REHABILITATION EXERCISE AND PSYCHOLOGICAL SUPPORT AFTER COVID-19 INFECTION

Statistical Analysis Plan

Version 2.0

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APPROVAL

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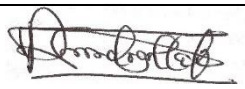
	Signature: 	Date: 03/11/2022

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Abbreviations

Abbreviation	Explanation
AE	Adverse Event
CI	Confidence Interval
COM-B	Capability, Opportunity and Motivation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CRF	Case report form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
IES-6	Impact of Event Scale – 6
IES-R	Impact of Event Scale – Revised
IPAQ-SF	International Physical Activity Questionnaire short form
IQR	Interquartile range
ITT	Intention-to-treat
MET	Metabolic equivalent task
MI	Multiple Imputation
NIH	National Institute for Health
PIS	Patient Information Sheet
PP	Per protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Post-traumatic stress disorder
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
TBC	To be confirmed
USA	United States of America
WCTU	Warwick Clinical Trials Unit

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Roles and responsibilities

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Role: To develop the statistical analysis plan and conduct the final analysis.

Data Monitoring Committee (DMC)

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1 INTRODUCTION

This document details the proposed presentation and analysis for the main results from the multi-centre randomised controlled trial REGAIN (ISRCTN 11466448) which aims to investigate the clinical and cost-effectiveness of an intensive, on-line, supervised, group, home-based rehabilitation programme (REGAIN) vs best practice usual care, to support the long-term physical and mental health recovery of people discharged from hospital (more than three months) after COVID-19 infection.

The results reported in the funder report and main paper(s) will follow the strategy set out here. Any subsequent analysis of a more exploratory nature will not be bound by this strategy and will be detailed in a separate statistical analysis plan (SAP). Suggestions for subsequent analyses by oversight committees, journal editors or referees, will be considered carefully in line with the principles of this analysis plan.

Any deviations from the final, approved SAP will be described and justified in the final report to the funder. The statistical analysis will be carried out by an identified, appropriately qualified and experienced medical statistician, who will ensure the integrity of the data during their processing.

2 BACKGROUND INFORMATION

2.1 Rationale for trial

Early data from COVID-19 survivors shows that a proportion of people experience persistent cognitive impairment, and pulmonary hypertension in those with thromboembolic problems [1]. For the 45% of people hospitalised with COVID-19 in the UK who are estimated to require prolonged support from health and social care [2], a multitude of physical, psychological and social needs have been identified [1]. For hospitalised patients, long-term physical and psychological consequences are also prominent [3]. A further feature is the disproportionate infection rate and progression to severe illness in Black, Asian and minority ethnic groups [4]. We have no data on whether ethnicity affects the prevalence or pattern of long-term sequelae from COVID-19.

To tackle the multiple long-term physical and mental health consequences of COVID-19, it is clear that a complex, multi-disciplinary, physical and psychological rehabilitation intervention should be tested. Importantly, this must be delivered at the appropriate point in the recovery timeline. It must also be cost-effective and deliverable at scale whilst adhering to continued general population infection control measures. Further, it must address ethnic and cultural health inequalities.

Please refer to latest version of the protocol: presently 7.0, 18 January 2022.

2.2 Objectives of the trial

2.2.1 *Primary objective*

The primary objective of this study is to determine whether the online, supervised, group REGAIN rehabilitation intervention improves health-related quality of life (HRQoL) at three months post-randomisation compared to best-practice usual care in patients with ongoing COVID-19 symptoms.

2.2.2 *Secondary objectives*

Secondary objectives of the study are to determine if the REGAIN intervention compared to best-practice usual care in patients with ongoing COVID-19 symptoms impacts on the following outcomes over 12 months. Outcomes listed below are measured at three, six and 12 months:

1. HRQoL (**primary at three months)**
2. Dyspnoea
3. Cognitive function
4. Health utility
5. Physical activity
6. PTSD symptom severity
7. Depressive and anxiety symptoms
8. Work status
9. Health and social care resource use
10. General health
11. All-cause mortality.

2.3 Trial design

REGAIN is a multi-centre, randomised controlled trial (RCT) testing the clinical and cost-effectiveness of the REGAIN intervention vs. best practice usual care. The trial design includes:

1. An intervention development phase, to confirm feasibility, refine online intervention delivery and manualised practitioner training, and prepare study set-up.
2. An internal pilot phase, with formative process evaluation, to test recruitment and study procedures.
3. A main trial with embedded process evaluation.

2.4 Eligibility

2.4.1 *Inclusion criteria*

1) UK resident;
2) Aged ≥18 years;
3) ≥ 3 months after any hospital discharge related to COVID-19 infection, regardless of need for critical care or ventilatory support;
4) Substantial, as defined by the participant, COVID-19 related physical and/or mental health problems;
5) Access to, and ability/support to use, email, text message, internet video, including webcam and audio;
6) Ability to provide informed consent;

7) Able to understand spoken and written English, Bengali, Gujarati, Urdu, Punjabi, or Mandarin themselves or with support from family/friends.

2.4.2 *Exclusion criteria*

1) Exercise contraindicated*
2) Severe mental health problems preventing engagement**
3) Previous randomisation in the present study
4) Patient already engaging in, or planning to engage in a conflicting NHS delivered rehabilitation programme in the next 12 weeks
5) A member of the same household has previously been randomised in the present study

* As advised by a clinical member of the research team or REGAIN practitioner
** As judged by a clinical member of the research team or the REGAIN practitioner

2.5 Interventions

Patients are randomised into one of two groups: the REGAIN Intervention or best practice usual care.

2.5.1 *Study Interventions*

The REGAIN intervention has three components:

1. **Individual assessment:** up to one-hour, on-line, one-to-one assessment with a REGAIN practitioner (Clinical Exercise Physiologist/Physiotherapist), trained and supported by a health psychologist, to holistically assess participant needs, introduce the programme, and provide individualised exercise advice. All participants are directed to freely available on-line programmes published by NHS England (https://www.yourcovidrecovery.nhs.uk/).

   Participants with case level mental health disorders (depression/anxiety/PTSD), as identified from baseline questionnaires (IES-6 score ≥11; HADS Anxiety score ≥11; HADS Depression score ≥11), will be directed to their GP for treatment/advice. These symptomatic participants will continue in the study intervention as long as the practitioner considers their mental health problems would not preclude engagement.

2. **On-line, home-based, exercise rehabilitation:** Up to 30 minutes exercise two to three times per week for eight weeks; individualised and progressive multi-modality exercise at a manageable intensity (regulated with breathlessness and perceived exertion scales).

   Participants are encouraged to attend one live on-line group exercise session every week for eight weeks led by a REGAIN practitioner, using equipment-free exercise to improve cardiovascular fitness, strength, balance, and co-ordination. These sessions are

undertaken in discrete groups. Participants remain in the same group for the 8-week programme. If requested, some groups can be single sex.

For the remaining 1-2 exercise sessions per week, participants are encouraged to access online, pre-recorded video sessions, graded by ability and exercise modality.

3. **Psychological support:** Over the eight-week intervention period, participants attend six on-line group sessions each lasting for up to one hour, led by a trained REGAIN practitioner supported by a health psychologist.

Best practice usual care

A thirty-minute, on-line, one-to-one consultation with a REGAIN practitioner, trained and supported by a health psychologist. All study participants, in both intervention arms, are directed to freely available on-line programmes published by NHS England (https://www.yourcovidrecovery.nhs.uk/).

2.6 Definitions of primary and secondary outcomes

2.6.1 *Primary outcome*

Health-related quality of life measured using the PROMIS® 29+2 Profile v2.1 (PROPr) at three months post-randomisation. This measure is part of a portfolio of outcomes developed and validated by the National Institute for Health (NIH) (USA); the Patient-Reported Outcomes Measurement Information System. It is a reliable generic outcome measure validated for on-line use [6-8] generating a single overall score (from -0.2 to 1) plus physical function, anxiety, depression, fatigue, sleep disturbance, social roles/activities, pain interference, cognitive function and pain intensity sub-scales. A higher score indicates better quality of life.

Justification for timing of primary outcome

Long-term outcomes are important, however, any intervention effects will be maximal soon after completion of the intervention. We have set our short-term follow-up at three months as we are confident that those randomised to the REGAIN intervention will complete the eight-week treatment phase in this time period. If there is no evidence of effect at three months, then a meaningful effect at one year is unlikely. Assessing the primary outcome at three months after randomisation is more efficient than seeking an effect at one year, as attrition is likely to be lower.

2.6.2 *Secondary clinical outcomes*

The following outcomes will be measured at 3, 6 and 12 months post-randomisation.

1. HRQoL: PROMIS® 29+2 Profile v2.1 (PROPr) at 6 and 12 months post randomisation. This form includes all 29 items from PROMIS® 29 Profile v2.1, plus two Cognitive Function abilities items. The 29 items from PROMIS® 29 Profile v2.1 are from the following forms;

Items	Number of items
PROMIS SF v2.0 Physical Function	4
PROMIS SF v1.0 Anxiety	4
PROMIS SF v1.0 Depression	4
PROMIS SF v1.0 Fatigue	4
PROMIS SF v1.0 Sleep Disturbance	4
PROMIS SF v1.0 Ability to Participate in Social Roles and Activities	4
PROMIS SF v1.0 Pain Interference	4
Cognitive Function SF v2.0	2
PROMIS SF Pain Intensity	1

A single overall preference score ranging from -0.2 to 1 (perfect or ideal health) is generated using sub-scores from the multiple forms. Zero indicates as state equal to death and a negative value indicates worse than death. This outcome will be scored anonymously using the HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice), as recommended by the PROMIS Adult Profile Scoring Manual.

2. Dyspnoea: PROMIS dyspnoea severity Short Form. Exertional dyspnoea is a commonly reported symptom in COVID-19 survivors, thus specific questions have been added [9]. The dyspnoea short form includes 10 questions, with each response ranging from 0 to 3, giving a total raw score ranging from 0 to 30 (higher scores indicate worse severity). This measure will be scored using the HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice).

3. Cognitive function: Neuro-QoL Short Form v2.0 - Cognitive Function [13]. Given the high incidence of cognitive impairment in COVID-19 survivors we have added additional PROMIS questions, to obtain a measure of cognitive function. The Cognitive function short form has 8 items, with total raw scores ranging from 8 to 40 (higher scores indicate better cognitive function). This measure will be scored using the HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice).

4. Health utility: Euroqol EQ-5D-5L [10]. Validated, generic HRQoL measure consisting of five dimensions, each with five levels. Each combination of answers can be converted into a health utility score. It has good test-retest reliability, is simple to use, and gives a single preference-based index value for health status that can be used for cost-effectiveness analysis. A statement by NICE highlighted serious concerns regarding the EQ-5D-5L tariffs published by Devlin et al [11]. For that reason, the crosswalk value set will be used to map from the EQ-5D-5L to EQ-5D-3L using previously used and more reliable tariff values. The EQ-5D score ranges from <0-1 where a higher score reflects better quality of life.

5. International Physical Activity Questionnaire (IPAQ short-form). The IPAQ is a well-established activity measure reported as metabolic equivalent task (MET)-minutes per week derived from duration of walking, moderate and vigorous exercise [12] The questionnaire will be scored using the IPAQ Scoring protocol (https://sites.google.com/site/theipaq/scoring-protocol).

6. PTSD symptom severity: The Impacts of Events Scale-Revised (IES-R) a 22 item self-report measure of difficulties people sometimes face after stressful life events. It has been widely used in studies of survivors of ICU admission, including COVID admissions. It is part of recommended outcomes for studies of respiratory failure survivors [13-15]. The IES-R is scored by summing the response to each of the 22 questions, which each range from 0 (not at all) to 4 (extremely), making a total score range of 0-88. A score of ≥11 on the IES-6, an abbreviated version extracted from the longer 22-item IES-R, will be taken to be indicative of case level disorder.

7. Depressive and anxiety symptoms: Hospital Anxiety and Depression Scale (HADS). A 14-item questionnaire from which anxiety and depression subscales can be derived. 7 item sub-score values ≥11 points identify case-level anxiety/depression. The HADs is widely used and a well validated measure in clinical populations [16]. The scores are simply summated to give an anxiety and depression score both ranging from 0-21 where a higher score reflects more severe symptoms of anxiety and depression.

8. Death measured using GP record. Data will be requested from general practices on completion of the trial.

Timing and format of data collection

Patient reported outcomes are collected online at baseline pre-randomisation, and at three months, six months and 12 months post-randomisation. Participants receive an email notification and/or text message to remind them to complete the online questionnaires at each follow-up time point. In the case of non-response to text messages, participants are contacted by telephone for collection of two core outcomes: the PROPr (primary outcome) and EQ-5D-5L.

Fluency in English is not an inclusion criterion for this study. For those not fluent in English, we will aim to collect all outcomes (or as many as possible) verbally at each follow-up. As a minimum, a core data outcome set including the PROMIS® 29+2 Profile v2.1 (PROPr) and EQ-5D-5L questionnaires will be collected orally by a bilingual researcher, where necessary, to ensure that those not fluent in English are able to contribute participant reported outcomes to the study. The EQ-5D-5L is well validated for verbal administration.

Long-term follow-up beyond 12 months: Consent will be sought from participants to hold their personal data, and at the end of the 12-month follow-up period, to request a copy of the participant's medical record from their GP. This will only be requested if the participant has not responded to the 12-month follow-up or if we know the participant has died. This will provide information on GP consultations and include copies of any hospital discharge letters allowing us to accurately cost in-patient care costs. Where appropriate, we will triangulate data from GP records and any participant self-report to achieve a robust estimate of health service activity and mortality.

2.6.3 *Symptoms sub-study*

Study sites identifying patients will record information on patient hospital admission data including length of hospital stay and ventilation type. This will be pseudonymised using a screening ID number assigned to each patient by the study site. Any patients approached by a study site will provide their screening ID number and using this screening ID number, for those patients consenting to the study, WCTU will request pseudonymised data for that individual from the study site that approached the participant. Ongoing COVID-19 symptoms will be collected during the initial online eligibility assessment, supplemented by the external clinical expertise from the TSC and DMC. This will allow us to compare selected factors including patient characteristics and COVID-19 admission characteristics, and ongoing COVID-19 symptoms profile of those who take part in the study. Where possible, this sub-study will be undertaken.

2.7 Hypothesis framework

For each of the primary and secondary outcomes, the null hypothesis will be that there is no true difference in treatment effect between the intervention arms.

2.8 Sample size

We had no data on which to base a sample size estimation for the study. There are no normative data for the PROPr quality of life scores in this Covid-19 population and no external indication of what might be a worthwhile benefit from the intervention on quality of life outcomes for this population. American values for the general population in the USA are a mean score of 50 (1-100 scale) with an SD of 10. Whilst not our preferred practice, we have used the approach of looking for a small to moderate standardised mean effect size of 0.3. Allowing for a clustering effect in the intervention arm, we assume that a group size will consist of a maximum of eight participants. Then assuming an intra cluster coefficient (ICC) of 0.01, 90% power and type I error rate of 5%, with a 10% loss to follow-up, we require 535 participants. This equates to 272 participants in the intervention arm across up to 34 intervention groups and 263 participants in the control arm (control:intervention = 1:1.03), using computations recommended by Moerbeek [17].

The sample size was revised as requested by the data monitoring committee (DMC) in the DMC meeting (14 January 2022). However, following this meeting because of the change in recruitment strategy and thus the large recruitment from the NHS Digital mass mailouts there was no need to update the sample size. The recruitment of the trial was completed in few months following the meeting and finally 585 participants were recruited. We overrecruited to compensate the higher lost to follow-up (15%) in the observed data.

2.9 Randomisation

Randomisation is undertaken automatically by the WCTU system following completion of the baseline questionnaire using a computer-generated randomisation sequence, performed by minimisation and stratified by:

1. age (i. <65; ii. ≥65 years),
2. level of hospital care (i. ICU/HDU; ii. ward),
3. case level mental health disorder (i. IES-6 PTSD score ≥11/24 or HADS Anxiety sub-score ≥11/21 or HADS Depression sub-score ≥11/21; ii. IES-6 PTSD score <11/24 and HADS Anxiety sub- score <11/21 and HADS Depression sub- score <11/21).

Participants are randomised strictly sequentially at study level.

2.10 Data collection schedule

All data are entered directly by participants, UHCW staff, REGAIN practitioners or WCTU study team members onto a secure online study database hosted by WCTU as outlined in the data management plan and in accordance with the Warwick SOPs. Data entered onto the online study database are considered source data. This will be stored safely and securely. On all study-specific documents, other than the completed consent form, the participant will be referred to by the study participant number, not by name. Various methods will be used to chase missing data including phone, text and email. The procedures for managing this will be outlined in the data management plan and appropriate consent will be sought to contact participants. Data will still be collected for participants who discontinue or deviate from the intervention protocol, unless they withdraw their consent.

Table 1: Study assessments and data collected at Trial time points

	Pre-randomisation		**Post-randomisation**			
Online assessment	**1**	**2**	**3**	**4**	**5**	**6**
Assessment time point	**Screening**	**Enrolment (Baseline)**	**Intervention Delivery 0- 8 weeks (+/- 2 weeks)**	**3m (± 2w)**	**6 m (± 1 m)**	**12 m (± 1 m)**
Invitation letter and flyer posted	✓					
Initial Eligibility Assessed	✓					
Concomitant Illnesses		✓				
Eligibility check* (telephone)		✓				
Informed consent		✓				

	Pre-randomisation		Post-randomisation			
Online assessment	**1**	**2**	**3**	**4**	**5**	**6**
Assessment time point	**Screening**	**Enrolment (Baseline)**	**Intervention Delivery 0- 8 weeks (+/- 2 weeks)**	**3m (± 2w)**	**6 m (± 1 m)**	**12 m (± 1 m)**
Patient Demographics		✓				
PROMIS® 29+2 Profile v2.1 (PROPr)		✓		✓	✓	✓
PROMIS dyspnoea		✓		✓	✓	✓
PROMIS Neuro-QoL		✓		✓	✓	✓
EQ-5D-5L		✓		✓	✓	✓
IPAQ-SF		✓		✓	✓	✓
IES-R		✓		✓	✓	✓
HADS		✓		✓	✓	✓
Intervention			✓			
Adverse events			✓			
Overall health		✓		✓	✓	✓
Death						✓

* Eligibility check will be performed in person over the telephone by clinical member of the research team at UHCW. All other assessments and information will be completed by the participant online.

For long term follow-up assessments, consent will be sought from participants to keep their personal data. Consent will also be taken to request a copy of the participant's medical record from their GP, should they not respond to the 12-month follow-up questionnaire, or have died at the end of the study follow-up period. This will provide information on GP consultations and include copies of any hospital discharge letters allowing us to accurately cost in-patient care costs. Mortality data will be gathered from GP records at 12 months.

2.11 Data monitoring and interim analysis

All study data will be supplied in strict confidence to the independent DMC for independent assessment and evaluation. The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC meeting frequency will be guided by the DMC chair but will be suggested to be six months into the recruitment phase and regularly thereafter, as directed by the DMC chair. Confidential reports containing recruitment, protocol compliance, safety data and informal interim assessments of outcomes will be

reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated. The membership of the DMC has been approved and appointed by the NIHR.

There are no formal interim analyses for this study.

2.12 Trial reporting

The trial will be reported in line with the CONSORT (Consolidated Standards *o*f *R*eporting *T*rials) statement[18].

3 ANALYSIS

3.1 Subject population

3.1.1 Intention-to-treat

The primary analysis and any secondary analyses will be applied to an all-randomised population on an intention-to-treat (ITT) basis. That is, any subject randomised into the trial, regardless of whether they received trial intervention and regardless of protocol deviations, unless specified.

3.1.2 Missing data

Whilst every effort will be made to ensure complete data collection, it is inevitable that some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. The nature and pattern of the missingness will be carefully considered, including whether data can be treated as missing completely at random. If judged appropriate, missing data will be imputed using the multiple imputation facilities available in statistical analysis software.

If imputation is undertaken, the resulting imputed datasets will be analysed, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variable will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal, or other protocol violations will be stated, and any patterns summarised. If the missing data is considered missing at random or missing completely at random, we will use imputation techniques, such as Multiple Imputation by Chained Equations (MICE), to impute missing data. The number of imputed datasets will be determined by the proportion of missing data. Usually 10-20 datasets would be sufficient for 10-30% missing data [19].

More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

4 DESCRIPTIVE ANALYSES

4.1 Participant throughput

Screening data will be checked to identify any characteristic differences between those individuals in the trial, those ineligibles, and those eligible but withholding consent. A CONSORT chart illustrating participant flow throughout the trial will also be produced which will describe the following: number of participants randomised, allocated to each intervention, delivered and not delivered intervention, lost to follow-up, and included in ITT analysis population at different time points.

4.2 Baseline comparability of randomised groups

Baseline data will be summarised to check comparability between treatment arms. The number and percentage will be presented for categorical variables. The mean and standard deviation or the median and the interquartile range (IQR) will be presented for continuous variables, or the range if appropriate. There will be no tests of statistical significance performed nor confidence intervals calculated for differences between randomised groups on any baseline variable.

4.3 Losses to follow-up

The number and percentage of participants lost to follow-up before 12 months post-randomisation will be reported for each randomised group.

4.4 Adherence to treatment

The number and proportion of patients who did and did not receive the intervention they were allocated to will be reported. Full compliance with the online, exercise and psychological REGAIN intervention will be defined as attending the initial assessment, plus attending four out of six psychological support sessions, AND five out of eight live exercise sessions.

5 COMPARATIVE ANALYSES

All analyses will be conducted as ITT unless otherwise specified.

The screening data collects; Date of admission, Date of discharge and ventilation support (highest level of ventilation support during admission: Invasive ventilation [highest level]/Non-invasive ventilation/CPAP [lowest level]). A CONSORT chart illustrating participant flow throughout the trial will also be produced. Standard statistical summaries will be presented for the primary outcome measure and all secondary outcome measures.

For continuous outcomes, mean treatment difference with 95% confidence interval (CI) will be reported. For categorical outcomes, odds ratio with 95% CI will be reported. Plots will also be produced for the primary outcome and some of the secondary outcomes to check the comparability between treatment arms.

5.1 Primary analysis

5.1.1 *Primary outcome*

The main analyses will be for overall treatment effect. The primary analysis will use a linear regression (heteroscedastic) model to estimate the treatment effects (95% confidence intervals (CI)), adjusted for baseline as well as adjusted for stratification variables, important patient-level covariates and group effect. The reason for using heteroscedastic model is the variance is different between the arms as the control arm is non-clustered and the intervention arm is clustered [20]. In the trial, the control arm receives individual therapy whereas the intervention arm receives group therapies. The groups or therapist effect will be treated here as random effects. If there is negligible group and centre effect, then the usual linear regression will be used for the analysis.

The main analysis will be carried out on the stratification variables such as:

- Age (continuous)
- Level of hospital care (i. ICU/HDU; ii. ward)
- Case level mental health disorder (i. IES-6 PTSD score ≥11/24 or HADS Anxiety sub-score ≥11/21 or HADS Depression sub-score ≥11/21; ii. IES-6 PTSD score <11/24 and HADS Anxiety sub- score <11/21 and HADS Depression sub- score <11/21)

5.2 Secondary analyses

For the primary outcome, we will also use a linear regression (heteroscedastic) to estimate the treatment effect, without adjustment of any covariates but adjusting the therapist random effects.

All secondary continuous outcomes (including the health economic outcomes, EQ-5D-5L index and VAS scores) will be analysed using the linear regression (heteroscedastic) specified in the primary analysis method, with the same adjustment. An unadjusted analysis will also be conducted for each outcome.

We will assess the impact of compliance on outcomes using a CACE (Compliers average causal effect) analysis for the primary outcome. CACE models evaluate the average effect of the intervention in participants who comply with their allocated treatment. This preserves randomisation groups and eliminates introducing any potential confounders introduced by PP analysis.

For categorical outcomes, odds ratio with 95% CI will be reported. We will also plot the data over time, with the mean and confidence intervals, for some of the secondary outcomes such as the International Physical Activity Questionnaire (IPAQ short-form).

5.3 Subgroup analyses

Exploratory subgroup analyses will examine the interaction of treatment assignment with the pre-specified subgroups, including:

1. Age group (<65 vs >=65)
2. Level of hospital care (Critical care vs Ward)

3. Depression (HADS depression score <11 vs >=11)
4. Anxiety (HADS anxiety score <11 vs >=11)
5. PTSD (IES-r <11 vs >=11)
6. Ethnicity (BAME vs non-BAME)
7. Wave of pandemic (1st Wave: March 2020, 2nd Wave: September 2020, 3rd Wave: TBC)
8. Method of recruitment (NHS digital mailouts vs others)

These subgroup analyses will be conducted in the observed dataset on the basis of ITT population. The analyses will use hierarchical linear regression model with adjustment for covariates in the primary analysis. The overall significance of the interaction will be reported. Estimated treatment difference in each subgroup will be reported with mean treatment difference with 95% CI.

5.4 Sensitivity analyses

5.4.1 Additional covariate analysis

The sensitivity analysis on the primary outcome will be carried out on the additional variables such as:

- Sex (Male, Female, Other, Prefer not to say)
- BMI (Continuous)
- Ethnicity (White, Black Caribbean, Black African, Black Other, Indian, Pakistani, Bangladeshi, Chinese, Mixed- White and Black Caribbean, Mixed- White and Black African, Mixed- White and Asian, Prefer not to say, Other)∗

∗ Sex and *Ethnicity categories may be grouped together if numbers are too low*

5.4.2 Imputed analysis

The primary analysis will be replicated to analyse the imputed datasets. if imputation is deemed appropriate. The pooled results will be reported.

5.4.3 CACE analysis

Also, it is likely that non-compliance will occur (i.e. exercise sessions not attended or participant requests for treatment) during the trial. Careful monitoring of non-compliance will be conducted. If large numbers of treatment non-compliance are observed, Complier-Average Causal Effect (CACE) models or other appropriate methods will be used. The CACE analysis will also be replicated using different definitions of compliance.

5.5 Significance levels and adjustments of p-values for multiplicity

Treatment effects will be presented, with appropriate 95% confidence intervals, for both the unadjusted and adjusted analyses. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). All analyses will be conducted as ITT unless otherwise specified. No adjustment of p-values in the analysis as there is no multiple comparison in the analyses.

5.6 Statistical software employed

All analyses will be conducted using Stata/SE version 17 (or later), SAS version 9 (or later), or R version 4 (or later).

6 SAFETY DATA

The frequency and percentage (%) of serious adverse events (SAE) and adverse events (AE) in the trial will be reported by treatment with the following details: the event type, severity assessment, expectedness and relatedness to intervention will also be summarised/analysed by treatment arm.

7 ADDITIONAL EXPLORATORY ANALYSIS

Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be exploratory in nature and will be documented in a separate statistical analysis plan.

8 DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

None yet.

9 REFERENCES

9.1 Trial documents

Dummy tables can be found in the separate document.

9.2 Other references

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