REGAIN
REHABILITATION EXERCISE AND PSYCHOLOGICAL SUPPORT AFTER COVID-19 INFECTION

PROTOCOL

Rehabilitation Exercise and psycholoGical support After covid-19 InfectioN' (REGAIN): a multi-centre randomised controlled trial

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TABLE OF CONTENTS **PAGE**

TABLE OF CONTENTS 7
STUDY SUMMARY 10
LIST OF ABBREVIATIONS/GLOSSARY 12
1. BACKGROUND 14
1.1 Epidemiology and burden of the condition 14
1.2 Existing knowledge 14
1.3 Hypothesis 15
1.4 Need for a study 15
1.5 Ethical considerations 16
1.6 CONSORT 18
1.7 Assessment and management of risk 18
2. STUDY DESIGN 18
2.1 Study summary and flow diagram 18
2.2 Aims and objectives 21
2.2.1 Primary objective 21
2.2.2 Secondary objective 21
2.2.3 Symptoms sub-study objective 21
2.2.4 Process Evaluation objective 21
2.3 Outcome measures 22
2.3.1 Efficacy 22
2.3.2 Symptoms sub-study 23
2.4 Eligibility criteria 24
2.4.1 Inclusion criteria 24
2.4.2 Exclusion criteria 24
2.5 Participant identification / Screening 24
2.6 Eligibility and informed consent 25
2.6.1 Consent for qualitative interviews 26
2.7 Site Staff Training 27
2.8 Randomisation 27
2.8.1 Randomisation 27
2.8.2 Post-randomisation withdrawals and exclusions 28
2.9 Study interventions 28
2.9.1 Study treatment(s) / intervention(s) 28
2.9.2 Compliance 31
2.10 Concomitant illness and medication 32

2.10.1 Concomitant illness 32
2.10.2 Concomitant medication 32
2.11 Co-enrolment into other trials 32
2.12 End of study 32
3. METHODS AND ASSESSMENTS 33
3.1 Schedule of delivery of intervention and data collection 33
3.2 Long term follow-up assessments 34
3.3 Symptoms sub-study 34
3.4 Embedded process evaluation 34
4. ADVERSE EVENT MANAGEMENT 35
4.1 Definitions 35
4.1.1 Adverse Events (AE) 35
4.1.2 Serious Adverse Events (SAEs) 35
4.2 Recording Adverse Events and Reporting Serious Adverse Events 36
4.2.1 Recording and reporting period 36
4.2.2 Recording Adverse Events 36
4.2.3 Reporting Serious Adverse Events 36
4.2.3.1 SAEs that are exempt from reporting 37
4.2.4 Determination of causality and expectedness for SAEs 37
4.2.4.1 Expected Serious Adverse Events 37
4.2.5 Follow-up of reported SAEs 38
4.3 Responsibilities 38
4.4 Notification of deaths 39
4.5 Reporting urgent safety measures 39
5. DATA MANAGEMENT 39
5.1 Data collection and management 40
5.2 Database 40
5.3 Online video platform 41
5.4 One-to-one consultation platform 41
5.5 Data storage 41
5.6 Data access and quality assurance 41
5.7 Data Shared with Third Parties 42
5.8 Archiving 42
6. STATISTICAL ANALYSIS 42
6.1 Power and sample size 42
6.2 Statistical analysis of efficacy and harms 42
6.2.1 Statistics and data analysis 42
6.2.2 Planned recruitment rate 43

6.3 Subgroup analyses 43
6.4 Health economic evaluation 43
6.5 Qualitative data analysis 44
7. STUDY ORGANISATION AND OVERSIGHT 44
7.1 Sponsorship and governance arrangements 44
7.2 Ethical approval 45
7.3 Peer Review 45
7.4 Study Registration 45
7.5 Notification of serious breaches to GCP and/or study protocol 45
7.6 Indemnity 46
7.7 Study timetable and milestones 46
7.8 Administration 46
7.9 Trial Management Group (TMG) 46
7.10 Trial Steering Committee (TSC) 46
7.11 Data Monitoring Committee (DMC) 47
7.12 Essential Documentation 47
7.13 Financial Support 47
8. MONITORING, AUDIT AND INSPECTION 47
9. PATIENT AND PUBLIC INVOLVEMENT (PPI) 48
10. DISSEMINATION AND PUBLICATION 49
11. REFERENCES 50
12. APPENDICES 53
12.1 Appendix 1 - Logic model for the REGAIN psychological intervention. 53

LIST OF TABLES PAGE

Table 1 Study assessments ……..33
Table 2 SAE Causal relationship …….....……..37

LIST OF FIGURES PAGE

Figure 1 Study flow diagram 20

STUDY SUMMARY

Study Title	Rehabilitation Exercise and psycholoGical support After covid-19 InfectioN' (REGAIN): a multi-centre randomised controlled trial
Short study title	REGAIN
Clinical Phase	Phase III
Study Design	Multi-centre randomised controlled trial with embedded process evaluation and health economic evaluation
Study Participants	Adults aged 18 years and older with ongoing COVID-19 sequelae more than three months after hospital discharge
Planned sample size	535 people randomly allocated to receive the REGAIN intervention or control; 1.03: 1 allocation
Treatment Duration	Eight weeks post randomisation
Follow-up Duration	12 months post randomisation
Planned Study Period	01 Nov 2020 to 31 August 2022
Objective	To run a multi-centre RCT testing the clinical and cost-effectiveness of an intensive, on-line, supervised, group, home-based rehabilitation programme to support long-term physical and mental health recovery (REGAIN) vs. best-practice usual care discharged from hospital (>3/12) after COVID-19 infection.
Outcomes Primary Secondary	Assessed at baseline pre-randomisation, three, six and 12 months post-randomisation. Health-related quality of life (HRQoL): PROMIS® 29+2 Profile v2.1 (PROPr) measured at three months post-randomisation 1. HRQoL: PROMIS® 29+2 Profile v2.1 (PROPr) at six and 12 months post randomisation. 2. Dyspnoea: PROMIS dyspnoea severity short form v1.0 3. Cognitive Function: PROMIS Neuro-QoL Short Form v2.0 4. Health Utility: Euroqol (EQ-5D-5L)

	5. Physical activity. International Physical Activity Questionnaire short form (IPAQ-SF) 6. PTSD symptom severity: Impact of Event Scale - Revised (IES-R) 7. Depressive and Anxiety Symptoms: Hospital anxiety and depression scale (HADS) 8. Work Status: Time lost from work (paid/unpaid) and patient-borne health care costs. 9. Health and Social Care resource use: Participant self-report, NHS and GP records 10. General health – Participant self-reported assessment of overall health 11. Death – NHS and GP records	
Sub-studies	Objectives	Outcome Measures
Symptoms Sub Study	To explore the relationship between personal characteristics and in-hospital care, and subsequent ongoing COVID-19 symptoms and other health problems	Ongoing COVID-19 symptoms, Ethnicity, Age, Gender, Duration of hospital stay, Need for high flow oxygen/continuous positive airways pressure/ventilation
Process evaluation Qualitative	To explore and contextualise participant and practitioner experience of the study and intervention delivery, barriers and enablers, to inform interpretation of quantitative data and facilitate wider implementation	Semi-structured interviews with participants and practitioners

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
CACE	Compliers Average Causal Effect
CI	Chief Investigator
CONSORT	*Cons*olidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
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
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
MRC	Medical Research Council
NHS	NHS
NIHR	National Institute for Health Research
ORCHA	Organisation Review of Care and Health Apps (ORCHA)
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient & Public Involvement
PROMIS	PROMIS – add as this is primary outcome
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

UHCW	University Hospitals Coventry and Warwickshire NHS Trust
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

At least 80 thousand people in the UK have been discharged from hospital by the NHS after treatment for COVID-19. Many will return relatively quickly to good health and a normal life [1]. However, a substantial proportion of people will have ongoing health problems. These problems are multi-systemic [2] including motor, cognitive, neurological, musculoskeletal, respiratory and cardiovascular as well as depression, anxiety, and post-traumatic stress disorder (PTSD) [3]. In April 2020, the NHS predicted that 45% of people discharged from hospital would need some ongoing support from health and/or social care [4]. In June 2020, Public Health England confirmed that the virus, and its treatment, would have a lasting impact on the health of survivors [1]. The actual proportion with long-term health problems after the initial recovery phase remains unknown. However, the scale of the COVID-19 pandemic means that many thousands of people globally will require long-term multi-disciplinary support and rehabilitation. Our COVID-19 patient partners highlighted issues including protracted recovery, multiple sequelae and perception of little post-discharge support.

There is little specific provision to support short-term recovery at home for COVID-19 survivors. Moreover, there are few, rehabilitation or structured support programmes for COVID-19 survivors who continue to have physical and mental health problems several months after hospital discharge. Where programmes exist, their potential benefit is unproven. Research is needed now to find out how best to help long-term COVID-19 survivors who have ongoing physical and mental health problems. Multi-disciplinary physical and psychological rehabilitation may be beneficial in improving people's quality of life. However, the size of the problem, now considered by some to be a rehabilitation pandemic [5], requires the testing of approaches to multi-disciplinary rehabilitation that can be delivered at scale.

Traditional centre-based NHS rehabilitation services do not have the capacity to support the numbers of people recovering from COVID-19 [1]. Resources are insufficient to deliver rehabilitation services within a traditional intensely supervised and facility dependent model of care. This, in combination with issues relating to continued restrictions on movement and extended closure of existing rehabilitation services, means it is imperative that alternative long-term support strategies are explored. 'Virtual' (on-line) rehabilitation may offer an alternative to traditional face-to-face rehabilitation. However, existing virtual rehabilitation platforms are not sufficiently specialised or developed to treat people recovering from COVID-19, and their clinical and cost-effectiveness has not been tested in randomised controlled trials (RCTs). Our patient partners, most of whom were not previously active on-line, said they had become confident in the use of on-line video technology during the pandemic.

1.2 Existing knowledge

People recovering from acute respiratory distress syndrome frequently develop substantial long-term morbidity [6]. Physical and psychological sequelae can affect quality of life (QoL) for years [7] with almost half of people not returning to work within 12 months of discharge [6]. Multiple studies investigating the 2002-2004 Severe Acute Respiratory Syndrome (SARS) epidemic showed reduced walking distance at three and six months compared to population norms [8]. One in six survivors had impaired pulmonary function at 24 months and SF-36 QoL domain scores were reduced [9]. Another study (N=189) found the prevalence of depression, anxiety and PTSD to be 14%, 18%, and 6% respectively [10]. A chronic post-SARS syndrome has been described, characterised by persistent fatigue, diffuse myalgia, weakness, depression, and sleep disturbance [11].

Early data from COVID-19 survivors shows a broadly similar pattern along with 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 [4], a multitude of physical, psychological and social needs have been identified [1]. For hospitalised, but less severely affected 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 [12]. We have no data on whether ethnicity affects the prevalence or pattern of long-term sequelae from COVID-19.

Targeted exercise-based rehabilitation is beneficial for people with COPD [13] and survivors of SARS [14]. A quasi-experimental study (N=72) in COVID-19 survivors reported positive results on multiple outcomes [15]. On international trial registries, small RCTs (N=30-50) are assessing centre-based and on-line rehabilitation protocols for COVID 19 survivors. The majority aim to recruit participants immediately post-discharge, and none are UK-based. There are no large multi-centre RCTs assessing the clinical and cost-effectiveness of comprehensive, supervised, on-line, home-based physical and mental health rehabilitation. Choosing the optimum time to intervene to improve long-term outcomes is important. Early intervention targeting mental health problems is likely to be ineffective due to a high rate of spontaneous resolution[16]. Moreover, international guidance does not support early pulmonary rehabilitation for COVID-19 [1].

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.

1.3 Hypothesis

Research question: What is the clinical and cost effectiveness of an intensive, on-line, supervised, group, home-based rehabilitation programme that supports long-term physical and mental health recovery for people discharged from hospital (>3/12) after COVID-19 infection?

Aim: To assess the clinical and cost-effectiveness of the 'Rehabilitation Exercise and psycholoGical support After covid-19 InfectioN' (REGAIN) intervention compared to best-practice usual care (single session of advice only) for people recovering from COVID-19.

Objectives: To run a definitive multicentre RCT testing the clinical and cost-effectiveness of REGAIN vs. a single session of advice, including:

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

1.4 Need for a study

To date, research has understandably focused on the immediate need for life-saving health interventions. Research has addressed the basic biology and epidemiology of COVID-19 and concentrated on early efforts to develop evidence-based treatments and vaccination. Early evidence that some treatments, such as dexamethasone, effectively reduce mortality in selected patients,

emphasises the importance of longer-term support for the increasing proportion of those affected who survive to hospital discharge [17].

The large number of people affected over a short time frame means that many people in the UK are now facing a rehabilitation challenge. This has physical, psychological and economic consequences at individual and societal levels. While interventional research rapidly develops, the proposed REGAIN intervention has the potential to guide recovery and re-entry to economic productivity for those living with the longer-term consequences of COVID-19.

Long-term rehabilitation interventions are not currently offered to COVID-19 survivors. To our knowledge, there are no rehabilitation interventions currently being tested in the UK for people who have not fully recovered more than three months or longer after hospital discharge. This group are likely to require intensive support as they may be at high risk of chronic physical and mental health problems.

Many COVID-19 survivors return to normal activities within a few weeks [4]. Thus, universal early intensive rehabilitation only has the potential to help a sub-set of people. Selecting those people who have not recovered after three months is likely to be a more efficient and cost-effective approach to rehabilitation. Furthermore, it may only be after a protracted recovery that many people, who were previously well, are likely to require, and be accepting of, a psychologically informed behavioural intervention.

We need to deliver this study rapidly to inform long-term care for COVID-19 survivors and to achieve the greatest benefit for patients and society. To do this efficiently at a time when restrictions to normal life are likely to continue for some time, and to take advantage of the recent shift in acceptability of virtual health care, REGAIN will be run completely on-line. On-line recruitment, outcomes assessment and intervention delivery means we can have a national sampling frame, approaching very large numbers of potential participants in a short period.

Assuming a positive result from REGAIN, we will have an intervention suitable for immediate implementation nationally and internationally. Implementation of a successful programme has the potential to substantially reduce the chronic burden of COVID-19 in a large number of survivors, who, in the current unique pandemic environment, may not have access to normal social and primary/community care support. Apart from the direct benefits for those concerned, improving the general health of survivors has the potential to reduce demand on health and social services more widely and improve economic productivity.

1.5 Ethical considerations

The study will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and University of Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the Data Protection Act 2018.

Study participants will be enrolled via two routes of entry, either by direct approach of the patient by a participant identification centre (PIC) or by self-referral. Before approaching potential study participants, each PIC will ensure that the local conduct of the study has the agreement of the relevant NHS Trust Research & Development (R&D) department and written confirmation is received by Warwick Clinical Trials Unit (WCTU).

All direct approaches to potential participants made by PIC sites will be from clinical care teams and all identifiable data will be held within NHS sites until participants have registered their interest in participating and provided their contact details.

We will ensure that study recruitment staff are trained in GCP and consent procedures.

Relevant data will be entered directly by participants into a secure online database provided by WCTU, although in some instances, data may be entered into the database by study staff at UHCW or WCTU during follow-up telephone calls with study participants. These data will be considered as source data for the study.

For the symptoms sub-study, routinely collected, pseudonymous, data will be obtained by PIC sites on the total number of patients discharged with COVID-19. Consent for WCTU to hold core source data (age, gender, ethnicity, length of stay, ventilation type) will be sought from all patients accessing the secure REGAIN database.

Any routine data collected for the symptoms sub-study and GP records (if collected for particular participant) will also be considered source data. Direct access to source data will be granted to authorised representatives from the sponsor, host institutions and the regulatory authorities to permit study related monitoring, audits and inspections.

Study staff will ensure that participants' anonymity is maintained. Participant identifiable information will be stored securely on the electronic database. All data will be stored securely and will only be accessed by study staff and authorised personnel. The study will comply with relevant UK data protection legislation, which requires data to be pseudonymised as soon as it is practical to do so. Identifiable data will be deleted within 6 weeks of completion of the study, specified as the point of withdrawal or completion of the 12 month follow-up questionnaire.

One ethical consideration is that people of different ethnicities can take part in the study. Participants who are not fluent in spoken or written English will be eligible to take part. Participant information sheets and consent forms will be translated into the following languages; Bengali, Gujarati, Urdu, Punjabi and Mandarin. When confirming consent for those not fluent in English, a bilingual researcher will speak to the participant to ensure a full explanation of the study and to confirm understanding. An NHS accredited translator will be included in the one-to-one advice consultation (control arm) and the individual assessment (intervention arm). On-demand online videos will also be translated in those languages mentioned above. Participants who are not fluent in English will be encouraged to attend live online exercise sessions with a friend or relative who can translate for them. For the psychological support sessions we will arrange bespoke small online group sessions with an REGAIN practitioner and NHS accredited translator. 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.

Mindful of the likely high prevalence of case level mental health symptomology in this population, REGAIN practitioners seeing people in both arms of the study will be provided with selected findings from the baseline questionnaires. Those with suspected mental health symptoms (depression/anxiety/PTSD), based on high scores reported on one or more of the HADS Anxiety sub-scale, HADS Depression sub-scale, and IES-6 within the baseline questionnaire, will be flagged and patients will be directed to their GP for advice as per the participant information sheet and also by the REGAIN practitioner. Participants with suspected mental health disorders (based on symptom

score cut-points) who do not attend their first treatment session will be contacted via a letter by the REGAIN study team and advised to see their GP, even if they no longer wish to take part in the study. We will provide all GPs with a letter explaining their patient is taking part in the study and notification of their treatment allocation. This letter will also provide the baseline screening scores for two measures only, the HADS and IES-6 questionnaires. Additional reports will be provided to GPs at the 3, 6 and 12 month follow-up time points for those patients who score highly on one or more of the HADS Anxiety sub-scale, HADS Depression sub-scale or IES-6 questionnaires.

1.6 CONSORT

The study will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement [18].

1.7 Assessment and management of risk

Exercise carries a very small risk of complications. All participants will be assessed for any underlying health conditions or severe complications related to COVID-19. Participants will be excluded from the study at the eligibility stage where exercise is clearly contraindicated, as assessed by a clinical member of the research team. A further assessment will be undertaken by the REGAIN practitioner, through discussion with the patient about their current health, at the time of the initial online intervention assessment. Any additionally identified contra-indications at this stage will result in withdrawal from the study. The REGAIN practitioner will advise on an exercise regime appropriate for each participant's ability. All participants will be advised to have another person nearby for the initial exercise sessions. We will encourage this wherever possible.

All intervention sessions will be led by staff experienced in assessment, prescription and delivery of exercise for multi-morbid clinical populations.

For the exercise programme, weekly troubleshooting will assess safety, progress, changes to health, and any adverse effects. This will take place during a 10 minute 'debrief' after each live online exercise session every week. Participants will have the opportunity to attend the troubleshooting session at least weekly to discuss any issues with the REGAIN practitioners and other participants. There will also be time to discuss these issues after each of the group behavioural sessions, and participants may contact the REGAIN practitioners or the study team via email or telephone with any further queries.

2. STUDY DESIGN

2.1 Study summary and flow diagram

REGAIN is a multi-centre, randomised controlled study testing the clinical and cost-effectiveness of the REGAIN intervention vs. best practice usual care, including:

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

Around 20 NHS trusts, prioritising ethnically diverse localities, will be set up as Participant Identification Centres (PIC). The study team based at UHCW and Warwick Clinical Trials Unit (WCTU) will recruit participants who have registered their interest. The intervention and control sessions will be led by staff at the UHCW community exercise rehabilitation centre (Atrium Health, Coventry).

Study overview: Adults admitted to hospital with COVID-19 who were discharged more than three months previously will be identified by clinical care teams from hospital records at PIC sites. The PIC sites will contact all patients discharged over three months previously. Confirmation of clinical status via hospital and NHS systems will be performed immediately prior to the mail out to ensure that patients have not died since their hospital discharge. People with substantial ongoing health problems after COVID-19 will also be able to self-refer to the study. The study will not recruit two patients from the same household.

Those with substantial ongoing COVID -19 sequelae, as defined by the participant, who are eligible for the study will be invited to participate.

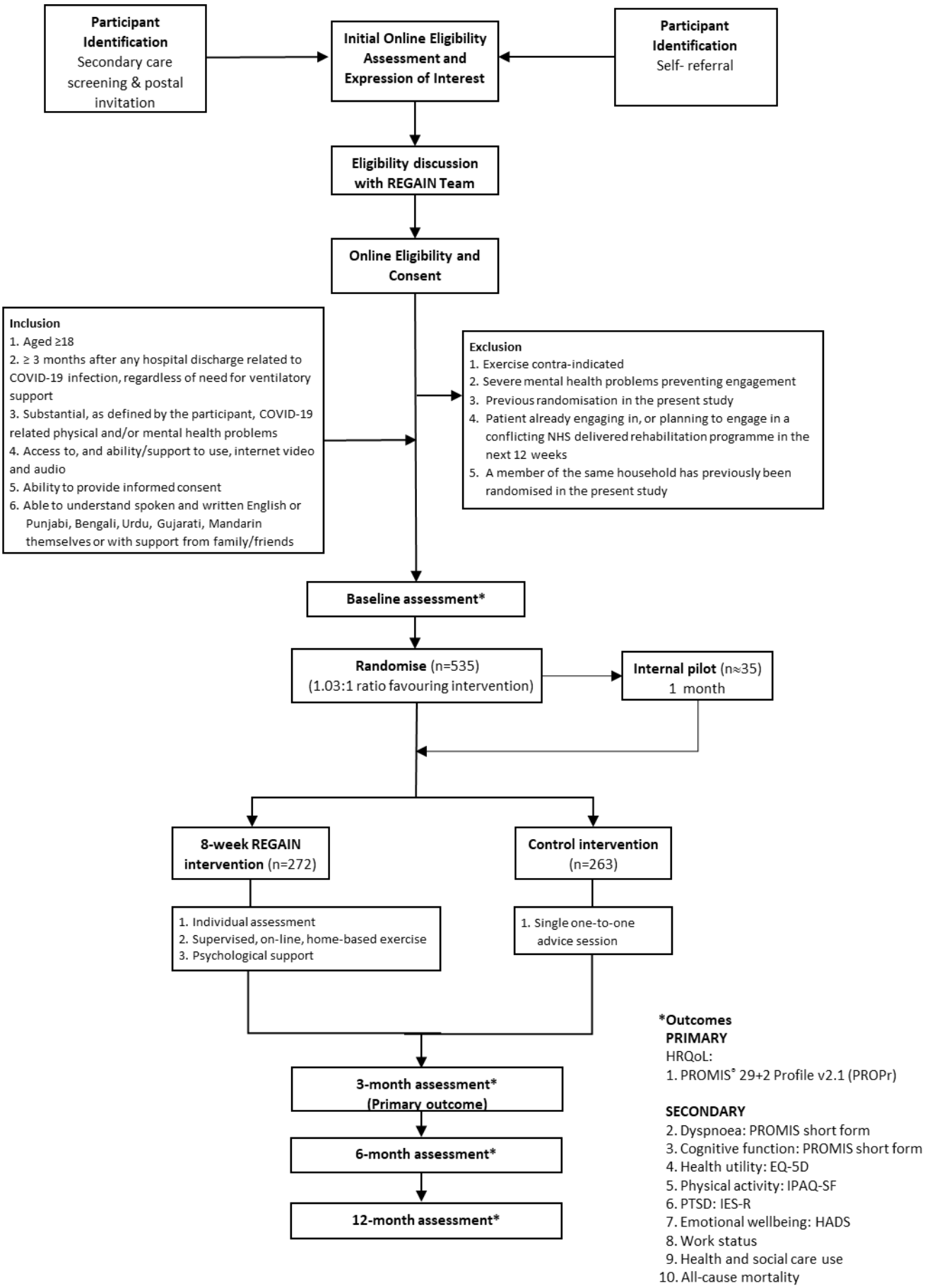
We aim to recruit 535 participants, who will be randomised to the REGAIN intervention or best practice usual care only on a 1.03:1 basis using a computer-generated randomisation sequence, performed by minimisation and stratified by age, level of hospital care (ICU/HDU or ward), and case level mental health symptomology based on scoring of the HADS Anxiety sub-scale, HADS Depression sub-scale and IES-6.

Outcomes will be assessed at baseline pre-randomisation and at three, six and 12 months post-randomisation. The primary outcome will be HRQoL measured using the PROMIS® 29+2 Profile v2.1 (PROPr) at three months post-randomisation. Data will be collected directly from study participants using online data collection via the password protected REGAIN website.

Pre-pilot: A small pre-pilot feasibility phase (n= 6-10) will be undertaken to complete development of intervention and study materials, refine online recruitment processes, pilot practitioner training, and confirm feasibility of intervention delivery using live and recorded online sessions. Over one month, the constituent parts of the REGAIN intervention will be tested with six to ten participants recruited from our PPI group. These participants will not be allocated a REGAIN study number and no data from these participants will be analysed as part of the study outcomes. The purpose of this pre-pilot will be to refine and test the online delivery of intervention and control materials, including participant and practitioner manuals, and staff training procedures, and to commence preparation for main study set-up. This will allow us to confirm the feasibility of all aspects of the study and make final alterations prior to the internal pilot.

Internal pilot: In a one-month internal pilot (n=35), recruiting from multiple PIC sites and running seamlessly into the main study, participant recruitment and retention will be confirmed. This will also provide provisional data on the fidelity of the intervention, its safety, and participant compliance and experiences.

Figure 1 Study flow diagram



2.2 Aims and objectives

The aim of this study is to assess the clinical and cost effectiveness of an intensive, on-line, supervised, group, home-based rehabilitation programme (the REGAIN intervention) compared to best practice usual care (single advice session only), to support long-term physical and mental health recovery for people discharged from hospital more than three months after COVID-19 infection.

2.2.1 Primary objective

The primary objective of this study is to determine if the REGAIN rehabilitation intervention improves HRQoL at three months post-randomisation compared to best-practice usual care in patients with ongoing COVID-19 symptoms.

2.2.2 Secondary objective

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:

1. HRQoL
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.

2.2.3 Symptoms sub-study objective

To report on the characteristics of people discharged from hospital with COVID-19, we will ask participating NHS Trusts to provide pseudonymous key demographic data to allow comparison of recruited and non-recruited patient cohorts. We will record and compare selected factors including patient factors (ethnicity, age, gender) and COVID-19 admission characteristics (duration of hospital stay, need for high flow oxygen/continuous positive airways pressure/ventilation), and ongoing COVID-19 symptom profile.

2.2.4 Process Evaluation objective

1) To explore the experiences of participants in the intervention and control groups, including enablers of, and barriers to, lifestyle change amongst participants.

2) To highlight any contextual issues that may affect the outcome or delivery of the study and/or intervention.

2.3 Outcome measures

2.3.1 Efficacy

Primary Outcome:

Health-related quality of life (HRQoL) 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 [19-21] generating a single overall score plus physical function, anxiety, depression, fatigue, sleep disturbance, social roles/activities, pain interference, cognitive function and pain intensity sub-scales.

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 will be lower.

Secondary Outcomes:

The following outcomes will be measured at three, six and 12 months post-randomisation.

1. HRQoL: PROPr
2. Dyspnoea: PROMIS dyspnoea severity Short Form [21]. Exertional dyspnoea is a commonly reported symptom in COVID-19 survivors, so we have added specific questions to the longer HRQoL PROMIS measure.
3. Cognitive function: PROMIS Neuro-QoL Short Form v2.0 - Cognitive Function [21]. In light of the apparent high incidence of cognitive impairment in COVID-19 survivors we have added additional PROMIS questions, to obtain a specific measure of cognitive function.
4. Health utility: Euroqol EQ-5D-5L [22]. 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.
5. International Physical Activity Questionnaire (IPAQ short-form). A well-established activity measure reported as metabolic equivalent task (MET)-minutes per week derived from duration of walking, moderate and vigorous exercise [23]
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 [24-26]. 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. Commonly used and well validated measure in clinical populations [27].
8. Work status: Time lost from work (paid/unpaid) and patient-borne health costs.

9. Health and social care resource use: participant self-report and NHS records. The primary health-economic analysis will concentrate on direct intervention and healthcare/personal social services costs, while wider impact (societal) costs will be included within the sensitivity analyses. Participants will complete resource use questionnaires at all follow-up points, to collect resource use data associated with the interventions under examination. We will request a copy of the participant's medical record from their GP at the end of the study follow-up 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 participant self-report to achieve a robust estimate of health service activity. Consent will be obtained for access GP records.
10. General health – Participant self-reported measurements of current overall health and comparison of current health to health 12 months prior.
11. Death measured using GP.

Follow-up: Patient reported outcomes will be collected online at baseline pre-randomisation, three months, six months and 12 months post-randomisation. Participants will 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, two key outcomes, the PROPr (primary outcome) and EQ-5D-5L will be collected by telephone. 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: 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.

2.3.2 Symptoms sub-study

We will request and store pseudonymised data from PIC sites to provide useful information on sample representativeness. Anonymised data on sex, age, ethnicity, length of stay and ventilation type of discharged patients will be requested from each site. . All patients identified through PIC sites that are completing online screening, including those who are deemed ineligible for the study, will be asked for consent for UHCW and WCTU to hold this data and link this to data collected as part of the study. Patients who consent to this will provide their screening ID number, which will be assigned to them by the PIC sites, enabling WCTU to link with the pseudonymised data for that individual. Ongoing COVID-19 symptoms will be collected during the initial online eligibility assessment and expression of interest. This will allow us to compare characteristics of those who take part in the study with those who have recovered from COVID-19 post-discharge and/or who do not want to participate.

2.4 Eligibility criteria

Patients are eligible to be included in the study if they meet the following criteria:

2.4.1 Inclusion criteria

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

** Self-reported and/or adjudged by a clinical member of the research team or the REGAIN practitioner

2.5 Participant identification / Screening

Patients will be identified via two routes: (i) clinical care teams at each PIC (NHS hospital trust) will screen hospital discharge data and identify potential participants for contact by mail; and (ii) via self-referral.

Patient Identification Centres

PICs will send potential participants an invitation letter and infographic invitation flyer allocating a screening ID number. This will direct participants to the study website. These resources will be brief, providing only the most important detail required, and will be written in plain English. On each resource there will be a sentence in each of the five specified non-English languages directing the potential participant to the study website where the invitation flyer and participant information sheet (PIS) will be available in their preferred language. The invitation letter and REGAIN study website will instruct potential participants to read the PIS, and if they are interested in taking part in the study, to access the online database to register. For those whose first language is not English, there will be an option to request a phone call from a bilingual research associate. This option will be written in five languages on the study portal: Bengali, Gujarati, Urdu, Punjabi and Mandarin.

The online database will direct potential participants to a series of screening questions to determine their initial eligibility for the study.

If a potential participant is not eligible for the study, a message will appear on screen to inform them that the REGAIN study is not suitable for them. These people/patients will be advised to refer to the NHS 'yourcovidrecovery' website.

If the participant is initially considered eligible, they will be asked to complete an expression of interest form and enter their contact details including their first name, surname, address, post code, telephone number(s), email address, GP name and GP address. A GP address must be provided in order for the potential participant to register interest into the study. This is required so that the participants GP can be contacted if any medical concerns are raised during the initial eligibility and consent telephone call. The potential participant will be instructed that a member of the REGAIN team will be in touch via telephone to confirm their suitability for the study.

Once the potential participants have completed the online eligibility form, both the people who are suitable and those that are not will be asked separately if they consent to UHCW and the University of Warwick holding and linking routinely collected hospital administrative data; including demographic information and information regarding their COVID-19 treatment during their hospital stay with data collected as part of the study. These data will be used for the symptoms sub-study to allow comparison with the recruited cohort of study participants. WCTU will arrange for the PIC sites to securely transfer routine data collected for all participants approached for the study, which will be pseudonymised and identified only using the screening ID number. If a participant does not consent to this data being held at UHCW and WCTU and linked to data collected as part of the study this data will be deleted.

Self-referral

The study will be promoted though local media/social media, relevant charities and on the study website. A REC-approved study flyer will also be used to promote the study. People suffering from ongoing COVID-19 related symptoms following hospital discharge will be able to self-refer. Self-referred patients will be directed to the REGAIN website and follow the same process as described above for PIC referrals.

2.6 Eligibility and informed consent

When a potential participant has registered their eligibility and expression of interest for the REGAIN study via the online database, the WCTU REGAIN study team and the site team based at UHCW will receive an alert. An appropriately trained clinical member of the site team (listed on the study delegation log) will then telephone the potential participant on their main telephone contact number. The REGAIN site team member will conduct a further eligibility screen and complete an online eligibility form with the potential participant. The REGAIN site team member will ensure the potential participant has read the PIS, understands what is involved and has had the chance to ask any questions before starting the eligibility questions.

If the potential participant is eligible for the REGAIN study, they will automatically receive a link via text or email (whichever they have specified is their preference) to an electronic consent form. The team member will explain the purpose of the consent form and summarise the key points. The patient will be able to complete the consent form in their own time, although the link will only be active for three weeks from the date sent. Upon clicking the link to the consent form, the participant will be issued with an authentication code via text or email, ensuring only the intended patient can access the consent form via the sent link. Potential participants will need to confirm they have read each of

the consent items before agreeing to take part in the study. A copy of the fully signed consent will then be sent to the patient via email. Once the consent form has been completed, the participant will be able to access the baseline questionnaire from the same link. Once both the consent form and baseline questionnaires have been completed by the patient, they will be automatically randomised into the study by the online system.

Pregnancy is not an exclusion criterion for REGAIN. These potential participants will be recruited to the study if eligible and participants who confirm pregnancy following enrolment will remain in the study. All participants randomised to the intervention arm, including those who are pregnant, will receive a one-to-one consultation with a REGAIN practitioner where exercise will be tailored to their ability, however, the exercise intervention is deemed safe for those who are pregnant. These participants will be monitored for adverse events as per Section 4.

GP notification: After randomisation, the participant's GPs will be informed by letter that they are taking part in the study, informed of the participant's baseline HADS and IES-6 questionnaire scores and notified of which treatment arm they have been allocated to.

Responsibility: The PI at UHCW will retain overall responsibility for informed consent and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, qualified and competent.

When confirming consent for those not fluent in English, a NHS accredited translator or bilingual researcher will be present to ensure that participants receive a full explanation of the study and to confirm their understanding, according to Warwick SOP 7.

New information: Any new information that arises during the study, that may affect participants' willingness to take part, will be communicated to all participants. If deemed necessary, the participant will be contacted by the relevant researcher and asked whether they still wish to continue participating in the study. If required a revised PIS and consent form will be made available on the REGAIN website and the participant may be asked to read, consider and sign the consent form online.

Decline/withdrawal: Participants will have the option to withdraw from the study and/or the intervention at any time, if for any reason they change their mind without giving reasons and without prejudice to any further treatment. This will be recorded on a withdrawal form. The right of a potential participant to refuse participation without giving reasons will be respected and recorded on the withdrawal form. A reason will be documented if participant is willing to offer one.

Willingness to continue in the study will also be monitored, and recorded throughout the intervention period by researchers conducting the interventions.

2.6.1 Consent for qualitative interviews

At the beginning of the study, participants will be asked for their consent to be contacted at a later stage about an interview with a researcher. Although consent will be recorded for everyone on entry to the REGAIN study, only some participants will be contacted for interview. If they are selected to be interviewed, they will be contacted by phone or text message to invite them to participate. They will be directed to the study website where they can download another information sheet and separate consent form for the qualitative study. These forms will be in English and translated into the following languages; Bengali, Gujarati, Urdu, Punjabi and Mandarin. If the participant is interested, they will be asked to complete the online consent form. Following this initial contact, a member of the study team will contact the participant to discuss the study, answer any questions they may have and if they remain happy to proceed, then arrange a date for

the interview to take place. The interviewer will confirm the consent form has been completed before the interview is conducted by telephone or video call.

2.7 Site Staff Training

Staff training will be documented on training logs held at WCTU and UHCW. Study responsibilities will be documented on delegation logs to be held at WCTU and UHCW. The CI will retain overall responsibility for conduct of the study.

Intervention practitioners: Practitioners delivering the REGAIN intervention will be Clinical Exercise Physiologists or Physiotherapists with appropriate professional registration, relevant continued professional development (CPD), and good clinical practice (GCP) training. An exercise lead (exercise physiologist/physiotherapist) at UHCW will be responsible for ensuring study procedures are followed and standardised for intervention delivery.

REGAIN training: All intervention practitioners will undergo one day of REGAIN intervention training. This training will ensure an appropriate level of clinical knowledge and skills for exercise rehabilitation in COVID-19 patients. Training will be delivered by a health psychologist, to upskill practitioners on delivery of the psychological component of the intervention. Training will be supplemented with a comprehensive practitioner intervention manual. Access to health psychology expertise and support will be maintained and monitored throughout the duration of the study. The exercise lead at UHCW will be responsible for ensuring additional practitioners are appropriately trained and familiarised with the manual. Full training will be provided by the REGAIN research fellow and health psychologist for new staff, as needed. Should any clinical (physical or mental) issue require escalation, REGAIN practitioners will follow the appropriate local clinical guidelines.

REGAIN Practitioner manual: This detailed manual will guide practitioners through each component of the intervention, with graphics, flowcharts and detailed written instructions. It will also include general information about the study, key components of GCP, and contact details of the study team. The content will reflect information delivered during the training for REGAIN intervention practitioners.

Exercise intervention: To enhance practitioners' knowledge of exercise prescription, ensuring intervention efficacy and safety, the manual will provide an overview of key evidence and exercise guidance. To provide a level of standardisation, parameters within which the exercise intervention should be delivered and progressed will be detailed.

Psychological support intervention: The manual will give a detailed description of each psychological topic, with hints and tips of questions to ask, and the aims of each session. The content will map onto the intervention participant manual, allowing the practitioner to tailor the discussion.

2.8 Randomisation

2.8.1 Randomisation

Pre-randomisation eligibility checks will be carried out to ensure that potential participants meet the eligibility criteria and are not randomised in error. Consent for entry into the study must have been completed prior to randomisation. Subjects will be randomised once they have been registered as eligible for randomisation on the web-based system and completed their baseline questionnaire.

Participants with case level mental health disorder, identified from baseline HADS and IES-6 questionnaires (screening scales for anxiety, depression, PTSD) will be directed to their GP for treatment. This will be included in the PIS. They will continue in the study intervention as long as the REGAIN practitioner and/or the participant consider that their mental health does not preclude engagement with interventions.

Randomisation will be undertaken automatically by the 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),
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 <11/14 **and** HADS Depression sub- score <11/21).

Participants will be randomised strictly sequentially at study level.

2.8.2 Post-randomisation withdrawals and exclusions

Participants may decline to continue involvement in the study at any time, without prejudice. This will not affect the standard of care they receive. For participants withdrawing from the study, data obtained prior to the point of withdrawal, will be retained for the final analysis unless explicitly withdrawn at the participant's request. For participants who withdraw, a withdrawal CRF will be completed.

Participants may be withdrawn from the study, at any time, at the discretion of the investigator /practitioner based at UHCW or the Trial Steering Committee due to safety concerns.

2.9 Study interventions

2.9.1 Study treatment(s) / intervention(s)

Best practice usual care (Control) intervention: A thirty-minute, on-line, one-to-one consultation with a REGAIN practitioner, who will be trained and supported by a Health Psychologist during the study, will be given as the control intervention. All study participants will be directed to freely available on-line programmes published by NHS England (https://www.yourcovidrecovery.nhs.uk/). If case level mental health disorder (depression/anxiety/PTSD) is identified from baseline questionnaires, participants will also be referred to their GP for treatment/advice.

Participants with suspected mental health disorders who do not attend their one-to-one consultation will be contacted by letter and advised to see their GP. GPs will receive a letter for participants where case level mental health disorder is met specifying which symptoms were reported and at which time-point. The letter will not indicate a diagnosis, rather, will present the questionnaire data allowing the GP to decide on appropriate treatment.

We recognise the challenge of recruiting to studies where the usual care arm receives no additional treatment or care, despite understanding issues around equipoise. Our patient partners consistently raise this issue. Therefore, for our control arm, the intervention can be described as 'best-practice usual care', in the form that is currently recommended by the NHS (yourcovidrecovery.nhs.uk) and also an individual practitioner consultation, with general advice on safe and effective physical activity. A 30-minute consultation will allow practitioners to discuss individualised ways in which

participants can undertake physical activity at home. Participants will not be provided with a structured exercise plan, rather directed to good quality freely available on-line NHS resources detailing ways in which physical activity can be safely and effectively incorporated into their everyday lives. No specific psychological techniques will be used to support this. Doing this allows us to offer the usual care group a standardised form of best current practice, whilst retaining the aim of the study comparing outcomes in people who receive comprehensive support, with people who do not. This approach of comparing two study interventions also reduces the risk of resentful demoralisation in the control group which might introduce bias [35].

REGAIN Intervention: The REGAIN intervention has three components -

1. **Individual assessment:** One-hour, on-line, one-to-one assessment with a REGAIN practitioner (Clinical Exercise Physiologist/physiotherapist), who will be trained and supported by a health psychologist during the study, to holistically assess participant needs, introduce the programme, and provide individualised exercise advice. All participants will also be 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 also be directed to their GP for treatment/advice. These symptomatic patients will continue in the study intervention as long as the practitioner considers their mental health problems would not preclude engagement.

   Participants with suspected mental health disorders who do not attend their first treatment session will be contacted by letter and advised to see their GP. GPs will receive a letter for participants where case level mental health disorder was met specifying screening scores for HADS and/or IES-6.

2. **On-line, supervised, 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 will be encouraged to attend at least 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. Where possible, groups will be arranged to allow those of similar age, ability, gender, and cultural needs to exercise together as a group. This approach will allow us to maximise the acceptability of the programme to people from different minority ethnic groups. It may also promote adherence to exercise sessions.

The REGAIN exercise intervention will be facilitated by trained practitioners using:

   a. Participant manual with instruction on safe and effective exercise, and an online downloadable logbook to record completed exercise.
   b. Pre-recorded sessions, graded by ability, available to participants on the REGAIN website.
   c. Live (end-to-end encrypted, password protected, on-line) sessions led by REGAIN practitioners to allow participants to complete group exercise with real time instruction/feedback.

3. **Psychological support:** Over the eight-week intervention period, participants will attend six on-line group sessions each lasting for up to one hour, led by a REGAIN practitioner who will be trained and supported by a health psychologist during the study. Core theoretical principles used

to inform the psychosocial content, structure and delivery include the bio-psychosocial model of behaviour change [28, 29], Michie's behaviour change wheel and taxonomy [30], Michie's COM-B model (Capability, Opportunity and Motivation), and psychological theories of self-efficacy (perceived confidence in ability to engage and implement the strategies learnt) [31], cognitive behaviour-change, and motivational interviewing [32]. The logic model for the psychological intervention can be found in Appendix 1.

The group support element draws on social learning principles promoting behaviour change through peer support. It is necessary to engage participants in the thought processes needed to interpret their own experiences of COVID-19 by providing time for discussion and reflection and then a summary of key information to promote cognitive functioning. We will explore expectations which may include the meaning of recovery, impact on social networks and relationships, including family and friends and goals to rebuild life to promote executive functioning (Capability). These sessions, delivered on-line rather than in person, will allow participants to engage in the programme from the safety and convenience of their chosen location.

Each week will cover different topics providing strategies to help recovery from the effects of Covid-19. We will incorporate motivational interviewing techniques to promote direct behaviour change through awareness and management of emotional responses to participants' own experiences of COVID-19 which may include fear, stress and low mood. Education will be combined with cognitive behavioural approaches to action management and change, with online worksheets between sessions to consolidate learning. Our PPI support group will share stories of recovery and rehabilitation. For the mental health disorders likely to be common in this group of patients (depressive and anxiety disorders including PTSD), this provides a rational intervention for an established mechanism of symptom development.

Informed by the British Psychological Guidance [33] for management of those recovering from COVID-19 and PPI input, the sessions will cover the following topics:

1: Introduction, expectations, motivation and goal setting

2: Fear avoidance and pacing

3: Management of emotions (perceived stigma, mood/unhelpful thoughts)

4: Recovery and sleep, sleep management strategies

5: Understanding stress and anxiety and management strategies

6: Managing setbacks and long-term behaviour change and future goals

Each session will include a facilitated group discussion, with interactive components. To prevent on-line fatigue, sessions will last up to 60 minutes. Participant resources will include a professionally produced online workbook highlighting key topics and providing the opportunity for reflection and learning between sessions. This will be supplemented with pre-recorded on-line short video content available to participants via the study online video platform.

REGAIN practitioner training: We have extensive experience of training and upskilling staff to deliver rehabilitation and behaviour change programmes (SPHERe, I-WOTCH, PULSE)[34, 35]. We will adapt and combine experiences from these trials to deliver a physical and psychological intervention for COVID-19 survivors.

Safety: All supervised sessions will be led by staff experienced in assessment, prescription and delivery of exercise for multi-morbid clinical populations. Pre- and post-exercise session poll questions will be completed by participants during each supervised session to capture any adverse events during the session and since the previous supervised session. Weekly troubleshooting after the live exercise sessions and the group behaviour change sessions will assess safety, progress, health, and any adverse effects. Participants will be advised to initially have another person nearby during exercise. If a participant fails to attend two consecutive intervention appointments a REGAIN practitioner will attempt to contact them via telephone or email in order to ascertain their welfare.

Intervention/control delivery: The multicentre REGAIN study will be delivered nationwide from a single central study 'hub'. The UHCW community exercise rehabilitation centre at Atrium Health delivers NHS cardiac, pulmonary, vascular, heart failure, cancer and other long-term condition rehabilitation services for Coventry and surrounding areas. Further, it is a clinical academic centre of excellence currently co-ordinating and delivering a number of nationally funded clinical exercise rehabilitation trials. The centre has the capacity, infrastructure and multi-disciplinary expertise to deliver the REGAIN study. Practitioners trained in the REGAIN intervention will be able to deliver the programme to groups of participants anywhere in the country using pre-recorded and live exercise and behaviour change sessions.

2.9.2 Compliance

Compliance with REGAIN intervention: Attendance at live online exercise sessions and the psychological support sessions will be logged by the online platform for each participant every week. Participants will be identified using their email address. Data will also be recorded detailing the number of times an individual has clicked onto an online video and the amount of time they have spent viewing each video. The completion of intervention (individual assessment, online live exercise sessions, psychological support sessions and online and guided home exercise plan,) and control sessions will be recorded as one measure of compliance.

Definition of compliance with intervention

The impact of compliance on outcomes will be assessed using a CACE (compliers average causal effect) analysis. A detailed statistical analysis plan will be written and approved by the Data Monitoring Committee (DMC) including definitions of full and partial compliance for the intervention group.

Fidelity: The majority of live exercise sessions and psychological support sessions will be audio-recorded (practitioner only) to reduce the risk of those delivering the intervention behaving differently when being recorded. The psychological support sessions will be audio-recorded and scored against criteria. From these sessions, a purposively selected subset (10%) of recordings will be analysed across relevant intervention sessions. This will enable assessment of fidelity, and an understanding of areas and issues that generated discussion.

The control group individual practitioner appointment will also be audio recorded and scored against criteria.

2.10 Concomitant illness and medication

2.10.1 Concomitant illness

At the start of the study, potential participants will be screened during their eligibility assessment for any concomitant illnesses. If the illness influences the potential participant's eligibility to continue in the study (e.g. serious mental health problems that preclude participation in a group intervention) the investigator will be informed and they will not be eligible to participate.

2.10.2 Concomitant medication

Participants will be asked to record any medications they are taking, for COVID related problems, at each follow-up time point (baseline, three, six and 12 months).

2.11 Co-enrolment into other trials

Co-enrolment of REGAIN participants onto other interventional studies will be considered where there is no possible conflict with the REGAIN study objectives. A list of appropriate and agreed studies will be produced at a national level to guide co-enrolment. In addition, the CI will review the protocols for other studies at sites e.g. interventional studies and will consider co-enrolment in conjunction with the Trial Management Committee where appropriate.

2.12 End of study

The study will end when all participants have completed their 12-month follow-up. As part of the process evaluation, n=25 participants in the control arm and n=25 from the intervention arm will be interviewed **after** their three-month follow-up.

The study will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the study ceases

The Research Ethics Committee will be notified in writing within 90 days when the study has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 1. Study assessments

	Pre-randomisation		Post-randomisation			
Online assessment	**1**	**2**	**3**	**4**	**5**	**6**
Assessment time point	**Screening**	**Enrolment/ randomise (Baseline)**	**Intervention Delivery**	**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		✓				
Patient Demographics		✓				
Medication Use				✓	✓	✓
PROMIS® 29+2 Profile v2.1 (PROPr)		✓		✓	✓	✓
PROMIS dyspnoea		✓		✓	✓	✓
PROMIS Neuro-QoL		✓		✓	✓	✓
EQ-5D-5L		✓		✓	✓	✓
IPAQ-SF		✓		✓	✓	✓
IES-R		✓		✓	✓	✓
HADS		✓		✓	✓	✓
Work status		✓		✓	✓	✓
Intervention			✓			
Adverse events			✓			
Overall health		✓		✓	✓	✓
Death						✓
Health and Social Care resource use				✓	✓	✓

	Pre-randomisation		Post-randomisation			
Online assessment	**1**	**2**	**3**	**4**	**5**	**6**
Assessment time point	**Screening**	**Enrolment/ randomise (Baseline)**	**Intervention Delivery**	**3m (± 2w)**	**6 m (± 1 m)**	**12 m (± 1 m)**
Semi-structured interviews (Process evaluation)				✓		

* 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.

3.2 Long term follow-up assessments

Long-term follow-up: Consent will be sought from participants to keep their personal data, and at the end of the study follow-up period request a copy of the participant's medical record from their GP 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. Mortality data will be gathered from GP records at 12 months.

3.3 Symptoms sub-study

PIC sites will be asked to send information to WCTU on recorded ethnicity, age, gender, duration of hospital stay and type of ventilation received for any participants that complete an initial screen form and provided consent for this. This data will be sent to WCTU in a pseudonymised format with the participant identified using the screening ID number.

These data will not be collected from those patients screened via the self-referral route of study entry.

3.4 Embedded process evaluation

Semi-structured interviews with participants: Information about interviews will be provided to all participants during study recruitment. Participants will be asked to consent (or not) to being contacted around three months after they have entered the study to share their views and experiences of the intervention and control. Participant interviews will be completed online and online verbal consent will be taken and documented prior to the interview taking place.

Interviews will be conducted by a qualitative Research Fellow from WCTU, on the phone/video-call as appropriate.

Pilot study

Interviews with up to five people in each arm recruited to the internal pilot to check intervention acceptability, and identify obstacles or facilitators to participation, uptake and completion. We will

use this internal pilot to optimise recruitment and retention by identifying challenges, and solutions which will be discussed with our patient partners. The model used for interviews in the pilot study will differ from the main study in that participants will be interviewed within three months of randomisation rather than after three months.

Main Study

Intervention and control participants will be interviewed to investigate their experiences, contextualise quantitative findings, and explore factors that helped or hindered participation, thus informing interpretation and wider implementation. Interviews will take place after the three month follow-up outcome data collection, so that the interview itself does not introduce bias to the analysis. A purposive sample of up to n=25 intervention and n=25 control participants will be interviewed at three months post randomisation to ensure a diverse range of perspectives are included. Our sample size of up to 25 per group follows guidance [36] indicating that while code saturation ('when researchers have *heard it all*') was reached at nine interviews, 16 to 24 interviews were needed to reach meaningful saturation ('*to understand it all*'). The interviews will use a topic guide that will include participant experiences of COVID-19, and any obstacles or enablers to participation, adherence and recovery. We will explore what components were used/dropped/never used, and views on the guided home exercise content. The interviews will last about one hour, be digitally recorded on an encrypted recorder.

We will aim to include up to three participants per arm who do not speak English in our interviews. They will be interviewed by staff who have interviewing skills and relevant language skills. They will be interviewed in their first language, this will be transcribed verbatim. The transcript will then be translated into English, then back translated and the back translation compared to the original transcript. This approach will be informed by recent work in this area [37-42].

Practitioner interviews: At the end of the study, all consenting REGAIN practitioners will be interviewed (~n=5) about their experiences of delivering the interventions/best usual care, what worked well, what helped, and what was challenging. These interviews will last up to one hour, be digitally recorded, and piloted during the internal pilot.

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence involving a participant, which does not necessarily have a causal relationship with the intervention or study.

4.1.2 Serious Adverse Events (SAEs)

A SAE is any untoward medical occurrence that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Intervention is required to prevent one of the above or is an important medical condition

4.2 Recording Adverse Events and Reporting Serious Adverse Events

4.2.1 Recording and reporting period

Intervention group: All AEs and SAEs that occur during or within 24 hours of a REGAIN live online session or an on-demand exercise session (supervised or unsupervised) should be recorded on the AE log by the exercise practitioner.

Usual care group: The usual care group will be asked about anything that might constitute a Serious Adverse Event at the time of their three-month follow-up. It will not be possible to collect a comparison dataset for the usual care group within this period without contaminating the control intervention. This is a pragmatic study and the participants will not be contacted during the intervention period, unlike the intervention group. It is important not to contact the usual care group more than is necessary so as not to introduce bias. We anticipate a low risk of adverse events arising from best practice usual care i.e. an NHS website and a single session of advice.

4.2.2 Recording Adverse Events

Participants in the intervention group will have the opportunity to indicate whether or not they have experienced AEs by completing both pre- and post-exercise session poll questions. Responses indicating the participant has potentially experienced an adverse event will be evaluated by the practitioner and the participant contacted to confirm the details. Practitioners should also monitor for any information volunteered by a participant at any time during a live exercise session. Participants in the intervention group will also have contact details (generic email address and phone number) for the study team and practitioners. Whilst participants will not be actively encouraged to report AEs via this route, they may seek advice and help from the team which may result in AEs being disclosed/discussed. Any AEs will be recorded on the AE log unless they fulfil the criteria for a 'Serious Adverse Event' in which case they will be reported to WCTU via the SAE form (see section 14.2.3 below).

4.2.3 Reporting Serious Adverse Events

All AEs should be assessed by the research practitioner to determine if they meet the criteria to be reported as a 'serious adverse event' as defined in section 4.1.2. If any of the adverse events meet this criteria, they will be reported to WCTU by emailing WCTUQA@warwick.ac.uk using the Serious Adverse Event form within 24 hours of becoming aware of it. If the 3 month questionnaire for a control group or REGAIN intervention group participant indicates events that may fulfil an SAE, then they should be contacted for further information and an SAE form completed if applicable.

A clinical assessment of whether the event has a causal relationship to the intervention should be made and recorded on the form by the practitioner. All SAEs should be reported irrespective of their relationship to the intervention unless they are exempt from reporting (see section 4.2.3.1).

For each **SAE** the following information will be collected:

- full details in medical terms and case description using CTCAE V5.0
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (relatedness to intervention), in the opinion of the practitioner

4.2.3.1 SAEs that are exempt from reporting

The following events that would usually fulfil the criteria for 'serious' do **not** need to be reported as per section 1.2.3:

- Treatment, which was elective or pre-planned, for a pre-existing condition, not associated with any deterioration in condition
- General care, not associated with any deterioration in condition

4.2.4 Determination of causality and expectedness for SAEs

Two independent causality assessments will be performed (i.e. relationship to study intervention). The practitioner will submit an assessment of their clinical opinion on causality upon submission of the SAE report using the classifications in SAE table 2 below. The CI will then do a separate causality assessment on reported events on behalf of the sponsor. These two assessments should be independent of each other.

If either party suspect there is a possibility that the event is related to the intervention then a delegate on behalf of the Sponsor will assess whether or not this is expected using the information in 4.2.4.1 below. For any related and unexpected serious adverse events, WCTU will report this to the REC within 15 days of receipt.

4.2.4.1 Expected Serious Adverse Events

Due to the limited knowledge of the long-term health problems in COVID-19 survivors, there are no Serious Adverse Events that would be expected in exercise intervention for the population included in this study.

Table 2. SAE Causal relationship

Relationship to study medication	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study intervention). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study intervention). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

4.2.5 Follow-up of reported SAEs

Practitioners will monitor for changes to unresolved SAEs via intervention poll responses or through close contact with the participant. If a practitioner becomes aware of any change of condition or other follow-up information it should be emailed to WCTUQA@warwick.ac.uk on the Serious Adverse Event Follow-Up form as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached where possible.

4.3 Responsibilities

Practitioners:

Checking for AEs when participants attend for exercise session or via pre- and post-exercise poll responses:

1. Using clinical judgement in assigning seriousness and causality
2. Ensuring that all SAEs are recorded and reported to the Sponsor via Warwick QA within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that reported SAEs are chased with WCTU if a record of receipt is not received within 2 working days of initial reporting.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the study, including an ongoing review of the risk / benefit.
2. Using clinical judgement in assigning causality
3. Immediate review of all related and unexpected SAEs
4. Review of specific SAEs in accordance with the study risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Production and submission of annual reports to the relevant REC.

Sponsor or delegate:

1. Central data collection and verification of SAEs, according to the study protocol.
2. Expectedness assessment of related SAEs
3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
4. Reporting safety information to the independent oversight committees identified for the study (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.

5. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
6. Notifying Investigators of related and unexpected SAEs that occur within the study.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

4.4 Notification of deaths

All deaths, when they are identified, will be reported to the sponsor by the REGAIN practitioner, overseen by the CI, irrespective of whether the death is related to disease progression, the intervention, or an unrelated event.

Staff at the UHCW community exercise rehabilitation centre and WCTU may become aware of deaths that occur during the study however the majority of deaths will be identified by accessing GP records for those non-responders at 12 months post-randomisation.

4.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

5. DATA MANAGEMENT

Personal data collected during the study will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018.

Personal identifying information will be collected on the online application and stored at WCTU for contacting the patient to: confirm eligibility and consent: complete and send a letter to the participants GP at baseline and at subsequent follow-up time points if one or more of HADS Anxiety sub-score, HADS Depression sub-score and IES-6 reveal possible case level mental health disorders; for intervention delivery (control and intervention arm); contact participants for follow up purposes; contact potential participants to take part in the interviews; and to request a copy of the participant's medical record from their GP. Information will be accessed via the online application by staff at UHCW (the community exercise rehabilitation centre) in order to contact the participants and deliver the study (intervention and control). Handling of personal and confidential data will be clearly documented in the participant information sheet and consent obtained.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick SOPs (Warwick

SOP 15 part 1) and the UK regulatory framework. There is no reason to expect this situation to occur in this study more than any other.

5.1 Data collection and management

The CRFs and questionnaires will be developed by the Trial Manager in consultation with the CI, Statistician, Health Economist and other relevant members of the study team to collect all required study data.

All data will be entered directly by participants, 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 will be source data. This will be stored safely and securely. Personal identifiable information will be stored separately to other data collection forms. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number, not by name.

For SAE reports, anonymised paper CRFs may be completed by UHCW staff and returned via email to WCTU for data checking and quality assurance purposes by study team members at WCTU and Sponsor representatives at UHCW. The participant will be referred to by the study participant number/code, not by name. If printed these forms will be stored in locked filling cabinets within WCTU accessible only to authorised staff from the study team. Electronic data will be stored in a secure area of the computer with access restricted to staff working on the study.

Various methods will be used to chase missing data including phone, text and email. Participants will receive an email notification and/or text message to remind them to complete the online questionnaires at each follow-up time point. If a participant has not completed a follow-up questionnaire within the anticipated time frame, the REGAIN study team will initially contact the participant via telephone to encourage them to complete the missing data and to provide support where required. A link to the study database may be provided via email to facilitate data completion. If data remain missing following this initial data chase, the REGAIN study team will contact the participant after a pre-defined period of time via telephone in order to attempt to collect core outcome measurements only (PROPr and EQ5DL). Where necessary a bilingual researcher will assist with the collection of missing data from participants who are non-English speakers. 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 (section 2.9.2). For any participants who do not respond to the 12 month follow-up questionnaire, WCTU will request a copy of the participant's medical record from their GP. Identifiable data will be deleted within 6 weeks of completion of the study, specified as the point of withdrawal or completion of the 12 month follow-up questionnaire.

5.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate study staff.

5.3 Online video platform

An external online video platform will be used for the REGAIN study interventions. This platform will enable live streaming of intervention sessions and the hosting of on-demand, pre-recorded content. A Data Protection Impact Assessment will be completed in order to identify and minimise risks associated with the online platform. The online platform will be GDPR compliant and Organisation for Review of Care and Health Apps (ORCHA) accredited. Any data that is stored, including the participant's email address, will be encrypted in accordance with NHS Digital guidance and storage will be NHS cloud compliant, conform to ISO 9001/27001/27017/27018 standards and meet the G-Cloud (UK Government) standard.

Private groups will be created on the online platform and administrative access to these given only to UHCW/UoW approved staff. Admins will authorise participant's access to the private groups and participants will be asked for their consent to share utilisation metrics with the group admin. Participants may choose to use a nickname on the online platform to remain anonymous to other members.

5.4 One-to-one consultation platform

The UHCW Trust approved patient video-platform will facilitate all one-to-one consultations between the REGAIN practitioner or qualitative interviewer and a study participant. This will include the best practise usual care advice consultation in the control group, the individual assessment component of the REGAIN intervention and the qualitative interviews. This platform will enable secure patient staff video consultations and operates fully in compliance with GDPR, DCB0129 and DCB0160.

5.5 Data storage

All essential documentation and study records will be stored at WCTU in conformance with the applicable regulatory requirements and access to stored information (electronic and paper) will be restricted to authorised personnel. Electronic data will be stored on password protected university computers in a restricted access building. All data will be stored in a designated storage facility within the WCTU.

5.6 Data access and quality assurance

The majority of data will be received directly from participants who will enter their data into the online study database. Following the completion of an expression of interest (EOI) form (which includes an initial eligibility check) participants will be contacted using the contact details that they have provided on the EOI form to confirm eligibility. Participants will complete an online consent form. After the collection of the baseline demographic data for each participant and following randomisation all data will be pseudonymised. Confidentiality will be strictly maintained and names, addresses or personal identifiable information will not be disclosed to anyone other than the staff involved in running the study. All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms will be held in secure, locked filing cabinets within a restricted area of WCTU. Participants will be identified by a participant number only on the paper forms. Direct access to source data (online study database) will be available for study-related monitoring or audit by UHCW or WCTU for internal audit or regulatory

authorities. The PI must arrange for retention of study records on site in accordance with GCP and local Trust's policies.

Direct access to source data/documents will be required for study-related monitoring. For quality assurance, the data and results will be statistically checked. A full data management plan will be produced by the study manager and statistician to outline the data monitoring checks required.

5.7 Data Shared with Third Parties

Requests for data sharing will be managed in accordance with University of Warwick SOP 15 Part 3. The datasets generated during and/or analysed during the current study are/will be available upon request after publication of the main study results. The publication of a study protocol, study results and study data will comply with the NIHR standard terms and will follow Warwick SOP 22: Publication & Dissemination.

5.8 Archiving

Study documentation and data will be archived for at least ten years after completion of the study. Study documentation and data held by NHS PIC sites will be stored in line with their local trust policy.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

We have no data on which to base a sample size estimation. There are no normative data for the PROPr quality of life scores in this 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 will use 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 patients. Then assuming an intra cluster coefficient 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 groups and 263 patients in the control arm (control:intervention = 1:1.03), using computations recommended by Moerbeek [43].

6.2 Statistical analysis of efficacy and harms

6.2.1 Statistics and data analysis

A detailed statistical analysis plan will be written and approved by the Data Monitoring Committee (DMC).

Data will be summarised and reported as per CONSORT, using intention-to-treat analyses.

For the primary outcome measures, treatment effects (with 95% Confidence Intervals) will be estimated using hierarchical linear regression models, Both unadjusted and adjusted (for stratification variables and important patient-level covariates) will be presented. We will estimate and adjust for site effects as a random variable in the model. Other secondary outcomes which are

continuous will be analysed in a similar way. Secondary outcomes which are categorical will be analysed using logistic regression models. We will assess compliance using Compliers Average Causal Effect (CACE) analysis. In the case of missing outcome data, we will compute sensitivity analyses using imputation techniques to examine the impact of missingness.

There are no formal interim analyses for this study.

6.2.2 Planned recruitment rate

A minimum recruitment rate of 67 participants per month will be required, based on a recruitment target of 535 participants over 8 months. Patients will be identified from roughly 20 PIC sites in addition to patients identified via self-referrals. The target recruitment rate for the study has been discussed with and agreed by the Trial Management Group (TMG). We are unable to estimate the numbers of self-referrals to the study at this stage. We will have data on proportion of self-referrals after the internal pilot study.

6.3 Subgroup analyses

Pre-specified, exploratory sub-group analysis will include age, need for critical care support, depression, anxiety, PTSD and ethnicity. The sub-group effects will be assessed using regression modelling with the interaction term of sub-group and treatment. As the sub-groups are not powered, the results will be reported using 95% confidence intervals.

6.4 Health economic evaluation

A prospectively planned economic evaluation will be conducted from a NHS and personal social services perspective, according to the recommendations of the NICE reference case [44].

Participants' health service contacts will be recorded at three, six and 12 months, including healthcare, local authority-provided day care and NHS residential services. Time lost from work (paid/unpaid) and patient-borne health costs (e.g. wheelchair by type, home adaptations, feeding aids, walking aids, home-help, support from relatives) will also be recorded, examining a broader social perspective. Participants will be encouraged to use an electronic or paper calendar to help recall this information at follow-up. Healthcare resource use will be costed using most recently available published national reference costs, reflated to a common year [45, 46].

Generic health-related quality-of-life will be assessed at baseline, three, six, and 12 months using the EQ-5D-5L questionnaire. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis [47]. Using the trapezoidal rule, the area-under-the-curve of health status scores will be calculated, providing patient-level QALY estimates. Reflecting the one year timeframe, costs and QALYs will be undiscounted.

Mechanisms of missingness of data will be explored and multiple imputation methods will be applied where appropriate to impute missing data. Imputation sets will be used in bivariate analysis of costs and QALYs, using the STATA MI framework. Within-study (12 month) incremental cost per QALY estimates and confidence intervals will be estimated [48-51]. Findings will be analysed and visualised in the cost-effectiveness plane, as cost-effectiveness acceptability curves, net monetary benefit and value of information analysis. At the time of writing no method is available to analyse one-arm clustering within a bivariate regression framework. Ignoring clustering may result in some over-precision of findings if the clustering effect is significant, although have limited scope to

systematically bias findings. The importance of clustering will be explored within a hierarchical univariate sensitivity analysis of net monetary benefit (NMB) at varying thresholds of willingness to pay. If incremental costs and benefits are non-convergent within the study follow-up then extrapolated modelling will be considered.

6.5 Qualitative data analysis

The semi-structured interviews with ~n=25 intervention group, ~n=25 control and ~n=5 practitioner's will be digitally recorded, subject to the permission of each participant/practitioner, pseudonymised, and transcribed verbatim. Framework analysis will be used to analyse the data [52]. This will involve:

- Data familiarisation: listening to digital recordings, reading transcripts, and re-reading field notes;
- Identifying a thematic framework: key issues and themes identified and an index of codes is developed;
- Indexing: this index is applied to all data;
- Charting: a summary of each passage of text is transferred into a chart to allow more overall and abstract consideration of index codes across the data set and by each individual;
- Mapping and interpretation: understanding the meaning of key themes, dimensions and broad overall picture of the data and identifying and understanding the typical associations between themes and dimensions. We will remain vigilant for any new themes emerging from the data as we progress. The computer package NVivo 12 will be used to organise the data.

The charting process provides an opportunity to code data from numerous perspectives. The computer package NVivo 11 will be used to organise the analysis.

The findings of the qualitative work will be reported as a separate chapter in the final report but will also be incorporated in the discussion to bring together a synthesis of all the results, thus helping to explore and explain the overall 'value' of the interventions. Quantitative and qualitative data will be integrated using a mixed methods matrix' where quantitative responses can be compared to interview data and recorded on a matrix. This is particularly useful to reveal gaps between quantitative and qualitative insights.

From the intervention delivery recordings (initial practitioner assessment, the exercise familiarisation session and the psychological support sessions) and control (1:1 session) recordings, a purposively selected subset (10%) of recordings will be analysed, with a checklist to assess fidelity and using the qualitative approach detailed above to help understand which areas generated discussion and what issues were discussed. Intervention fidelity will be assessed using the tenets highlighted by Mars et al.

7. STUDY ORGANISATION AND OVERSIGHT

7.1 Sponsorship and governance arrangements

University Hospitals Coventry and Warwickshire NHS Trust will act as Sponsor for the study and undertake the responsibilities as defined by the UK Policy Framework For Health and Social Care Research and Good Clinical Practice guidelines. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the study design, conduct, data analysis and interpretation and plans for publication and dissemination of results.

Study management will be undertaken at Warwick Clinical Trials Unit, the University of Warwick. A sub-contract agreement is in place between UHCW and WCTU who will provide full research management services. This will specify whose SOPs will be adhered to for each aspect of the study.

PIC agreements will also be in place between the Sponsor and each research site, with clear delegation of roles and responsibilities.

7.2 Ethical approval

All ethical approvals will be sought using the Integrated Research Application System. The study will be conducted in accordance with relevant regulations and guidelines. Before enrolling people into the study, each study site must ensure that the local conduct of the study has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to send out invitation letters for the study until written confirmation of R&D agreement is received by the co-ordinating team. Substantial protocol amendments (e.g. changes to eligibility criteria) will be communicated by the study team to relevant parties i.e. investigators, participants, NHS Trusts and study registries once approved. Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. The REC and sponsor will be notified of the end of the study (whether the study ends at the planned time or prematurely). The CI will submit a final report to the required authorities with the results, including any publications, within one year ending the study.

7.3 Peer Review

This study was peer reviewed by NIHR COVID-19 Recovery and Learning cross programme commissioning board.

7.4 Study Registration

The study will be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) Register.

7.5 Notification of serious breaches to GCP and/or study protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the study; or
(b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase and will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that study; or
(b) the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach

7.6 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick has Public Liability and Clinical Trials insurance cover in place to cover its own legal liabilities arising from the Study, including for any harm caused to participants by the design of the research protocol.

7.7 Study timetable and milestones

	Month	Recruitment
Set-up	0* – 1	n/a
Pre-pilot phase	1 – 2	n/a
Pilot study	2 – 3	35
Main recruitment	2 – 9	500
Primary Outcome	5 – 12	n/a
Follow-up	5 – 22	n/a
Process Evaluation	3 – 16	n/a
Analysis	14 – 17 / 23 – 24	n/a

**Month 0 estimated to commence 01st September 2020.*

7.8 Administration

The study co-ordination will be based at WMS/WCTU, University of Warwick.

7.9 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the study, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

The full remit and responsibilities of the TMG will be documented in the Charter which will be signed by all members.

7.10 Trial Steering Committee (TSC)

The study will be guided by a group of respected and experienced personnel and trial methodologists as well as at least one 'lay' representative. The TSC will have an independent chair-person. Meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the study will take responsibility for:

- Major decisions such as a need to change the protocol for any reason

- Monitoring and supervising the progress of the study
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the study

The membership of the TSC is shown on page 5.

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.11 Data Monitoring Committee (DMC)

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 three months into the recruitment phase and regularly thereafter, as directed by the DMC chair. Confidential reports containing recruitment, protocol compliance, safety data and 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 study should be amended or terminated. The membership of the DMC will be approved and appointed by the NIHR.

DMC meetings may also be attended by the CI and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.12 Essential Documentation

A Trial Master File will be set up in accordance to Warwick SOP 11 - 'Essential Documentation' and held securely at WCTU. Investigator Site Files will be prepared electronically and the content for the investigator site files will be uploaded to the study website (https://warwick.ac.uk/regain) for sites to download. UHCW will hold and maintain a Sponsor oversight file.

7.13 Financial Support

The study has been funded by a grant from NIHR Recovery and Learning programme further to a commissioned call (NIHR: 132046).

8. MONITORING, AUDIT AND INSPECTION

The study will be monitored by the Research and Development Department at UHCW as representatives of the lead Sponsor, and by the Quality Assurance team at WCTU as representatives of the study coordinating centre and academic lead, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring

will be specified in a study monitoring plan determined by the risk assessment undertaken prior to the start of the study. A Trial Monitoring Plan will be developed and agreed by the TMG and TSC based on the study risk assessment, including on site monitoring if applicable. Processes to be considered in the monitoring plan will include participant enrolment, consent, eligibility, and allocation to study groups; adherence to study interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. The plan will be available from the study coordination centre and will also be lodged with the sponsor. Whilst the monitors work in the same institution as the study team (WCTU), they will act independently in this role.

If the UHCW community exercise rehabilitation centre are persistently late in reporting SAEs, or there is evidence that the study protocols and procedures are not being adhered to (as assessed by the CI or the TMG) an on-site monitoring visit may be triggered where this is possible. The sponsor will ensure investigator(s) and/or institutions will permit study-related monitoring, audits and REC review, providing direct access to source data/documents as required. Monitoring will be performed by exploring the study dataset or performing central monitoring procedures and/or site visits, as defined in the study monitoring plan. Staff at WCTU and UHCW community exercise rehabilitation centre are obliged to assist the sponsor in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

We are setting up a reference group of COVID-19 survivors (>3/12 post-discharge) from the recently established COVID-19 follow-up clinic at UHCW. The PPI group will advise on intervention content, study processes and outcomes. As part of setting up this group, we will identify two further COVID-19 survivors to join the Trial Management Group and Steering Committee.

Our lay co-applicants will sit on the trial management group (TMG), initially meeting monthly and subsequently quarterly, and will have a pivotal role in steering the conduct of the study. They will review the ethics application to ensure that study documentation e.g. participant information sheet, is user appropriate. They will be given the opportunity to engage in study publicity and the dissemination of findings through appropriate channels i.e. social media, lay conferences, public engagement events, service provider events, newsletter articles. They will be viewed as members of the research team, with experience and skill that can contribute fully to the successful conduct of the study, and will be asked to be involved in measuring and reporting research impact. A role description and terms of reference for lay co-applicants has been produced in collaboration with our lay partners and the UHCW Patient and Public Research Advisory Group (PRAG). This will ensure that both parties understand the nature and extent of the collaboration, and their expectations of each other.

In addition to reviewing ethics documentation, we will ask our lay partners to work closely with the research team, acting as critical reviewers, in finalising the resources for REGAIN - practitioner manual, the home exercise guidance material, and the control group information. This is essential to ensure creation of feasible, acceptable and participant friendly resources. They will also help develop the interview topic guide and will contribute to the interpretation of qualitative data analysis.

Lay co-apps and partners will be supported by the Chief Investigator, study coordination team, and through the peer support of lay partners on existing clinical trials. Comprehensive training and

support will be provided by UHCW NHS Trust R&D department who run regular lay seminars, group training and social events through the PRAG, with governance from PALS. All activity will be appropriately reimbursed at INVOLVE rates, for which there is adequate provision in the budget. Lay partners will also benefit from training and support from Warwick CTU's existing one-day face-to-face training programme for patient and public partners which was developed in collaboration with a patient partner from another study who suggested the original need for, and content of, the course.

10. DISSEMINATION AND PUBLICATION

We will publish the primary analysis on three months outcomes as soon as possible after these are available to ensure they immediately inform practice. Full results of the study will be prepared by the research team and lay partners and submitted to funders as a final report. Findings will be submitted to peer-reviewed journals and disseminated to the medical and exercise rehabilitation communities. We will publish papers in open-access journals describing the development and refinement of the REGAIN intervention, and the study protocol, as per recommended guidance for transparent reporting, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org), the NIHR standard terms, and Warwick SOP 22: Publication & Dissemination. UHCW NHS Trust as Sponsor will review and approve all publications. We will submit abstracts to national and international conferences.

The REGAIN intervention will be fully manualised and available for public access once the study has completed. If appropriate, we will develop a practitioner training programme to support the implementation of REGAIN.

Our lay partners will help prepare the final report and assist with dissemination of study results. We will produce a lay summary for participants and the hospitals/centres involved. Results will be publicised via the study website and social media. At the end of the study, we will host a joint investigator and participant event to promote key findings. The REGAIN study will be relevant to the NHS thus outputs will follow the usual route into the NHS system and wider society.

HRA guidance on information for participants at the end of a study will be followed:

https://www.hra.nhs.uk/about-us/consultations/closed-consultations/guidance-participant-information-end-study-consultation/

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12. APPENDICES

12.1 Appendix 1 - Logic model for the REGAIN psychological intervention.