FULL TRIAL TITLE: Randomised evaluation of rehabilitation after acute proximal humerus fracture: a multi-centre, non-inferiority, randomised trial to compare the clinical and cost-effectiveness of a self-directed rehabilitation programme versus physiotherapist-supervised rehabilitation (usual care) for adults with a proximal humerus fracture

SHORT TRIAL TITLE: Randomised evaluation of rehabilitation after acute proximal humerus fracture

TRIAL ACRONYM: Error! Bookmark not defined.REACH

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Contents

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2 ORGANISATIONAL INFORMATION

Chief Investigator:	**Dr David Keene** Associate Professor in Trauma and Orthopaedics University of Exeter Refer to the KEY TRIAL CONTACTS section for contact details.
Sponsor:	University of Exeter Refer to the KEY TRIAL CONTACTS section for contact details.
Clinical Trials Unit:	The trial is managed by Oxford Trauma and Emergency Care (OxTEC). Oxford Clinical Trials Research Unit (OCTRU) Botnar Research Centre, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LF
Funder:	The trial is funded by the National Institute for Health and Care Research (NIHR). Refer to Funding and support in kind section for full details of all funding source
Co-applicants:	The following are co-applicants on the trial grant and have contributed to the trial design and development of the protocol: **Professor Matthew Costa (co-lead for the trial)** Professor of Orthopaedic Trauma Surgery University of Oxford ✉ matthew.costa@ndorms.ox.ac.uk **Mr Stephen Gwilym** Associate Professor & Consultant Orthopaedic Surgeon University of Oxford ✉ steve.gwilym@ndorms.ox.ac.uk **Dr Juul Achten** Research Manager University of Oxford ✉ juul.achten@ndorms.ox.ac.uk **Professor Stavros Petrou** Professor of Health Economics University of Oxford ✉ stavros.petrou@phc.ox.ac.uk **Dr Duncan Appelbe** Senior Research Information Specialist University of Oxford ✉ duncan.appelbe@ndorms.ox.ac.uk

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Additional Protocol contributors:	**Susan Dutton** OCTRU Lead Statistician & grant co-applicant (now retired from role), Oxford Clinical Trials Research Unit University of Oxford **Clare Calvert** OCTRU Head of Pre-Trial Operations Produced first draft of Protocol
CTU involvement	This trial will be coordinated by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford.
Conflict of Interest statement:	None of the co-applicants or Protocol contributors listed above have declared a potential conflict of interest.
Confidentiality Statement:	In accordance with the NIHR Open Access policy, the Protocol will be published and made freely and openly accessible to all.

3 KEY TRIAL CONTACTS

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4 PROTOCOL APPROVAL AND SIGNATORIES

This Protocol has been approved by the Sponsor, Chief Investigator (CI) and Lead Trial Statistician. Approval of the Protocol is documented in accordance with OCTRU Standard Operating Procedures (SOPs).

All parties confirm that findings of the trial will be made publicly available through publication without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any important deviations and serious breaches of good clinical practice (GCP) from the trial as planned in this Protocol will be explained.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

A break (fracture) to the bone of the upper arm at the shoulder (proximal humerus) is a painful injury. It results in a sudden loss of use of the arm with recovery taking many months. Most injuries occur in people over 50 years of age after a fall, due to reduced bone strength, and are usually treated with a sling, although some fractures may need surgery.

At the moment, people are asked to see a physiotherapist a number of times to help with recovery after a proximal humerus fracture. Attending physiotherapy appointments can however be very difficult, especially for people who live alone or have poor social support networks. Driving is not possible and public transport is a struggle due to low confidence after a fall. A one-off advice session, with clear verbal and written instructions and videos of exercises patients can do at home, could be an alternative to attending physiotherapy clinic for multiple sessions. Providing high-quality advice so people can manage their own recovery could be less of a burden for patients and their carers who might use fewer healthcare resources.

Before widely using an alternative advice approach, it is important to know that people receiving a one-off advice session would not be disadvantaged in their recovery compared with people having a series of physiotherapy appointments.

The REACH trial aims to find out the best way to support recovery and will compare the recovery of patients who receive a single advice session with a health professional and access to a workbook and videos to use at home, with the recovery of patients who are referred to see a physiotherapist. After 6 months, patients' shoulder function and quality of life will be compared between the two groups.

6 TRIAL SYNOPSIS

Full Trial Title:	Randomised evaluation of rehabilitation after acute proximal humerus fracture: a multi-centre, non-inferiority, randomised trial to compare the clinical and cost-effectiveness of a self-directed rehabilitation programme versus physiotherapist-supervised rehabilitation (usual care) for adults with a proximal humerus fracture
Short Title:	Randomised evaluation of rehabilitation after acute proximal humerus fracture
Trial Acronym:	REACH
Trial Design:	The REACH trial is a multi-centre, two-group, parallel design, non-inferiority randomised controlled clinical trial with an embedded health economic evaluation.
Trial Aim	The aim of the REACH trial is to compare the clinical and cost-effectiveness of a self-directed rehabilitation programme versus physiotherapist-supervised rehabilitation (usual care) for adults with non-surgically managed proximal humerus fractures.
Trial Participants/ Target Population:	The REACH trial will recruit adults aged 16 years and over with non-surgically managed proximal humerus fractures. Refer to the PARTICIPANT ELIGIBILITY CRITERIA section of the main body of the Protocol for full eligibility criteria.
No. of trial groups:	Two
Intervention(s):	**Self-directed rehabilitation** (provision of high-quality self-management advice) Participants allocated to this group will receive detailed advice by a health professional and a workbook and website with a set of exercises that can be progressed independently.
Comparator:	**Physiotherapist-supervised rehabilitation** (usual care) Participants allocated to this group will receive usual fracture clinic advice and a referral to physiotherapy.
Planned Sample Size:	1214 participants (607 per group).
Target no. of research sites:	At least 24 NHS hospitals.
Countries of recruitment:	UK
Planned recruitment duration:	Recruitment is expected to last for 25 months (including a pilot phase of 9 months).

<table>
<tr><td>Duration of intervention/treatment:</td><td colspan="2">Participants randomised to receive self-directed rehabilitation will be given a REACH workbook and directed to the trial website. Participants will undertake an exercise programme, which they can tailor based on their current level of pain and function, and their recovery goals. They will be provided with advice to continue with the self-management exercise programme for at least four months.</td></tr>
<tr><td>Follow-up duration:</td><td colspan="2">Each participant will be followed up for six months from randomisation.</td></tr>
<tr><td></td><td>Objective</td><td>Outcome Measure</td></tr>
<tr><td>Primary objective and outcome measure:</td><td>To compare shoulder pain and function between treatment groups.</td><td>Patient-reported shoulder-related pain and function at six months after randomisation measured by the Oxford Shoulder Score (OSS).</td></tr>
<tr><td>Additional objectives and outcome measures:</td><td colspan="2">Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main body of the Protocol for full trial objectives and outcome measures.</td></tr>
</table>

7 ABBREVIATIONS

AE	Adverse Event
AUC	Area under the curve
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMP	Data Management Plan
DSMC	Data and Safety Monitoring Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IP	Intellectual Property
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention To Treat
MAR	Missing at random
MCID	Minimum clinically important difference
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
OSS	Oxford Shoulder Score
OxTEC	Oxford Trauma and Emergency Care
PI	Principal Investigator
PIS	Participant information sheet
PPI	Patient and Public Involvement
PROMIS	Patient Reported Outcome Measurement Information System
R&D	Research and Development
REDCap	Research Electronic Data Capture
QA	Quality Assurance
QALY	Quality Adjusted Life-Years
REACH	Randomised Evaluation of rehabilitation and Acute proximal Humerus fracture
RCT	Research Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEE	Self-Efficacy to Exercise
SFQ	Site Feasibility Questionnaire
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File

TMG	Trial Management Group
TSC	Trial Steering Committee
UE	Upper Extremity
VAS	Visual Analogue Scale

8 BACKGROUND INFORMATION AND RATIONALE

8.1 Background and rationale

Proximal humerus (shoulder) fractures are painful injuries, resulting in a sudden life-changing reduction in physical function and mental wellbeing. Approximately 24,000 people suffer a proximal humerus fracture in the UK each year (1). Most of these fractures are related to reduced bone density (osteoporosis) with over 85% occurring after a fall from standing height in people aged 50 years and over (2, 3). A year after a proximal humerus fracture, 27% of patients report poor upper limb function (4), struggling with pain and difficulties carrying, lifting and reaching. Patients' quality of life is reduced (5). Looking after people with upper limb fractures is expensive for the National Health Service (NHS), costing £1.4 billion in 2017 (6).

National Institute for Health and Care Excellence (NICE) fracture guidelines recommend non-surgical management for most patients with a proximal humerus fracture (7). The REACH trial is for the majority of patients who are treated without the need for surgery.

Standard practice in the UK is for a sling to be applied and then to refer patients with a proximal humerus fracture to a clinic for outpatient physiotherapist-supervised rehabilitation (1, 8). The number of physiotherapy sessions varies but typically consists of four to eight clinic appointments focusing on advice and exercise prescription. However, people often report finding it difficult to attend physiotherapy appointments. Driving is not possible after this injury and public transport can be a struggle due to low confidence and sling use. To attend appointments people become reliant on family, friends, and carers. Travel to outpatient appointments also bears a substantial carbon footprint (9).

NHS information indicates that physiotherapy sessions after proximal humerus fractures cost £326 per patient, so with an estimated 24,000 people having this fracture each year (1), total £7.8 million each year, making physiotherapy the largest healthcare cost for patients treated non-operatively.

Provision of high-quality advice at the fracture clinic visit to support self-directed rehabilitation could be an alternative to attending physiotherapy. Enabling people to manage their own recovery could be less of a burden for patients and use less healthcare resources. Self-directed rehabilitation interventions have recently been found to be successful for non-traumatic shoulder pain (NIHR Health Technology Assessment (HTA) GRASP) (10). There is a clear evidence gap and need to evaluate such interventions in the acutely fractured population.

8.2 Review of existing evidence

Despite physiotherapist-supervised rehabilitation being usual care in the UK for this injury, there is insufficient evidence to assess whether this approach improves recovery after proximal humerus fracture. A 2022 Cochrane review found insufficient evidence to make recommendations about rehabilitation after sling immobilisation (11). A 2021 review concurred (12). There have been only two Randomised Control Trials (RCTs) (13, 14). Bertoft et al. included 20 participants with non-surgically treated proximal humerus fractures and compared instructions on self-exercise with 9 sessions of usual care physiotherapy (13). Lundberg et al. included 42 participants with non-surgically treated proximal humerus fractures and compared instruction on self-exercise with 9 sessions of usual care physiotherapy (14). These trials found no evidence of a difference in function or harms but were too small to draw firm conclusions and had methodological shortcomings.

A review of trial registries (clinicaltrials.gov, ISRCTN) found one trial (NCT03498859), also identified as the only relevant ongoing trial by the recent Cochrane review. The trial, based in Scandinavia, recruited 72 participants aged 60 years and over and compared self-directed exercises with 10

sessions of physiotherapy. This trial was published in 2024 (15). While the findings indicate a self-directed rehabilitation approach is acceptable, it will not be sufficient to change UK NHS practice.

8.3 Why this research is needed now

The REACH trial will find out if self-directed rehabilitation results in non-inferior outcomes when compared to usual care, i.e. supervised rehabilitation, for people with proximal humerus fractures. This research addresses two of the top three priorities from a James Lind Alliance Priority Setting Partnership (16):

- What is the best physical rehabilitation programme for people over 50 with an upper limb fracture when it no longer needs to be kept still?
- What type of information should patients over 50 with an upper limb fracture be given and how should this be provided?

If patients can be managed effectively with a single advice session rather than a course of physiotherapy sessions, this would be less of a burden to patients, their family, friends and carers. It would also likely reduce costs of treatment to the NHS and reduce pressures on rehabilitation services. However, if no evidence is found to show self-directed rehabilitation is non-inferior, this will provide robust evidence to support commissioning of supervised physiotherapy for this injury. This evidence is crucial as physiotherapy services are dealing with an increasing lack of capacity in terms of funding and staffing. The REACH trial will provide evidence to guide future updates to NICE fracture guidelines (7) and inform decisions about rehabilitation for this common injury for commissioners, clinicians and patients.

9 OBJECTIVES AND OUTCOME MEASURES

9.1 Aim

The aim of the REACH trial is to compare the clinical and cost-effectiveness of a self-directed rehabilitation programme versus physiotherapist-supervised rehabilitation (usual care) for adults with non-surgically treated proximal humerus fractures.

9.2 Primary objective and outcome measure

Table 1: Primary objective and outcome measures

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To compare shoulder pain and function between treatment groups at 6 months post-randomisation	Patient-reported shoulder-related pain and function measured by the Oxford Shoulder Score (OSS)	6 months post-randomisation	OSS questionnaire	Participant questionnaire (entered directly into trial database or as paper questionnaire)

9.3 Secondary objectives and outcome measures

Table 2: Secondary objectives and outcome measures

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure	Data required	Source data (including location)
To compare shoulder pain and function between treatment groups at 2 and 4 months post-randomisation	OSS	Baseline* (retrospective pre-injury and post-injury), 2 and 4 months post-randomisation	OSS questionnaire	Participant questionnaire (entered directly into trial database or as paper questionnaire)
To compare upper extremity physical function between treatment groups	Patient-reported upper extremity function as measured by the Patient Reported Outcome Measurement Information System (PROMIS) Physical Function (Upper Extremity) score	Baseline*, 2, 4 and 6 months post-randomisation	PROMIS questionnaire	Participant questionnaire (entered directly into trial database or as paper questionnaire)
To compare health-related quality of life between treatment groups	Patient-reported health-related quality of life as measured by the EuroQol 5 Dimensions EQ-5D-5L	Baseline* (retrospective pre-injury and post-injury) 2, 4 and 6 months post-randomisation	EQ-5D-5L questionnaire	Participant questionnaire (entered directly into trial database or as paper questionnaire)
To compare self-efficacy to exercise between treatment groups	Patient-reported confidence in ability to exercise as measured by the Self-Efficacy to Exercise (SEE) Scale	Baseline*, 2, 4 and 6 months post-randomisation	SEE Scale questionnaire	Participant questionnaire (entered directly into trial database or as paper questionnaire)
To compare the rates of complications between treatment groups	Bespoke participant questionnaire and site-completed Case Report Forms (CRFs)	Up to 6 months post randomisation	Participant questionnaire at 2, 4 and 6 months; Medical records	Participant questionnaire (entered directly into trial database or as paper questionnaire) and medical records

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure	Data required	Source data (including location)
To assess costs and comparative cost-effectiveness	Bespoke participant resource use questionnaire; Site treatment log; EQ-5D-5L	2, 4 and 6 months post-randomisation.	Resource use questionnaire; treatment CRF; EQ-5D-5L questionnaire	Participant questionnaire (entered directly into trial database or as paper questionnaire)

* Baseline scores taken at time of consent, no later than 21 days after injury.

9.4 Exploratory objectives/additional mechanistic objectives outcomes

There are no additional exploratory/mechanistic objectives/outcomes in this trial.

9.5 Use of core outcome sets

There are currently no core outcome sets for proximal humerus fracture.

9.6 Primary outcome – Shoulder pain and function

Shoulder pain and function will be assessed using the OSS, a 12-item questionnaire, each item with a five-level response (0 to 4) and overall score of 0 to 48 (higher better). It has high internal consistency, reliability and validity in UK populations (17, 18).

9.6.1 Choice of primary outcome/justification for the follow-up period

The primary outcome measure is a region-specific patient-reported functional outcome measure – the OSS (17). The 6-month follow-up covers the time period within which active rehabilitation occurs and the recovery trajectory is set.

9.7 Secondary outcome(s)

9.7.1 Upper extremity function

Upper extremity function will be assessed using the PROMIS Physical Function (Upper Extremity)(19, 20). PROMIS questionnaires are administered electronically. They are a computer adaptive test, which are dynamic tests based on item response theory. A mathematical model adapts the sequential questions asked based on a participants' previous response. A tailored set of questions is therefore asked from a large item pool. PROMIS instruments are scored from 0 to 100 with 50 points representing the mean score for the US general population, higher scores indicate better function. Participants with no internet access will be able to complete a paper-based version of the PROMIS questionnaire (PROMIS Physical Function Upper Extremity Short Form, 7a). This questionnaire has been found to be valid in the context of upper limb fractures in the UK (21, 22) and has been successfully used in trials involving participants with similar demographics to the target population (23).

9.7.2 Confidence to exercise

The SEE Scale (24) is a 9-item tool assessing confidence to exercise measured on a 0 to 10 scale. This participant-reported questionnaire (total scores range from 0 to 90, higher scores indicate higher self-efficacy for exercise) will be used to assess the participants' confidence in their ability to exercise.

9.7.3 Health-Related Quality of Life

The EuroQol 5 Dimensions (EQ-5D-5L) is a validated, generalised and standardised instrument comprising a Visual Analogue Scale (VAS) measuring self-rated health and a health status classification system, consisting of a five-level response (no problems, some problems, moderate

problems, severe problems and unable) for five domains related to daily activities: (i) mobility, (ii) self-care, (iii) usual activities, (iv) pain and discomfort and (v) anxiety and depression (25). Responses to the health status classification system are converted into an overall score using a published utility algorithm for the UK population. The EQ-5D-5L utility scale, recommended for application in the UK, ranges from a negative score, −0.594 (reflective of a patient's health-related quality of life being worse than death), 0 (death), to 1 (perfect health). A respondent's EQ-VAS gives self-rated health on a scale where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0).

9.7.4 Complications

Participants will be asked to report at 2, 4 and 6 months about any increase in pain after shoulder exercises lasting more than one week and requiring initiation of pain medication or increase in pain medication or consultation with medical doctor.

Recruitment centres will be asked to review the participants medical records and report on any of the following complications up to 6 months post-randomisation:

- diagnosis of Complex Regional Pain Syndrome
- diagnosis of venous thrombosis
- diagnosis of pulmonary embolism
- diagnosis of a post-traumatic neurovascular injury (including neuropathy/nerve palsy)
- diagnosis of post-traumatic (secondary) frozen shoulder (arthrofibrosis)
- surgery to the injured shoulder

9.7.5 Health and personal social service resource use

Bespoke resource use questionnaires will be used to assess the number of primary and secondary care consultations, further shoulder x-rays and scans, surgery and over-the-counter pain medication prescribed, and use of broader hospital and community health and social services. It will also be used to describe out-of-pocket expenses, and work absences.

10 TRIAL DESIGN AND SETTING

The REACH trial is a pragmatic, multi-centre, two-group, parallel design, non-inferiority randomised controlled clinical trial with an embedded health economic evaluation.

The trial will recruit 1214 adult patients (607 in each trial group) with non-surgically managed proximal humerus fractures from approximately 24 NHS hospitals in the UK. Participants will be randomised to receive physiotherapist-supervised rehabilitation as per usual care (control group) or self-directed rehabilitation (intervention group) by the provision of high-quality self-management advice.

A trial flow chart is provided in APPENDIX 1 – TRIAL FLOW CHART.

Potentially eligible participants can be identified and provided with information about the trial in the emergency department or minor injuries unit at first presentation, or at a subsequent outpatient/virtual trauma and orthopaedic appointment (fracture clinic). Consent will be obtained at the point where strict shoulder immobilisation is discontinued at a routine clinical review appointment. Patients will be excluded if consent cannot be obtained within the first 21 days post-injury. Following consent, participants' baseline data will be collected and participants will be randomised to either self-directed rehabilitation or physiotherapist-supervised rehabilitation.

Participants randomised to physiotherapist-supervised rehabilitation (usual care) will be referred to outpatient physiotherapy following the fracture clinic review at which consent is obtained. Reflective of usual care physiotherapy for people with a proximal humerus fracture, it is anticipated that participants will be offered a minimum of three sessions with a physiotherapist over 4 months. When completing the Site Feasibility Questionnaire (SFQ), recruitment centre staff will be asked to provide information about their hospital's standard referral pathways to physiotherapy for this patient population (i.e. who makes the referral, where/when is it made and the duration of current waiting time to first appointment).

Participants randomised to self-directed rehabilitation (intervention) will receive high-quality advice and a set of exercises that can be progressed independently by participants as they make progress through milestones in their recovery for at least 4 months. A workbook and website hosting the exercises will also be provided to support participants, and where appropriate their family, friends and carers. The advice will be introduced by a health professional (physiotherapist, nurse or surgeon) during the routine fracture clinic visit where consent has been obtained. Clear guidance will be provided when and where additional advice or clinical input should be sought in case of lack of progression or if they have concerns.

All participants will be followed up for the trial for 6 months post-randomisation; they will be sent questionnaires electronically to collect outcome data at 2, 4 and 6 months post-randomisation, with telephone and/or paper follow-up if required. Participants in the usual care group will additionally be contacted either electronically or by phone call and be asked to report on physiotherapy session attendance approximately every 3 weeks.

10.1 Recruiting centres

Participants will be recruited from at least 24 NHS secondary care hospitals.

Refer to section 27, "Identification and management of participating sites" for information on identification and management of sites.

10.2 Collection of outcome data and follow-up assessments

Data will be collected electronically at baseline. Follow-up questionnaires will be administered primarily electronically with an option of telephone and/or postal follow-up if required. Participants completing questionnaires electronically will be sent a hyperlink via email and/or text to an electronic CRF at the specific follow-up time points.

Refer to section 17, "Trial assessments/procedures and data collection" for full details of outcome data collection and follow-up assessments.

10.3 Countries of recruitment

UK.

10.4 Duration of participant involvement

Participants will be in the trial for approximately 6 months from randomisation to last trial follow-up.

10.5 Post-trial treatment/care and follow-up

Apart from random allocation to the mode of rehabilitation, participants will receive standard NHS care.

10.6 Central review procedures

Not applicable for this trial.

10.7 Use of clinical registries and NHS England data
No data of this type is to be accessed for this trial.

10.8 Expected recruitment rate
The predicted recruitment rate is 3 participants per centre per month. This rate is based on hospital audit data and experience of recruitment rates achieved in previous trauma rehabilitation trials in this setting.

A 9-month internal pilot in 9 recruitment centres will confirm the willingness of hospital trusts, clinicians and patients to take part in the proposed RCT by assessing whether the projected recruitment rate can be achieved.

10.9 Equality, diversity and inclusion for trial participants
Using the NIHR-INCLUDE ethnicity framework and the key questions worksheet developed by Trial Forge (www.trialforge.org) (26) to carefully consider key under-served populations in trauma research, Patient and Public Involvement (PPI) partners and clinical stakeholders at centres with diverse catchment populations were consulted. It was evident from this work that people from more deprived areas with lower educational levels are a key group that can be less engaged with health services after trauma.

As trauma centres have large catchment areas, most centres have a diverse population in terms of urban, rural and coastal areas and a range of socioeconomic groups. However, there are higher levels of social deprivation in different regions of the UK, hence we will ensure trauma centres from diverse regions of the UK are involved. The central trial team have collaborated with over 100 hospitals on trauma trials in diverse regions with the UK and have access to heat maps of regional socio-demographics and historical research activity via the supporting local Clinical Research Network, which will aid site recruitment planning.

The central trial team will prepare trial materials in different formats to allow for informed consent discussions to be accessible for a large audience. Written materials will be created in normal and large fonts, information will be available in visual formats such as infographics and explainer videos, with voiceovers and subtitles which can be played at various speeds.

10.10 End of trial
The end of trial is the point at which all data relating to the trial primary and secondary outcomes have been entered and all queries resolved.

The Sponsor and the CI reserve the right to terminate the trial earlier at any time. In terminating the trial, they must ensure that adequate consideration is given to the protection of the participants' best interests.

11 PARTICIPANT ELIGIBILITY CRITERIA
11.1 Timing of eligibility assessment
Eligibility will be assessed upon initial entry into the trial and confirmed at the point of randomisation.

11.2 Overall description of trial participants
The REACH trial will recruit adults aged 16 years and over with non-surgically managed proximal humerus fractures.

Written informed consent must be obtained before any trial specific procedures are performed. Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the PI based on the below criteria.

11.3 Inclusion Criteria

A patient will be eligible for inclusion in this trial if **ALL** of the following criteria apply:

- Aged 16 years or over
- Has a diagnosis of a proximal humerus fracture which is to be managed non-surgically

11.4 Exclusion Criteria

A patient will not be eligible for the trial if **ANY** of the following apply:

- Has a concurrent neurological injury leading to a significant deficit in the affected arm
- More than 21 days have elapsed since the fracture
- Other upper limb injury which may reasonably be expected to impact shoulder rehabilitation and affect responses to patient-reported outcome measures
- Is unable to adhere to the trial procedures.

11.5 Rationale for inclusion and exclusion criteria

Broad eligibility criteria allow for the results of the trial to be generalisable to a wide population.

Exclusion criteria have been chosen to exclude factors that may confound results. Before age 16, bones are still growing and their pathology after a fracture and recovery are demonstrably different from those of adult patients. Approximately 3 weeks from injury, bone healing has already started progressing and the effect of being treated in one or other group of the trial is likely to be less evident.

11.6 Pre-trial screening tests or investigations

There are no pre-trial screening tests for inclusion in the trial.

11.7 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a randomised trial. There will be no waivers regarding eligibility (i.e. each participant must satisfy all the eligibility criteria). Changes to the approved inclusion and exclusion criteria may only be made by a substantial amendment to the Protocol.

Before entering a patient into the trial, the PI or delegated individual will confirm eligibility. If unsure whether the potential participant satisfies all the entry criteria and to clarify matters of clinical discretion, the PI or delegated individual should contact the central trial team, who will contact the CI or designated clinicians as necessary. If in any doubt the CI must be consulted before recruiting the patient. Details of the query and outcome of the decision must be documented in the Investigator Site File (ISF) and Trial Master File (TMF).

11.8 Clinical queries and Protocol clarifications

Every care has been taken in drafting this Protocol. Contact the central trial team for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the central trial team. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all trial investigators for information as necessary. For urgent safety measures or changes that require Protocol amendment see section 28.7, “Urgent safety measures”.

12 SCREENING AND RECRUITMENT

Participation will be offered regardless of the patients' gender, sexual orientation, marital status, ethnicity, religion or beliefs, disability or socio-economic status.

12.1 Participant Identification

Participants will be screened and approached about the trial from a minimum of 24 NHS hospitals in the UK.

The following methods will be used to identify potentially eligible participants:

- Identification in the emergency department or minor injuries unit or via virtual or outpatient trauma and orthopaedic services.
- Advertising of the trial in fracture clinics directing potential participants to the local site research team for further information.

12.1.1 Identification of participants in the emergency department or minor injuries unit or via virtual or outpatient trauma and orthopaedic services (fracture clinic)

Potentially eligible patients identified during their initial attendance at the emergency department or minor injuries unit at recruiting centres will be provided with a Participant Information Sheet (PIS) by a member of their usual care team (who may also be a member of the site research team) and asked to consider the trial. Potentially eligible patients can also be identified at routine follow-up appointments in fracture clinic (in person or virtual) that take place within 21 days of the injury.

Where their usual care clinician is not a member of the site research team, potential participants will be asked if it would be acceptable for their name and contact details to be passed to the local research team to discuss the trial.

12.1.2 Identification through trial advertising material

Posters advertising the trial will be displayed in electronic and/or paper formats as allowed in participating sites. All advertising material will be approved prior to use.

12.2 Re-screening if a potential participant does not meet eligibility criteria first time

If a potential participant does not meet the eligibility criteria at first assessment, they can be re-screened at any time up to 21 days post-injury.

12.3 Use of screening logs

A screening log (within the Research Electronic Data Capture (REDCap) trial database) will be used to record information about the number of patients assessed for eligibility and/or approached for the trial and if provided, the reasons for exclusion or declined consent.

The following data, in addition to the eligibility criteria, will be collected on the screening log: age, sex at birth, deprivation index and ethnicity. A screening number will be assigned to each patient screened. Screening data will be reviewed by the central trial team to assess whether representative samples of patients are being approached and to ensure no selection bias occurs in any of the centres with regard to approach and inclusion/exclusion of specific groups of patients. Continued training of site staff on accurate and inclusive screening and recruitment will be through newsletters, regular Q&As and top tips, and refresher sessions. Investigator meetings will be planned, as they have proved successful in the past in ensuring appropriate sampling of patients.

13 TRIAL INTERVENTION AND COMPARATOR

13.1 Self-directed rehabilitation (intervention)

Participants allocated to self-directed rehabilitation will be provided with high-quality self-management advice and a set of simple exercises that can be progressed independently as they make progress through milestones in their recovery. The advice will be introduced by a health professional (i.e. physiotherapist, nurse or surgeon) during their routine fracture clinic visit when restrictions on moving the shoulder are lifted, typically within two weeks post-injury. Protocol adherence for the intervention will be met when the health professional has delivered the advice and materials. The health professional will complete an electronic checklist (Treatment delivery CRF) indicating whether all aspects of intervention delivery have been completed.

A richly illustrated workbook and website hosting exercise videos will support participants and where appropriate their family, friends and carers. We have worked closely with the REACH PPI Advisory Group to ensure the supporting materials are accessible and user friendly. Commonly used methods to support independent exercise adherence will be used, including goal setting and using a workbook to progress these independently, and provision of an exercise diary. Participants will be provided with a phone number in case of concerns.

It is anticipated that a small proportion of participants will experience fracture or recovery complications, which may necessitate a fracture clinic review or referral to physiotherapy. These actions are allowable in the protocol (i.e. is not a deviation or reason for withdrawal). Participants will be asked to report any outpatient visits and/or referrals to physiotherapy for their index injury after they have been allocated their treatment.

The exercise programme will be consistent with what is offered in physiotherapy currently but structured in a simple way so that participants can tailor their own progress based on their current level of pain and function, and their functional goals. A clinical reference group of health professionals involved in proximal humerus fracture rehabilitation with a range of experience levels and the PPI Advisory Group have been involved in reviewing all intervention materials.

13.2 Physiotherapist-supervised rehabilitation (usual care)

A referral to outpatient physiotherapy will follow the fracture clinic appointment for participants allocated to physiotherapist-supervised rehabilitation, as per usual care. Protocol adherence for the usual care group will be met when the referral for physiotherapy is made. The date of referral will be recorded on the trial database.

It is the expectation that the initial appointment will be as soon as possible after referral, as per local appointment availability. Supporting rehabilitation guidance will be provided for the treating physiotherapists. Guidance will emphasise that trial participants allocated to physiotherapist-supervised rehabilitation should receive usual care. Reflective of usual care physiotherapy for proximal humerus fracture, study guidance will outline that it is expected that participants will be offered a minimum of three sessions with a physiotherapist over 4 months. There will be no upper limit on the number of sessions. Physiotherapists will, as per their usual practice, support participants with a progressive exercise programme focusing on recovery of movement, muscle strength, and function. Participants will be asked to report the number of physiotherapy sessions they have attended (see Table 4).

To provide an indication of current usual physiotherapy provided we will request, during the pilot phase only, additional information on those participants receiving physiotherapy at their recruiting NHS Trust. We will ask research/physiotherapy teams to report on the number of sessions provided,

grade of physiotherapist leading the sessions, the duration of the sessions and if available the type of exercises performed and any adjunct treatment provided.

13.3 Concomitant care

Other aspects of health and social care including further contact with fracture clinic will continue as normal. As per usual care, participants in both groups can contact their treating hospital with any problems experienced and re-assessment/review conducted if there is any clinical concern about fracture complications.

Records will be made of additional treatments provided in relation to the index fracture, including fracture clinic care or additional rehabilitation provided by the NHS or privately.

13.4 Intervention quality assurance and fidelity

All clinical staff delivering the manualised intervention will, where feasible, be trained to enhance standardisation. Training can be delivered face-to-face or through online/written materials and trained individuals will be added to a site training log. There will be fidelity assessments by completion of the Treatment delivery CRF for each participant and site monitoring where required. In addition, direct observation or audio-recordings of a subsample of self-directed rehabilitation sessions will be assessed to ensure fidelity is maintained. More intensive site training and monitoring will be put in place if there are any issues identified during central monitoring, during site visits or audio-recordings.

Additional contacts with fracture clinics and physiotherapy services will be monitored for both treatment groups. Self-directed rehabilitation website access will be via unique user log-ins. Participants will be asked in their 2, 4 and 6 month follow-up questionnaires to indicate how many times in the preceding week they have done exercises for their injured arm. Interventions will be reported in accordance with Template for Intervention Description and Replication (TIDieR) guidelines (27).

14 INFORMED CONSENT

14.1 Consent procedure

A member of the clinical team will initially approach the potential participant. Informed consent will be sought and if a person approached is willing to give consent, it will be collected by a member of the local research team listed on the delegation log from each participant before they undergo any trial-related procedures or interventions related to the trial.

If a patient is interested in the REACH trial, they will be introduced to a member of the local trial research team, and presented with the PIS, directed to an ‘explainer video’, a public website containing all relevant information and given a verbal explanation of the trial procedures. The patient will then be given the opportunity to discuss issues related to the trial with the clinical team and family and friends ensuring that the potential participant has sufficient time to consider participating or not. They will then be asked to sign an electronic Informed Consent Form (ICF).

14.2 Time allowed to decide to take part

Potential participants will have to decide within 21 days of injury.

14.3 Completion of the ICF

The potential participant and the Investigator (or authorised designee) must personally sign and date the current approved version of the ICF.

The ICF will be offered to participants in clinic as an electronic form on a tablet device, or in some cases a laptop or desktop computer (with the ICF being completed directly in the trial database,

REDCap). A simple electronic signature will be obtained, either achieved by a finger tracing across a tablet device or using an electronic stylus on a tablet device or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen.

Where the participant has an email address they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the participant does not have or does not provide an email address the site research team will be able to print a copy of the signed ICF and provide this to the participant. A copy of the electronic ICF downloaded from the trial database will be placed in the ISF and a copy in the participant's medical record.

On the rare occasion that a potential participant is not attending their routine follow-up appointment in person, remote eConsent (using REDCap) may be obtained in accordance with OCTRU's SOP for obtaining consent. Where remote consent will be used, potential participants will be asked to provide an email address for receiving consent documents prior to obtaining written informed consent. Potential participants will receive a unique link via email to an electronic ICF which may then be completed remotely. Once completed this form will be countersigned by a member of the site research team authorised to do so and then sent, via email, to the participant as a PDF document. A member of the site research team will be required to countersign all ICFs completed remotely, in the same way as for paper forms. Patients who decide not to consent will have their email address deleted from the study systems by the central trial team. Patients that do consent to trial participation will receive a copy of the fully completed ICF via email once this has been countersigned.

14.4 Optional aspects of consent

Participants will be required to give their consent for all aspects of trial participation in order to take part in the study.

14.5 Individuals lacking capacity to consent

Individuals lacking capacity to consent to trial participation will not be eligible to enter the trial.

14.6 Participants who lose capacity during the trial

In the rare event that a participant, who has previously given consent, loses capacity, the participant will be withdrawn from the trial. De-identified data already collected with consent would be retained and used in the trial. No further data would be collected nor any other research procedures carried out on or in relation to the participant.

14.7 GP (General Practitioner) notification

GPs will be notified of participants' participation in the trial. GPs can also refer to physiotherapy, so it is important for them to be aware of participation in the study.

14.8 Re-consenting

Should there be any subsequent amendment to the final protocol which might affect a participant's involvement in the trial, continuing consent will be obtained using an amended ICF which will be signed by the participant.

15 RANDOMISATION

15.1 Timing of randomisation

Randomisation will only be performed when informed consent has been obtained, eligibility confirmed, and baseline questionnaires completed.

15.2 Randomisation procedure

Eligibility will be reconfirmed at randomisation. Participants will be randomised using the REDCap Randomisation Module provided within the core code of the REDCap application. This module has been validated for use by OCTRU and is accessed via the REACH REDCap trial database.

Participants will be randomised to one of the following two treatment groups:

Table 3: Treatment groups

Group	Description
Self-directed rehabilitation (intervention)	Detailed advice from a trained health professional and a workbook and website with a set of exercises that can be progressed independently.
Physiotherapist-supervised rehabilitation as per usual care (control)	Usual fracture clinic advice and referral to physiotherapy

Upon randomisation of a participant the central trial team and a member of the site research team will be notified by an automated email. Patients who are being consented using the remote consent method will be called by the site research team following randomisation and informed of their allocation.

Full details of the randomisation procedure will be stored in the Randomisation and Blinding Plan in the confidential statistical section of the TMF.

15.3 Randomisation methodology

Participants will be randomly allocated to the treatment options via automated, secure (encrypted), web-based randomisation provided by the Oxford Clinical Trials Research Unit (OCTRU) using a REDCap platform. Minimisation will be implemented with a 1:1 allocation ratio using the REDCap-Minimization module.

Randomisation will be performed using a minimisation algorithm (or randomisation schedules) to ensure balance between the two treatment groups using stratification factors:

- Age (<50 years/≥50 years)
- Recruiting centre

The first few participants will be randomised using simple randomisation, to seed the minimisation algorithm, and a non-deterministic probabilistic element will be included to prevent predictability of treatment allocation. The randomisation schedule will be designed by the OCTRU trial statistician and full details will be detailed in the Randomisation and Blinding Plan.

15.3.1 Justification for stratification factors

After the age of 50, bone mineral density decreases steadily in males, while in females there is an initial decline between the ages of 50 and 65, with a further decline in the age groups thereafter (28). In the UK incidence of humeral fractures increase steadily from 50 years of age, more so for females (29). These studies provide strong evidence that people aged 50 and over become increasingly vulnerable to fragility fractures of the proximal humerus.

Stratification within these two age boundaries will ensure that a similar proportion of people with fracture due to fragility are randomised to each group. Similarly, stratification by centre will ensure

that each centre has a similar proportion of participants allocated to each group and any clustering effect related to the centre itself will be equally distributed in the trial groups.

15.4 Back-up randomisation/registration procedure

There is no back-up randomisation procedure for this trial.

16 SUB-STUDIES/TRANSLATIONAL STUDIES/MECHANISTIC STUDIES

There are currently no planned sub-studies or translational studies or mechanistic studies.

17 TRIAL ASSESSMENTS/PROCEDURES AND DATA COLLECTION

The trial flow chart can be found in APPENDIX 1 – TRIAL FLOW CHART of this protocol.

17.1 Overview

Table 4 shows scheduled assessments for the trial.

After consent, baseline demographic data as well as patient-reported outcome measures will be collected prior to randomisation. Data collection will be completed by the participant, a member of the research team will be available to assist if required.

After randomisation, patient-reported outcomes, resource use and health-related quality of life, Complications and shoulder exercise data will be collected from participants via electronic or postal questionnaires at 2, 4 and 6 months. Additional data collection on physiotherapy session attendance will be collected from those participants allocated to the usual care group. Recruitment centres will be asked to review the participants' medical records and report complications up to 6 months post-randomisation. Data collection will be centrally managed by the central trial team at the University of Oxford.

17.2 Trial questionnaires

Participants will be sent a link to complete their trial questionnaires electronically where possible. Any link to a questionnaire sent to a participant either by email or text is unique to a participant and their time point/questionnaire in the trial. For those participants indicating that they will be unable to complete questionnaires electronically, data will be collected through telephone interview or via postal questionnaire. Where paper-based questionnaires are used, data will be entered into the trial database by the central trial team.

Clear guidance will be provided about how to complete each part of the questionnaire. If the participant does not complete the follow-up questionnaires, they will receive a reminder email, text and/or postal reminder, followed by one or more phone calls by the central trial team to offer assistance in the completion of the questionnaires or to complete the questionnaires over the phone. This will reduce drop out. The follow-up strategy will be described in the Data Management Plan. The central trial office may also phone participants to resolve data queries.

Table 4: Schedule of assessments

Assessments	≤21 days post-injury	3, 5 wks	2 mnths	11, 14 wks	4 mnths	20, 23 wks	6 mnths
Confirmation of eligibility Informed Consent	X						

Injury details and medical history	X						
Oxford Shoulder Score (OSS)	Pre-injury and Post-injury Baseline		X		X		X
PROMIS Physical Function (Upper Extremity)	Baseline		X		X		X
Self-efficacy (confidence) to Exercise (SEE)	Baseline		X		X		X
Health-related quality of life (EQ-5D-5L)	Pre-injury and Post-injury Baseline		X		X		X
Complications			X		X		X*
Resource use questionnaire			X		X		X
Exercise information			X		X		X
Physio attendance (usual care group only)		X	X	X	X	X	X
Further physio delivery information (*pilot phase – where physiotherapy is provided by the recruiting NHS Trust*)							X

Retrospective pre-injury baseline OSS and EQ-5D-5L will be collected at time of consent.
**Additional site reported questionnaire*

17.3 Data Collection

Data will be collected as described at each of the time points defined below.

17.3.1 Baseline

Baseline data will be collected prior to randomisation, with the exception of physiotherapy referral information, which will be post-randomisation.

Data sourced/collected by local research team	**Data directly reported by participants**
• Participant demographics • Injury details and medical history • Physiotherapy referral information (usual care group only): date and location (recruiting trust or community)	• OSS questionnaire – pre-injury and post-injury baseline • PROMIS Upper Extremity questionnaire – baseline • EQ-5D-5L questionnaire – pre-injury and post-injury baseline • SEE questionnaire – baseline

17.3.2 Follow-up assessments/subsequent visits

3 & 5 weeks post-randomisation (usual care only)

Data sourced/collected by local research team	Data directly reported by participants
n/a	Physiotherapy appointments attended

2 months post-randomisation

Data sourced/collected by local research team	Data directly reported by participants (patient-reported outcomes)
Ad hoc – Serious Adverse Event (SAE) CRF completion, Death notification	• OSS questionnaire • PROMIS Upper Extremity questionnaire • SEE Scale questionnaire • EQ-5D-5L questionnaire • Resource use questionnaire • Complications and exercise information questionnaire • Physiotherapy attendance

11 & 14 weeks post-randomisation (usual care only)

Data sourced/collected by local research team	Data directly reported by participants
n/a	Physiotherapy appointments attended

4 months post-randomisation

Data sourced/collected by site research team	Data directly reported by participants (patient-reported outcomes)
Ad hoc – SAE CRF completion, Death notification	• OSS questionnaire • PROMIS Upper Extremity questionnaire • SEE Scale questionnaire • EQ-5D-5L questionnaire • Resource use questionnaire • Complications and exercise information questionnaire • Physiotherapy attendance

20 & 23 weeks post-randomisation (usual care only)

Data sourced/collected by local research team	Data directly reported by participants
n/a	Physiotherapy appointments attended

6 months post-randomisation

Data sourced/collected by site research team	Data directly reported by participants (patient-reported outcomes)

• Complications (Medical Notes) • Further physio delivery information (*pilot phase – where physiotherapy is provided by the recruiting NHS Trust*) Ad hoc – SAE CRF completion, Death notification	• OSS questionnaire • PROMIS Upper Extremity questionnaire • SEE Scale questionnaire • EQ-5D-5L questionnaire • Resource use questionnaire • Complications and exercise information questionnaire • Physiotherapy attendance

17.4 Qualitative assessments

No qualitative research is currently planned as part of the trial.

17.5 Withdrawal

Withdrawal of consent means that a participant has expressed a wish to withdraw from the trial altogether or from certain aspects of the trial only. The type of withdrawal will be collected on the CRF labelled 'Withdrawal'.

The Withdrawal CRF should be completed to document the reasons for withdrawal, if provided, the level of withdrawal and who the decision to withdraw was made by.

Where a participant expresses a wish to withdraw from the trial, the research team will record the level of withdrawal – a) no longer willing to complete trial questionnaires (data will still be collected for study purposes) or b) full withdrawal (data collection will stop).

Participants may also be withdrawn from the trial (or aspects of the trial) by their clinician if they believe the participant needs to be withdrawn to safeguard the safety or wellbeing of the participant.

A decision to no longer adhere to the trial procedures by either participants or clinician (i.e. not attend scheduled physiotherapy sessions, no interaction with the provided materials, referral to physiotherapy, later surgery or other complications) will not be considered a trial withdrawal.

The site research team can request withdrawal of a participant by email to the central trial team. Appropriate action will be taken by the trial teams (centrally and by the local research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used and analysed as explained in the PIS. Investigators should continue to follow-up any ongoing SAEs to resolution in the CRF in accordance with the safety reporting section.

Withdrawn participants will not be replaced.

18 BLINDING AND CODE BREAKING

18.1 Blinding

It is not possible to blind trial participants or those delivering the interventions. Those involved in the care of participants or delivery of the interventions will not be involved in outcome data collection or analysis. The outcome data will be collected directly from the participants. Table 5

provides an overview of the blinding status of all individuals involved in the conduct and management of the trial.

Table 5: Blinding status of those involved in trial conduct and management.

Role in trial	Blinding status	Additional information
Participants	Not blinded	Not possible due to the nature of the intervention.
Site research staff including PI	Not blinded	Not possible due to the nature of the intervention.
CI	Blinded for those at sites other than their own, except for any SAE causality assessment	It is not possible to blind the CI as they may be the primary clinician for those participants recruited at their site, however, they will be blinded to allocations for participants at other sites. In instances where SAEs are reported, the CI will become unblinded to complete the full causality assessment.
Database programmer	Not blinded	The database programmer is responsible for the management of the REDCap database and will have access to all unblinded datasets.
Central trial team	Not blinded	Members of the central trial team will not be blinded to treatment allocations as site staff may require support for randomisation, or participants may contact the trial team directly. SAE reports will also be handled by the trial management team which will contain allocation information. Staff calling participants to collect outcome data will receive training and follow scripts to ensure a consistent approach.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the trial randomisation system and database to ensure data quality and undertake central monitoring activities.
Trial Statistician and Senior Trial Statistician	Not blinded	The trial statistician and senior trial statisticians will have access to treatment allocations or data needed for generating the Data and Safety Monitoring Committee (DSMC) closed reports and the final analysis and will remain blinded while performing any data cleaning.
Health Economist	Not blinded	The trial health economist and senior health economist will have access to treatment allocations for the final analysis.

18.2 Code break/ unblinding

Not applicable for this trial.

19 SAMPLES

This trial Protocol does not involve any taking of new biological samples or any use of pre-existing samples.

20 IMAGES

This trial protocol does not involve any taking of new images.

21 SAFETY REPORTING

21.1 Safety reporting period

Safety reporting for each participant will begin from randomisation and will end when the participant has reached their final follow-up time point, at 6 months post-randomisation.

21.2 Definitions

Table 6: Definitions of adverse events

Adverse event (AE)	Any untoward occurrence in a clinical trial participant. *Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the trial procedures, whether or not considered related to the procedures.*
Related AE	An event that resulted from administration of any of the research procedures.
SAE	An AE that: • results in death • is life-threatening [1] • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect; or • is otherwise considered medically significant by the Investigator [2].
Unexpected Related Serious Adverse Event	An SAE related to the trial (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the Protocol as an expected occurrence).

[1] participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

[2] Medical events that may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

21.3 Foreseeable AEs

For this trial, foreseeable AEs will be recorded by participants or site staff but will not need to be reported immediately. These will be recorded on participant and site-reported CRFs up to 6 months post-randomisation. The foreseeable AEs for this trial have been identified as:

- increase in pain after shoulder exercises lasting more than one week and requiring initiation of pain medication or increase in pain medication or consultation with medical doctor
- diagnosis of Complex Regional Pain Syndrome
- diagnosis of venous thrombosis
- diagnosis of pulmonary embolism
- diagnosis of a post-traumatic neurovascular injury (including neuropathy/nerve palsy)
- diagnosis of post-traumatic (secondary) frozen shoulder (arthrofibrosis)
- surgery to the injured shoulder

21.4 Non-reportable SAEs/AEs

AEs that are unrelated to the intervention will not be reported. AEs deemed related to the intervention that do not meet the SAE definition and are not classed as foreseeable as per section 21.3, will also not be reported.

21.5 Reporting of SAEs from sites to the central trial team

Only those adverse events that meet the definition of SAEs, are not listed as foreseeable AEs, and are considered by the site investigator to be related (possibly, probably, or definitely, see Table 7) to the trial intervention or any of the research procedures will be reported immediately to the central trial team as follows:

SAEs will be reported by the site research team using the SAE form within the REDCap trial database as soon as they are aware of the event. The central trial team is automatically notified of the SAE report through the database. If the electronic system on REDCap fails, sites will be asked to print out the SAE CRF from the PDF version contained in their Electronic Investigator Site File (eISF). They will use this hard copy to complete the event details using wet-ink and then scan and send a copy to the central team via email.

21.6 Assessment of SAEs by the PI (or delegate)

The PI (or delegated individual) is responsible for assessing all reported SAEs for seriousness, causality and expectedness.

21.6.1 Relatedness/causality

The assessment of "relatedness" to the trial intervention is the responsibility of the PI at site or an agreed designee according to the following definitions:

Table 7: Relatedness and causality

Relationship to intervention	Attribution (Causality)	Description
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

For the purpose of safety reporting interventions are defined as self-directed rehabilitation or physiotherapist-supervised rehabilitation.

21.7 Review of SAEs by the Sponsor/Clinical Trials Unit (CTU) Nominated Person

An appropriately qualified person will review the SAE and raise any queries with the reporting site. If the site has not provided an assessment of causality and has not responded to the query, it will be assumed that the event reported is related to the trial procedures/intervention. The site will be encouraged to respond and if a response is not provided, the CI will be consulted by the central trial team and the central trial team will complete the Sponsor part of the SAE report.

21.8 Reporting of SAEs to the Research Ethics Committee (REC)

All SAEs that are assessed as related and unexpected will be submitted to the REC within 15 days of the CTU/Sponsor becoming aware of the event.

21.9 Unblinding of SAEs for reporting to the REC

Not applicable as the trial team are already unblinded.

21.10 Follow-up of SAEs

If the SAE is an unexpected, related event then follow up information must be provided as requested by the central trial team. A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available.

22 PREGNANCY

If a participant does become pregnant during their participation in the trial, it does not need to be reported due to the nature of the intervention as concluded in the risk assessment of the trial.

23 STATISTICAL CONSIDERATIONS

23.1 Statistical Analysis Plan (SAP)

The statistical aspects of the trial are summarised here with details fully described in a SAP that will be drafted early in the trial and finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Trial Statistician in accordance with the current OCTRU SOPs. Any changes or deviations from the original SAP will be described and justified in any protocol amendments, final report and/or publications, as appropriate.

23.2 Sample Size/Power calculations

The primary outcome measure is the OSS at 6 months post-randomisation. Previous studies have demonstrated a minimum clinically important difference (MCID) of 5 points and a standard deviation of 12 (1). One method for choosing the non-inferiority margin is to take half the MCID and this is the method used in this trial. In real terms, a 2.5 point worse score equates to dropping one level on more than two of the twelve questions e.g. moving from little to moderate difficulty in more than two functional tasks such as household shopping and hanging clothes in a wardrobe. To ensure the acceptability of this margin with patients and clinicians we undertook consultations with stakeholder representatives. A 5% worse outcome overall (2.5/48) would be acceptable to avoid the burden of multiple outpatient visits and is sufficient to change clinical decision making. Primary outcome data provided by 970 participants at 6 months will provide 90% power at 2.5% (1-sided) significance to detect whether self-directed rehabilitation is non-inferior to standard physiotherapist-supervised rehabilitation based on a non-inferiority margin of 2.5. Allowing 20% loss to follow-up yields an overall sample size of 1214 (607 per group).

23.3 Description of Statistical Methods

Standard descriptive statistics will be used to summarise the baseline participant demographic characteristics by treatment group using means with standard deviation or medians with interquartile ranges as appropriate for continuous variables and numbers with percentages for binary or categorical variables. It is anticipated that all statistical analyses will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical software.

A non-inferiority trial aims to demonstrate that a new treatment is not clinically worse than the active control by more than a predefined amount and therefore the interest is one-sided. The new treatment may be better than the control, but it must not be inferior. We therefore define a maximum difference between the two groups in a given direction we are prepared to tolerate and

still consider the new treatment clinically not inferior to the standard treatment. This difference is the non-inferiority margin (Δ_M). We then test the null hypothesis that a difference greater than Δ_M exists in favour of the control (H_0: $\Delta \geq \Delta_M$). This is assessed by constructing a 95% confidence interval for the difference between the two treatments (Δ) which should be above the non-inferiority margin for the new treatment to be declared non-inferior and reject the null hypothesis in favour of the alternative (H_A: $\Delta > -\Delta_M$). To estimate Δ, the primary outcome measure, OSS at 6 months will be compared between treatment groups as the dependent variable in a mixed effects linear regression model adjusting for the minimisation factors (age and centre). A fixed effect will be used to account for age and a random effect will be included to account for any heterogeneity due to recruitment centre.

The primary analysis will be performed using a treatment policy, in which all randomised participants with available data are analysed according to their treatment allocation regardless of whether intercurrent events occur (30, 31). Given the nature of the interventions as described in Section 13, any trial-specific intercurrent events which are likely to occur in the trial setting and not in routine clinical practice are expected to be non-significant. For example, it is possible for participants in both self-directed rehabilitation and usual care groups to access further physiotherapy treatment. To assess the impact of such intercurrent events or similar on the non-inferiority conclusion, we will consider defining additional secondary estimands. Details of the estimands and estimator strategy will be defined in the SAP and finalised following a blinded review of the data before the primary outcome analysis data lock (32).

Additional analyses including data from all timepoints in a multilevel linear regression model will be used to explore the recovery trajectory between the two groups for the OSS score using the area under the curve (AUC) based on a summary statistics approach (33). Similar mixed effects linear regression models will be used to analyse continuous secondary outcomes (PROMIS, EQ5D- 5L, SEE Scale) over time. The number and proportion of participants experiencing complications will be summarised by treatment group and compared using an adjusted logistic regression model if sufficient complications occur.

Results will be reported in line with the CONSORT statement and any appropriate extensions and will be described fully in a separate SAP. A single final unblinded statistical analysis will take place after all follow-up has been completed, and sufficient time has been allowed for data collection and cleaning.

23.4 Inclusion in analysis

The principal analysis will be performed on the ITT population as defined above, analysing participants with available outcome data in their randomised groups.

23.5 Subgroup analysis

Pre-specified subgroup analyses will be finalised in the SAP. These will include exploring the possible treatment effect modification of age group (<50 years or ≥50 years) as a clinically important factor. Analyses will use treatment by factor interactions. Results from these analyses will be viewed as exploratory and interpreted with caution.

23.6 Interim analyses

The main outcomes will be analysed as stated in the analysis plan once the trial follow-up has been completed. No formal interim analyses of treatment effect are planned for any of the trial outcomes and will be performed only where requested by the DSMC.

23.7 Stopping rules

As no formal interim analyses are planned, no stopping rules have been incorporated into the trial design. An independent DSMC will review the accumulating data at regular intervals and may recommend pausing or stopping the trial in the event of safety concerns.

23.8 Level of Statistical Significance

Non-inferiority comparisons will use one-sided 2.5% significance which is equivalent to the lower bound of the 95% confidence interval being compared to the non-inferiority margin. If the Self-directed rehabilitation is found to be non-inferior to physiotherapist-supervised rehabilitation then superiority will also be tested at 2.5% (1-sided) significance. The remaining superiority comparisons and secondary outcome analyses will use a two-sided 5% significance and 95% confidence intervals throughout.

23.9 Procedure for accounting for missing data

The trial will attempt to collect data as completely as possible. Any missing data will be summarised by treatment group and patterns analysed. Unavailable observations due to missed questionnaires or to a participant leaving the trial prematurely are assumed to be similar to observed outcomes from similar participants at the same time points (i.e. missing at random (MAR)). The multilevel mixed effects regression model including all participants with outcome data at other timepoints, and adjusted for minimisation factors or important prognostic factors is expected to produce unbiased results under a MAR mechanism (34) and therefore we do not anticipate using multiple imputation for missing outcome data in the analysis. The potential impact of informative missing data (missing not at random) on the treatment effect in the OSS at 6 months will be investigated using Stata's 'rctmiss' command or similar approaches if there is sufficient or differential missing data.

23.10 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any deviation(s) from the original SAP will be described in the final statistical report.

23.11 Internal pilot/Decision Points

An internal pilot is planned that will progress seamlessly to the definitive trial if predefined progression criteria are reached. Data from the internal pilot trial will contribute to the final analysis. The purpose of the internal pilot is to ensure that the projected site enrolment rate and recruitment rate can be achieved.

Stop-go criteria for the pilot phase are given in Table 8 together with the definitions of how each will be measured. The criteria will be reviewed after 9 months of recruitment.

Table 8: Stop-go criteria for internal pilot phase.

No. of participants recruited	No. sites opened	Recruitment rate/site/month	Progression guidance
≥200	9	3	Continue with trial – no action required
100-199	5-8	1.5-2.9	Continue with trial – action required: • Review recruitment strategies, consider modification and monitor closely
≤99	≤4	≤1.4	Review with funder

The Trial Management Group (TMG) will closely monitor the progression criteria during the internal pilot, and together with the Trial Steering Committee (TSC) and DSMC will perform a full review towards the end of the internal pilot. Guided by the TSC, the funder will make the final decision to terminate the trial.

The internal pilot trial will mirror the procedures and logistics undertaken in the main definitive trial. It is intended that the study will progress seamlessly into the main phase, with internal pilot participants included in the final analysis. Should a decision be made to stop the trial any data collected would be presented, and together with the funder it would be decided upon whether participants would be followed up as per protocol.

24 HEALTH ECONOMIC EVALUATION

A prospective economic evaluation, conducted from NICE's recommended NHS and personal social services perspective (20) is integrated into the trial. A health economics analysis plan will be drafted early in the trial and finalised prior to the final analysis data lock. Primary research methods will be followed to estimate the costs of the management methods, including the costs of physiotherapists and other health professionals, physiotherapy sessions in outpatient departments, support materials and associated administrative activities. Broader resource utilisation will be captured through patient questionnaires completed at baseline and at 2, 4 and 6 months post randomisation. Unit costs for resource inputs identified will largely be derived from national reference tariffs, although primary research that uses established accounting methods may also be required. EQ-5D-5L responses will be used to generate quality adjusted life-years (QALYs) based upon baseline-adjusted utility curves using the trapezoid rule. Utility weights for EQ-5D-5L health states will be estimated using an interim crosswalk algorithm (35) until a national tariff set for the EQ-5D-5L is formally recommended by NICE. Regression methods, accounting for clustering effect, with multiple imputation of missing data if evidence supports missing at random assumption as the base-case missingness mechanism, will be conducted for costs and QALYs to generate within-trial estimates of incremental cost-effectiveness associated with the self-directed rehabilitation programme. Sensitivity analyses will be undertaken to assess the impact of areas of uncertainty surrounding components of the economic evaluation.

The sensitivity analyses will include re-estimation of cost-effectiveness under alternative missing data mechanisms, and re-estimation of cost-effectiveness assuming a broader societal perspective. The latter will incorporate direct costs to trial participants, economic values for informal care provided by family and friends and economic values associated with productivity losses; the values of these broader resource consequences will be informed by responses to questions in the patient completed questionnaires.

If incremental costs and benefits are not convergent over the trial follow-up period of the main randomised controlled trial, decision-analytic modelling will be used to extrapolate the impact of the self-directed rehabilitation programme beyond the follow-up period. Accepted guidelines for good practice in decision-analytic modelling will be followed (36). A de novo model structure will capture progression using health states that represent the important natural history and clinical- and event-related activity following proximal humerus fracture and its management methods, the appropriate model type (e.g., Markov or discrete-event simulation approach) and the appropriate analytical framework (e.g., cohort analysis versus individual-level simulation). Parameter inputs will be informed by data from the main randomised controlled trial supplemented by data from targeted

literature searches. Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis.

Cost-effectiveness acceptability curves will be used to show the probability of cost-effectiveness of the self-directed rehabilitation programme at alternative cost-effectiveness thresholds held by decision-makers.

25 DATA MANAGEMENT

The data management aspects of the trial are summarised here with details fully described in the trial-specific Data Management Plan. See section 29, "Participant confidentiality" for information on management of personal data.

25.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. Source data is outlined in section 9.

25.2 Location of source data

The location of source data in the trial is listed in the tables within section 9.

25.3 CRFs

The Investigator and trial site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. All appropriate Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed ICF, the participant will be referred to by the trial participant number, not by name.

25.4 Source data to be recorded directly on the CRFs

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data).

25.5 Non-CRF data

All trial data will be recorded on the CRFs. No additional data will be held outside of the CRFs.

25.6 Access to Data

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor and host institution to permit trial-related monitoring, audits and inspections. The data submitted by trial participants directly via the trial database (i.e. electronic participant reported outcomes) will also be made available to the participating site that recruited the participant; this is detailed within the PIS so that participants are aware of who will have access to this data.

Members of the trial team will only be able to access data that they need to, based on their roles and responsibilities within the trial.

25.7 Data Recording and Record Keeping

The CRFs will be designed by members of the trial management team which will include the CI, trial statistician(s) and trial manager.

Data will, wherever possible, be collected in electronic format with direct entry onto the trial database by site staff or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit

trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic ICFs, will be held on a server located in an access-controlled server room at the University of Oxford.

The database and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the trial PIS.

Personal identifiable data will be kept separately from the outcome data obtained from or about the patients. Participants will be identified by a trial ID only.

Data captured during phone calls to participants or from paper-based trial questionnaires returned to the trial office will be entered into the trial database by suitably trained central trial team staff. Full details of this process will be recorded in the Data Management Plan. Identifiable data will only be accessible by members of the research team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant (e.g. for sending follow-up reminders for online form completion or telephone follow-up).

25.8 Electronic transfer of data

Any electronic transfer of data during the course of the trial will be strictly controlled in accordance with OCTRU's SOP for Secure Information/Data Transfer.

26 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The TMG will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of randomisation, trial entry procedures and data collection. OCTRU has a QA team who will monitor this trial by conducting audits of the TMF. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the central trial team. Additionally, the trial may be monitored, or audited by the Sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and SOPs.

A trial-specific data management and monitoring plan will be in place prior to the start of the trial.

26.1 Risk Assessment

This Protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the trial opens. The known and potential risks and benefits to participants have been assessed in comparison to those of usual care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the trial or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

26.2 Trial monitoring

Monitoring will be performed by the central trial team according to a trial-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the trial will permit trial-related monitoring and provide direct on-site access to all trial records and facilities if required. They will provide adequate time and

space for the completion of monitoring activities.

Trial sites will be monitored centrally by checking incoming data for compliance with the Protocol, consistency, completeness and timing. The case report form data will be validated using appropriate set criteria, range and verification checks. The trial site must resolve all data queries in a timely manner as specified in the Data Management Plan. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the trial site for resolution.

Trial sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the trial. The central trial team will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports or data discrepancies will be sent to the site in accordance with OCTRU SOPs and the trial monitoring plan. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

Intervention delivery will be monitored periodically during the internal pilot phase of the trial to ensure fidelity. Site visits and/or audio recording of interventions will be conducted. Permission will be sought from the trial participants to observe or record treatment sessions. Verbal consent will be provided and recorded. CRFs will also be used to monitor intervention fidelity. Data will be collected on intervention content delivery to facilitate monitoring and reporting. The sites will regularly receive feedback from quality assurance activities to help maintain and improve fidelity.

26.3 Audit and regulatory inspection

All aspects of the trial conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits or inspections may occur at any time during or after the completion of the trial. Investigators and their host Institution(s) should understand that it is necessary to allow auditors direct access to all relevant documents, trial facilities and to allocate their time and the time of their staff to facilitate the audit visit. Anyone receiving notification of an audit that will (or is likely to) involve this trial must inform the central trial team without delay.

26.4 Trial committees

26.4.1 Trial Management Group (TMG)

A TMG will be established for the trial and operate in accordance with a trial-specific TMG charter. The TMG will manage the trial, including the clinical and practical aspects and will meet approximately monthly to assess progress. Other specialities and individuals will be invited as required for specific items or issues.

26.4.2 Data and Safety Monitoring Committee (DSMC)

An independent DSMC will be established for this trial. The DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the trial. The DSMC will meet regularly throughout the trial at time-points agreed by the Chair of the Committee and the CI. At a minimum this will be on an annual basis. The DSMC will review the data generated, including all safety data, and make recommendations as to whether the Protocol should be amended to protect patient safety. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

26.4.3 Trial Steering Committee (TSC)

The TSC, which includes independent members, provides overall supervision of the trial on behalf of the funder. The TSC will act in accordance with a TSC charter which will outline its roles and responsibilities. Full details including names will be included in the TSC charter. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the trial.

The TSC will consider, and act, as appropriate, upon the recommendations of the DSMC.

27 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

27.1 Identification of recruitment sites

Recruitment sites will be selected based on suitability to conduct the trial. Potential sites will be invited to complete a SFQ which will be used by the TMG to assess suitability of the site for the trial; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

27.2 Trial site responsibilities

The PI (the Principal Investigator, or lead clinician for the trial site) has overall responsibility for the conduct of the trial but may delegate responsibility where appropriate to suitably experienced and trained members of the site research team. All members of the site research team must complete a delegation log provided by the central trial team prior to undertaking any trial duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

27.3 Trial site set up and activation

The PI leading the participating trial site is responsible for providing all required core documentation. Mandatory site training which is organised by the central trial team (see below) must be completed before the site can be activated. Training in the trial processes will be administered at site initiation visits delivered either in person or online by the central CTU trial team. The central trial team will check to confirm that the site has all the required trial information and documentation and is ready to recruit. The site will be notified once they are activated on the trial database and are able to begin recruiting participants.

27.4 Training

Training in the trial processes will be administered at site initiation visits (delivered face to face or online) by the central trial team.

27.5 Trial documentation

The central trial team will provide an electronic ISF to each participating site containing the documents needed to conduct the trial. The central trial team must review and approve any local changes made to any trial documentation including patient information and ICFs prior to use. Additional documentation generated during the course of the trial, including relevant communications, must be retained in the site files as necessary to reconstruct the conduct of the trial.

28 ETHICAL AND REGULATORY CONSIDERATIONS

28.1 Declaration of Helsinki

The Investigator will ensure that the trial is conducted in accordance with the principles of the Declaration of Helsinki.

28.2 Guidelines for Good Clinical Practice and compliance

The Investigator will ensure that the trial is conducted in accordance with relevant regulations and with the principles of GCP, the UK Data Protection Act and all other applicable regulatory and governance frameworks including the UK Policy Framework for Health and Social Care Research.

28.3 Ethical conduct of the trial and ethical approvals

The Protocol, patient information sheet, ICF and any other information that will be presented to potential trial participants (e.g. advertisements or information that support or supplement the informed consent process) will be reviewed and approved by an appropriately constituted, independent REC.

28.4 NHS Research Governance

Once Health Research Authority (HRA), Health and Care Research Wales (HCRW) and/or Research and Development (R&D) trial-wide review in Scotland and Northern Ireland approvals are in place for the trial, sites will confirm capability and capacity to participate in the trial, and the sponsor will provide green light confirmation to each site.

28.5 Protocol amendments

All amendments will be generated and managed according to the CTU SOPs to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators as applicable for the amendment type. The only exceptions are for changes necessary to eliminate an immediate hazard to trial participants (see below).

It is the Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the trial. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

28.6 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the Protocol are not allowed. Changes to the approved Protocol need prior approval unless for urgent safety reasons.

A trial related deviation is a departure from the ethically approved trial Protocol or other trial document or process or from GCP or any applicable regulatory requirements. Deviations from the Protocol will be captured within the trial database either using a Protocol deviation form or via suitably designed fields within a Protocol deviation CRF which will be extracted from the trial database and reviewed regularly by the TMG. Deviations will be handled and reviewed in a timely manner in accordance with a trial-specific Data Management Plan and Monitoring Plan.

The PI must promptly report any important deviation from GCP or Protocol to the central trial team. Examples of important deviations are those that might impact on patient safety, primary or secondary endpoint data integrity, or be a possible serious breach of GCP.

28.7 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the central trial team IMMEDIATELY if the trial site initiates an urgent safety measure.**

The notification must include:

- date of the urgent safety measure;
- who took the decision; and
- why the action was taken.

The Investigator will provide any other information that may be required to enable the central trial team to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The central trial team will follow written procedures to implement the changes accordingly.

28.8 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this Protocol on hold for short periods for administrative reasons **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of participants already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The central trial team will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

28.9 Serious Breaches

A “serious breach” is a breach of the Protocol or of the conditions or principles of GCP which is likely to affect to a significant degree:

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

(b) the scientific value of the research.

Investigators must notify the central trial team within one working day if any serious breach of GCP is suspected. The central trial team will review the event and, if appropriate will report a serious breach to the REC and the NHS host organisation within 7 days of the central trial team becoming aware of the breach.

28.10 Trial Reports

This Protocol will comply with all current applicable REC and Sponsor reporting requirements.

28.11 Transparency in Research

Prior to the recruitment of the first participant, the trial will be registered on a publicly accessible database (ISRCTN), which will be kept up to date during the trial, and results will be uploaded to the registry within 12 months of the end of the trial declaration. A Final Report will be submitted to the REC containing a lay summary of the trial results which will be published on the HRA website.

The results of the trial will be published and disseminated in accordance with section 34.

28.12 Use of social media

Social media (e.g. Twitter/X feeds) may be utilised to promote the trial and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment by a site, etc.).

29 PARTICIPANT CONFIDENTIALITY

29.1 Collection and use of personal identifiable information

Contact details (participant name, email address, postal address and phone numbers) will be collected in this trial for the following purposes, and where an activity is optional, only with the specific consent of the participant:

- sending of follow-up questionnaires and any reminder messages, by post, phone, email and/or text
- sending a copy of the completed ICF by email (for any participants that consent electronically and wish to receive a copy by email)
- collection of NHS number/Community Health Index (CHI) number/H&C number
- enabling access to the intervention materials (for the self-directed rehabilitation group)
- sending a welcome letter with a small low-value item such as a trial branded keyring or pen to all participants

The PIS explains what contact details will be collected and how these will be used.

Where remote eConsent is used, participants will be asked to give their permission verbally for a link to the consent documentation to be sent to their email address or an email address they provide.

29.2 Use of audio/visual recording devices

Audio recordings of the intervention delivery of a subset of trial participants will be reviewed by a member of the central trial team to enable completion of a quality assurance checklist. Audio recordings of treatment will be made digitally on password-protected devices. They will be stored on secure servers at the University of Oxford, identified by a trial ID and/or initials only and will only be accessible to the CI and those members of the Oxford research team who have been authorised to do so by the CI. The audio recordings will be retained for 12 months after being received and analysed as part of intervention quality assurance and then deleted. It is necessary to retain the recordings for this period as they are the source data and help us to assess treatment delivery. Access to them is required in case these are needed to refer back to these during intervention monitoring.

29.3 Storage and use of personal data

Personal data during the trial will be stored and used in accordance with OCTRU's SOP for confidentiality, protection and breach of personal data in relation to research participants. This ensures that all personal data collected during the trial is recorded, handled and stored in such a way that it satisfies the requirements of the UK General Data Protection Regulation (GDPR) and requires data to be anonymised as soon as it is practical to do so.

All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal data of participants will be minimised wherever possible by the use of a unique participant trial number on trial documents and any electronic databases.

Personal data on all documents will be regarded as confidential. The trial staff will safeguard the privacy of participants' personal data.

The use of all personal data in the trial will be documented in a trial-specific data management and sharing plan which details what and where personal data will be held, who will have access to the data, when personal data will be anonymised and how and when it will be deleted.

The Investigator site will maintain the patient's anonymity in all communications and reports related to the research.

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a Protocol deviation.

29.4 Access to participants' personal identifiable data during the trial

Access to participants' personal identifiable data will be restricted to individuals authorised to have access. This includes:

- members of the research team at participating trial sites with delegated responsibility by the site PI, and
- members of the central trial team involved in the conduct and management of the trial where this is necessary for their role

Research staff that are not part of the participant's direct care team will not have access to personal identifiable data until the participant has given their consent to take part in the trial or the participant has indicated to their direct care team that they wish to be contacted by a member of the site research team. Permission for this will be recorded in the participant's medical notes.

The PIS clearly describes who will have access to the participant's personal identifiable data during the trial and explicit consent is obtained from trial participants for such access.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the trial being looked at by individuals from the Universities of Oxford and Exeter, from regulatory authorities and from the NHS Trust(s), where it is relevant to their taking part in this trial; only authorised individuals will be granted access and only where this is necessary for their role.

29.5 Destruction of personal identifiable data

Consent for the storage and use of personal identifiable data (which includes ICFs) will be obtained from participants as detailed in the PIS and ICF.

Personal identifiable data will be destroyed as soon as it is no longer required. The time point for this destruction is detailed in the trial data management plan and is in accordance with OCTRU SOPs which comply with the UK GDPR.

29.6 Participant Identification Log

The site research team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

30 PUBLIC AND PATIENT INVOLVEMENT

30.1 PPI in trial design and Protocol development

The UK Trauma and Emergency Care PPI group were involved in several research prioritisation exercises, where rehabilitation of upper limb fragility fractures was a consistent priority.

During the trial development work PPI representatives described the particular challenges of recovering from shoulder trauma and wearing a sling. The challenges of attending outpatient physiotherapy clinic appointments were described as being a major issue during recovery, as people could not drive, and public transport was a struggle due to low confidence, use of a sling, and pain and weakness in the arm.

A high-quality self-directed rehabilitation approach so that people could manage their own recovery had great appeal, if there were robust evidence that outcomes are not worse than the current usual care (physiotherapist-supervised rehabilitation). There was support for shoulder pain and function as the primary outcome. The use of patient-reported outcomes at two-monthly intervals was considered a good balance between keeping contact and not being excessively burdensome. Remote trial follow-up was strongly preferred given the issues mentioned above with hospital visits. However, digital access and health literacy were noted as important potential barriers to trial participation so there was broad support for offering accessible and clear intervention materials and follow-up questionnaires in both paper and electronic format.

In response to the concerns of trial participants, including those who declined participation in trauma research, and the UK Musculoskeletal Trauma PPI group, we will provide:

- clear and simple patient information, delivered at appropriate moments, understandable by people with a range of health literacy levels
- web resources including explainer videos, with accessibility options for ease of reading
- access to clinicians with detailed knowledge of the trial
- a postal option to enable those with lower-level IT skills or less IT access to participate in the trial.

The PPI members of the management group have been specifically involved in producing:

- trial PIS and explainer animation
- CRFs
- recruitment and consenting procedures
- patient posters
- intervention workbooks and website
- trial explainer animation.

30.2 Dissemination of trial results

Findings of the trial will be made available to participants via the study website and social media. The PPI Advisory Group will lead trial updates and dissemination to patients or service users, carers, and the wider population directly through their extensive network of patient advocacy organisations and charities. They will help generate a plain language summary of the results for patients and the public, which will also be used as the basis for an infographic and a results explainer animation video.

31 EXPENSES/PAYMENTS TO PARTICIPANTS

No payments will be made to trial participants for taking part in this trial.

32 SPONSORSHIP, FINANCE AND INSURANCE

32.1 Sponsorship

The Sponsor, University of Exeter, will provide written confirmation of Sponsorship.

32.2 Funding and support in kind

Table 9 provides a summary of all funding and support in kind for the trial.

Table 9: Funding for the trial

Funder(s)	Financial and non-financial support given
NIHR HTA Programme	NIHR153139

32.3 Insurance

The Sponsor (University of Exeter) has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Aviva Insurance Ltd.). NHS indemnity operates in respect of the clinical treatment that is provided.

33 CONTRACTUAL ARRANGEMENTS

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

34 PUBLICATION AND DISSEMINATION

34.1 Publication plan

The Sponsor will retain ownership of all data arising from the trial.

Publication and dissemination of trial results will be in accordance with OCTRU SOPs and irrespective of trial findings.

The trial Protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (37, 38). The trial results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The trial will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT) (39) including any applicable extensions to this. The TIDieR statement will be used for reporting the intervention (27, 40).

The statistical and health economics analysis plans will be published in an open-access format before the final trial analysis.

34.2 Trial results and dissemination

All data will be presented such that no individual participants can be identified. This trial will provide the first robust clinical and cost-effectiveness evidence regarding self-directed versus supervised rehabilitation for people with proximal humerus fracture.

The results will inform updates to the NICE guideline NG38: Fractures (non-complex).

An investigator webinar will be held to feed the trial results back to the trial sites. We also plan to present results at annual British Orthopaedic Association and Association of Trauma and Orthopaedic Chartered Physiotherapists congress, the British Elbow and Shoulder Society conference, and international Orthopaedic and Fragility Fracture meetings.

34.3 Dissemination of trial results to participants and the public

The trial website and social media will share news on trial progress and eventually the trial results. The PIS includes a link to the trial website where participants will be advised that the results will be published. The PPI co-applicants, along with the wider PPI Advisory Group, will support development of lay summaries, a short animation video and an infographic, and actively reaching wider patient networks. Findings will be shared with patients and the public more widely through local and national charity newsletters. Posters will also be prepared with input from the broader PPI Group for inclusion at any workshop, focus group or conference where relevant national PPI is involved or discussed.

34.4 Authorship

Authorship of any publications arising from the trial will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from this trial must acknowledge the contribution of participants, the funder, OCTRU, OxTEC and the Sponsor.

35 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY (IP)

Ownership of IP generated by this trial vests in the University of Exeter. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

36 ARCHIVING

36.1 Minimum Mandatory archiving period

It is the University of Exeter's policy to store de-anonymised data sets for 3 years, in accordance with GDPR.

Investigators may not archive or destroy trial essential documents or samples without written instruction from the central trial team.

36.2 Archiving responsibilities/procedure

During the trial and after trial closure the Investigators must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request, for the minimum period as specified above.

36.3 Central trial team TMF

All paper and electronic data including the TMF and trial database will be retained and archived in accordance with OCTRU SOPs which are compliant with the UK GDPR.

36.4 ISF and participant medical records

The ISFs will be archived at the participating site. The medical files of trial participants must be retained for the mandatory archiving period stated above and in accordance with the maximum period of time permitted by the participating site. Sites should comply with the documentation retention specified in the clinical trial agreements (or equivalent) issued by the trial Sponsor.

36.5 Retention of data sets

Trial data and associated metadata will be held electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory

archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

37 DATA SHARING

The trial statistician and health economist may retain copies of anonymised datasets for the purpose of data sharing in accordance with the trial data sharing plan.

37.1 Retention of anonymised datasets

Upon completion of the trial, anonymised research data may be shared with other organisations on request to the CI and in accordance with the data sharing policies of OCTRU, the Sponsor and funder. Anonymised data will be kept for a minimum of 10 years following publication in accordance with the Concordat on Open Research Data.

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39 VERSION HISTORY

Previous versions of this Protocol and a summary of the changes made are provided in the table below:

Protocol version no.	Protocol date	Summary of key changes from previous version
N/A		1st version of the Protocol

APPENDIX 1 – TRIAL FLOW CHART