iRehab

Remote rehabilitation after intensive care

PROTOCOL

Remote multicomponent rehabilitation compared to standard care for survivors of critical illness after hospital discharge: a randomised controlled assessor-blind clinical and cost-effectiveness trial with internal pilot (iRehab).

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This protocol has regard for current HRA guidance and content.

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The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Protocol Version Log

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Summary of Changes N/A. Initial protocol sent to REC, not approved.		
2.0	10th May 2022	18th May 2022
Summary of Changes Removal of pregnancy from exclusion criteria.		
3.0	28th September 2022	18th October 2022
Summary of Changes Updates to trial team contact details Recruitment start date of 1st October 2022 Clarification around AEs and SAEs Addition of reporting hospital readmissions		
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Summary of Changes Further clarification around AEs and SAEs Updates to trial team Addition of information for data sharing with co-enrolled trials Addition of email for contacting patients		
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Summary of Changes Inclusion of TFAQ questionnaire Option to re-collect EQ-5D data if required Updates to process evaluation		

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TRIAL SUMMARY

Full Title	Remote multicomponent rehabilitation intervention in survivors of critical illness post hospital discharge: a randomised controlled assessor-blind clinical and cost effectiveness trial with internal pilot.
Short title	Remote Rehabilitation After Intensive Care (iRehab)
Duration of Trial	1st January 2022 – 31 December 2024 (36 months)
Clinical Phase	Phase III
Trial Design	Pragmatic, randomised (allocation ratio 1: 1.17), controlled, assessor blind, multi-centre trial with internal pilot and embedded process evaluation.
Research question:	What is the clinical and cost effectiveness of a remote multicomponent rehabilitation intervention compared to standard care in survivors of critical illness following discharge from hospital after an Intensive Care Unit admission (ICU)
Trial Participants	Adults within 12 weeks of hospital discharge after treatment of a critical illness requiring ICU care and mechanical ventilation for ≥48hours
Planned sample size	428 participants (197 control: 231 intervention) from at least 30 UK sites
Intervention	Six-week remote multi-component, individualised, rehabilitation intervention incorporating: weekly symptom management; targeted exercise; psychological support; and peer support and Information.
Control	Standard care offered at each site
Outcomes Primary: Secondary:	Measured pre-randomisation, eight weeks, six months post-randomisation Health-related Quality of Life: EQ-5D-5L at eight weeks Physical Function: 30 second sit to stand test Illness Perception: Brief Illness perception questionnaire (BIPQ) Fatigue: Fuctional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale Anxiety and Depression: Hospital Anxiety and Depression Scale (HADS) Healthcare and social care utilisation Safety: Serious Adverse events Acceptability and Process Evaluation: Theoretical Framework of Acceptability Questionnaire
Follow-up	Remote follow up at eight weeks and six months (26 weeks)

Process evaluation	Qualitative interviews with up to 40 participants from intervention and standard care arms, and up to30 health care professionals (intervention team members, trial management group members, CTU staff, NHS staff involved in the trial and/or rehabilitation service delivery). Acceptability of rehabilitation or treatments that participants received explored using the Theoretical Framework of Acceptability Questionnaire (TFAQ).

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	**Explanation**
AE	Adverse Event
CACE	Complier Average Causal Effect
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	European Quality of Life – 5 Dimensions
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health Related Quality of Life
HSC	Health and Social Care
HSCT	Health and Social Care Trust
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICU	Intensive Care Unit
IRAS	Integrated Research Application System
ISO	International Organisation for Standardisation
ISRCTN	International Standard Randomised Controlled Trial Number
LTFU	Lost to Follow-up
MRC	Medical Research Council
NICE	National Institute Clinical Excellence

NIHR	National Institute for Health and Care Research
NHS	National Health Service
ORCHA	Organisation for Review of Care and Health Apps
PAG	Patient Advisory Group
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient & Public Involvement
QA	Quality Assurance
QALY	Quality of Life Years
QOL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SF-36	Short Form 36 Health Survey Questionnaire
SOP	Standard Operating Procedure
TFAQ	Theoretical Framework of Acceptability Questionnaire
TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

The UK Intensive Care National Audit and Research Centre, described approximately 172,000 admissions to critical care units in England, Wales, and Northern Ireland, with approximately 129,000 patients surviving critical illness discharged from acute hospitals over one year (April 2019 to March 2020) (1).The consequences of critical illness are substantial and multifactorial, and often encompass physical deconditioning, respiratory and swallowing problems, reduced activities of daily living, cognitive and mental health impairments, fatigue, and declines in health-related quality of life (HRQoL) (2-8). In the UK, one in four people recovering from critical illness experience an unplanned hospital readmission within 90 days of discharge, substantially higher rates of readmission than hospitalised patients without an ICU stay (9). At a societal level, nearly half of ICU survivors fail to return to work after 12 months, (10-11) with UK data highlighting the increase in social care support required (11). Therefore there is a need to intervene to improve the long term health of patients discharged home after intensive care. Identifying ways to support people returning home after a stay in ICU has been ranked a key priority for research by patients, their families, and researchers (12).

Guidance has recommended remote rehabilitation as standard of care for critically ill survivors following COVID-19 (13,14). There is no evidence to support the delivery of remote rehabilitation to the broader population of survivors of critical illness, despite its use and anecdotal evidence of acceptability across many disease populations. This trial will provide evidence on whether remote rehabilitation is clinically and cost-effective for survivors following critical illness post-ICU care. This trial will provide high quality evidence regarding the effectiveness of remote rehabilitation on health-related outcomes and whether rehabilitation should be implemented more widely across the NHS or withdrawn if there is no evidence of improved outcomes for patients.

1.2 Existing knowledge

National Institute for Health and Care Excellence (NICE) guidance currently advises that the recovery pathway following critical illness should include regular assessment of physical and non-physical morbidity, goal setting, multi-professional rehabilitation input according to individualised needs, and transition of information between care delivery stages (15). However, this practice has either been applied poorly or not at all following hospital discharge, and rehabilitation services post-critical illness in the UK are ad hoc, geographically inconsistent, and variable in terms of structure, content, and format of delivery (16). A survey of 242 UK hospitals conducted in 2020 found that few responding hospitals offered a post-discharge physical rehabilitation programme (31/176, 18%) (17).

Exercise programmes can aid physical recovery in people with chronic obstructive pulmonary disease, chronic fatigue, and congestive heart failure (18-20). Our Cochrane systematic review found that evidence for the effectiveness of post-hospital discharge rehabilitation interventions for survivors of critical illness was inconclusive (21, 22). Nonetheless, findings from qualitative studies suggest that individual's experience of participating in rehabilitation programmes is markedly positive across domains of health, wellbeing, and perceived rate and quality of recovery (23). This suggests that the primary indicator of clinical effectiveness for these complex, multifactorial interventions may lie not only in objective markers of physical symptoms, but in measures reflecting broader aspects of quality of life. Individual's needs after critical illness are multifaceted (24) and we found that people

specifically re-enforced the need for multicomponent rehabilitation as well as a more individualised approach (25).

1.3 Need for a trial

There is evidence to support the rehabilitation of critically ill patients within ICU, but a paucity of literature to support rehabilitation following discharge from ICU and hospital (26). Of the four Cochrane systematic reviews that explore rehabilitation after critical illness, there are no trials that address remote rehabilitation or technology enhanced care for post-hospital discharge rehabilitation in survivors of critical illness. No such trials are currently registered. Technology-enabled care has been shown to be effective and accessible for delivery of rehabilitation in other illnesses and settings e.g. cardiac rehabilitation, balance rehabilitation in older people, chronic obstructive pulmonary disease (27-35) but this needs to be tested in people after critical illness before widespread implementation in the NHS. We also need feasible methods and alternative approaches to provide rehabilitation to patients during ongoing pandemic restrictions. Our proposed intervention includes strategies to improve recovery, collectively delivered in an efficient format for ease of user-accessibility in a modern health service. The active intervention will be delivered remotely and accommodates accessibility issues, including ethnic diversity as well as being acceptable for those from more deprived socioeconomic areas. Therefore, it provides a real opportunity to scale a rehabilitation service to be available to everyone in the UK who could benefit, irrespective of geographic location, ethnicity or income.

In summary, this trial provides an opportunity to deliver a definitive trial for the pragmatic evaluation of a remote multicomponent rehabilitation programme targeting survivors of critical illness following discharge from the ICU in whom post-hospital morbidity is substantial. This trial will be the first to systematically test a technology-driven remote approach to evaluate the clinical and cost-effectiveness of a rehabilitation intervention in patients recovering from critical illness after ICU care.

1.4 Hypothesis

Hypothesis: For people following a hospital admission that included admission to an ICU for a critical illness, a six-week remote multicomponent rehabilitation intervention improves health-related quality of life, physical function, fatigue, mood, and other health-related outcomes after eight weeks, compared to best practice standard care.

1.5 Aims and objectives

1.5.1 Aim

The overall aim of this trial is to investigate, in survivors of critical illness following discharge from hospital after an Intensive Care Unit (ICU) admission, the effects of a six-week remote multicomponent rehabilitation intervention compared to standard care on health-related quality of life at eight weeks post-randomisation.

1.5.2 Objectives

Trial objectives are:

a) To investigate the effects of a six-week remote multicomponent rehabilitation intervention compared to standard care on physical function, illness perceptions, fatigue, anxiety, depression, and adverse events at eight weeks post-randomisation.
b) To investigate longer term effects of a six-week remote multicomponent rehabilitation programme compared to standard care on health-related quality of life, physical function, illness perceptions, fatigue, anxiety, and depression at six months post-randomisation.
c) To determine explanatory factors influencing outcomes via an embedded process evaluation.
d) To evaluate the cost-effectiveness of the multicomponent rehabilitation intervention compared to standard care over six months follow-up.

2. TRIAL DESIGN

2.1 Trial Summary

Trial Design: Pragmatic, randomised (allocation ratio 1: 1.17), controlled, assessor blind, multi-centre trial with internal pilot and embedded process evaluation.

Setting: At least 30 NHS hospitals across UK.

Population: Adults (≥18years) within 12 weeks of discharge from hospital that included an ICU admission for critical illness, requiring mechanical ventilation ≥48hours.

Sample size: 428 participants (control n= 197; intervention: n=231).

Intervention: Six week multicomponent, rehabilitation intervention, delivered remotely by a core intervention team. In brief, the intervention includes four components: weekly symptom management; targeted exercise; psychological support and information/peer support.

Control: Standard Care, **not** involving structured rehabilitation.

Outcomes: primary - health-related QoL at eight weeks post-randomisation; secondary outcomes: health-related QoL (at six months), physical function, fatigue, anxiety and depression, healthcare resource use at eight weeks and six months post-randomisation and intervention acceptability at 8 weeks

Internal pilot: An internal pilot will test recruitment processes and intervention-related procedures, with planned seamless transition to the main trial, after review and approval of stop-go criteria. The internal pilot phase will include qualitative interviews with participants taking part in the rehabilitation intervention, intervention team members and trial staff

2.2 Outcome measures

2.2.1 Justification for primary outcome

The trial primary outcome is **health-related quality of life**, measured using the EQ-5D-5L at **eight weeks** post-randomisation. Health-related QoL is multidimensional, encompassing components of physical, psychological, emotional, and social wellbeing. The EQ-5D-5L is the recommended measure for assessing quality of life in core outcome sets for longer-term outcomes following respiratory failure and physical rehabilitation in critical illness (36, 37). Systematic reviews confirm the EQ-5D-5L to be similarly robust compared with other longer measures, such as the SF-36 (38, 39). The scale measures mobility, self-care, usual activities, pain/discomfort, and anxiety/depression from no problems to severe problems. These domains and the visual analogue scale (VAS 0-100mm) capturing health utility are widely used for health economic evaluation. The scale was responsive to change in a study assessing multicomponent rehabilitation in post-critical illness patients (40), and has been validated for telephone completion. Importantly, our PPI group endorsed quality of life as an important outcome to reflect recovery after critical illness. Our PPI partners also confirmed assessment time-points were appropriate and feasible from a patient perspective. Follow-up time-points of eight weeks and six months mirror previous rehabilitation research, including remotely delivered interventions, with six months being of adequate duration to capture changes over time (41).

2.2.2 Justification for secondary outcomes

People typically report a range of symptoms and disability with varying levels of severity and magnitude after critical illness (2-11, 23-25). It is important to capture how rehabilitation may impact upon multiple symptoms, using measures feasible for remote data collection, including postal, online, and/or telephone follow-up (42,43), 38-40, 44). Our trial outcomes are similar to outcomes included in other studies investigating remote pulmonary rehabilitation and remote exercise testing (42, 43). Secondary outcomes in iRehab include valid and reliable tools to measure physical strength (8,45,46), fatigue and emotional wellbeing, including symptoms of anxiety and low mood (46,47). Health and social care data will be collected for health economic analyses.

Efficacy

Primary outcome
Health-related quality of life – EQ-5D-5L (38-40, 44) measured at eight weeks post-randomisation.

Secondary outcomes
Secondary outcomes will be measured at eight weeks and six months.

- Physical Function – 30 second sit to stand test (45)
- Illness Perception – Brief Illness Perception Questionnaire (46)
- Fatigue – Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale (8)
- Anxiety and Depression – Hospital Anxiety and Depression Scale (HADS) (47)
- Intervention acceptability data will be collected as recommended the MRC guidance for evaluating complex interventions (75)

Safety

- We will collect data on serious adverse events as described in Section 4.

Others

- Healthcare and social care utilisation questionnaire for health economic analyses

Timing of outcome assessments
All measures will be collected at baseline (pre-randomisation), **eight weeks** and **six months** post-randomisation. The eight-week follow-up is one to two weeks after planned completion of the rehabilitation programme.

Follow-up outcome assesments
Follow-up questionnaires will be completed **remotely online or by telephone** (or postal as exception) at eight weeks and six months, coordinated by WCTU trial office. An email and/or text message will be sent to participants asking them to click on a link which will take them to the online questionnaire portal or they will receive a call to arrange a time to complete the questionnaire verbally via phone. The 30-second sit-to-stand test will be captured by a iRehab researcher using remote consultation and will be conducted as soon as possible aiming to complete it within one week from the completion of the patient reported outcomes. Reminders will be sent to non-responders after two weeks following WCTU processes. The minimum core data set will include the EQ-5D-5L at eight weeks and six months.

2.3 Trial Flow Diagram

2.3.1 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (48).

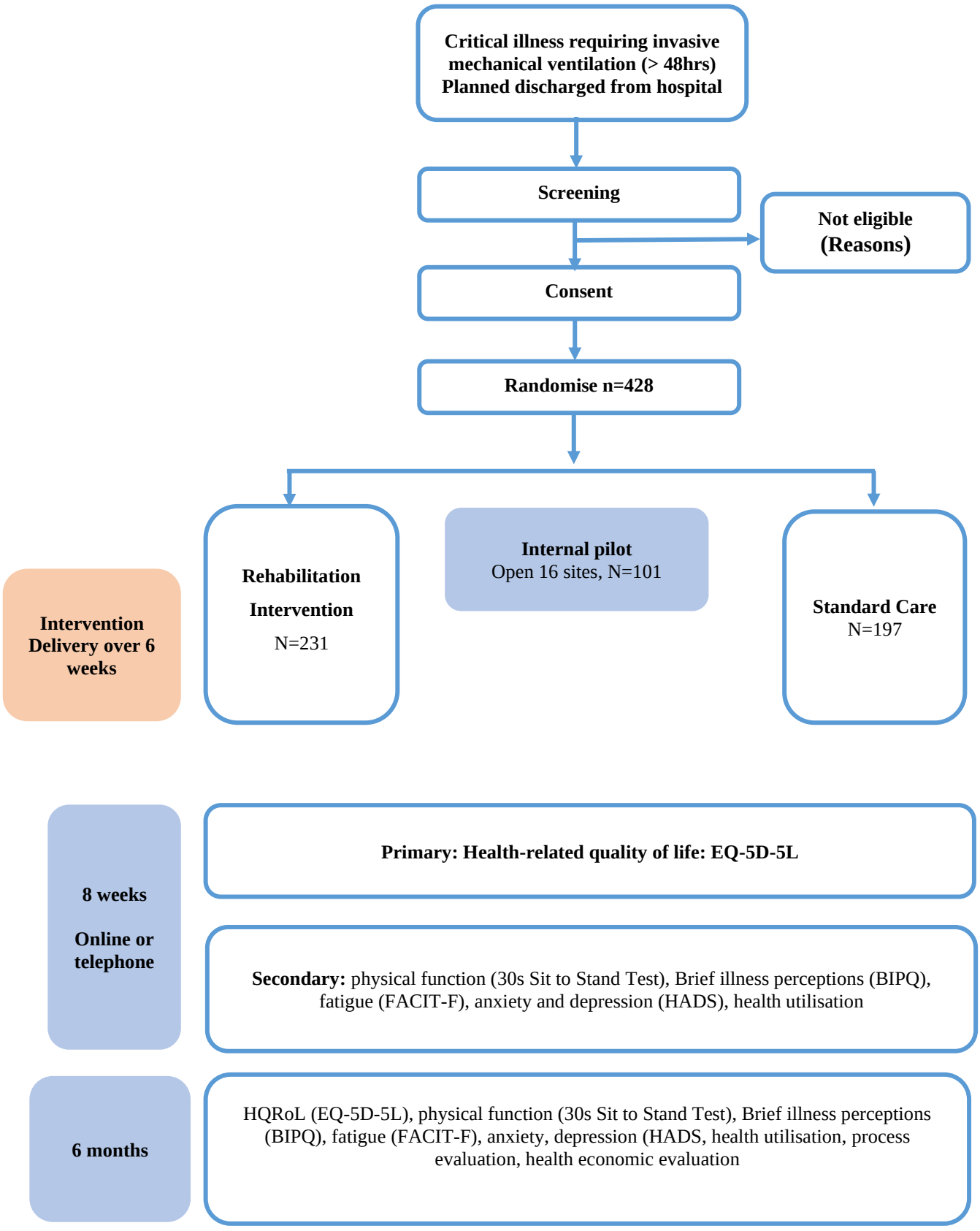

Figure 1 – Trial Flow Diagram

2.4 Participant eligibility criteria

Justification for inclusion/exclusion criteria

People who received invasive mechanical ventilation for 48 hours or longer during an ICU admission, are eligible to participate. The inclusion criteria for iRehab were selected based on evidence for poor recovery after mechanical ventilation for 48 hours or longer (24,25,41). Data from our post-ICU study found that most people started a prescribed rehabilitation intervention within six weeks, and all were able to commence the intervention within 11 weeks post-hospital discharge (41). This study informed the recruitment timeframe of consent **within 12 weeks of hospital discharge** after care in ICU requiring at least 48 hours of continuous mechanical ventilation. However, some people may remain on hospital wards post-ICU care, for days or weeks, or months, before being discharged home.

People are eligible for inclusion if they meet **all** the following criteria:

2.4.1 Inclusion criteria

1. Aged ≥ 18 years
2. Received continuous invasive mechanical ventilation for 48 hours or longer
3. Are within 12 weeks following discharge home from hospital at time of consent
4. Understands spoken English or has family member/friend/other present to translate trial materials
5. Able to participate in the intervention and with trial procedures (e.g. using equipment such as telephone)

2.4.2 Exclusion criteria

1. Declined consent or unable to provide consent.
2. Previous randomisation into the present trial.
3. Participating in another rehabilitation or self-management support trial
4. Contra-indication to exercise
5. Severe mental health problems that preclude participation in a group intervention
6. Discharged to a rehabilitation unit, or care home with/without nursing care
7. Prisoners

2.5 Recruitment procedures

Number of hospital sites: At least 30 UK hospitals.

Site Eligibility

Hospital sites will be asked to complete an expression of interest for the trial. Sites that do not offer structured active rehabilitation programmes will be eligible to participate.

Hospital sites that offer rehabilitation will be assessed for eligibility. Hospitals that exclusively offer active rehabilitation, whether online or face-to-face, as usual care after ICU or hospital discharge will not be eligible.

Ethnic/sociodemographic representation

We will recruit participants through at least 30 hospitals across the UK. Our aim is to ensure wide geographical spread to promote ethnic diversity and sociodemographic inclusivity. Trial interventions will be delivered remotely to help suit underserved groups. We have considered strategies from the INCLUDE project, to invite groups that are at risk of being underserved in research groups (49). We will implement strategies to simplify recruitment and consent procedures e.g., local trial champions will be identified to assist with understanding specific cultures within each site. We will undertake active scrutiny of the trial screening and recruitment logs to help ensure we are not unconsciously excluding anyone and if needed develop strategies to overcome this.

2.5.1 Participant identification and screening

Potential participants will usually be identified via clinical teams/site trial champion at hospital sites who, with agreement from local NHS Trust Research and Development will screen for eligible people. Eligible people may be identified through patient electronic databases at each of the trial sites, referrals or while attending follow-up clinics. Hospital electronic registers/databases will be used to identity people by date of hospital discharge post-ICU care. A further check will be required to ensure potential participants received mechanical ventilation for 48 hours or longer.

- People discharged from ICU to wards who appear to satisfy the inclusion criteria will be approached close to hospital discharge and, provided with written information about the trial and an opportunity to ask questions. Agreement will be sought to be contacted again after they have been discharged from hospital.

- If they are within the specified timeframe (0-12 weeks post hospital discharge) people may also be screened and identified whilst attending hospital follow-up clinics. Those appearing to satisfy the inclusion criteria will be given written information about the trial at the follow-up clinic and an opportunity to ask questions. Agreement will be sought to be contacted again after they have had time to review the trial information.

- People discharged home who appear to satisfy the inclusion criteria who were not approached prior to hospital discharge will be sent a trial invitation letter and written information about the trial which will include a link to the trial website. A follow up phone call will be made to provide an opportunity to ask questions.

- People who self-refer will be considered for the trial provided eligibility criteria can be verified. The trial will be promoted though local/national media/social media, relevant charities and on the trial website. Eligibility for self-referred patients will need to be confirmed via hospital clinical or research teams with permission provided by the potential participants to source this confirmation, or by the potential participant directly contacting the hospital requesting they provide the confirmation.

2.5.2 Informed consent

If a person would like to participate, their initial eligibility will be checked by a suitably trained member of the hospital research team listed on the trial delegation log. The research team member will ensure the potential participant has read the patient information sheet (PIS), understands what is involved with the trial, is willing to be randomised and has had the chance to answer and discuss any questions before proceeding to consent.

Consent to join the trial will usually be taken, by telephone or video call, once the participant has returned home. Consent will be taken by an appropriately delegated member of the research team. Potential participants will be asked to confirm they have read each of the consent items before agreeing to take part in the trial. The consent items include agreement for the trial team to hold contact details, such as addresses, telephone numbers, mobile telephone numbers, email addresses and contact details of next of kin. Potential participants will be asked to confirm that they have contacted the next of kin and that the next of kin has agreed for the trial team to hold their contact details for the purposes needed. A copy of the completed consent form will then be sent to the potential participant via email or post. This model for consent has become widely accepted in clinical trials (50). Completion of consent will be confirmed on the WCTU database.

A letter will be sent to the participants GP and the hospital from which they were discharged to inform them of the participants recruitment into the trial.

The PI retains overall responsibility for informed consent at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent. Where participants are identified via self-referral a designated member of the research team or WCTU team will be PI.

Optional consent for qualitative interviews

During consent for the trial, participants will be asked for their consent to be contacted at a later stage about an interview with a researcher. This consent will be optional and only a subset of participants will be contacted for interview. If they are selected for interview, participants will be contacted to invite them to consider the interview and they will be provided with an interview PIS. If they choose to participate, the researcher will take verbal consent for interview from the participant prior to the interview being conducted by telephone or video call.

Consent for qualitative practitioner interviews

The iRehab trial intervention will be delivered by a central intervention team. During the pilot and main trial and with their consent, we will interview the intervention team members, trial staff and practitioners involved in the rehabilitation service delivery.

Consent of participants non-fluent in English

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

The Participant Information Sheets and Consent Forms will be translated into Welsh or provided bilingually where this is requested by a participant, to comply with the Welsh Language Act 1993.

2.5.3 Site staff training

The trial team will train site staff on trial processes and procedures including patient identification, screening, consent and CRF completion. Site staff must demonstrate and document a willingness to comply with the protocol, standard operating procedures, trial specific procedures, the principles of Good Clinical Practice (GCP) and regulatory requirements. Site staff must be prepared to participate in trial-specific training including a remote Site Initiation Visit. Materials will be provided to participating sites in advance of training.

2.5.4 Baseline data collection

Site staff: After participant consent, research staff at sites will be asked to complete an online case report form (CRF). This will capture the participant's contact details, including contact telephone number and email, alongside participant demographic information and medical history. We require clinical data on illness severity at ICU admission using the 'acute physiology and chronic health evaluation II' (APACHE II) score, co-morbidities, pre-ICU admission functional status, duration of mechanical ventilation, duration of ICU and hospital stay. These clinical data will be extracted from hospital records.

Participants: After providing consent, a baseline assessment trial pack, including a copy of the baseline questionnaire, instructions on the sit-to-stand test and a pulse oximeter to measure blood oxygen levels, will be provided by post and/or email to trial participants. The trial participants will also be sent an email and/or text link to access and complete the baseline assessment questionnaire directly online. Participants will be asked to complete the baseline questionnaires online, but they will also be supported to complete this by telephone, if preferred. When the researcher contacts the participant by telephone, email, text, WhatsApp and/or their preferred method of contact the participant to arrange the sit to stand test, the participant will then have a reference copy while the researcher records the participant's response and enters it onto the trial database. All methods of contact will be done by a trial-specific phone, smart mobile phone or PC.

Participants will also be asked to complete the 30-second sit-to-stand test during an online video call (e.g. MS TEAMs) or telephone call with the independent assessor based at WCTU. This call will be within 1-2 weeks of contact, as soon as possible, after consent for the trial.

Once the EQ-5D-5L is complete, participants will have four weeks to complete any remaining questionnaires and the sit to stand test. If the sit to stand test is arranged after these four weeks, the participant will be asked to re-complete the EQ-5D-5L with a member of the research team, to ensure the data is the best reflection of their current health.

2.6 Randomisation

After consent and baseline data collection, participants will be randomised to either standard care only or the rehabilitation intervention. Randomisation will use a minimisation algorithm stratified by (i) hospital site and (ii) duration of continuous invasive mechanical ventilation (≤7 days : >7 days). The target allocation ratio will be 1.17: 1 (Intervention: Control) using a weighted random element to minimise the imbalance. The randomisation schedule will be generated using a computerised system developed by WCTU. Allocations will be done centrally by WCTU to ensure allocation concealment. The randomisation process will allocate a unique trial identification number to each participant in accordance with the computer-generated trial randomisation schedule. To maintain confidentiality, all CRFs, trial reports and communication regarding the trial will identify participants using the unique identification numbers only.

2.6.1 Randomisation confirmation

Automatic emails confirming participant randomisation will be sent directly to the participant, intervention delivery team, recruiting site research team and WCTU trial management team. The intervention delivery team will only be notified of participants randomised into the intervention arm.

2.6.2 Monitoring of screening data

Following randomisation, the site research team should ensure that the participant's details are updated onto the local site's participant screening log.

Sites will maintain screening logs with numbers of potential participants meeting inclusion criteria for the trial but not entered into the trial and, where possible, data on reasons for non-approach or non-enrolment. We will scrutinise screening and recruitment logs at monthly intervals and discuss with recruitment sites during the internal pilot period. Screening logs will also be monitored regularly throughout the main trial. We will compare data from screened but excluded patients against screened and recruited participants, using anonymised screening logs from sites. Strategies will be considered to overcome potential recruitment barriers and to mitigate against unconscious bias.

2.6.3 Clinical team notification

After randomisation, the participant's GPs, and consultant responsible for their in-patient care will be informed by letter that they are taking part in iRehab trial. A GP letter, with interpretation, will also be sent out at baseline, 8 weeks or 6 months if a participant scores ≥11 on the HADS questionnaire, this can occur at any timepoint however only be sent out once (i.e. if triggered at baseline and 8 weeks, this letter would just be sent out at baseline).

2.6.4 Post-randomisation withdrawals / discontinuation

All participants have the right to withdraw from the iRehab trial at any time if for any reason they change their mind. A participant can discontinue from trial treatment, and they can also choose to withdraw from the trial. There are different levels of withdrawal: a) withdraw consent for future trial involvement b) withdraw consent for future trial involvement and for use of previously entered data. For participants withdrawing completely from the trial, we will retain all data obtained to date of withdrawal, unless the participant explicitly requests for data not to contribute to final analyses.

Wherever possible, we will obtain a reason for discontinuation or withdrawal on trial CRFs although the right of a participant who does not want to give reasons will be respected. For participants wishing

to withdraw from the intervention during the pilot study, we will ask whether they would be willing to explore their experiences of the intervention. There will be a dedicated trial email and helpline which anyone taking part in the trial can access and which will be answered by the WCTU trial team.

Participants may be discontinued from the trial intervention or be withdrawn from the sit-to-stand element of outcome data collection, due to safety reasons, at the discretion of the chief investigator, and lead intervention team (Ulster University/Belfast Health and Social Care NHS Trust).

2.6.5 Incidental findings

Given the high morbidity rate in this patient population, we do not anticipate reporting incidental findings relating to participants' medical conditions or general health to hospital teams or to GPs. Incidental findings relating to participants' medical conditions or general health, will be discussed with the lead medical clinician on the research team, and communicated to the participant as required. We have a clearly defined process for handling incidental findings from questionnaires that assess symptoms of anxiety and depression (potential case-level anxiety and depression – scores $\geq$8/14 HADS) during the baseline, eight weeks or six-month assessment. These cut-off points will be pre-programmed into the trial database. Should participants exceed these clinical cut-offs on completion of any questionnaires, the WCTU trial team will be informed, and the participant's GP will be notified in line with trial procedures.

2.7 Trial interventions

2.7.1 Comparator - Standard Care

Standard NHS care, without active rehabilitation, will be the trial comparator. Hospitals offering active structured physical rehabilitation as part of usual care, will not be eligible to participate. For participants randomised to standard care, no further intervention will be offered after completion of baseline assessment and randomisation, other than usual NHS care. Data on healthcare resource use will be collected from all participants over the six-month trial period. We will record what standard care has been received at an individual level for all participants across the trial period, and as well as resource use across the trial period.

2.7.2 Rehabilitation intervention

Rationale for programme content: The rehabilitation intervention was informed by the MRC framework for complex interventions (51), views from patients after ICU discharge (23-25), and psychological theory, including Leventhal's Common-Sense Model of Self-regulation (52). The aim of the iRehab programme is to support and promote self-management by communicating with participants referred for intervention, clarifying their illness symptoms, offering treatment, and working together to develop action plans (18). Qualitative research (23, 24, 25) found that people experience common and varied symptoms after critical care, including dysphagia (53), breathlessness (54), fatigue (55), and reduced appetite (56). The iRehab programme will address these symptoms and care pathways will be prescribed. The exercise component is based on a tested exercise intervention for people after critical care (41).

Overview of rehabilitation programme: A patient centred structured, individually tailored, multi-component intervention delivered remotely to trial participants by an iRehab trained intervention team over six weeks. To support this trial participants will be provided with participant manual(s). The intervention includes core components delivered as a rehabilitation 'package' and is designed to allow for progression, according to individual ability. The intervention delivery will be supported by a detailed intervention manual and the intervention will be reported in accordance with the TIDieR checklist and guide (57). An overview of the rehabilitation programme is presented in Table 1.

Programme duration: six weeks from first appointment. Intervention sessions will be arranged via telephone, email, text, WhatsApp and/or their preferred method of contact or at a previous session.

Mode of delivery: Remote delivery facilitated by online platforms i.e. Microsoft Teams or Zoom, supported with video platform BEAM© or via telephone.

Format: Weekly one-to-one remote needs assessment to identify individual participant symptoms and provide management plans and strategies to best support their recovery. Participants will be encouraged to attend a weekly group-based remote exercise session and a group-based remote support session (iRehab Café).

Intervention team: the iRehab intervention will be delivered by an intervention team of iRehab trained practitioners with expertise in the management of critical illness and specialist rehabilitation. The core team will include at least three staff members, managed centrally to deliver the intervention.

Referral to intervention: Participants randomised to the iRehab intervention will be notified by email or by telephone. The intervention delivery team will be notified by email that a participant has been randomised to the rehabilitation intervention. This email will contain relevant information needed to commence the intervention including contact details.

First intervention appointment

The first telephone or video consultation appointment will be arranged as soon as possible after the intervention team are notified of participant details and randomisation. Ideally, the participant will be contacted within one week of notification, maximum of three weeks. The participant will be helped to identify any symptoms of relevance to them in their recovery, to recommend the most appropriate components to best support their recovery. An appropriate individualised management plan will be set for each participant. An overview of the intervention programme is presented in Table 1).

Table 1 – Overview of iRehab rehabilitation programme

Timing	Session format	Content
Week 1	1-to-1 appointment, online	• Explain programme • Assess symptoms and identify needs • Provide Individual symptom management • Agree and start exercise and activity plan • Agree review appointments

	Independent or online group/recorded exercise session	• Home exercise plan/attend group exercise session /access recorded exercise sessions
	Online peer support group (iRehab café)	• Attend peer-support café
Weeks 2 to 6	1-to-1 appointment, online	• Weekly review of symptoms and progression through treatment plans • Continue needs assessment, symptom management and psychological support • Continue exercise and activity plan • Agree review appointments
	Independent or online group/recorded exercise session	• Home exercise plan or attend group exercise session/access recorded exercise sessions
	Online peer support group (iRehab café)	• Attend peer-support café
Week 6	Final 1-to-1 weekly session to include review and discharge	• Encourage participant to continue with prescribed management plans • Identify further sources of support • Discharge from intervention.

There are four broad components to the iRehab intervention:

Component 1: Weekly focused discussion and expert guidance to determine individual symptoms and management plans

At each weekly appointment, participants will report any symptoms affecting their recovery, and an appropriate personalised management plan will be agreed. Standardised treatment strategies, individualised to the patient's needs will be provided e.g. difficulty swallowing, breathlessness, fatigue, reduced appetite and other symptoms.

The intervention team member will help participants to set goals and incorporate the strategies for symptom management, exercise, and psychological wellbeing into an individualised action plan for the week ahead. Participants will continue with their individual rehabilitation techniques at home and progress will be reviewed and plans amended at the weekly appointments.

Component 2: Exercise and physical activity plans

At the first appointment (or as soon as possible), participants will be prescribed a progressive exercise and physical activity programme. This aims to address physical weakness, deconditioning and reduced function. Participants will work with the intervention team to agree goals and create action plans for their exercise and physical activity. Progression towards achieving these will be monitored and supported weekly, with discussion of strategies to overcome barriers (41, 58). Participants will be helped with their exercise/physical activity programme at the weekly appointments. They will be offered the use of a Fitbit (step counter) to help with the activity component if suitable. They will also be encouraged to complete an additional exercise session (either group based or individually).

Component 3: Psychological wellbeing support

At each weekly appointment participants will be supported to manage psychological symptoms e.g. anxiety or low mood, by undertaking a wellbeing activity, such as relaxation or a specific taught strategy. Symptoms will be assessed, and specific taught strategies or activities will be incorporated into the patient action plan. These will be reviewed weekly (59, 60).

Component 4: Group based peer support sessions and other information needs

Participants will also be encouraged to attend a weekly group-based peer support session at the remote, online iRehab Café. This will provide an opportunity to meet with other participants who have been in ICU, share and discuss challenges, and share strategies that helped them with aspects of their recovery. It will be facilitated by one of the intervention team. A loose topic guide will be used to support the intervention team member to facilitate the session. Based on individual needs and/or preference participants will be provided with information about critical illness, the critical care journey, how and when to seek help, and ongoing peer support (59-61).

Intervention training: The intervention team will receive bespoke training, either face-to-face or online training, to deliver the iRehab intervention during the set-up phase (months 0 to six) in preparation for intervention delivery during the internal pilot. This will be delivered by the intervention development team. This will include a detailed intervention manual for the intervention team, supporting materials for trial participants, presentations, rehearsals, and interactive problem solving via case studies prior to delivering the intervention. We will include certification of the intervention team to deliver the intervention and they will be supported with frequent and ongoing mentorship throughout the trial as well as training updates.

Quality Assessment: To minimise performance bias in intervention delivery, the core components will be standardised and incorporate protocols to guide overarching delivery, whilst still enabling flexibility in how they are applied to individual participants. The team delivering the intervention will have access to the detailed intervention manual to support delivery and will receive training and certification for intervention delivery. A subset of individual and group intervention delivery sessions will be recorded and reviewed for quality control purposes and to ensure the fidelity of the intervention delivery as part of the trial process evaluation (see Process Evaluation, section 2.8). Checklists will be developed for quality assessment, informed by existing frameworks (62,63).

2.8 Internal pilot study

The **aim** of the internal pilot study will test processes and procedures with planned seamless transition to recruiting to the main trial (64, 65). Participants enrolled in the internal pilot will be included in the analysis of the main trial.

2.8.1 Internal pilot

The nine-month internal pilot phase will be used to test recruitment procedures, confirm and refine recruitment rates, assess protocol compliance, refine procedures for outcome data collection, and test procedures for referral to, delivery of and fidelity with the iRehab intervention. Protocol compliance will be evidenced by the quality and completeness of data returned to the trial office, including baseline and eight-week outcome completion. We will review all data collected to inform

the decision to transition from pilot to main trial. We will evaluate numbers of potential participants approached, reasons for non-eligibility and uptake to the trial to consider accessibility, reach and engagement.

Adherence to standard care and rehabilitation intervention will be assessed during this phase. Uptake and adherence to the active intervention will be evidenced by number of referrals made, number of iRehab intervention sessions attended and reasons for withdrawals amongst those randomised to iRehab intervention. We will monitor time from randomisation to referral to intervention, time from referral to first rehabilitation appointment, number and format of sessions attended and adherence to the programme over six weeks.

2.8.2 Process evaluation: internal pilot

During the internal pilot our process evaluation will explore the intervention in terms of what is working and what is not working, and we will check that our fidelity criteria and procedures enable us to fully assess all aspects of intervention delivery. We will record what standard care has been received at an individual level for all participants across the internal pilot study period. Details of the processes are covered in a Standard Operating Procedure separate to this this protocol.

2.8.3 Qualitative interviews

During both the internal pilot phase and main trial, qualitative interviews will allow in-depth exploration of the acceptability of trial interventions. A similar methodology and analytical approach will be used for interviews conducted in the pilot and main trial.

Participants: In the pilot phase, we will invite up to 15 participants taking part in the iRehab intervention for interview, after they have been discharged from the six-week intervention. We will sample participants from a range of recruiting sites, who consented to be contacted for qualitative interview at baseline, striving to interview those of different ages, gender, and ethnicity. We will explore participant views about the perceived helpfulness of the different components of the remote intervention as well as any standard care they have received during this time. Where possible, we will aim to explore reason for discontinuation for any participant who discontinued the intervention before six-weeks. We will interview a sample of participants from the standard care arm to explore their views about their care.

Intervention team: We will interview members of the intervention team, to explore their views about the remote intervention in practice. Staff delivering the intervention will be interviewed during the pilot and main trial. Where possible, at the end of the main trial, we will interview practitioners involved in rehabilitation service delivery in the UK, to explore their views about remote rehabilitation services and the implementation of trial findings.

Trial Staff/ Site research champions: Where possible, we will follow up with trial staff/site champions to explore their views about the trial processes, including recruitment.

Qualitative data collection and analysis: Qualitative data collection and analysis in the internal pilot study will follow the same methodology and plan for analyses as described for the main trial (Section 7.2). Findings from qualitative interviews will be reviewed by the trial team and oversight committees, to inform decision for progression to main trial.

2.8.4 Stop-go criteria

After completion of the internal pilot phase and consideration of recruitment monitoring data and intervention-related data, summary reports will be generated for circulation to oversight committees. The stop-go decision will be made by the funder, following consultation with the TMG, TSC, DMC and NIHR. Data from the internal pilot will inform this decision, from approximately nine months from pilot opening. The recommended traffic light system will be used to guide decisions regarding progression of the trial based on pilot recruitment data, based on an average recruitment rate of 0.8 participants per centre/ per month:

- **Green:** progress from pilot to main trial; review screening logs at sites achieving less than 100%, assess any barriers to recruitment, share strategies from high recruiting sites, review intervention throughput and adherence (see Table 2).

- **Amber:** explore screening logs**,** assess barriers to recruitment at all sites, share strategies from sites that are recruiting well, open additional sites to recruitment, adaptations to intervention delivery to encourage uptake and adherence.

- **Red:** decision whether to progress to main trial will be made by the DMC, TSC and the NIHR.

Table 2 - Detail of internal pilot phase conducted during first nine months of recruitment, based on opening 16 sites and recruiting n=101 participants

	Red	Amber	Green
Recruitment aim (n=101 participants, up to 16 sites)			
Total number of participants recruited	<50	50-100	101*
Sites recruited	<8	8-15	16
% Threshold	<50%	51-99%	100%
Completeness of outcome measures at 8 weeks (of those recruited to trial*)			
% Threshold of those reaching 8-week timepoint	<75%	75-90%	>90%
Engagement with intervention of those recruited (of those recruited to trial*)			
% Threshold engagement of those allocated to intervention	<50%	51-75%	>75%

* Where engagement with the intervention for the pilot study is interpreted as attendance at first/one session

2.8.5 Process evaluation: Main trial

Embedded process evaluation will continue from the internal pilot throughout the main trial, to explore whether the iRehab and standard care arm interventions were implemented as intended and allow us to understand and explain any factors that may influence trial outcomes (51, 66).

The process evaluation will involve:

a) Trial process data: ongoing monitoring of trial data will continue from the pilot phase, with evaluation of numbers of people approached, randomised, reasons for non-eligibility, proportion discontinuing from interventions and overall trial attrition. These will be reviewed and discussed at monthly TMG meetings and will allow us to interpret accessibility, reach and engagement.

b) Intervention fidelity: a sample of recorded intervention sessions from the main trial will be evaluated for quality assessment purposes and intervention fidelity. A checklist will be adapted to monitor intervention fidelity (62,63). Key components will include training and certification of the intervention team to deliver the intervention, monitoring directly throughout the trial and retraining as required (41, 58, 63).

c) User acceptability survey. Participants in the intervention will be asked about the perceived helpfulness of the different components of the remote rehabilitation intervention using a short questionnaire Theoretical Framework of Acceptability Questionnaire (TFAQ) administered after the intervention. The online platform used for live and recorded exercise sessions will include a single question on satisfaction with session; these data will be collected throughout intervention delivery. Participants in the standard care arm will be asked about their opinion of the care they received at their 8-week follow-up using a short questionnaire (TFAQ) administered via an online link. The questionnaires (TFAQ) could, if preferred, be completed over the phone with a member of the research team or returned via post or email for data entry.

d) Standard care survey. On completion of trial recruitment and participant follow-up, a single page survey will be sent to all sites to request information on whether any structured rehabilitation was provided over the trial period. This will help us understand usual care in each of the trial sites, and whether this changed over the time during the trial. We will also record what standard care has been received at an individual level for all participants across the trial period.

e) Qualitative interviews: Qualitative semi-structured interviews will allow in-depth exploration of the acceptability of the intervention and the components.

-Participants. In the main trial, we will conduct an additional 20 semi-structured interviews (n=10 participants from iRehab intervention and n=10 from standard care). Invitation to interview will be after completion of primary outcome data collection, thus from eight weeks onwards. Interviews with participants in the standard care arm will be conducted at a similar time point and will also explore

their views about being in the trial and their care e.g. whether any other strategies for recovery support were sought.

-We will interview the the intervention delivery team to explore their views about the remote intervention in practice and to explore the acceptability of the intervention and the components. Where possible, at the end of the main trial, we will interview NHS staff/academics involved in rehabilitation service delivery in the UK, to explore their views about remote rehabilitation services and the implementation of trial findings.

- Trial staff/ research champions: where possible, we will follow up with site champions to explore their views about trial processes, including recruitment.

Details of the processes are covered in a SOP separate to this protocol.

Qualitative data collection
Optional consent to be approached for qualitative interview will be collected at baseline on entry to the trial. People invited to take part in the qualitative study will receive a separate information sheet about the study and give consent specifically for the interview study. Interviews will be conducted by an experienced qualitative researcher, independent from the intervention delivery team. Interview topic guides will be developed, to ensure similar areas are covered and discussed in each interview. Interviews will be held via video conferencing or by telephone and will be audio recorded, transcribed, and checked for accuracy and anonymity.

For interviews with the intervention team, intervention materials will be referred to, to aid recall and generate discussion. Details of the processes are covered in a SOP separate to this protocol.

Qualitative data analysis
Interview transcripts will be analysed using framework analysis (67).

While each component of the process evaluation will be undertaken and analysed separately, the findings will be triangulated to integrate the qualitative findings and the trial outcomes, and we will explore the mechanistic pathways for any treatment effects (66).

2.8.6 Compliance/contamination

Compliance (adherence) with trial interventions will be monitored throughout the trial. Uptake and adherence to the active iRehab intervention will be evidenced by number of sessions referred to and attended, over the six-week intervention delivery period (41). This is a complex multicomponent individualised intervention, but the expectation is that each participant will engage in at least one intervention session per week over the six-week period. Definitions of full and partial adherence to the iRehab intervention will be refined during the pilot phase informed by data from the process evaluation. We anticipate this to be: full adherence = engaged with five or more sessions (out of six); partial adherence = engaged with one to four sessions; and non-attendance = none.

2.9 Allocation concealment

Participants' treatment allocation is revealed at randomisation via email to the participant themselves and the lead intervention team. Treatment allocation should be concealed from the independent assessor performing the outcome assessments at baseline and follow-up.

At the eight-week and six-month follow-up assessments, participants will be asked to not reveal their allocation to the independent assessor. If allocation is revealed, the assessor will record this on the appropriate CRF.

To minimise performance bias in the intervention arm, the core components will be protocolised to guide overarching delivery, whilst still enabling flexibility for individual participants. The intervention development team will provide training to practitioners, as described in Section 2.5.3 above.

2.10 Concomitant illness and medication

2.10.1 Concomitant illness

We anticipate comorbidity to be high in this post-ICU population. If any illness influences the potential participant's eligibility to participate in the trial (e.g. serious mental health problems that preclude participation in a group intervention) the principal investigator will be informed and a decision reached regarding about whether or not they are eligible to participate. Once recruited and consent has been obtained, if any illness influences the potential participant's eligibility to continue in the trial this will be discussed with the trial team and the participant may need to discontinue treatment and/or withdraw from collection of data.

2.10.2 Concomitant medication

Participants will be asked to identify any medications they are taking at baseline and any changes in medication will be recorded across the trial, i.e., at each follow-up time point (eight weeks and 6 months) thereafter.

2.11 Co-enrolment into other trials

Participants in this trial may be eligible for co-enrolment in other studies, and this will be decided on a case-by-case basis by the Chief Investigator and TMG of iRehab and any respective studies. The WCTU trial office should be informed if co-enrolment is being considered. Any co-enrolment agreements records retained by WCTU and details of co-enrolment should be documented in the CRF.

2.12 End of trial

The trial will end when all participants have completed their six-month follow-up and related trial activities have been completed.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Recommended by the 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.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

An overview of schedule of trial assessments is given in Table 3.

Table 3 – Schedule of delivery of data collection

	Pre-randomisation		**Post-randomisation**			
	Screening	**Baseline**	**Intervention**	**Follow-up**		
Weeks ± No. Days	**Weeks 0-12**		**Weeks 1-6**	**Week 8**	**8-26 weeks**	**Week 26**
Check eligibility	✓	✓				
Consent participant		✓				
Clinical data collection (by site)						
APACHE II score		✓				
Medical history		✓				
Co-morbidities		✓				
Pre-ICU admission functional status		✓				
Duration ventilation		✓				
Length of ICU stay		✓				
Length hospital stay		✓				
Participant data collection						
EQ-5D-5L		✓		✓		✓
30sec Sit-to-Stand		✓		✓		✓
BIPQ		✓		✓		✓
FACT-F		✓		✓		✓
HADS		✓		✓		✓
Health and social care use				✓		✓
TFAQ				✓		
Randomisation		**R***				
Intervention delivery			✓			
Process evaluation						

	Pre-randomisation		Post-randomisation			
	Screening	Baseline	Intervention	Follow-up		
Weeks ± No. Days	**Weeks 0-12**		**Weeks 1-6**	**Week 8**	**8-26 weeks**	**Week 26**
					✓	
Participant self-report/Site data collection						
AEs		✓	✓	✓		✓
SAEs		✓	✓	✓		✓

*Randomisation after consent and participant baseline data collection. Refer to outcome section for questionnaire measures.

4. ETHICAL CONSIDERATIONS

The trial will be conducted in 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 Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the UK GDPR and Common Law Duty of Confidentiality.

Ethical approval will be sought using the Integrated Research Application System prior to commencing this trial. Sites will only be permitted to enrol patients into the trial once all required agreements are in place. Key ethical issues that we have considered for this trial relate to (i) eligibility and access to underserved groups, and (ii) information governance relating to the remote intervention delivery.

As discussed in Section 2.3, the trial has broad inclusion criteria to ensure the trial offered to all patients post-ICU that might benefit from rehabilitation. We will review characteristics of those recruited and compare these to the overall population of adults in ICU. We will develop strategies to address invitation bias.

The iRehab trial uses remote consent and delivery of the rehabilitation intervention, including prescription and delivery of exercise, as well storage of personal data. We will ensure that the trial information governance strategy is developed including risk assessments that optimise patient safety for remote delivery (68-70).

5. ADVERSE EVENT MANAGEMENT

5.1 Definitions

5.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with the treatment/intervention.

AEs exempt from recording
These are common AEs associated with exercise and will not be recorded as AEs for this trial (Table 4)

Table 4 – Common AEs associated with exercise

Events
Breathlessness
Light headedness/dizziness
Muscle stiffness/soreness
Tiredness/fatigue
Oxygen desaturation (that resolves with appropriate management e.g. rest, breathing exercises, inhaled medications)

For the **intervention group,** AEs listed in Table 4 that are identified during or after the intervention, will be recorded on the intervention notes (not on an AE form), for clinical purposes only. For all participants, AEs listed in Table 4 identified during outcome assessment will be recorded on the iRehab database.

Any AEs that are not listed in Table 4 should be recorded using the Adverse Event eCRF. Recording should be done by the intervention team, outcome assessor or investigator site, as appropriate, within 48 hours of becoming aware of the AE. All AEs should be assessed to see if they constitute a 'Serious' adverse event as per section 5.1.2 below. If they do, they will be reported by the mechanism in section 5 and not recorded on the AE form.

5.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

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

SAEs exempt from reporting
The following SAEs listed in Table 5 are common in the clinical population being studied and **do not** require reporting to the Clinical Trials Unit as an SAE for this trial, but will be recorded as part of follow-up data collection in the participant questionnaires or in the relevant section(s) of the CRF (such as the hospital readmission CRF):

Table 5 – Common SAEs in the clinical population being studied that are exempt from reporting

Events
Hospitalisation, or death, for pre-existing conditions e.g. respiratory exacerbation and infection, or a complication related to the initial ICU admission
Treatment, which was elective or pre-planned, for a pre-existing condition, not associated with any deterioration in condition

5.2 Assessing and Reporting AEs, SAEs and related SAEs

5.2.1 Recording and assessing AEs/SAEs

All **AEs** and **SAEs** (unless otherwise specified) occurring from the time of **informed consent** until 8 weeks post randomisation and during the 8 week and 6-month outcome assessment appointments, must be recorded (AE)/reported (SAE) (where events are usually within 48 hours of the assessment appointment).

During the baseline, eight- week or six-month assessment all participants will be asked about anything that might constitute an AE or SAE by the independent assessor performing the assessment. AEs/SAEs occurring during the intervention delivery in the intervention group will be determined through patient report at each weekly online catch-up session.

All SAEs, except for those listed in Table 5, should be initially reported by the site, the outcome assessor or a member of the intervention delivery team, as appropriate. A copy of the SAE form should be sent to the WCTU trial team via the trial database and the WCTU QA Team will be notified by the WCTU trial team. WCTU should be informed **within 24 hours** of any party becoming aware of the event.

Once received, the trial management team at WCTU will review the SAE. Information will be requested from the recruiting site to provide further detail on the SAE if required. If the patient was treated for the SAE at the investigator site that recruited the patient, WCTU will send the SAE on to the investigator site for completion within 2 working days (if not already reported by the site). If not then WCTU will contact the patient or the patients GP for further information where applicable.

For each **SAE** the following information will be collected from the intervention team, assessor and/or investigator site (as appropriate):

- details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome

- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the site Principal Investigator and Chief Investigator(s) on the SAE form using Table 6.

Table 6 – SAE causal relationships

Relationship to trial intervention	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention e.g. within 48 hours). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

5.2.2 Related SAEs

Any SAEs that are assessed as related to the intervention will be reported according to the WCTU protocol.

5.2.3 Expected SAEs

There are no expected serious adverse events previously documented for this intervention. Therefore, any that are assessed as having a causal relationship to the intervention will not undergo expectedness assessment and will automatically be expedited to the REC as per section 5.2.4 below.

5.2.4 Reporting SAEs

The trial management team at WCTU will liaise with the intervention team/outcome assessor/investigator site to compile all the necessary information. Once the SAE form has been completed, causality will be independently assessed by the Chief Investigator (or delegate). SAEs that are deemed to be possibly, probably or definitely related to the trial interventions or outcomes assessments (by either the intervention team/outcome assessor/investigator site or the CI), will be notified to the Research Ethics Committee (REC) and sponsor within 15 days. All such events will be reported to the TMG, Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings. All other recruiting sites in the trial must also be informed of the event and any implications for the trial.

5.2.5 SAE Follow-up

Any change of condition or other follow-up information should be sent to WCTU QA Team as soon as it is available or at least within 24 hours of the information becoming available. A member of the PI's trial team will be instructed to closely monitor each participant who experiences a SAE, until the outcome of the SAE has been determined. All participants experiencing SAEs will be followed-up until the event has been resolved or a final outcome has been reached as per protocol until the end of the trial.

5.2.6 Annual reporting

All SAEs will be recorded for inclusion in annual reports to the Research Ethics Committee.

5.3 Safety

If an AE/SAE occurs during the assessment or intervention, the person responsible for the patient should decide whether it is safe to continue the assessment/intervention, with or without modification, or whether it should be discontinued. SAEs will be reviewed/monitored by the TMG for trends.

The instructions for remote/home exercise will include appropriate warnings regarding when to stop exercise, e.g., chest pain, faintness, and dizziness, and a contact telephone number for the trial team. Participants will also be advised to follow usual procedures for any medical emergencies.

5.4 Responsibilities

Independent assessor/Intervention delivery team:

1. Checking for AEs/SAEs during participant assessments and treatment.
2. Ensuring that all AEs are recorded on the AE log and using clinical judgement in assigning seriousness and causality to AEs as applicable.
3. Ensuring that all SAEs are reported to Warwick CTU within 24 hours of becoming aware of the event and providing any additional information as appropriate.

Principal Investigator:

1. Using clinical judgement in assigning seriousness & causality to SAEs.
2. Ensuring that all SAEs received from WCTU are reviewed and appropriately reported back within 2 working days of receipt and providing further follow-up information as soon as available.
3. Ensuring that SAEs are recorded and reported to Warwick in line with the requirements of the protocol.

Chief Investigator / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using clinical judgement in assigning seriousness & causality of SAEs where it has not been possible to obtain local medical assessment.
3. Immediate review of all related SAEs
4. Review specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Production and submission of annual reports to the relevant REC.

Sponsor (or delegate):

1. Oversight of safety reporting process, review of cumulative safety data
2. Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (DMC and TSC) according to the Trial Monitoring Plan.
4. Expedited reporting of related SAEs to the REC within required timelines.
5. Notifying Investigators of related SAEs that occur within the trial.

Trial Steering Committee:

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

Data Monitoring Committee:

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

5.5 Hospital Readmissions

Investigator sites will be asked to report all hospital readmissions to the trial team via the eCRF. The trial team will use the date of the readmission to help determine, along with the investigator site, whether this constitutes an SAE.

5.6 Notification of deaths

All deaths will be reported to the sponsor (Ulster University) and WCTU irrespective of whether the death is related to disease progression, the intervention, or an unrelated event. These should be reported within 24 hours of a staff member becoming aware of the event to WCTU using the eCRF.

5.7 Reporting urgent safety measures

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

6. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the UK General Data Protection Regulation and Common law Duty of Confidentiality.

Personal identifying information and Confidential Patient Information will be collected via the WCTU online database. Participants' details will be stored and accessed by staff at WCTU, Ulster University, Belfast HSCT and The Queens University Belfast via the online database to contact the participants during the trial, allow postage of participant materials, enable delivery of the intervention and to conduct the qualitative interviews. Handling of personal and confidential data will be clearly documented in the participant information sheet and consent obtained.

The iRehab intervention delivery team at Ulster University and Belfast HSCT will also keep records of participant contact details and medical health information for those participants randomised to the iRehab intervention. This is required for trial delivery to ensure participants are exercising at the appropriate level and to be used if a medical emergency occurs. These records will be stored securely and will not be passed on to anyone outside of the intervention delivery team.

Disclosure of confidential information will only be considered if there is an issue which may jeopardise the safety of the participant or another person, according to Warwick SOPs (Warwick SOP 15 part 1) and the UK regulatory framework. There is no reason to expect this situation to occur in this trial more than any other.

6.1 Data collection and management

Trial CRFs and participant questionnaires will be developed to collect all trial data. These CRFs will be developed by the WCTU trial management team in consultation with the CI, statistician, health economist and other relevant members of the trial team.

We will use the standard WCTU web-based application for trial management to record participant data in accordance with the trial protocol. The CRFs will be developed by WCTU team and made available to the participating sites as either paper or electronic CRFs (eCRFs) for ease of data collection; supporting materials will also be available to staff. All documents will be stored safely with restricted access to maintain confidentiality. On all trial-specific documents, other than the consent form, the participant will be referred to by a unique trial-specific number/patient identifier/code in any database, not by name. The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant data protection regulations and standard operating procedures (SOPs). A monitoring plan and risk assessment will be devised to protect participant safety

and integrity of trial data. Routine monitoring procedures will be conducted the frequency of which will be determined by each sites rate of recruitment and safety of permitting staff to conduct visits.

Various methods will be used to track missing data including phone, text, and email. Participants will receive a reminder to complete the online questionnaires at each time point alongside a video/telephone call from the independent assessor at WCTU. If a participant has not completed a questionnaire at the follow-up assessment timepoint the independent assessor will encourage them to complete the questionnaire online or provide support for this to be completed via phone (using the reference copy of the questionnaires previously provided). If data remain missing, the independent assessor will make further contact with the participant to attempt to collect the outcome measurements with priority for the core measures.

Data will still be collected for participants who discontinue or deviate from the protocol, unless they withdraw their consent (section 2.1.2). For any participants who do not respond to the follow-up assessment calls or who are known to have died, WCTU will request a death notification form be completed by the recruiting hospital site.

Identifiable data that we no longer require or information that could identify anyone by name will be deleted 12 months after trial completion (last follow-up for last participant). We will have to keep non-identifiable (pseudonymised) data for up to 10 years.

6.2 Database

The iRehab 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.

6.3 Online group video platform

An external online video platform (Beamfeelgood) will be used with the iRehab trial intervention. This platform will enable live streaming of the group intervention sessions. A Data Protection Impact Assessment will be completed and approved by Ulster University and Belfast HSCT to identify and minimise associated risks. The online platform is GDPR compliant, and Organisation for Review of Care and Health Apps (ORCHA) accredited. Any data that is stored, including the participant's email address, will be encrypted in accordance with NHS England guidance and storage will be NHS cloud compliant, conforming to ISO 9001/27001/27017/27018 standards and the G-Cloud (UK Government) standard.

Private groups will be created on the online platform and administrative access to these given only to approved staff in the intervention delivery team and WCTU. Administrative users will authorise participant's access to the private groups and participants will be asked for their consent to share utilisation metrics with the University of Warwick, Ulster University and Belfast HSCT.

Participants in the intervention arm will be asked to set up an account and profile where they agree to the terms and conditions of Beamfeelgood and consent to the University of Warwick, Ulster University and Belfast HSCT having access to any of their data collected through the platform. Participants may choose to use a nickname on the online platform to remain anonymous to other members.

This online video platform will collect and store data on participants attendance at classes and any answers relating to post-exercise session online poll questions. This information will be stored against the participants name and email address on Google data studio and held until the end of the trial. The iRehab team (University of Warwick and University of Ulster/Belfast HSCT) will be given access to this data as required to monitor attendance, safety and for analysis of compliance.

6.4 Data storage

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 WCTU. Electronic data will be stored on password protected university computers.

Separate records required for intervention delivery will be securely stored at Ulster University and Belfast HSCT for participants randomised to the intervention delivery arm.

All trial records and documentation related to the qualitative interviews will be stored and analysed by staff based at The Queens University Belfast. These records will not be transferred to WCTU.

6.5 Data access and quality assurance

Confidentiality will be strictly maintained and names or addresses of participants 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. Any paper forms with participant-identifiable information will be held in secure, locked filing cabinets within a restricted area of WCTU, Ulster University, Belfast HSCT or The Queens University Belfast, wherever the activity is taking place. Participants will be identified by a participant number only where possible. The PI must arrange for retention of trial records on site in accordance with GCP and local Trust's policies for the length of time stated in the protocol. 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 management team and statistician to outline the data monitoring checks required.

6.6 Data Shared with Third Parties

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 trial will be available upon request after publication of the main trial results. The publication of a trial protocol, trial results and trial data will be in line with the NIHR standard terms and will follow Warwick SOP 22: Publication & Dissemination.

6.7 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial. Trial documentation and data held by recruiting NHS sites will be stored for 10 years in line with their local trust policy.

7. STATISTICAL ANALYSIS

7.1 Power and sample size

The total sample size for iRehab will be **428 participants**. Using our primary outcome of EQ-5D-5L utility score at eight weeks, our target difference is 0.08 with a standard deviation of 0.2 (i.e. an effect size=0.4) (71). If we assume that there are on average seven therapists for the intervention delivery and a clustering effect will exist (ICC=0.01) and allowing for 30% loss to follow up (LTFU), a total of 428 (control: 197 and intervention: 231) participants will be required. This uses the Morbeek's formulation (72) and an unequal randomisation of the ratio of 1: 1.17. A difference of 0.08 on the primary outcome is a justifiable clinical effect. We will endeavour to minimise losses to follow-up. If we achieve a 15% loss to follow-up, we will be able to detect a smaller effect size (up to 0.37) at 90% power.

7.2 Statistical analysis of efficacy and harms

7.2.1 Statistics and data analysis

The main statistical analysis will be based on intention-to-treat. Data will be summarised and reported in accordance with CONSORT guidelines for RCTs. The impact of compliance on outcomes will be assessed using a CACE (complier average causal effect) analysis or other appropriate approach.

7.2.2 Statistical analysis plan

Summary of baseline data and flow of patients

Baseline data will be summarised by treatment arm, using means, standard deviations, medians, interquartile ranges for continuous variables and frequencies and proportions for categorical variables. Screening data will be summarised descriptively between the randomised patients, those ineligible and those eligible but not consented. A CONSORT diagram will be presented to show the patient flow throughout the trial (50).

Primary outcome analysis

The primary outcome will be summarised using means, standard deviations, medians and interquartile ranges. Linear regression will be used to estimate the treatment effect with 95% confidence interval, with and without adjustment for important patient-level covariates and site effect, by intention-to-treat. The impact of compliance will be assessed using CACE analysis or other appropriate approach.

Secondary outcome analysis

Secondary outcomes will be summarised using means, standard deviations, medians and interquartile ranges. Linear regression will be used to estimate the treatment effect with 95% confidence interval, with and without adjustment for important patient-level covariates and site effect.

7.3 Subgroup analyses

Subgroup analysis which are specified a priori include (a) duration of mechanical ventilation and (b) age (2, 6, 73). The primary outcome will be examined in relation to these subgroups using an interaction in the model with treatment and sub-group effect.

7.4 Interim analysis and criteria for early termination of the trial

The frequency and timing of the interim analysis will be reviewed and agreed by the DMC. Detailed stopping rules will be developed and specified in the SAP. The interim analysis will be conducted by trial statistician(s). The DMC will review unblinded interim data and make their decision to terminate the trial early based on the statistical evidence or safety concerns. The trial team will remain blinded to allocation during the trial unless necessary.

7.5 Subject population

The primary and secondary analyses will be conducted based on an all-randomised population by intention-to-treat.

7.6 Procedure(s) to account for missing or spurious data

Whilst every effort will be made to minimise missing data, it is inevitable that some data will be missing. We will monitor the level of and reasons for missingness in the primary outcome. The nature and pattern of missingness will be carefully considered. If deemed necessary, an appropriate imputation method, e.g., multiple imputation, will be applied to impute missing data. The imputed datasets will be analysed as a sensitivity analysis. Further details will be given in the statistical analysis plan.

7.7 Other statistical considerations

Any additional statistical considerations in the trial will be described in the statistical analysis plan.

7.8 Health Economic Evaluation

A prospective within-trial economic evaluation, adhering to NICE Reference Case recommendations (67) will compare intervention with standard care. Healthcare resource use data will include in-patient and community care health service contacts during the six-month follow-up period, collected via trial CRFs and costed using the most recently available published reference costs. Generic HRQoL will be assessed at baseline, eight weeks and six months using the EQ-5D-5L, with responses converted to health status scores using the NICE-recommended UK value set and sensitivity analyses conducted using alternative tariffs if this is likely to be useful for decision-making (74). Patient-level QALY estimates will be calculated using the trapezoidal rule. Analyses will

explore and manage data missingness in line with the approach described in section 7.6. Every effort will be made to minimize missingness, but if appropriate, a suitable method such as multiple imputation will be used to account for missingness. Bootstrapped bivariate regression will estimate and visualize incremental cost-effectiveness ratios, acceptability curves and net monetary benefit. If findings are non-convergent at six months, we will explore the sensitivity of cost-effectiveness to extrapolation of costs and benefits beyond the trial time horizon, via a suitable decision model or parametric survival analysis model. Value of information analysis will be conducted to explore the sensitivity of health economic recommendations to additional research. Sensitivity analyses will also explore the impact of broadening the decision perspective beyond the NICE reference case to include indirect costs such as the impact on productivity. Additional secondary cost-effectiveness analyses will also explore the unit cost of any achieved reductions in fatigue or anxiety/depression resulting from the intervention.

8. TRIAL ORGANISATION AND OVERSIGHT

8.1 Sponsor and governance arrangements

The trial sponsor is Ulster University. The University of Warwick will act as the co-ordinating centre and will employ the trial management team and in collaboration with the Chief Investigator will manage the day-to-day running of the trial, collecting and managing the data.

8.2 Ethical approval

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

8.3 Trial Registration

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

8.4 Notification of serious breaches to GCP and/or trial protocol

A ‘serious breach’ is a breach which is likely to effect, to a significant degree:

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

If a serious breach occurs, the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

8.5 Indemnity

NHS indemnity 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 provides indemnity for any harm caused to participants by the design of the research protocol.

8.6 Trial timetable and key milestones

Start date: 1st January 2022 (month 1).

	Month	**Recruitment**
Set-up	1-9	n/a
Pilot study	10-18	101
Main study	19-27	428 (total)
Follow up	28-33	n/a
Analysis	34-36	n/a

Project year	Year 1				Year 2				Year 3			
Year	Jan-Dec 2022				Jan – Dec 2023				Jan – Dec 2024			
Quarters	1	2	3	4	1	2	3	4	1	2	3	4
Month	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D	J-M	A-J	J-S	O-D
REC approval												
HRA/site approvals												
Site set up												
Recruit Trial Staff												
Database set up												
Intervention refinement												
Recruitment: pilot												
Recruitment: main												
Follow up												
Process evaluation												
PAG	X	X	X		X			X			X	
TMG	X	X	X	X	X	X	X	X	X	X	X	X
DMEC		X			X						X	
TSC		X			X						X	
Data analysis												
Reports to funder, manuscript preparation												

Figure 2 – Gantt Chart of research timetable

8.7 Administration

The trial management team will be based at WCTU, University of Warwick.

8.8 Trial Management Group (TMG)

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

8.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists, researchers, clinicians, and academics with relevant experience and at least one PPI member. The TSC will have an independent Chairperson. Face to face or remote meetings will be held at regular intervals determined by need but not less than once a year; this will include a meeting scheduled at the end of internal pilot. Routine business is conducted by email, post or teleconferencing.

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

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

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

8.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC meeting frequency will be guided by the DMC chair but will be suggested to be three months into the recruitment phase, at the end of the pilot study, and regularly thereafter as directed by the DMC chair. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated. The membership of the DMC will be approved and appointed by the NIHR.

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

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

8.11 Essential Documentation

A Trial Master File will be set up according to Warwick SOP 11 and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

8.12 Financial Support

The trial has been funded by a grant from the NIHR Health Technology Assessment (HTA): 132871.

9. MONITORING, AUDIT AND INSPECTION

- A Trial Risk Assessment will be conducted by the Trial Manager, Senior Project Manager, Trial Statistician, Chief Investigator (or delegated representative) and WCTU QA Team.
- A Trial Monitoring Plan will be developed and agreed by the TMG based on the trial risk assessment.
- A data management plan will be developed and agreed by the CI.
- The trial will be audited by WCTU's QA team as per Warwick SOPs.

10. PATIENT AND PUBLIC INVOLVEMENT (PPI)

We will form a Patient Advisory Group (PAG) who will be involved throughout the trial, from set-up to completion. We have a PPI co-applicant (EW) as part of the research team. We recruited our PPI co-applicant from Public Involvement Enhancing Research (PIER) which is an established group of PPI members aiming to assist HSC R & D Division Northern Ireland with implementing PPI in research. EW will represent PPI on the Trial Management Group (TMG) and will support co-applicant JB to lead our PAG (which will have independent representation on our TSC). JB and EW will link with co-applicants AW and KK who will work to ensure diversity involvement in PPI more generally with the Centre for Black and Minority Ethnic by accessing their existing patient and community partners to ensure their views are represented.

One of our PAG members (PC) will join the TSC, to ensure PPI the interests of patients continue to be central during the active phases of our trial.

The PAG will comprise approximately six members. Other members will be recruited from our existing patient advisors as well as from PPI forums, e.g., PIER, support groups, ICU steps and from the Centre for BME health community partners panel (facilitated by AW & KK). BME health community partners panel has representatives with different backgrounds from across the East Midlands, who have received training in research methods, and can contribute to the production and review of trial resources.

Training and support for all PPI members in the PAG will be offered to help with understanding of trial and trial procedures, and to optimise opportunity for meaningful input. This will include e.g. access to formal training programmes such as Building Research Partnerships, on-line courses, and attendance at relevant conferences. Dr Gail Johnston is a Programme Manager with the HSC R& D

Division PHA, Northern Ireland and Lead in PPI in Research; Gail has agreed to help the team to co-ordinate the set up and running of the PAG and advise about training for PPI members.

Examples of active contribution by the PAG include informing best practice guidance on lay language to explain the trial to patients and relatives when identifying patients for the trial, preparing materials including recruitment materials to optimise equity of access, advising on how the approach to delivery of the intervention needs to be refined at individual level to be cognisant of specific circumstances.

In addition to more frequent meetings with our PAG during the set-up stages of the trial, we will meet with our PAG 2-3 times per year (and more frequently if needed or requested) to consider any PPI-related issues that have arisen during the trial conduct as well as update on the ongoing progress of trial.

We will include our PPI colleagues when planning dissemination activities once the trial findings become available. Their input will help ensure findings are presented in a format that is accessible to a wide audience and includes a range of opportunities for presenting trial results in person to patients and family members e.g. at support group meetings or via community or charity events, and use of social media. We will encourage and support our PPI co-applicant (EW) to co-present at academic and clinical conferences and forums.

11. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial co-investigators and collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of clinical teams and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

We will collaborate with our PAG once the trial findings become available to plan information and engagement activities. Our PAG will help ensure findings are presented in a format that is accessible to a wide audience. This includes a range of opportunities for presenting trial results in person to patients and family members e.g. at support group meetings or via charity events, and via social media. Our end of trial information will include information about how those that have participated in the trial can access the results. We will encourage and support our PPI co-applicant (EW) to co-present at academic and clinical conferences and forums. Key findings will be posted on the trial and institutional websites, and we will work with institutional communication offices to prepare press releases as appropriate.

The results of the trial will be shared widely by our multi-professional team and published in international, high impact factor, journals, and presented at relevant national and international conferences. Results will be circulated via relevant patient and family networks following discussion with and input from our patient advisory group, and participants will be able to request a copy of the

results through contacting the local trial team. This trial provides a real opportunity to scale a rehabilitation service to be available to everyone in the UK who could benefit, irrespective of geographic location.

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