The most common reasons given for "other" were: (i) told about it by a friend or relative; (ii) Long Covid groups; and (iii) staff emails/newsletters at hospitals/health boards.

If eligible, participants then went on to complete the electronic informed consent form. If those interested in participating were unable or unwilling to use the internet, they could phone the central research team for assistance in form completion. Data for age, gender, sex at birth, ethnicity, household information, highest educational qualification, employment, use of any community-based health and social care services or mental health services in the last 3 months status, positive covid test. We gathered data on the number of Long Covid symptoms lasting for 12 weeks or longer across 10 organ systems as defined by Davis et al. [27] who surveyed n=3762 participants with confirmed (diagnostic/antibody positive; n=1020) or suspected (diagnostic/antibody negative or untested; n=2742) Covid-19, from 56 countries, with illness lasting over 28 days and onset prior to June 2020. These included cardiovascular symptoms, dermatological symptoms, gastrointestinal symptoms, head/ears/eyes/nose or throat symptoms, immunological symptoms, musculoskeletal symptoms, pulmonary symptoms, reproductive symptoms, systemic symptoms (e.g. fatigue, fever, sweats, coldness), mood and emotion symptoms, cognitive dysfunction, headaches, memory issues, sensory issues, sleep issues, language and speech issues and smell or taste issues.

Randomisation and blinding. Participants were individually allocated to either the LISTEN intervention or usual care study arm (control group) in a 1:1 ratio using simple randomisation stratified by site. This was implemented via the LISTEN secure remote web database. The randomisation sequences were generated by the trial statistician in Stata 17 using permuted blocks of randomly varying sizes between 2 and 10. Participants were randomised by the central trial team following the completion of baseline assessments. Email notifications were sent to the participant and their allocated site advising them of their group allocation. It was not possible to blind participants or practitioners to group allocation. Statistical and health economic analyses were conducted blind to group allocation.

The LISTEN intervention. The LISTEN personalised self-management support intervention[19] was co-designed with 28 people living with Long Covid and nine HCPs working in Long Covid services. The protocol for the intervention co-design[28] and the subsequent intervention[19] are reported and elsewhere in accordance with the Template for Intervention Description and Replication (TIDieR).[29] Underpinned by social cognitive theory and self-efficacy principles[30] to build belief in individual capability, the LISTEN intervention was adapted and drew upon theory and evidence from Bridges Self-Management to enhance the knowledge, skills and confidence of people to manage everyday life with symptoms of Long Covid.[31] In the intervention, key sources of self-efficacy included goal mastery and vicarious peer modelling experiences, with self-efficacy a proposed mediator of change. In this approach to self-management, interactions by HCPs become less directive and more

collaborative, facilitating individuals' problem-solving skills. The LISTEN programme theory highlighted self-efficacy, gaining control and stability of symptoms and knowledge about living day-to-day with Long Covid as key mechanisms of impact. We hypothesised this would result in greater capacity to engage in regular activities that form the basis of daily life, better symptom management and improved emotional wellbeing.

The LISTEN intervention was underpinned by eight core principles developed and refined through co-design stages. Participants accessed up to six one-to-one personalised self-management sessions with a trained LISTEN HCP. The content of sessions were tailored to individuals ongoing needs and priorities and delivered in accordance with the intervention core principles. These included attentive listening, and supporting reflection on everyday strategies, problem solving and feelings of success. Participants also received the LISTEN handbook available as a hard copy or interactive PDF. The handbook consisted of five sections including narratives of people living with Long Covid, symptoms, challenges and solutions to managing, navigating social encounters, space for reflection and further resources. The six sessions were remotely delivered through video conferencing software (e.g., Microsoft Teams or Zoom) or by telephone, and could each last up to one hour. While six sessions were offered, minimum session adherence was four, this number was arrived at through discussions during co-design stages and PPIE meetings and considered the minimum required to establish a collaborative relationship and address core intervention principles. Participants were given the choice of number and frequency of sessions, time of the day and mode of delivery (online or telephone) based upon their needs. Participants were initially required to complete all sessions within a 10-week period. However, it was observed that sessions could take up to 12 weeks to complete due to factors relating to severity of symptoms, competing pressures such as work, and participant and HCP availability. Therefore, intervention delivery time was extended to 12 weeks early into the trial to accommodate greater flexibility for sessions. Before delivering the LISTEN intervention sessions to participants, 72 HCPs comprising nurses, physiotherapists, occupational therapists and assistant psychologists completed eight hours of training in the LISTEN core intervention principles, plus use of the LISTEN handbook. To supplement the initial eight hours of training, and to maintain intervention delivery fidelity, HCPs were also given access to an additional support and resource package. This 'wrap-around support package' provided resources and interactive events hosted through a Microsoft Teams channel available only to trained practitioners. The virtual platform contained supporting video files, audio files and documents, including podcasts, frequently asked questions and quick guides. Recordings from the 35 approximately bi-monthly, virtual 'top-up' question and answer events were also stored on this platform as additional resources.

Usual care. Participants randomised to the usual care group (control arm) of the study received NHS routine care as available to them in their region. The availability of Long Covid care varied geographically, and services differed in size, modality of delivery and clinical speciality (e.g., respiratory, neurology). NHS services for Long Covid evolved during the trial with the introduction of a tiered system. Care in each tier varied ranging from self-management resources (tier 1), GP support, referral to Long Covid services (e.g., respiratory, ear, nose and throat) or referral to highly specialised services (e.g., cardiovascular complications, severe autoimmune dysfunction; tier 4).[32-34] Trial recruitment ceased prior to the integration of Long Covid care into NHS Integrated Care Boards.[35] Participation in the LISTEN study did not guarantee or 'fast track' access to NHS services. However, where possible, the LISTEN team signposted participants to local NHS services if they

requested information. Access to and perceptions of NHS usual care were explored as part of an embedded process evaluation. This will be reported elsewhere (manuscript in submission).

Outcomes. Outcomes were measured at baseline, six weeks (for purposes of health economic evaluation only) and three months (all outcomes) post randomisation. The primary outcome measure was the Routine Activities scale score (RASS) of the Oxford Participation and Activities Questionnaire (Ox-PAQ) at three months[36], a fully validated, patient-reported outcome measure developed specifically to assess participation and activity in individuals with chronic health problems. Secondary outcomes were emotional wellbeing (Ox-PAQ Emotional Wellbeing scale score (EWSS)), social engagement (Ox-PAQ Social Engagement scale score (SESS)), health-related quality of life (Short Form-12 (SF-12) Health Survey[37]), fatigue (Fatigue Impact Scale (FIS)[38]) and perceived self-efficacy to predict coping with daily struggles and adaptation after experiencing stressful life events (Generalised Self-Efficacy Scale (GSES)[39]) with additional Covid-19 context specific questions (see supplementary material), which enabled exploration of the key anticipated mediators of intervention outcome. Information on health utility was captured using the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire that includes five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[40] Adverse events (AEs) related to psychological distress and any events meeting the definition of a serious adverse event (SAEs) were recorded. Three brief validated scales, namely the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM) and Feasibility of Intervention Measure (FIM) were used to assess the fitting, suitability, likability and match of the intervention.[41] Detail for each of the LISTEN trial outcome measures including number of items, range, minimum important difference (MID) and direction of effect are provided in Supplementary Tables S3 and S4.
Adherence to the LISTEN intervention was defined as attendance at three or more of the one-to-one personalised self-management sessions. Fidelity of intervention delivery was assessed in a purposively selected sub-sample of recorded sessions against a pre-defined fidelity checklist which reflected the eight core intervention principles. Results of the intervention fidelity, alongside findings from participant interviews and HCP focus groups undertaken as part of a detailed embedded mixed methods process evaluation will be reported elsewhere (manuscript in submission).

Sample size. We aimed to detect a minimum clinically important standardised effect size of 0.32[42] between randomised arms in the primary outcome of the RASS domain of the Ox-PAQ with 90% power whilst controlling the two-sided type I error level at 5%. This relates to a within group MID of 7.51[42]. A conventional individually randomised trial would have required 414 participants (based on a two-sample t-test), but since the intervention was expected to be delivered by up to 24 community rehabilitation teams, we also took potential clustering in the intervention arm into account.[43,44] Assuming an intraclass correlation coefficient (ICC) of 0.03 in the intervention arm, 24 clusters with 10 participants each in the intervention arm and 234 participants in the usual care arm (i.e., a total of 474 participants) was required for 90% power. This was calculated using the method of Moerbeek and Wong[45] as implemented in version 0.7.0 of the R package 'clusterPower'[46]. Assuming 15% loss to follow-up, the overall recruitment target was set to 558.

Data collection. Study data were collected and managed using REDCap electronic data capture tools hosted at Yale University.[47, 48] Outcomes were self-reported and mostly completed online. All site staff had password protected accounts for REDCap to access participant records and complete intervention session notes, and withdrawal and safety forms.

Enablers to trial participation and inclusivity. Inclusivity considerations were integral to the trial process. Narratives and experiences from a wide variety of people from different backgrounds, contexts, ages and genders were captured through online co-design meetings and interviews and were included in the LISTEN handbook to enhance relatability to different groups. Data were collected on gender, age, sex at birth and ethnicity of trial participants. To enable a diverse population to participate in the trial, and with support of the LISTEN PPIE group, multiple steps were implemented. Firstly, the LISTEN intervention handbook was posted to all participants in hard copy and the option to receive the intervention by phone was provided. One-to-one personalised support sessions were offered to participants in both English and Welsh languages. This allowed participation and access to the intervention for Welsh speaking participants. Next, the trial was set up for individuals to self-refer into, thus improving accessibility. The remote delivery of intervention sessions, via a secure web video conferencing system or telephone, and the flexibility of scheduling sessions were designed to further maximise access of the intervention for all. For those with debilitating symptoms and/or physical impairments, remote delivery and inclusivity methods (e.g., breaks, shorter sessions and cameras off) were used to enhance the feasibility and accessibility of the intervention. All our participant materials were developed with guidance from Diversity and Ability, a social enterprise, led by and for disabled people who support groups to create inclusive cultures within their activities. Finally, for baseline and follow-up questionnaire completion, and the reading of key study documents, additional support and measures were available. For instance, members of the research team and site staff supported participants by taking verbal informed consent and gave support completing forms over the telephone. On the recommendation of the LISTEN PPIE group, all study materials were audio recorded for any additional accessibility needs.
Statistical analyses. Participant characteristics and outcome scores at baseline were summarised descriptively by randomised allocation (usual care or LISTEN intervention). In scoring the SF-12 v1 US version in our population, responses to items BP2 and SF2 were set to missing due to incorrect response options provided during survey administration. We worked with the license providers (Quality Metrics) to ensure that the survey and the PCS and MCS scores were correctly scored and interpreted as per the validated outcome measure. The primary analysis used the intention-to-treat (ITT) population. A linear mixed-effect regression model was fitted with RASS at 3 months as dependent variable, randomisation group and baseline RASS as independent variables, and a random centre effect to provide the estimated mean difference of the RASS at 3 months for the intervention group compared with the usual care group alongside a 95% confidence interval (CI) and p-value (Model A). The regression model accounted for clustering due to centres in both groups. The effectiveness of the intervention on the total scores of the secondary outcomes (EWSS, SESS, SF-12, FIS, EQ-5D-5L, GSES) at 3 months follow-up, adjusted for baseline, were assessed using similar mixed-effect models as for the primary outcome analysis. In a post hoc responder analysis, we created a binary outcome based on whether or not participants achieved a change of at least 7.51 (MID) in Ox-PAQ RASS and used a mixed-effect logistic regression model with randomisation group as independent variable and a random centre effect to compute and odds ratio (OR) for the intervention group versus usual care with 95% CI.

Recognising the potential impact of age, gender, ethnicity, employment status, and number of long Covid symptoms, we adjusted the primary and secondary outcome analyses for age, gender, ethnicity, employment status, and number of Long Covid symptoms, in a secondary pre-specified analysis, (Model B). We also explored pre-specified subgroup analyses for gender and ethnicity;

however, due to the lack of statistical power, we do not report these results here. To assess the impact of missing data, we conducted a sensitivity analysis using multiple imputation using chained equations with the assumption of missingness at random (MAR), creating 20 imputed datasets and combining them according to Rubin's rules. Imputation models included trial arm, centre, participant age, gender, qualification level, employment status, participant reporting a positive Covid test, and number of long Covid symptoms as independent variables. The assumption of clustering in the intervention arm only was evaluated with both homoscedastic and heteroscedastic models. Based on the post estimation of ICC and AIC for models fit, clustering was considered in both arms and results from the above models reported. The detailed statistical analysis plan was finalised before any analysis was performed using Stata version 17 and is presented in supplementary materials.

Results.

The LISTEN trial was open to recruitment between June 2022 and November 2023 with 15 primary and secondary care NHS centres and one non-NHS site within England set up as individual sites and NHS sites in Wales (covering all seven Health Boards and one non-NHS site) set up as a single site. The trial was ended once it had recruited fully, and the last recruited participant had completed their final follow up assessment. Potential participants completed the expression of interest form, and only if eligible, progressed to consenting and baseline data collection. Individuals did not progress to baseline if they: (1) were hospitalised for Covid; (2) reported Long Covid symptom duration less than 12 weeks; (3) had not consulted with their GP; (4) reported another life limiting condition; or (5) were participating in another Long Covid trial. They also did not progress if trial teams were unable to allocate a participant to a participating research site. Baseline characteristics of the total sample and by study arms are presented in Table 1. Gender (self-described) and sex (assigned at birth) for our total sample at baseline is presented in Supplementary Table S5.

<Table 1 here>

Our sample broadly matched that of Office for National Statistics (ONS) data for the condition with a greater prevalence of Long Covid in women and most likely to affect those aged 35-69 years. Despite statistical uncertainty, ONS data suggest Long Covid is more prevalent in White ethnic groups than in people of Black, Asian or Mixed ethnicity.[6] The LISTEN participants were overwhelmingly from White ethnicities, despite our use of multiple strategies to recruit from across diverse ethnic communities.[10] Overall, 42.2% were in full-time employment and 22.3% in part-time employment. The majority had been educated to GSCE level and above, and were living with a partner (31.4%), or partner and children (29.4%). Only 20.4% or 11.8%, respectively had accessed community health and social care, or community mental health services in the three months prior to enrolling in the LISTEN trial. Across both groups, 88.1% had received a positive Covid-19 test and had experienced a median of 12 different symptoms related to their Long Covid. Across the trial, 554 participants were randomised to either the trial intervention (n=277) or usual care (n=277). Two hundred and eleven participants in the LISTEN group and 221 in usual care group completed the six-week follow-up, and at the three-month follow-up, completions in the LISTEN and usual care groups were 210 and 200, respectively (see Figure 1 for CONSORT flow chart and Supplementary Tables S6, S7, S8, S9 and S10 which detail withdrawals and loss to follow up).

<Figure 1>

Participants who received the LISTEN intervention perceived it to be acceptable, feasible and appropriate (see Table 2). Adherence to the LISTEN intervention was good, with 76% of those allocated to receiving the intervention meeting the criteria for adherence (i.e., attending at least three sessions) and only 12% not attending any sessions (see Table 3 and Supplementary Table S11). There were seven AEs reported in the LISTEN intervention group and three in the usual care group. Of the seven intervention group participants, only one discontinued the intervention and was referred to the local mental health crisis team. There were two SAEs reported in the LISTEN intervention group and one in the usual care group. None of the reported SAEs were considered related to the intervention (see Supplementary Table S12 and S13 for details of AEs and SAEs).

<Table 2>

<Figure 2>

Outcomes at the three-month follow-up are presented in Table 4. The individual datapoints for each participant at baseline (x-axis) and follow up (y-axis) for the Ox-PAQ RASS are shown in Figure 2. Our primary analysis indicated that those who had received the LISTEN intervention had greater capacity for daily activities as assessed by the Ox-PAQ RASS at three months (adjusted mean difference (95% CI) -2.68 (-5.38, 0.02), p=0.052). The adjusted mean difference (95% CI) in a per-protocol analysis which included participants attending three or more sessions adjusted for the fixed effect of baseline outcome score and random effect of site was -2.79 (-5.57, -0.01), p=0.049 for the primary outcome (Ox-PAQ routine activities domain score). Participants also reported improved emotional wellbeing/mental health (Ox-PAQ EWSS -5.29 (-8.37, -2.20), p=0.001; SF-12 mental health component 2.36 (0.77, 3.96), p=0.004), reduced fatigue impact (FIS -7.93 (-11.97, -3.88), p<0.001), and increased self-efficacy (GSES 2.63 (1.50, 3.75), p<0.001). There were no between-group differences in social engagement (SESS -2.07 (-5.36, 1.22), p=0.218) or SF-12 physical health component (0.32 (-0.93, 1.57), p=0.612).

When adjusting further for the outcome score at baseline, age, gender, ethnicity, employment status and the number of Long Covid symptoms at baseline, there was a statistically significant improvement in the primary outcome (Ox-PAQ RASS) (-2.90 (-5.66, -0.15); p=0.039) when compared to scores of those allocated to usual care at the three-month follow-up. Similarly, scores were significantly lower in the EWSS domain of the Ox-PAQ, reflecting current emotional wellbeing (-5.89 (-8.99, -2.79); p<0.001), all three domains of the FIS and the overall FIS (-8.65 (-12.79, -4.52); p<0.001), the GSES with (2.79 (1.66, 3.93); p<0.001) and without (1.42 (0.54, 2.30); p=0.002) additional Covid-related items, and the mental health component of the SF-12 (2.36 (0.77, 3.96); p=0.001). There remained no between-group differences in social engagement (SESS -2.81 (-6.19, 0.57); p=0.103) which focusses on maintenance of personal and community relationships, or in the physical health component of the SF-12 (0.48 (-0.74, 1.71); p=0.440). Of the participants who provided primary outcome data (n=402), 161 (40.1%) reported achieving changes of at least 7.51 (MID) on the Ox-PAQ RASS and the odds of achieving this were higher in the those who received the LISTEN trial intervention (unadjusted OR=1.40 (0.94, 2.09); fully adjusted OR=1.46 (0.95, 2.25)).

Sensitivity analyses using multiple imputation for missing observations resulted in very similar effect estimates, 95% CIs and p-values indicating little effect of missing data on the results reported here (Supplementary Table S14 and S15).

<Table 3 here>

<Table 4 here>

Discussion

Here we report on the short-term impact of the LISTEN intervention, the first personalised self-management support intervention for people with Long Covid (and not hospitalised for initial Covid-19 infection) to be tested at scale across England and Wales. The LISTEN intervention was co-designed to focus on gaining control and stability of symptoms at a time when people were describing real helplessness andhopelessness. We hypothesised that those who received the LISTEN intervention would feel more in control of their symptoms which would then impact on their everyday life and emotional wellbeing. [10] Ratings of self-efficacy for chronic condition management were explored as part of our assessment of intervention fidelity. LISTEN participants reported improvements in self-efficacy, increased feelings of control of symptoms such as fatigue and pain and subsequent improvements in emotional wellbeing and quality of life. These findings must however be balanced with the limited understanding of how much change is clinically relevant in this study population and the preliminary single arm study in a small sample of people living with long term health conditions that informed our understanding of the LISTEN primary outcome. [42] We observed an average reduction of less than 3 points in the Ox-PAQ RASS for those receiving the LISTEN intervention compared with usual care, less than half the published MID for Ox-PAQ RASS of 7.51 points. Also, the 95% CI of the difference between arms includes a null effect (for the primary analysis) or very small and clinically insignificant improvements close to a null effect (for the additional adjusted analysis). Thus, whilst our data are supportive of our proposed mechanism of impact, we are not able to make firm conclusions about the LISTEN intervention leading to clinically meaningful benefit.

Trial participants rated the LISTEN intervention as acceptable, feasible and appropriate and 78% of those allocated to the intervention met the minimum criteria for adherence, an indicator of the success of this approach. A per-protocol analysis which included only participants who attended at least 50% (i.e., three or more) of their LISTEN intervention sessions did not alter the interpretation of our data. Importantly, the literature indicates that the quality of the interactions and support and level of personalisation received during the intervention sessions are more important in ensuring successful self-management intervention outcomes than the intensity (or dose/number) of sessions received. [12] Whilst our participants were able to receive up to six sessions with a trained practitioner with a view to enabling the collaborative relationship and encouraging opportunities for self-management activities and reflection on progress, in practice some participants did not need as many as six sessions for the intervention to be delivered as intended (i.e., with fidelity) and for participants to achieve the outcomes that they wanted.

The NICE guidelines for self-management and supported self-management for people with Long Covid (last updated January 2024) still focus primarily on advice, information and setting realistic goals.[2] Given the multiple components that might be included in Long Covid interventions, it is unsurprising that the rehabilitation intervention protocols (with or without inclusion of self-management support) registered to date typically involve cohort, case-controlled, before-and-after and non-randomised experimental studies, and include complex combinations of aerobic or strength exercises, tele-rehabilitation, cognitive rehabilitation, virtual reality rehabilitation, breathing exercises, cognitive behavioural therapy, mindfulness and various Long Covid-specific approaches including activity management and nutrition.[49] However, the recently published REGAIN trial provides the first evidence from a large prospectively registered randomised trial that an online, home-based, supervised, group multi-component physical and mental health rehabilitation

intervention[50] is effective in improving health-related quality of life in adults with Long Covid who were initially hospitalised.[51] The authors note that the relative contributions of the intervention components are unknown, but that rehabilitation efforts should target fatigue, pain interference, and depression.

When comparing the findings from REGAIN to the LISTEN trial, the key difference is that the REGAIN population were hospitalised whereas those enrolled in LISTEN were not hospitalised following the Covid-19 infection; this may explain the differences in these two trials in terms of participant demographics (REGAIN enrolled more men, fewer white and on average older participants who were hospitalised for Covid infection).[51] Interestingly, both trial interventions inferred positive outcomes for health-related quality of life as measured by the EQ-5D index, fatigue impact and emotional well-being.

Although access to self-management support can be integral to many rehabilitation programmes and is recommended by NICE, the core intervention principles and theoretical underpinnings are often unspecified, and the evidence for the individual self-management support components of rehabilitation in Long Covid is limited.[52] Personalisation of self-management support interventions has been shown to be a key indicator of success on both clinical and holistic outcomes and those that integrate collective and learnt strategies of people as well as a focus on 'what matters most', are critical when designing interventions ready for evaluation. In an emerging condition, such as Long Covid, it was vital to capture this learning and priorities for self-management support. Interviews with eighteen people living with Long Covid (who were members of the LISTEN co-design groups) indicated that seeking reassurance and knowledge, developing greater self-awareness through monitoring, learning from others about what had worked for them, building in moments of joy and purpose, and prioritising what is most meaningful, were all important in navigating life with Long Covid.[53]

Self-management (support) is also an integral part of treatments available for people living with complex long-term conditions and Long Covid appears similar. However, whilst there are other groups exploring self-management practices of people with Long Covid[54], and importantly which have informed outcome measure development[55], there are few interventions developed specifically for this group[19] or evaluations of such approaches. A search for registered trials and studies investigating isolated self-management support and/or education interventions for people with long Covid highlighted the LISTEN trial and to our knowledge, one other (https://clinicaltrials.gov/study/NCT05268523)[56] as the only registered randomised controlled trials focussing explicitly on self-management support. Whilst recognising interventions addressing specific symptoms such as cognitive and respiratory difficulties are in development and findings from studies will be emerging, currently there is no 'cure' for Long Covid. An intervention such as the LISTEN personalised self-management intervention, which can support some of the 1.9 million people in the UK living with Long Covid, could offer an opportunity for people to gain control of their symptoms and learn skills and knowledge to engage in and manage everyday meaningful activities.

Whilst our data highlights the value of personalised support from trained HCPs on self-management strategies to carry out everyday activities, we acknowledge the inherent limitations of this unblinded trial. Most of our trial population were female (approximately 72%) and from a white ethnic background (92%). Our analyses controlled for age, gender, ethnicity, employment status and number of Long Covid symptoms, but was not sufficiently powered to explore outcomes by gender

or ethnicity and as such our findings may have limited generalisability. We also did not examine the impact of factors such as health literacy or educational attainment. Potential participants self-referred to the trial by completing an expression of interest form on the trial website. Whilst telephone support was available, a level of digital exclusion cannot be discounted. Allowing self-certification of at least one symptom consistent with SARS-CoV-2 infection during the acute phase and close contact of a confirmed case of Covid-19 around the time of onset rather than providing evidence of a confirmed positive antigen test, as part of the self-referral process, may also have led to further ascertainment bias. Whilst it would have been interesting to explore outcomes according to recruitment source namely advertisement in press, letter/ referral from healthcare practitioner, social media and other, such an analysis would have been underpowered due to the small sub-groups. The short timeframe of the LISTEN trial is an additional limitation, as is the higher-than-anticipated loss to follow-up rate at the primary endpoint. Funder requirements meant that the outcomes reported here are limited to data collected at the three-month endpoint, and as such, an understanding of longer-term impacts and cost-effectiveness is lacking.

The trial was designed, and funding secured in 2021, at a time when there was no consensus on core outcomes for Long Covid research. We selected a primary outcome, namely the Ox-PAQ RASS, which reflected the multiple aspects of participation which could be impacted on by the wide-ranging symptoms of Long Covid. It is a psychometrically sound and valid patient reported outcome measure developed for use in a range of health conditions and valid for self-administration. It is theoretically grounded in the World Health Organization International Classification of Function and intended for use in the meaningful evaluation of interventions aimed at promoting participation and activity. Since that time, domains of importance for Long Covid outcomes have been published. Encouragingly, the outcome domains, namely fatigue, pain, cognitive, mental and physical health that were measured in LISTEN, alongside our focus on participation in daily living, are now recognised as being relevant and important in the field despite there being no consensus for any single instrument that assesses impact on daily life[57].

In a pragmatic unblinded effectiveness trial, such as ours, and indeed, as in most, if not all rehabilitation trials, we cannot exclude the potential for performance bias impacting our results. Participants could not be blinded to which intervention they were allocated to. This may have resulted in an element of behaviour change simply as result of being a participant in a trial. We were also aware that the confounding nature of a pandemic and healthcare provision itself resulted in variable offerings for usual care; our data were collected a time when the majority of long Covid clinics were set up in England and accessible in some but not all parts of Wales. It was not possible to standardise what usual care involved or was provided, and we could not control for contact time between groups. To ensure that this did not invalidate the main findings, we accounted for this variability of care in our pre-specified statistical analyses with the use of a mixed effect model with a random effect for the study centre. To further inform our understanding of trial outcomes, in relation to the intervention received, we captured consistency/inconsistency of usual care versus the trial intervention as a mechanism of impact in the trial process evaluation i.e. whether usual care included certain key characteristics that are reflected in the underpinning trial intervention logic model for example personalisation, being heard, supporting problem solving versus providing

information, diagnostics and monitoring. This mixed method process evaluation will be reported elsewhere (manuscript in submission).

In 2021, when LISTEN was conceived, Long Covid was a new, emerging condition, with a limited knowledge base to guide intervention approaches and variable or non-existent NHS services. Evidence generated in the LISTEN trial provides initial indications that a relatively brief, personalised self-management support intervention that integrates theoretical evidenced-based outputs and real-world lived experiences and contexts of non-hospitalised people with Long Covid can enable control of symptoms that may in turn lead to improvements in everyday activities and emotional wellbeing. We suggest that interventions for long Covid which provide personalised self-management support delivered by highly trained NHS staff may be preferable to 'one-off' advice and information sessions. There are however clear next steps to enable learning from this research, including formal exploration of what works for whom and in what circumstance. This could extend to examining the generalisability of our findings to different age and ethnic groups and studying the impact over a longer period.

Figure 1. CONSORT diagram showing the flow of participants through the LISTEN trial. Loss to follow up and partial withdrawals from questionnaires are reported at 6 week and 3 month follow up. Participants who did not complete the 6 week follow up but did complete the 3 month follow up (n=18 and n=10 respectively) are also indicated.

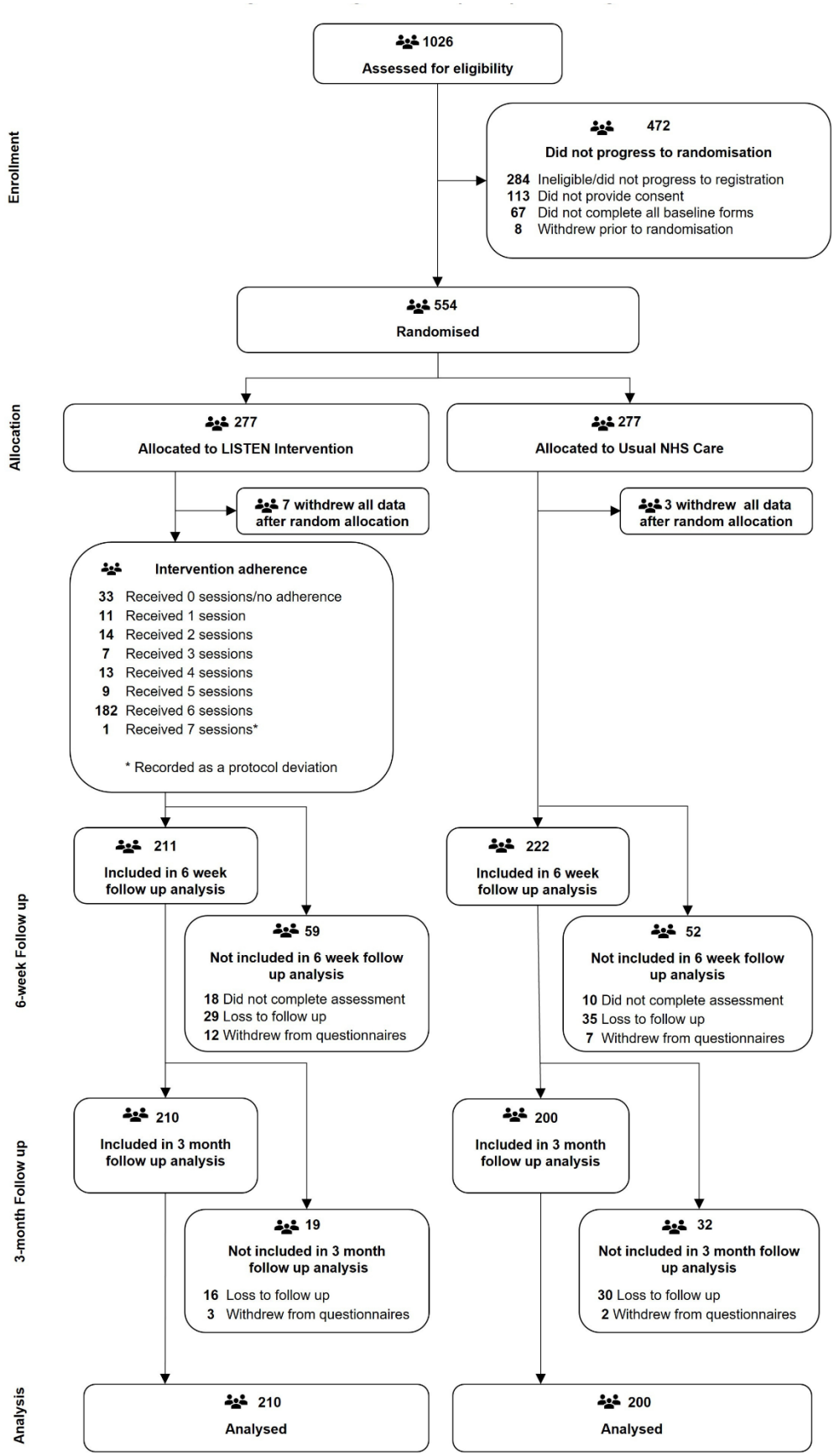
Enrollment
1026
Assessed for eligibility
472
Did not progress to randomisation
284 Ineligible/did not progress to registration
113 Did not provide consent
67 Did not complete all baseline forms
8 Withdrew prior to randomisation
554
Randomised
Allocation
277
Allocated to LISTEN Intervention
277
Allocated to Usual NHS Care
7 withdrew all data after random allocation
3 withdrew all data after random allocation
Intervention adherence
33 Received 0 sessions/no adherence
11 Received 1 session
14 Received 2 sessions
7 Received 3 sessions
13 Received 4 sessions
9 Received 5 sessions
182 Received 6 sessions
1 Received 7 sessions*
* Recorded as a protocol deviation
6-week Follow up
211
Included in 6 week follow up analysis
222
Included in 6 week follow up analysis
59
Not included in 6 week follow up analysis
18 Did not complete assessment
29 Loss to follow up
12 Withdrew from questionnaires
52
Not included in 6 week follow up analysis
10 Did not complete assessment
35 Loss to follow up
7 Withdrew from questionnaires
3-month Follow up
210
Included in 3 month follow up analysis
200
Included in 3 month follow up analysis
19
Not included in 3 month follow up analysis
16 Loss to follow up
3 Withdrew from questionnaires
32
Not included in 3 month follow up analysis
30 Loss to follow up
2 Withdrew from questionnaires
Analysis
210
Analysed
200
Analysed

Figure 2. Scatter plot of individual Ox-PAQ Routine Activities domain scores at baseline (x-axis) and three month follow up (y-axis) by treatment arm (intervention or control). The dashed diagonal line indicates no change between baseline and follow-up with data points below the dashed diagonal line indicating greater ability to participate in routine activities at follow-up compared to baseline (lower scores on RASS are a better outcome).

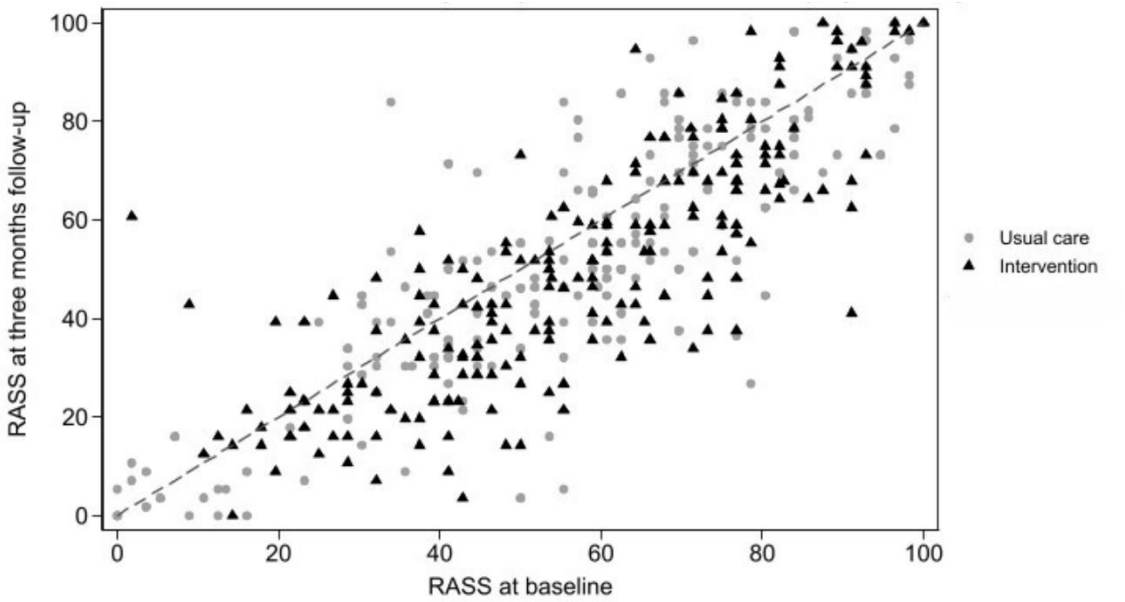

Table 1: Baseline characteristics of the total sample and by the study arms.

Characteristics	Total Sample (N=544) n (%)	Usual Care Arm (N=274) n (%)	LISTEN Intervention Arm (N=270) n (%)
Mean age (SD)	50.0 (12.3)	50.0 (12.1)	50.0 (12.5)
Missing	1 (0.2)	1 (0.4)	0 (0.0)
Gender:			
Female	394 (72.4)	199 (72.6)	195 (72.2)
Male	143 (26.3)	72 (26.3)	71 (26.3)
Other	7 (1.3)	3 (1.1)	4 (1.5)
Missing*	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity:			
White	505 (92.8)	255 (93.1)	250 (92.6)
Mixed or multiple ethnicity	15 (2.8)	8 (2.9)	7 (2.6)
Asian	15 (2.8)	5 (1.8)	10 (3.7)
Black	5 (0.9)	3 (1.1)	2 (0.7)
Other ethnicity	2 (0.4)	1 (0.4)	1 (0.4)
Missing	2 (0.4)	2 (0.7)	0 (0.0)
Living with:			
Alone	89 (16.4)	53 (19.3)	36 (13.3)
Partner	171 (31.4)	80 (29.2)	91 (33.7)
Children including adopted ones	58 (10.7)	33 (12.0)	25 (9.3)
Partner & children	160 (29.4)	78 (28.5)	82 (30.4)
Other family member	45 (8.3)	20 (7.3)	25 (9.3)
Non-family member	15 (2.8)	9 (3.3)	6 (2.2)
Missing	6 (1.1)	1 (0.4)	5 (1.9)
Dependents:			
None	349 (64.2)	179 (65.3)	170 (63.0)
Children aged ≤16	153 (28.1)	75 (27.4)	78 (28.9)
An adult reliant upon you for any support	36 (6.6)	17 (6.2)	19 (7.0)
Missing	6 (1.1)	3 (1.1)	3 (1.1)
Highest level of qualification			
No qualifications	12 (2.2)	5 (1.8)	7 (2.6)
1-4 GCSEs or equivalent	39 (7.2)	16 (5.8)	23 (8.5)
5+ GCSEs or equivalent	50 (9.2)	30 (11.0)	20 (7.4)
Apprenticeship	4 (0.7)	2 (0.7)	2 (0.7)
2+ A-levels or equivalent	73 (13.4)	31 (11.3)	42 (15.6)
Degree level or above	343 (63.1)	182 (66.4)	161 (59.6)
Other qualifications	17 (3.1)	7 (2.6)	10 (3.7)
Missing	6 (1.1)	1 (0.4)	5 (1.9)
Employment status:			

In full time education	28 (5.2)	13 (4.7)	15 (5.6)
In part time education	7 (1.3)	6 (2.2)	1 (0.4)
House person	13 (2.4)	8 (2.9)	5 (1.9)
Employed (full time)	230 (42.3)	121 (44.2)	109 (40.4)
Employed (part time)	121 (22.2)	54 (19.7)	67 (24.8)
Unemployed	58 (10.7)	28 (10.2)	30 (11.1)
Retired	82 (15.1)	42 (15.3)	40 (14.8)
Missing	5 (0.9)	2 (0.7)	3 (1.1)
In the past 3 months, use of any community-based health and social care services			
Yes	111 (20.4)	54 (19.7)	57 (21.1)
No	425 (78.1)	217 (79.2)	208 (77.0)
Missing	8 (1.5)	3 (1.1)	5 (1.9)
In the past 3 months, use of any community-based mental health services			
Yes	64 (11.8)	34 (12.4)	30 (11.1)
No	470 (86.4)	234 (85.4)	236 (87.4)
Missing	10 (1.8)	6 (2.2)	4 (1.5)
Positive Covid test:			
Yes	479 (88.1)	247 (90.1)	232 (85.9)
No	65 (12.0)	27 (9.9)	38 (14.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Number of Long Covid symptoms			
Median (IQR)	12 (9-14)	12 (9-14)	12 (10-14)
Range	1-18	1-18	1-18
Missing	0 (0.0)	0 (0.0)	0 (0.0)

* Self-identified gender categories were woman, man, transwoman, non-binary/genderqueer/agender/gender fluid, prefer not to say or other.
** Self-identified gender was missing for 1 participant and replaced with their sex at birth.

Table 2: Implementation outcomes completed by trial participants.

Implementation Measure	Median (IQR)
Acceptability of Intervention Measure (AIM) Score	17 (16-20)
The Intervention Appropriateness Measure (IAM) Score	16 (16-20)
Feasibility of Intervention Measure (FIM) Score	16 (16-19)

Table 3: Summary of LISTEN intervention adherence.

	Number of sessions	Number (%) of intervention group participants (total n=270)
Full adherence (n=212)	6	183* (67.8%)
	5	9 (3.3%)
	4	13 (4.8%)
	3	7 (2.6%)
Partial or no adherence (n=58)	2	14 (5.2%)
	1	11 (4.1%)
	0	33 (12.2%)

*One participant received a repeated 1st session due to a change in practitioner.

Table 4: Description of the outcomes and their comparison between the study arms at 3 months follow-up

	Baseline (N=544) Mean (SD)		Follow-up (N=410) Mean (SD)		Adjusted effect estimate β (95% CI)	p-value
Outcomes	**Usual Care Arm (n=274)**	**LISTEN Intervention Arm (n=270)**	**Usual Care Arm (n=200)**	**LISTEN Intervention Arm (n=210)**		
Primary outcome: Ox-PAQ Routine Activities domain score (range 0-100)	55.8 (23.0)	56.7 (22.5)	51.8 (26.4)	49.8 (24.3)	-2.68 (-5.38, 0.02) [a] -2.90 (-5.66, -0.15) [b]	0.052 **0.039**
Missing n (%)	4 (1.5)	2 (0.7)	1 (0.5)	2 (1.0)		
Secondary outcomes						
Ox-PAQ Emotional Wellbeing domain score (range 0-100)	58.5 (21.3)	60.6 (21.6)	54.7 (25.7)	50.6 (22.4)	-5.29 (-8.37, -2.20) [a] -5.89 (-8.99, -2.79) [b]	**0.001** **<0.001**
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Ox-PAQ Social Engagement domain score (range 0-100)	50.1 (24.8)	51.5 (26.2)	48.7 (26.5)	47.0 (26.0)	-2.07 (-5.36, 1.22) [a] -2.81 (-6.19, 0.57) [b]	0.218 0.103
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
FIS scores:						
Cognitive dimension (range 0-40)	22.8 (9.8)	23.2 (9.7)	21.6 (10.7)	19.9 (10.4)	-2.11 (-3.29, -0.92) [a] -2.34 (-3.56, -1.12) [b]	**0.001** **<0.001**
Physical dimension (range 0-40)	25.4 (9.0)	26.3 (8.6)	23.1 (10.1)	22.7 (9.5)	-1.53 (-2.63, -0.42) [a] -1.80 (-2.93, -0.67) [b]	**0.007** **0.002**
Social dimension (range 0-80)	41.2 (18.7)	43.2 (19.1)	39.2 (20.9)	36.5 (19.8)	-4.22 (-6.35, -2.09) [a] -4.63 (-6.81, -2.45) [b]	**<0.001** **<0.001**
Overall score (range 0-160)	89.3 (35.1)	92.7 (35.3)	83.9 (39.6)	79.1 (37.9)	-7.93 (-11.97, -3.88) [a] -8.65 (-12.79, -4.52) [b]	**<0.001** **<0.001**
Missing n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
EQ-5D-5L scores:						
Index score (range: 0-1)	0.52 (0.25)	0.49 (0.28)	0.53 (0.30)	0.53 (0.28)	0.03 (-0.01, 0.06) [a] 0.04 (0.00, 0.07) [b]	0.137 **0.046**
Missing n (%)	5 (1.8)	6 (2.2)	6 (3.0)	5 (2.4)		
VAS score (range: 0-100)	45.7 (20.9)	44.9 (20.8)	48.4 (23.7)	49.7 (21.6)	1.08 (-2.41, 4.56) [a] 2.72 (-0.80, 6.24) [b]	0.545 0.130
Missing n (%)	8 (2.9)	5 (1.8)	10 (5.0)	4 (1.9)		
GSES scores:						
Original 10 items scale (range 10-40)	26.9 (5.8)	26.3 (5.9)	26.5 (6.5)	27.5 (6.3)	1.25 (0.39, 2.11) [a] 1.42 (0.54, 2.30) [b]	**0.005** **0.002**
Covid 4 items scale (range 4-16)	9.7 (2.5)	9.3 (2.5)	9.7 (2.7)	10.8 (2.7)	1.31 (0.87, 1.75) [a] 1.38 (0.93, 1.82) [b]	**<0.001** **<0.001**
Original scale with Covid 4 items overall score (range: 14-56)	36.6 (7.5)	35.6 (7.6)	36.2 (8.5)	38.4 (8.2)	2.63 (1.50, 3.75) [a] 2.79 (1.66, 3.93) [b]	**<0.001** **<0.001**

Missing n (%)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)		
SF-12 scores:						
Physical health (range: 0-100)	32.3 (9.6)	31.9 (8.9)	33.1 (10.6)	32.8 (9.7)	0.32 (-0.93, 1.57) [a] 0.48 (-0.74, 1.71) [b]	0.612 0.440
Mental health (range: 0-100)	37.7 (10.8)	36.1 (10.2)	39.0 (11.2)	40.0 (10.6)	2.36 (0.77, 3.96) [a] 2.85 (1.23, 4.46) [b]	**0.004** **0.001**
Missing n (%)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)		

β: Regression coefficients (estimated difference of mean outcome scores at 3 months follow-up between the study arms) adjusted for baseline outcome scores ≈ (difference of mean outcome scores change in the study arms from baseline to 3 months follow-up)
(95% CIs): 95% confidence intervals
Ox-PAQ: Oxford Participation and Activities Questionnaire
SF-12: Short Form-12 items version 1
FIS: Fatigue Impact Scale
EQ-5D-5L: EuroQol Group health related quality of life questionnaire
VAS: Visual Analogue Scale
GSES: Generalised Self-Efficacy Scale
[a] Effect estimates, 95% CIs and p-values from linear mixed-effects models with the outcome scores at 3 months follow-up as dependent variable and study arm as independent variable, adjusted for the random effect of site and fixed effect of baseline outcome scores.
[b] In the models described in [a], effect estimates are further adjusted for the fixed effects of age, gender, ethnicity, employment status and the number of Long Covid symptoms at baseline. These additional covariate adjustments were pre-specified in the statistical analysis plan.

Author Contributorship Statement. MB, FJ and PP conceived the trial. MB, FJ, PP, RL, AE, AS, NS, JM, JF, MDA, BS are grant holders and contributed to the trial protocol. All authors had shared responsibility for trial delivery, interpretation of results and critically reviewing manuscript with specific focus on clinical trial methodology (MB, RL, PP, AE); intervention implementation and process evaluation and support for intervention delivery staff at site (FJ, FL, JF, AS, NS); statistics (PP, MR); health economics (BS, SH), trial and data management (CP, FL, AL) and public involvement (MDA, FJ, FL). MB wrote the initial draft of the manuscript supported by FJ, FL, CP, BS and PP. MB is the guarantor. All authors read, revised, and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Non-Author Contributor Statement. We are grateful for the contributions of the LISTEN Public and Patient Involvement and Engagement group comprising seven people (Anne Domeney, Ian Patel Carol Rowe, Judith Parsons, Rebecca Beltran, Elizabeth Treadwell, Maria Ines de Sousa de Abreu) with Long Covid who supported co-design, communications, trial recruitment and dissemination activities. We also acknowledge the input of staff at the Centre for Trials Research, Cardiff University (Penelope Farthing, Mandy Iles, Ffion Davies, Nicola Ivins, Calie Demougin, Christie Barlow) who supported the LISTEN trial across their respective remits of study administration, data collection and management, support for site staff in trial processes and intervention delivery. We are also grateful to our site Principal Investigators (Rachel Wallbank, Judith Hall, Jacky Jones, Leanne Durdle, Nick Wooding, Cheryl Finch, Laura Jenions, Thomas Williamson, Roisin Hyde, Constance Kendall, Jennifer Birch and Joshua Blake) for their commitment to the trial and its delivery.

Funding: This work is independent research funded by the National Institute for Health and Care Research (NIHR) [Long Covid Personalised Self-managemenT support- co-design and EvaluatioN (LISTEN), COV-LT2-0009]. The views expressed in this publication are those of the author(s) and not necessarily those of NIHR or The Department of Health and Social Care.
All researchers can confirm their independence from funders, and all authors, external and internal, had full access to all the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any commercial organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

Authors are chief investigators or co-investigators on various current research grants from the UK National Institute for Health and Care Research. The Centre for Trials Research receives infrastructure funding from Health and Care Research Wales. PRIME Centre Wales and the former Wales Covid-19 Evidence Centre (now Health & Care Research Wales Evidence Centre) receive infrastructure funding from Health and Care Research Wales. Up until March 2024 FJ's research was supported by the NIHR Applied Research Collaboration South London at King's College Hospital NHS Foundation Trust. MB was a member of the NIHR Health Technology Assessment Commissioned Funding Committee from 2020 to 2023 and is a current member of the NIHR Advanced Fellowship panel and MRC Clinical Fellowship Panel. PP is a current member of the MRC and NIHR Efficacy and Mechanism Evaluation Funding Committee.

FJ is the founder and CEO of Bridges Self-Management, a nonprofit social enterprise that was involved in the co-design of the LISTEN intervention and training of LISTEN intervention

practitioners. MB is recently appointed (25.04.24) as a non-executive board member of Bridges Self-Management. NS is Chief Editor, Frontiers in Health Services, Implementation Science Section.

Data sharing: Data are available on reasonable request from: ctrdatasamplerequests@cardiff.ac.uk. CTR is a signatory of AllTrials and aims to make its research data available wherever possible. Data requests undergo a review process to ensure that the proposal complies with patient confidentiality, regulatory and ethical approvals and any terms and conditions associated with the data.

Dissemination: We have delivered an extensive communication and engagement plan including publication of the trial and co-design protocols and a qualitative publication and intervention development publication co-written with PPIE colleagues. We have hosted three online knowledge exchange events attended by more than 300 people with Long Covid, NHS healthcare practitioners and academics. Summaries from the knowledge exchange webinars have been sent to more than 800 registrants. Several more publications are in review or being prepared for submission.

Ethical approval: This study was approved on 13th December 2021 by the Research Ethics Committee (REC) For Wales (Wales REC 7), recognised by the United Kingdom Ethics Committee Authority (UKECA), REC reference: 21/WA/0368. All participants provided informed consent to participate in this trial.

References.

1. Shah W, Hillman T, Playford ED, et al. Managing the long-term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ 2021;372: n136 http://dx.doi.org/10.1136/bmj.n136
2. NICE guideline [NG188]. COVID-19 rapid guideline: managing the long-term effects of COVID-19 [NG188]. Published: 18 December 2020 Last updated: 25 January 2024. www.nice.org.uk/guidance/ng188 (accessed 12.06.2024).
3. World Health Organisation. Post COVID-19 condition (Long COVID), 2022. https://www.who.int/europe/news-room/fact-sheets/item/post-COVID-19-condition (accessed 12.06.2024).
4. Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. Nature Reviews Microbiology 2023;21(3):133-46. doi: 10.1038/s41579-022-00846-2
5. Callard F, Perego E. How and why patients made Long Covid. Social Science & Medicine 2021; 268:113426. https://doi.org/10.1016/j.socscimed.2020.113426.
6. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 30 March 2023 https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/30march2023 (accessed 12.06.2024).
7. Alexandri E, Brooke A, Thoung C, et al. The economic burden of long COVID in the UK. Cambridge Econometrics. 2024. https://www.camecon.com/wp-content/uploads/2024/03/The-Economic-Burden-of-Long-Covid-in-the-UK_Cambridge-Econometrics_March2024.pdf (accessed 12.04.2024).
8. Byrne EA. Understanding Long Covid: Nosology, social attitudes and stigma. Brain, Behavior, and Immunity 2022;99:17-24.
9. Lancet Editorial. Facing up to long COVID. The Lancet;396(10266):1861. doi: https://doi.org/10.1016/S0140-6736(20)32662-3
10. Potter C, Leggat F, Lowe R, et al. Effectiveness and cost-effectiveness of a personalised self-management intervention for living with long COVID: protocol for the LISTEN randomised controlled trial. Trials 2023;24(1):75.
11. Lohse KR, Lang CE, Boyd LA. Is more better? Using metadata to explore dose–response relationships in stroke rehabilitation. Stroke 2014;45(7):2053-58.
12. Fu V, Weatherall M, McPherson K, et al. Taking Charge after Stroke: A randomized controlled trial of a person-centered, self-directed rehabilitation intervention. International Journal of Stroke. 2020;15(9):954-964. doi:10.1177/1747493020915144.
13. National Health Service (NHS). Your Covid Recovery. https://www.england.nhs.uk/2020/07/nhs-to-launch-ground-breaking-online-covid-19-rehab-service/(accessed 12.06.2024).
14. van Hooft SM, Been-Dahmen JM, Ista E, et al. A realist review: What do nurse-led self-management interventions achieve for outpatients with a chronic condition? Journal of Advanced Nursing 2017;73(6):1255-71.
15. de Silva D. Evidence: helping people help themselves. Health Foundation. 2011 (accessed 12.06.2024). https://www.health.org.uk/publications/evidence-helping-people-help-themselves
16. Ladds E, Rushforth A, Wieringa S, et al. Developing services for long COVID: lessons from a study of wounded healers. Clinical Medicine 2021;21(1):59-65. doi: 10.7861/clinmed.2020-0962.
17. World Physiotherapy. World Physiotherapy Response to COVID-19 Briefing Paper 9. Safe rehabilitation approaches for people living with Long COVID: physical activity and exercise. 2021. https://world.physio/sites/default/files/2021-06/Briefing-Paper-9-Long-Covid-FINAL-2021.pdf. (accessed 12.06.2024).
18. Austin J, Van Dijk J, Drossaert C. When theory meets users in co-design: four strategies towards synergy between bottom-up and top-down input in Boess, S., Cheung, M. and Cain, R. (eds.), Synergy DRS International Conference 2020, 11-14 August, Held online. https://doi.org/10.21606/drs.2020.152 (accessed 12.06.2024).

19. Jones F, Domeny A, Fish J, et al. Using co-design methods to develop new personalised support for people living with Long Covid: the 'LISTEN'intervention. Health Expectations. 2024;27: e14093. https://doi.org/10.1111/hex.14093.
20. Public Health England. Disparities in the risk and outcomes of COVID-19. PHE publications 2020 PHE publications gateway number: GW-1447. https://assets.publishing.service.gov.uk/media/5f328354d3bf7f1b12a7023a/Disparities_in_the_risk_and_outcomes_of_COVID_August_2020_update.pdf (accessed 12.06.2024).
21. Jones F, Poestges H, Brimicombe L. Building Bridges between healthcare professionals, patients and families: A coproduced and integrated approach to self-management support in stroke. NeuroRehabilitation 2016;39(4):471-80.
22. Jones F, Gage H, Drummond A, et al. Feasibility study of an integrated stroke self-management programme: a cluster-randomised controlled trial. BMJ open 2016;6(1): e008900.
23. Kulnik ST, Poestges H, Brimicombe L, et al. Implementing an interprofessional model of self-management support across a community workforce: a mixed-methods evaluation study. Journal of interprofessional care 2017;31(1):75-84.
24. Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for reporting outcomes in trial protocols: the SPIRIT-outcomes 2022 extension. JAMA 2022;328(23):2345-56.
25. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine 2013;158(3):200-07.
26. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. BMJ 2017;358
27. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. E Clinical Medicine 2021;38
28. Heaton-Shrestha C, Torrens-Burton A, Leggat F, et al. Co-designing personalised self-management support for people living with long Covid: the LISTEN protocol. PloS One 2022;17(10): e0274469.
29. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348
30. Bandura A. Self-efficacy: The exercise of control. New York: WH Freeman and Company, 1997.
31. Hancock NJ, Houghton J, Jones F. Integrating an approach to personalised self-management support in stroke and neurorehabilitation service contexts: People1st–a quality improvement initiative. Disability and Rehabilitation 2023;45(19):3034-45.
32. Sunkersing D, Ramasawmy M, Alwan NA, et al. What is current care for people with Long COVID in England? A qualitative interview study. BMJ open 2024;14(5):e080967.
33. Greenhalgh T, Darbyshire JL, Lee C, et al. What is quality in long covid care? Lessons from a national quality improvement collaborative and multi-site ethnography. BMC medicine 2024;22(1):159.
34. Greenhalgh T, Sivan M, Perlowski A, et al. Long COVID: a clinical update. The Lancet 2024;404(10453):707-24.
35. NHS England. Commissioning guidance for post-COVID services for adults, children and young people, 2023. https://www.england.nhs.uk/publication/national-commissioning-guidance-for-post-covid-services/ (accessed 25.08.2024).
36. Morley D, Dummett S, Kelly L, et al. Validation of the Oxford participation and activities questionnaire. Patient Related Outcome Measures 2016:73-80.
37. Jenkinson C, Layte R, Jenkinson D, et al. A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? Journal of Public Health 1997;19(2):179-86.
38. Frith J, Newton J. Fatigue impact scale. Occupational medicine 2010;60(2):159-59.
39. Schwarzer R, Jerusalem M. Generalized self-efficacy scale. J Weinman, S Wright, & M Johnston, Measures in health psychology: A user's portfolio Causal and control beliefs 1995;35(37):82-003.
40. Hegde S, Sreeram S, Bhat KR, et al. Evaluation of post-COVID health status using the EuroQol-5D-5L scale. Pathogens and Global Health 2022;116(8):498-508.

41. Weiner BJ, Lewis CC, Stanick C, et al. Psychometric assessment of three newly developed implementation outcome measures. Implementation Science 2017;12(1) doi: 10.1186/s13012-017-0635-3.
42. Morley D, Dummett S, Kelly L, et al. Measuring improvement in health-status with the Oxford Participation and Activities Questionnaire (Ox-PAQ). Patient Related Outcome Measures 2019:153-56.
43. Candlish J, Teare MD, Dimairo M, et al. Appropriate statistical methods for analysing partially nested randomised controlled trials with continuous outcomes: a simulation study. BMC medical research methodology 2018; 18:1-17.
44. Flight L, Allison A, Dimairo M, et al. Recommendations for the analysis of individually randomised controlled trials with clustering in one arm–a case of continuous outcomes. BMC Medical Research Methodology 2016; 16:1-13.
45. Moerbeek M, Wong WK. Sample size formulae for trials comparing group and individual treatments in a multilevel model. Statistics in medicine 2008;27(15):2850-64.
46. Kleinman K SA, Mojer J, et al. . clusterPower: Power calculations for cluster-randomized and cluster-randomized crossover trials. R package version 0.7.0. 2021.
47. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics 2009;42(2):377-81.
48. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. Journal of biomedical informatics 2019; 95:103208.
49. Fawzy NA, Abou Shaar B, Taha RM, et al. A systematic review of trials currently investigating therapeutic modalities for post-acute COVID-19 syndrome and registered on WHO International Clinical Trials Platform. Clinical Microbiology and Infection 2023;29(5):570-77.
50. Ennis S, Heine P, Sandhu H, et al. Development of an online intervention for the Rehabilitation Exercise and psycholoGical support After covid-19 InfectioN (REGAIN) trial. NIHR open research 2023;3
51. McGregor G, Sandhu H, Bruce 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;384
52. Brown K, Yahyouche A, Haroon S, et al. Long COVID and self-management. Lancet (London, England) 2022;399(10322):355.
53. Leggat FJ, Heaton-Shrestha C, Fish J, et al. An exploration of the experiences and self-generated strategies used when navigating everyday life with Long Covid. BMC Public Health 2024;24(1):789.
54. Haroon S, Nirantharakumar K, Hughes SE, et al. Therapies for Long COVID in non-hospitalised individuals: from symptoms, patient-reported outcomes and immunology to targeted therapies (The TLC Study). BMJ open 2022;12(4): e060413.
55. Hughes SE, Haroon S, Subramanian A, et al. Development and validation of the symptom burden questionnaire for long covid (SBQ-LC): Rasch analysis. BMJ 2022;377
56. Rybkina J, Jacob N, Colella B, et al. Self-managing symptoms of Long COVID: an education and strategies research protocol. Frontiers in Public Health 2024; 12:1106578.
57. Gorst SL, Seylanova N, Dodd SR, et al. Core outcome measurement instruments for use in clinical and research settings for adults with post-COVID-19 condition: an international Delphi consensus study. The Lancet Respiratory Medicine 2023;11(12):1101-14.