Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
REGAIN

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No

b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No

c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [x] Scotland
- [x] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
REGAIN

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

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

A3-1. Chief Investigator:

Title	Forename/Initials	Surname
Dr	Gordon	McGregor

Post	Associate Clinical Professor
Qualifications	BA(Hons), M.Phil, PhD
ORCID ID	0000 0001 8963 9107
Employer	University Hospitals Coventry and Warwickshire NHS Trust
Work Address	Department of Cardio-pulmonary rehabilitation UHCW Coventry
Post Code	CV2 2DX
Work E-mail	gordon.mcgregor@uhcw.nhs.uk
* Personal E-mail	
Work Telephone	02476 234 570
* Personal Telephone/Mobile	07772462255
Fax	

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

Title	Forename/Initials	Surname
Ms	Sharisse	Alleyne

Address	Warwick Clinical Trials Unit, Warwick Medical School University of Warwick Coventry
Post Code	CV4 7AL
E-mail	regain@warwick.ac.uk
Telephone	02476150285
Fax	

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	GM497120
Sponsor's/protocol number:	
Protocol Version:	V1.0
Protocol Date:	07/09/2020
Funder's reference number (enter the reference number or state not applicable):	132046
Project website:	https://warwick.ac.uk/fac/sci/med/research/ctu/trials/regain

Registry reference number(s):
The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

There is a substantial unmet need in the treatment and rehabilitation of people experiencing long-term effects from COVID-19. Existing NHS rehabilitation services have insufficient capacity to deal with demand, and delivery of rehabilitation healthcare in traditional group settings is currently suspended. However, virtual outpatient consultations have become commonplace in preference to face-to-face appointments. The implementation of personalised on-line consultation and treatment, whilst not well developed in the U.K., has been rapidly accelerated. On-line delivery of personalised rehabilitation may be beneficial for COVID-19 survivors who have ongoing physical and/or mental health

problems.

The objective of this trial is to run a multi-centre randomised controlled trial testing 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 (REGAIN) vs. best-practice usual care for people discharged from hospital (>3/12) after COVID-19 infection.

The intervention group will receive an eight-week, on-line, supervised, home-based, exercise rehabilitation programme with behavioural, motivational and mental health support. The intervention includes: 1) individual assessment; 2) supervised home-based exercise programme with pre-recorded and live sessions; 3) one-to-one and group on-line psychosocial and motivational support and education. The control group will receive a single, on-line, one-to-one, practitioner consultation with general advice on safe and effective physical activity.

Outcomes will be assessed at baseline, three, six and 12 months (post-randomisation). The primary outcome measurement is health related quality of life: PROMIS® 29+2 Profile v2.1 (PROPr) measured at three months post-randomisation.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

The trial 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.

Trial 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 trial participants, each PIC will ensure that the local conduct of the trial 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 individual data will be held within NHS sites. We will ensure that trial recruitment staff are trained in GCP and consent procedures.

Relevant data, including identifiable 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 trial staff at UHCW or WCTU during follow-up telephone calls with trial participants. These data will be considered as source data for the trial.

Participants who are not fluent in written English but speak one of the supported languages listed in the trial protocol will be eligible. Translation services will be used for these languages to enable non-English speakers to participate in the trial intervention and provide patient reported outcomes.

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 trial at the eligibility stage where exercise is clearly contraindicated, as assessed by the research nurse. 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 trial intervention. 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. Nevertheless, safety data and deaths will be closely monitored in all trial participants and these data presented to the DMC regularly. 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.

Emergency procedure: Participants will undertake live exercise and support sessions in discrete groups of up to 10 people. In advance of each session, the practitioner will have access to contact details for each participant. During the sessions, the practitioner will be able to see each participant individually on a large screen. In the event of an emergency, the practitioner will alert the designated 'co-pilot' for the session who will be able to communicate directly with the participant in question (via the live call or telephone) outside of the group, and alert the emergency services if

required.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☑ Qualitative research
- ☑ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

REGAIN is a multi-centre, randomised controlled trial 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 trial set-up
2. An internal pilot, with formative process evaluation, to test recruitment and trial procedures
3. A main trial with embedded process evaluation.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

Secondary objectives of the trial are to determine if the REGAIN intervention compared to best-practice usual care in patients with ongoing COVID-19 symptoms impacts:
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.

Sub-studies

Symptoms study objective:
To explore the relationship between personal characteristics and in-hospital care, and subsequent ongoing COVID-19 symptoms and other health problems.

Qualitative 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.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

At lease 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. However, a substantial proportion of people will have ongoing health problems. These problems are multi-systemic including motor, cognitive, neurological, musculoskeletal, respiratory and cardiovascular as well as depression, anxiety, and post-traumatic stress disorder (PTSD). In April 2020, the NHS predicted that 45% of people discharged from hospital would need some ongoing support from health and/or social care. In June 2020, Public Health England confirmed that the virus, and its treatment, would have a lasting impact on the health of survivors. 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, if any, 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, 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. 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.

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

Early data from COVID-19 survivors shows a broadly similar pattern along with persistent cognitive impairment, and pulmonary hypertension in those with thrombo-embolic problems. For the 45% of people hospitalised with COVID-19 in the UK who are estimated to require prolonged support from health and social care, a multitude of physical, psychological and social needs have been identified. For hospitalised, but less severely affected patients, long-term physical and psychological consequences are also prominent. A further feature is the disproportionate infection rate and progression to severe illness in Black, Asian and minority ethnic groups. 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 and survivors of SARS. A quasi-experimental study (N=72) in COVID-19 survivors reported positive results on multiple outcomes. 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. Moreover, international guidance does not support early pulmonary rehabilitation for COVID-19.

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

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

A multi-centre RCT testing 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 (REGAIN) vs. best-practice usual care for people discharged from hospital (>3/12) after COVID-19 infection.

Patients will be identified via two routes:
1. Participant Identification Centres
Clinical care teams at UHCW NHS Trust and each PIC site (NHS hospital trust) will screen hospital discharge data and identify potential participants for contact by mail. The sites will send potential participants an infographic flyer and invitation letter, (allocating a screening ID number) which will direct potential participants to the study website. 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 participant information sheet (PIS) and consent form 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 trial, 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 trial website: Bengali, Gujarati, Urdu, Punjabi and Mandarin.

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

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

If the participant is initially eligible they will be asked to enter their contact details including their first name, surname, address, post code, telephone number(s), email address, GP name and GP address. 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.

2. Self Referral
The study will be promoted though local/national media/social media, relevant charities and on the study website. 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 site referrals.

When a potential participant has registered their eligibility and provided their contact details for the REGAIN study via the online database, the WCTU REGAIN trial team and the REGAIN site team based at UHCW will receive an alert that a new potential participant has registered their interest. An appropriately trained clinical member of the REGAIN trial team (listed on the study delegation log) will then telephone the potential participant on their main telephone contact number. The REGAIN team member will conduct a full eligibility screen with the potential participant and complete an online eligibility form for the potential participant. The REGAIN 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 trial, 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 trial. A copy of the completed consent form 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.

Further to baseline assessment, a total of 535 participants will be randomised to the REGAIN intervention or best practice usual care on a 1.03:1 basis using a computer-generated randomisation sequence, performed by minimisation and stratified by age, assisted ventilation, and case level mental health disorder.

Best practice usual care will consist of a thirty-minute, on-line, one-to-one consultation with a REGAIN practitioner trained and supported a by Health Psychologist during the 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 be referred to their GP for treatment/advice.

REGAIN intervention (eight-weeks) includes:
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. 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, will also be directed to their GP for treatment/advice. These symptomatic patients will continue in the trial intervention as long as the practitioner considers their mental health problems would not preclude engagement.

2. On-line, home-based, exercise rehabilitation:
Up to 30 minutes exercise 2-3 times/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 one live on-line group exercise session every week for eight weeks led by a REGAIN practitioner, using equipment-free exercise to improve cardiovascular fitness, strength, balance, and co-ordination. These session will be undertaken in discrete groups. Participants will remain in the same group for the 8 week programme.

3. Psychosocial/motivational 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.

Outcomes will be assessed at baseline pre-randomisation, 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 trial participants using online data collection.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
PPI members have reviewed the patient facing documents submitted in this application to ensure the documentation was user appropriate.

A member of the ICUsteps Peer Support Group Charity is a listed co-applicant for this trial and has helped develop and refine the REGAIN protocol. Further PPI membership have been appointed to the TMG and will have a pivotal role in steering the conduct of the trial. They will be given the opportunity to engage in trial publicity and the dissemination of findings through appropriate channels i.e. social media, lay conferences, public engagement events, service provider events, newsletter articles. A role description and terms of reference for lay co-applicants has been produced This will ensure that both parties understand the nature and extent of the collaboration, and their expectations of each other.

Lay co-apps and partners will be supported by the CI, trial 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 with regular lay seminars, group training and social events through the Patient and Public Research Advisory Group (PRAG), with governance from PALS. All activity will be appropriately reimbursed at INVOLVE rates, for which there is adequate provision in the grant application. Lay partners will also benefit from training and support from UNTRAP (Universities/User Teaching and Research Action Partnership), an active organisation through which local communities engage in research and teaching in health and social care, at the University of Warwick.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☑ Inflammatory and Immune System
- ☐ Injuries and Accidents
- ☑ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☑ Respiratory
- ☐ Skin
- ☐ Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

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.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

1. Exercise contraindicated
2. Severe mental health problems preventing engagement
3. Previous randomisation in the present trial
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 trial

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Consenting	1	0	10 min	The Principal Investigator or delegated individual at each hospital sites
Questionnaires - Including PROMIS® 29+2 Profile v2.1, PROMIS dyspnoea severity short form v1.0, PROMIS Neuro-QoL Short Form v2.0, EQ-5D-5L, IPAQ-S, IES-r, HADS	3	0	45 mins	Performed by participant at home via trial database.
Qualitative interview	1	0	60 mins	Warwick CTU qualitative Research fellow with a sub-group of participants who consent to this (~n=25 intervention group, ~n=25 control)
Individual assessment to holistically assess participant needs, introduce the programme, and provide individualised exercise advice - Intervention group	1	0	60 mins	Conducted by REGAIN practitioner (Clinical Exercise Physiologist/physiotherapist), who will be trained and supported by a health psychologist during the study.
Supervised exercise rehabilitation sessions - intervention group	24	0	30 mins	REGAIN intervention practitioners.
Individual psychological support sessions - intervention group	6	0	60 mins	Conducted by REGAIN practitioner (Clinical Exercise Physiologist/physiotherapist), who will be trained and supported by a health psychologist during the study.
Best practice usual care - control group	1	0	30 mins	Conducted by REGAIN practitioner (Clinical Exercise Physiologist/physiotherapist), who will be trained and supported by a health psychologist during the study.

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

12 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

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 trial at the eligibility stage where exercise is clearly contraindicated, as assessed by the research nurse. 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 trial intervention. 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.

Emergency procedure: Participants will undertake live exercise and support sessions in discrete groups of up to 10 people. In advance of each session, the practitioner will have access to contact details for each participant. During the sessions, the practitioner will be able to see each participant individually on a large screen. In the event of an emergency, the practitioner will alert the designated 'co-pilot' for the session who will be able to communicate directly with the participant in question (via the live call or telephone) outside of the group, and alert the emergency services if required.

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.

Pregnancy is not an exclusion criterion for REGAIN. These potential participants will be recruited to the trial if eligible and participants who confirm pregnancy following enrolment will remain in the trial. These participants will be monitored for adverse events as per Section 4 of the protocol.

Guided home exercise will be conducted by intervention practitioners who will be specialist exercise physiologists or

physiotherapists, experienced in assessment, prescription and delivery of exercise in high risk clinical populations. Training in the standardised delivery of REGAIN will be provided. Warwick CTU and UHCW have extensive experience of training people to deliver complex interventions for chronic disorders. This, and experience of quality control of practitioner training, will ensure work is delivered to a high standard.

Over eight weeks participants in the intervention group will attend:
1. One-hour Individual Assessment

2. On-line, exercise rehabilitation
Participants will be encouraged to attend one live on-line group exercise session every week led by a REGAIN practitioner and complete up to 30 minutes exercise 2-3 times/week for eight weeks.

3. Psychosocial/motivational support
Six on-line 30-minute group sessions.

Home-based attendance of the online REGAIN intervention sessions will negate travel expenses and burden of journey time. Access to on demand exercise services will confer greater flexibility to participant's engagement with the trial intervention.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

Exercise rehabilitation may improve fitness, quality of life, breathlessness, fatigue, self-efficacy, emotional well-being, clinical status. 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.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

There will be no provision for continued supervised exercise and psycho-social and motivational sessions. Participants will be able to retain the study workbook which includes general information about the REGAIN study, guidance on the exercise and support sessions, space to record the dates and times of sessions, and worksheets to supplement the psychological support sessions.

Local services at each site may provide ongoing opportunity for supervised exercise for participants as paying customers of exercise, health and leisure services. This will be entirely dependant upon local provision and no guarantees of these opportunities can be provided.

A26. What are the potential risks for the researchers themselves? *(if any)*

We do not anticipate any risks to the researchers, all members of the research team will be suitability trained to deliver this study.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of social care or GP records, or review of medical records. Indicate whether this will be done by the direct care team or by researchers acting under arrangements with the responsible care organisation(s).*

Clinical care teams at each site (NHS hospital trust) will screen hospital discharge data and identify potential

participants for contact by mail.

The trial will be promoted though local media/social media, relevant charities and on the trial website. 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 for PIC referrals.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

(●) Yes ( ) No

Please give details below:
Potential participants will be identified by clinical teams at UHCW and each PIC site involved in the participants care who will screen hospital discharge data. Sites will send potential participants an invitation letter.

This will direct potential participants to the REGAIN website where they can access the patient information sheet. The invitation letter and website will instruct potential participants to read the patient information sheet, and if they are interested in taking part in the trial, to access the online database to register. The online database will ask potential participants a series of questions to determine their initial eligibility for the trial. If the participant is initially eligible they will be asked to complete and enter their contact details. 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 trial ahead of randomisation.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

All participant identification will be undertaken by trained NHS research staff within the hospital facility at each site, using approved clinical systems and
medical notes. All staff will abide by existing NHS and GDPR regulations. No identifiable personal information of patients will be transferred from the PIC sites to the trial team. Interested potential participants will register their interest by directly accessing the online database.

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

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

(●) Yes ( ) No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

(●) Yes ( ) No

If Yes, please give details below.
This is described in full detail in the patient information sheet and consent is specifically requested for this on the consent form.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

(●) Yes ( ) No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).
The trial will be promoted though the REGAIN participant flyer, local media/social media (including a trial Twitter

account), relevant charities and on the trial website. People suffering from ongoing COVID-19 related symptoms following hospital discharge will be able to self-refer.

A29. How and by whom will potential participants first be approached?

Identification and approach procedure:
1. Identify potential participants via clinical care teams at UHCW/PIC site or self-referral.
2. Sites will send potential participants an infographic flyer and invitation letter. The invitation letter will direct potential participants to the REGAIN website
3. The invitation letter and REGAIN study website will direct interested potential patients to read the patient information sheet which they will access via the REGAIN website
4. Potentially eligible patients will be directed to a 'suitability check link' on the study website which will link to the study database (initial screen). Here they will be asked a series of screening questions to determine their initial eligibility for the study and register their interest.
5. If a patient is initially considered eligible they will be asked to provide their contact details including their first name, surnameaddress, post code, telephone number (s),and email address, GP name and GP address.
6. Following successful completion of the suitability check (initial screen) a member of the REGAIN team will contact the patient via telephone to confirm their eligibility for the trial. The REGAIN 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. The trial team member will then explain the purpose of the consent form and summarise the key points with the participant.
7. Once an eligibility form has been completed the participant will receive a link to the online consent form. 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. Potential participants will need to confirm they have read each of the consent items before agreeing to take part in the study. .
7. A copy of the fully signed consent form will be sent to the participant via email.
8. Once the consent form has been completed, the participant will be able to access the baseline questionnaire from the same link. Once the consent form and baseline questionnaire have been completed by the participant they will be formally enrolled in the study.

A30-1. Will you obtain informed consent from or on behalf of research participants?

(●) Yes ( ) No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Consent process:
1. Potentially eligible patients will register their interest via the 'suitability check link' on the REGAIN website and provide their contact details including their first name, surname, address, post code, home telephone, mobile telephone and email address.
2. A member of the REGAIN team will contact the patient via telephone to confirm their eligibility for the trial and seek informed consent. The trial team member will then talk through each line of the consent form with the participant. The participant will be given as much time as they need to consider the trial and provide consent. If the potential participant would like to take part in the trial they will be asked to complete the online consent form.
3. A copy of the fully signed consent form will be sent to the participant via email.
4. The participant they will be directed to complete the baseline questionnaire. Once the consent form and baseline questionnaire have been completed by the participant they will be formally enrolled in the study.

Informed consent will be obtained by a suitably trained member of the research team as per the delegation log, after allowing sufficient time for the potential participant to consider their decision and ask questions about the trial, within two weeks of the patient's initial contact with the researcher.

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

When confirming consent for those unable to read English, a second person will be present to confirm correct explanation.

New information: Any new information that arises during the study will be reviewed by the TSC. If this new information may affect participants' willingness to take part in the study, it will be communicated to all participants. Participants will be contacted by a member of the REGAIN team and asked whether they still wish to continue participating in the study. Participants will be provided with an updated PIS and asked to complete a revised consent form as necessary.

Incidental findings: Incidental findings relating to participants' medical conditions or general health, will be discussed with the managing consultant, and communicated to the participant as required. We have a clearly defined process for handling incidental findings from our questionnaires that assess anxiety, depression and post-traumatic stress (potential case-level mental health diagnosis). Our psychiatric and health psychology co-investigators have identified cut-off points that are pre-programed into the trial database. Should participants exceed these clinical cut-offs on completion of the online questionnaires, the trial staff and REGAIN intervention/control practitioners (clinical exercise physiologists/physiotherapists) will be alerted. This information will be discussed with the participant during their initial one-to-one appointment with a REGAIN practitioner at baseline, or a separate call with a REGAIN practitioner will be arranged if identified during study follow-up. Further, as standard, the participant will be advised to make an appointment with their GP to discuss the incidental findings. Also during the initial one-to-one appointment with a REGAIN practitioner at baseline, symptoms and issues will be discussed with all participants, and onward referral to their GP initiated where appropriate.
Participants will be provided with contact details for the REGAIN trial team based at atrium health should they wish to report any concerns they may have.

Decline/withdrawal: People who have entered the study will still have the option to withdraw before treatment starts (i.e. between baseline assessment and the beginning of the intervention/ control), if for any reason they change their mind. The right of a potential participant to refuse participation without giving reasons will be respected and recorded on the screening log. The participant will remain free to withdraw at any time without giving reasons and without prejudice to any further treatment, and will be provided with a contact point where he/she may obtain further information about the trial.

Participants will be asked to consent (or not) to being contacted around three months after they have entered the trial to share their views and experiences of the intervention and control. Participant interviews will be completed online and online consent will be taken and documented prior to the interview taking place.

At the beginning of the study, participants will be asked if they consent to have photographs or short video clips taken for use at conference presentations or for study publicity. If they consent to this, participants may be approached to participate in the filming sessions to develop the video resources needed for the trial including promotional materials and publications. Patients will be approached by a study practitioner and an appropriate time and date will be arranged for photos/recordings to be taken.

The REGAIN study will be delivered online from a single central venue – UHCW NHS Trust. There will be 5 practitioners involved in delivery of the study (control and intervention). At the end of their time on the study, and with their consent, we will interview all of practitioners involved with the study. If more practitioners are involved in delivery, we will also interview them. Interviews will be conducted by a qualitative research fellow from Warwick CTU.

At the end of the trial, all REGAIN practitioners will be asked to consent to 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.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

The potential participant will be allowed up to three weeks from initial contact with the researcher in order to consider the trial and decide whether to take part.

Timing and appropriateness of obtaining consent will be closely monitored by the Trial Management Group (TMG) and reviewed by the independent Trial Steering Committee (TSC).

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

- (●) Yes
- ( ) No
- ( ) Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Recruitment to this study for patients already participating in other studies will be considered on a case by case basis. Patients on observational trials mirroring clinical care will be enrolled. If patients are on other interventional trials, they will only be approached about the current study if enrolment will not impact the outcome of either trial and if the burden on the patient is not significant.

Co-enrolment will be monitored by the Trial Management Group (TMG) and reviewed by the independent Trial Steering Committee (TSC).

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Written translations of patient facing documents, including the patient information sheet and consent form, are available in the following additional languages: Bengali, Punjabi, Gujarati, Urdu and Mandarin. An accredited NHS translator or bilingual research associate will assist consent and eligibility discussions in the aforementioned non-English languages. An accredited NHS translator will also be included in the one-to-one advice consultation (control arm) and the individual assessment (intervention arm). For the psychological support sessions we will arrange bespoke small group sessions with an NHS accredited translator.

Participants who are not fluent in English but do speak one of the aforementioned languages will be encouraged to invite a friend or relative to attend the on-line, supervised, home-based, exercise rehabilitation sessions in order to provide translation. Written translations of on-demand exercise materials will be provided via subtitles prepared by appropriate translators into the aforementioned non-English languages.

Translations of the trial case report forms (CRF) will not be available via the trial website, however, where required bilingual research associates will act as translators to contact the participant via telephone, to read through each question of the (CRF) and record the participant's responses via the trial website.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

The trial will initially open to recruitment within English PIC sites before expanding to the devolved nations, including Wales. During set up of Welsh PICs the trial team will liaise with Health and Care Research Wales and the local Health Board, who is responsible for providing translations of patient information sheets and consent forms where required. Additional translation services will be considered where required, as outlined in section A33-1.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Any new information that arises during the study will be reviewed by the TSC. If this new information may affect participants' willingness to take part in the study, it will be communicated to all participants. Participant will be contacted by a member of the REGAIN team and asked whether they still wish to continue participating in the study. Participants will be provided with an updated PIS and asked to complete a revised consent form as necessary.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- (●) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would

be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

◯ The participant would continue to be included in the study.

◯ Not applicable – informed consent will not be sought from any participants in this research.

◯ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☑ Access to medical records by those outside the direct healthcare team
- ☑ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☑ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☑ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☑ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☑ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☑ Laptop computers

Further details:
All information will be entered onto a secure online database, set up by the University of Warwick Clinical Trials Unit, that only authorised personnel will have access to. Case Report Forms, Consent Forms and the Trial Master File will be kept in locked filing cabinets in designated archive rooms in the University of Warwick's Clinical Trials Unit, to which only authorised personnel have access.

Direct quotations may be published during the dissemination of the research findings - these will be anonymised at all times.

Audio/visual recording will be used to produce on-demand exercise materials and case studies of participation in this research project. No personal data will be published in this process and the study consent form will include a section relating to this.

Qualitative interviews will be recorded and transcribed - both the recording and transcription will be fully anonymised.

All electronic devices will be password protected as per NHS and WCTU SOPs and as per GDPR.

Contact details may be shared with a third party text messaging service in order for participants to be contacted about the trial. Participants who are randomised to the REGAIN intervention arm will also be asked to register an account with a third party online video platform using their name and email address if they agree to the terms and conditions. This will enable the participants to access the intervention content. Participants will be asked to complete brief questionnaire polls via the online system before and after each supervised group exercise session. This will allow the REGAIN practitioner to collect information on adverse events. Information on data sharing with other organisations is detailed in the PIL and Consent Form.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Personal data collected during the trial will be handled and stored in accordance with GDPR and Data Protection Act 2018.

Handling of personal 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 Standard Operating Procedures and the UK regulatory framework. There is no reason to expect this situation to occur in this trial more than any other.

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 trial staff including the trial statistician.

All essential documentation and trial records will be stored at WCTU in conformance with the applicable regulatory requirements and access to stored information (paper and electronic) will be restricted to authorised personnel.

All data will be stored in a designated storage facility within the University Hospitals Coventry and Warwickshire and/or Warwick Clinical Trials Unit.

Electronic data will be stored on password protected university computers in a restricted access building.

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All data will be pseudo-anonymised after the collection of the baseline demographic data for each participant.

Confidentiality will be strictly maintained and names or addresses will not be disclosed to anyone other than the staff involved in running the trial. All electronic participant-identifiable information will be held on a secure, password protected database accessible only to essential personnel. Paper forms with participant-identifiable information 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/documents will be available for trial-related monitoring or audit by UHCW or Warwick CTU for internal audit, regulatory authorities or ethics committees. The principal investigator will arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

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

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Participants will consent to providing the trial management team with their contact details to enable follow-up questionnaires to be sent to the participants in the post, if required.

The majority of data will be received directly from participants who will enter their data into the online trial 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 consent. 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 pseudo-anonymised. 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 trial. 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 trial database) will be available for trial-related monitoring or audit by UHCW or WCTU for internal audit or regulatory authorities. The PI must arrange for retention of trial records on site in accordance with GCP and local Trust's policies.

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

Requests for data sharing will be managed in accordance with University of Warwick/WCTU policy on data sharing. The datasets generated during and/or analysed during the current study are/will be available upon request. The publication of a trial protocol, trial results and trial data will be in line with the NIHR standard terms and will follow WCTU SOPs.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Data analysis will be undertaken by the University of Warwick Clinical Trials Unit Statistical Team.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Dr	Gordon	McGregor
Post	Associate Clinical Professor		
Qualifications	BA(Hons), M.Phil, PhD		
Work Address	Department of Cardio-pulmonary rehabilitation University Hospitals Coventry & Warwickshire Coventry		
Post Code	CV2 2DX		
Work Email	gordon.mcgregor@uhcw.nhs.uk		
Work Telephone	02476 234 570		
Fax			

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ◉ 6 – 12 months
- ○ 12 months – 3 years
- ○ Over 3 years

A44. For how long will you store research data generated by the study?

Years: 10
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

As per UHCW NHS Trust policy, once the trial has come to an end and the analysis has taken place, trial documentation will be held for approximately 10 years. It is the responsibility of the CI to ensure the data is stored securely by a third party and is easily retrieved if required. All electronic pseudonymised patient information will be held on a secure, password protected database accessible only to essential personnel. Paper forms with patient identifiable information will be held in secure, locked filing cabinets within restricted areas at UHCW NHS Trust.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ○ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50-1. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted

in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ○ No

Please give details, or justify if not registering the research.
ISRCTN
University of Warwick website.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

☑ Peer reviewed scientific journals
☑ Internal report
☑ Conference presentation
☑ Publication on website
☑ Other publication
☑ Submission to regulatory authorities
☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
☐ No plans to report or disseminate the results
☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Identifiable data will not be used during the analysis of trial data. The data will be pseudonymised to facilitate the analysis of the data and no identifiable data will be published, only anonymised data.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.
Warwick CTU, with the lead clinical centre (UHCW) and lay partners, will jointly lead on strategies for knowledge dissemination and engagement within the NHS and wider public. All organisations will work together to ensure that clinically important findings are disseminated as widely as possible and, by working collaboratively, we will help facilitate the adoption of such outcomes within the NHS to enhance patient care. Towards the end of the trial, we will host a joint investigator and participant event to release and promote key trial findings.

The results of the trial will be made available once the final report is complete. An "End of Trial Letter" will be sent to participants making reference to the location of the results (likely to be directed to a website containing a lay summary of the results) and participants will be offered further information summarising the results of the trial if participants have indicated they wish to receive them.

5. Scientific and Statistical Review

A54-1. How has the scientific quality of the research been assessed?*Tick as appropriate:*

☑ Independent external review
☐ Review within a company
☐ Review within a multi−centre research group

- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
This study was peer reviewed by NIHR COVID-19 Recovery and Learning cross programme commissioning board.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title Forename/Initials Surname
	Prof Ranjit Lall
Department	Warwick Clinical Trials Unit
Institution	University of Warwick
Work Address	Warwick Clinical Trials Unit, Warwick Medical School
	University of Warwick
	Coventry
Post Code	CV4 7AL
Telephone	02476574650
Fax	
Mobile	
E-mail	R.Lall@warwick.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

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 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.

A58. What are the secondary outcome measures?*(if any)*

1. HRQoL: PROPr
2. Dyspnoea: PROMIS dyspnoea severity Short Form. 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. 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. 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
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. 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. Sub-score values ≥11 points identify case-level anxiety/depression. Commonly used and well validated measure in clinical populations.
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, participant self-report, and data held in participating hospitals to achieve a robust estimate of health service activity. Consent will be obtained for access to NHS and GP records.
10. Overall health – Participant self-reported measurements of current overall health and comparison of current health to health 12 months prior.
11. Death measured using GP and NHS records.

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 535
Total international sample size (including UK): 535
Total in European Economic Area:

Further details:
We aim to recruit 535 participants, who will be randomised to the REGAIN intervention or best practice usual care on a 1.03:1. This equates to 272 participants in the intervention arm and 263 patients in the control arm.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

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.

A61-1. Will participants be allocated to groups at random?

◉ Yes ○ No

If yes, please give details of the intended method of randomisation:
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 and IES-6.

Participants will be randomised strictly sequentially at trial level, as participants are eligible for randomisation.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

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.

Sub-group 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.

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.

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.

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. 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-trial (12 month) incremental cost per QALY estimates and confidence intervals will be estimated. 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 trial follow-up then extrapolated modelling will be considered.

Qualitative 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, pseudo-anonymised, and transcribed verbatim. Framework analysis will be used to analyse the data. 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.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Prof	Martin	Underwood
Post	Professor of Primary Care Research		
Qualifications	PhD MRCP		
Employer	University of Warwick		
Work Address	WCTU		
	WMS, Gibbet Hill Road		
	Coventry		
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Work Email	m.underwood@warwick.ac.uk		

	Title	Forename/Initials	Surname
	Prof	Julie	Bruce
Post	Professorial Fellow		
Qualifications	PhD		
Employer	University of Warwick		
Work Address	REGAIN Trial Team, WCTU		
	WMS, Gibbet Hill Road		
	Coventry		

Post Code	CV4 7AL
Telephone	
Fax	
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Work Email	Julie.Bruce@warwick.ac.uk

Title	Forename/Initials	Surname
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Post	Professor of Health Research
Qualifications	PhD
Employer	University of Warwick
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Post Code	CV4 7AL
Telephone	
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Work Email	kate.seers@warwick.ac.uk

Title	Forename/Initials	Surname
Assoc Prof	Harbinder	Sandhu

Post	Health Psychologist
Qualifications	PhD
Employer	University of Warwick
Work Address	Warwick Clinical Trials Unit, Warwick Medical School University of Warwick Coventry
Post Code	CV4 7AL
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Fax	
Mobile	
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Title	Forename/Initials	Surname
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Post	Consultant Psychiatrist
Qualifications	MB MD(Res)
Employer	Coventry and Warwickshire Partnership NHS Trust
Work Address	Wayside House Wilson Lane Coventry
Post Code	CV6 6NY
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Work Email	bartholomew.sheehan@covwarkpt.nhs.uk

	Title	Forename/Initials	Surname
	Dr	David	McWilliams
Post	Consultant Critical Care Physiotherapist		
Qualifications	BSc (Hons), MSc, PhD		
Employer	University Hospitals Birmingham NHS Foundation Trust		
Work Address	Critical Care, Queen Elizabeth University Hospital Mindelsohn Way Birmingham		
Post Code	B15 2TH		
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Mobile			
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	Title	Forename/Initials	Surname
	Assoc Prof	Joyce	Yeung
Post	Consultant Critical Care Physician		
Qualifications	MBChB, PhD, FRCA, FFICM		
Employer	University of Warwick		
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	Title	Forename/Initials	Surname
	Dr	Beatriz	Lara
Post	Consultant Respiratory Physician		
Qualifications	MD PhD		
Employer	University Hospitals Coventry and Warwickshire NHS Trust		
Work Address	Department of Cardiology and Respiratory UHCW, Clifford Bridge Rd Coventry		
Post Code	CV2 2DX		
Telephone			
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	Title	Forename/Initials	Surname
	Dr	Christina	Jones
Post	Research Manager		
Qualifications	PhD		
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Title	Forename/Initials	Surname
Prof	Ranjit	Lall

Post	Professor of Clinical Trials and Biostatistics
Qualifications	PhD
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Title	Forename/Initials	Surname
Dr	Chen	Ji

Post	Senior Research Fellow - Statistics
Qualifications	PhD
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Title	Forename/Initials	Surname
Miss	Katie	Booth

Post	Research Associate (Statistician)
Qualifications	MSc
Employer	University of Warwick
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Post Code	CV4 7AL
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Work Email	K.Booth@warwick.ac.uk

	Title	Forename/Initials	Surname
	Prof	James	Mason
Post	Professor of Health Economics		
Qualifications	PhD		
Employer	University of Warwick		
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Mobile			
Work Email	J.Mason@warwick.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Alastair	Canaway
Post	Health Economist		
Qualifications			
Employer	University of Warwick		
Work Address	Warwick Clinical Trials Unit, Warwick Medical School Gibbet Hill Road, University of Warwick Coventry		
Post Code	CV4 7AL		
Telephone			
Fax			
Mobile			
Work Email	A.Canaway@warwick.ac.uk		

	Title	Forename/Initials	Surname
	Ms	Rachel	Potter
Post	Senior Research Fellow		
Qualifications	PhD		
Employer	University of Warwick		
Work Address	Warwick Clinical Trials Unit, Warwick Medical School Gibbet Hill Road, University of Warwick Coventry		
Post Code	CV4 7AL		
Telephone			
Fax			
Mobile			
Work Email	r.potter@warwick.ac.uk		

	Title	Forename/Initials	Surname
	Mr	Stuart	Ennis
Post	Research Fellow		
Qualifications	MSc		
Employer	University of Warwick		
Work Address	Warwick Clinical Trials Unit, Warwick Medical School Gibbet Hill Road, University of Warwick Coventry		

Post Code	CV4 7AL
Telephone	
Fax	
Mobile	
Work Email	stuart.ennis@warwick.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- (●) NHS or HSC care organisation
- ( ) Academic
- ( ) Pharmaceutical industry
- ( ) Medical device industry
- ( ) Local Authority
- ( ) Other social care provider (including voluntary sector or private organisation)
- ( ) Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	UHCW NHS Trust
Given name	Becky
Family name	Haley
Address	Research & Development
Town/city	4th Floor Rotunda, ADA40007
Post code	CV2 2DX
Country	United Kingdom
Telephone	02476 966198
Fax	
E-mail	becky.haley@uhcw.nhs.uk

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [ ] Funding secured from one or more funders
- [x] External funding application to one or more funders in progress
- [ ] No application for external funding will be made

What type of research project is this?

- (●) Standalone project
- ( ) Project that is part of a programme grant
- ( ) Project that is part of a Centre grant
- ( ) Project that is part of a fellowship/ personal award/ research training award
- ( ) Other

Other – please state:

Please give details of funding applications.

Organisation	National Institute for Health Research
Address	Evaluation, Trials and Studies Coordinating Centre, University of Southampton Alpha House, Enterprise Rd Chilworth, Southampton
Post Code	SO17 1BJ
Telephone	02380597501
Fax	
Mobile	
Email	netspostawardsetup@nihr.ac.uk

Funding Application Status: ( ) Secured (●) In progress

Date Funding decision expected: 01/09/2020

Amount: £1,204,297

Duration

Years: 2

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

NIHR COVID-19 Recovery and Learning Cross Programme programme

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

(●) Yes ( ) No

Name: Warwick Clinical Trials Unit

Type of organisation:

( ) NHS (●) Academic ( ) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: Study management will be undertaken at Warwick Clinical Trials Unit, the University of Warwick.

Name: Beamfeelgood.com

Type of organisation:

( ) NHS ( ) Academic (●) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: An external online video platform, Beamfeelgood.com, will be used for the REGAIN study interventions

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Ms	Becky	Haley
Organisation	UHCW NHS Trust		
Address	Research & Development		
	4th Floor Rotunda, ADA40014		
	University Hospital, Coventry		
Post Code	CV2 2DX		
Work Email	R&DSponsorship@uhcw.nhs.uk		
Telephone	02476 966198		
Fax			
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

West Midlands

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/09/2020
Planned end date: 31/08/2022
Total duration:
Years: 1 Months: 11 Days: 31

A71-1. Is this study?

◉ Single centre
○ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- [x] England
- [ ] Scotland
- [ ] Wales
- [ ] Northern Ireland
- [ ] Other countries in European Economic Area

Total UK sites in study 1

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

[x] NHS organisations in England	1
[ ] NHS organisations in Wales	
[ ] NHS organisations in Scotland	
[ ] HSC organisations in Northern Ireland	
[ ] GP practices in England	
[ ] GP practices in Wales	
[ ] GP practices in Scotland	
[ ] GP practices in Northern Ireland	
[ ] Joint health and social care agencies (eg community mental health teams)	
[ ] Local authorities	
[ ] Phase 1 trial units	
[ ] Prison establishments	
[ ] Probation areas	
[ ] Independent (private or voluntary sector) organisations	
[ ] Educational establishments	
[ ] Independent research units	
[ ] Other (give details)	

Total UK sites in study: 1

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

◉ Yes ○ No

A73-2. If yes, will any of these organisations be NHS organisations?

◉ Yes ○ No

If yes, details should be given in Part C.

A73-3. Approximately how much time will these organisations expect to spend on screening records and/or provision

of information to potential participants, and how will the costs of these activities be funded?

Participant identification centres across the UK will receive £400 per site payment as part of the PIC agreement to cover the research costs which will include a database search to identify potential patients (60 mins), preparation of letters and mail out to these patients (200 mins) and minimal data collection (for the symptoms sub-study; 360 mins).

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

The study will be monitored by the Research and Development Department at University Hospitals Coventry and Warwickshire NHS Trust as representatives of the Sponsor and by the Quality Assurance team at Warwick Clinical Trials Unit as representatives of the trial management team, 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 trial 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 Trial Management Group (TMG) and Trial Steering Committee (TSC) based on the trial 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 trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. This plan will be available from the trial coordination centre and will also be lodged with the Sponsor. Whilst the monitors work alongside the CI and trial team (WCTU), they will act independently in this role. Sites persistently late in reporting SAEs, receipt of multiple late/poorly completed CRFs, or evidence from CRFs that the trial protocols and procedures are not being adhered to (as assessed by the CI or the TMG) may be considered triggers for on-site monitoring visits. The sponsor will ensure investigator(s) and/or institutions will permit trial-related monitoring, audits and REC review, providing direct access to source data/documents as required. Monitoring will be performed by exploring the trial dataset or performing central monitoring procedures and/or site visits, as defined in the trial monitoring plan.

Recruitment sites are obliged to assist the sponsor in monitoring the study. These may include hosting site visits, Recruitment sites 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.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

The Data Monitoring Committee (DMC) will be established in line with the charter set by Warwick Clinical Trials Unit and will be independently chaired and established in accordance with the principles of Good Clinical Practice and Warwick Clinical Trials Unit Standard Operating Procedures (SOPs). All Serious Adverse Events (SAEs) will be entered onto the Serious Adverse Event reporting form within 24 hours of the Investigator/research team becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and possibly related to the trial interventions will be notified to the Research Ethics Committee (REC) and Sponsor within 15 days. All such events will be reported to the Trial Management Group at their next meeting. Experience suggests that the nature of trial design is such that there is unlikely to be sufficient data available to make decisions regarding efficacy prior to the end of the recruitment phase of the study. This will in part be determined by the study recruitment patterns, which will be routinely monitored by DMEC, therefore they may decide that a narrow window of opportunity does exist to assess treatment efficacy. If so, they are at liberty under the DMEC charter to make recommendations and suggestions to the Trial Management and Steering Committees at end stage of the study.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The trial will be stopped prematurely if:
• Mandated by the Ethics Committee
• Following recommendations from the Data Monitoring Committee (DMC)
• Funding for the trial ceases

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

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

NHS indemnity (via UHCW) covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. 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.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☑ NHS indemnity scheme will apply (protocol authors with NHS contracts only)

☑ Other insurance or indemnity arrangements will apply (give details below)

NHS indemnity (via UHCW) covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. 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.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

NHS indemnity (via UHCW) covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. 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.

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

A79. Please select the level of commercial participation in this project.

◉ None
○ Industry funding, but not industry sponsored
○ Industry funding and industry sponsored
○ Industry sponsored, but not industry funded

A80. Please select the main subject area of research. Additional sub-topics may be selected, if required

☐ Age and Ageing
☐ Anaesthetics
☐ Cancer (includes malignant haematology
☐ Cardiovascular
☐ Clinical
☑ Critical Care
☐ Dementias and Neurodegenerative Diseases
☐ Dermatology
☐ Diabetes
☐ Ear, Nose and Throat
☐ Gastrointestinal
☐ Genetics
☐ Health Services Research
☐ Hepatology
☐ Immunology and Inflammation
☐ Infectious Disease and Microbiology
☐ Injuries and Accidents
☐ Medicines for Children (does not include Paediatrics)
☑ Mental Health
☐ Metabolic and Endocrine
☐ Musculoskeletal (Rheumatoid Arthritis is a separate category)
☐ Nervous System Disorders
☐ Non-malignant Haematology
☐ Ophthalmology
☐ Oral and Dental

- [ ] Paediatrics (does not include Medicines for Children)
- [ ] Primary Care
- [ ] Public Health Research
- [ ] Renal
- [ ] Reproductive Health and Childbirth
- [x] Respiratory
- [ ] Rheumatoid Arthritis
- [ ] Stroke
- [ ] Surgery
- [ ] Urogenital

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For further information please refer to guidance.*

Investigator identifier	Research site	Investigator Name	
IN1	◉ NHS/HSC Site ○ Non-NHS/HSC Site	Forename	Gordon
		Middle name	
		Family name	McGregor
Organisation name	UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE NHS TRUST	Email	gordon.mcgregor@warwick.ac.uk
Address	WALSGRAVE GENERAL HOSPITAL CLIFFORD BRIDGE ROAD COVENTRY	Qualification (MD...)	PhD
		Country	United Kingdom
Post Code	CV2 2DX		
Country	ENGLAND		

Participant Identification Centres

PIC Type	Centre	Individual(s)
○ NHS (England) ○ NHS (outside England) ○ Non-NHS		E-mail: