



Home-based Extended Rehabilitation for Older people (HERO)

Individually randomised controlled multi-centre trial to determine the clinical and cost effectiveness of a home-based exercise intervention for older people with frailty as extended rehabilitation following acute illness or injury, including embedded process evaluation.

Chief Investigator: Dr Andrew Clegg

Authors: Dr Andrew Clegg, Dr David Clarke, Bonnie Cundill, Professor Amanda Farrin, Professor Anne Forster, Dr Vicki Goodwin, Suzanne Hartley, Professor Claire Hulme, Michael Holland, Amanda Lilley-Kelly, Matthew Prescott, Phil Wright, Professor John Young

Co-ordinating Groups: Academic Unit of Elderly Care and Rehabilitation, University of Leeds
Bradford Royal Infirmary, Bradford, UK.
Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research,
University of Leeds, Leeds, UK.
Academic Unit of Health Economics, Leeds Institute of Health Sciences,
University of Leeds, Leeds, UK.
University of Exeter Medical School, Exeter, UK.

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1. KEY STUDY CONTACTS

Yorkshire Hub

Contact for queries relating to site participation and the HERO Intervention

Chief Investigator

Dr Andrew Clegg
Email: A.P.Clegg@leeds.ac.uk
Tel: 01274 38 2096

Trial Manager

Matthew Prescott
Email: Matthew.Prescott@bthft.nhs.uk
Tel: 01274 38 3424

Address

Academic Unit of Elderly Care and Rehabilitation
University of Leeds
Bradford Institute for Health Research (BIHR)
Temple Bank House
Bradford Royal Infirmary
Duckworth Lane
Bradford, BD9 6RJ

South West Hub

Contact for queries relating to site participation and the HERO Intervention

Co-investigator and Hub Lead:

Dr Victoria Goodwin
Email: V.Goodwin@exeter.ac.uk
Tel: 01392 262 745

Trial Manager:

Matthew Prescott
Email: Matthew.Prescott@bthft.nhs.uk
Tel: 01274 38 3424

Address

NIHR CLAHRC South West Peninsula (PenCLAHRC)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Exeter, EX1 2LU

Clinical Trials Research Unit (CTRU)

Contact for queries relating to NHS permissions, data collection and data management.

Trial Managers

Mrs Catriona Parker
Email: C.A.Parker@leeds.ac.uk
Tel: 0113 343 9241

Data Manager

Mrs Madeline Goodwin
Email: M.E.L.Goodwin@leeds.ac.uk
Tel: 0113 343 1480

Trial Statistician

Supervising Statistician

Mrs Bonnie Cundill
Email: B.E.Cundill@leeds.ac.uk
Tel: 0113 34 34848

Lead Methodologist

Prof Amanda Farrin
Director of Complex Interventions Division
Email: A.J.Farrin@leeds.ac.uk
Tel: 0113 343 8017

Project Delivery Lead

Suzanne Hartley
Head of Trial Management
Email: S.Hartley@leeds.ac.uk
Tel: 0113 343 8041

CTRU Address

Leeds Institute of Clinical Trials Research (LICTR)
Clinical Trials Research Unit, University of Leeds,
Leeds, LS2 9JT

Process Evaluation

Dr David Clarke

Academic Unit of Elderly Care and Rehabilitation
University of Leeds
Bradford Royal Infirmary
Bradford, BD9 6RJ

Email: D.J.Clarke@leeds.ac.uk
Tel: 01274 383441

Health Economist

Prof Claire Hulme

Health Economics Group
Institute of Health Research
University of Exeter Medical School, Exeter EX1 2LU

Email: C.T.Hulme@exeter.ac.uk
Tel: 0113 343 0875

Sponsor

Jane Dennison, Research Support & Governance Manager
Research Management & Support Office,
Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust

Telephone: 01274 38 2575

Mobile: 07779024387

Email: Jane.Dennison@bthft.nhs.uk

Other relevant contacts, including a list of co-applicants are detailed in Appendix 1.

2. STUDY SUMMARY

Study Title	Individually randomised controlled multi-centre study (with internal pilot) to determine the clinical and cost effectiveness of a home-based exercise intervention for older people with frailty as extended rehabilitation following acute illness or injury, including embedded process evaluation.	
Short title	HERO (Home-based Extended Rehabilitation of Older people)	
Study Design	Pragmatic multi-centre individually randomised study with a two level, partially nested hierarchical design, internal pilot with progression criteria and an embedded process evaluation and parallel cost-effectiveness evaluation.	
Study Participants	Older people (aged >65) with frailty admitted to hospital following acute illness or injury then discharged home directly from hospital or from intermediate care services.	
Planned Sample Size	718 (318 control and 400 intervention), adjusted to 742 in Protocol v5.0 (325 control and 417 intervention)	
Treatment duration	24 week home based intervention (HOPE Programme).	
Follow up duration	12 months	
	Objectives	Outcome Measures
Primary	To establish whether a home-based exercise intervention plus usual care as extended rehabilitation for older people with frailty improves health-related quality of life.	Measured using the physical component summary of the SF36 at 12 months post randomisation
Secondary	To establish whether the intervention improves mental health.	Measured using the mental component summary of the SF36
	To establish whether the intervention improves activities of daily living.	Measured using the Barthel Index of Activities of Daily Living and Nottingham Extended Activities of Daily Living scale.
	To establish whether the intervention reduces hospitalisation rates, care home admission rates, falls and overall health and social care resource use.	Measured using health care records, routine data, recording of living circumstances, self-report questionnaires, safety monitoring.
	To establish whether the intervention is cost-effective	Measured using differences in cost of service use between groups and the incremental cost effectiveness ratios (ICERs) using quality-adjusted life years (QALYs) derived from the EuroQol 5 dimension health questionnaire, 5 level (EQ-5D-5L) and the Short-form 6 dimension health index (SF6D).
	To understand how the intervention is experienced and understood by providers and recipients, and explore the organisational implications of embedding and sustaining the intervention in preparation for wider NHS roll-out.	Measured using an embedded mixed-methods process evaluation using a range of methods including documentary analysis, non-participant observation, and semi-

		structured interviews
Internal Pilot (4 Sites)	To assess whether the provision and acceptability of the intervention meet the pre-defined progression criteria thresholds.	Measured by intervention data collection forms (provision and acceptability assessed via the proportion of participants receiving their first home visit within three weeks and retention of intervention participants respectively)
	To assess whether study recruitment and six-month follow-up rates meet the predefined progression criteria thresholds.	Measured by recruitment rates and completion of the physical component summary of the SF36.
Intervention	The Home-based Older People's Exercise (HOPE) programme is a home-based exercise intervention for older people with frailty. It is a 12 week graded, progressive exercise intervention aimed at improving strength, endurance and balance that is presented to participants in an exercise manual and delivered by community-based physiotherapists and therapy assistants. Participants will receive weekly support through five face-to-face home visits and seven telephone sessions. The programme will be extended with weekly telephone calls for a further 12 weeks to ensure that participants are well-positioned for ongoing self-management following completion of the intervention.	

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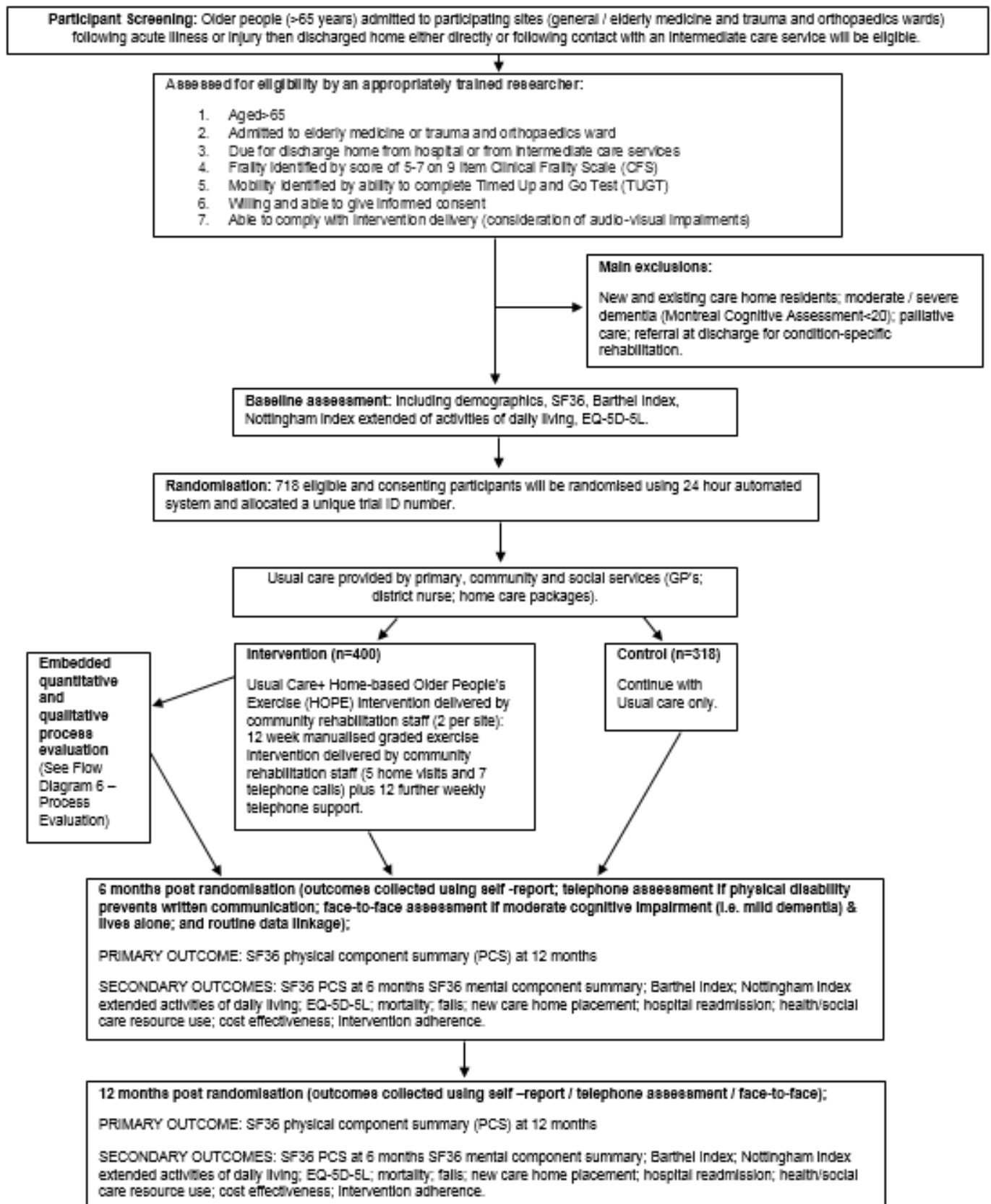
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4. LIST OF ABBREVIATIONS

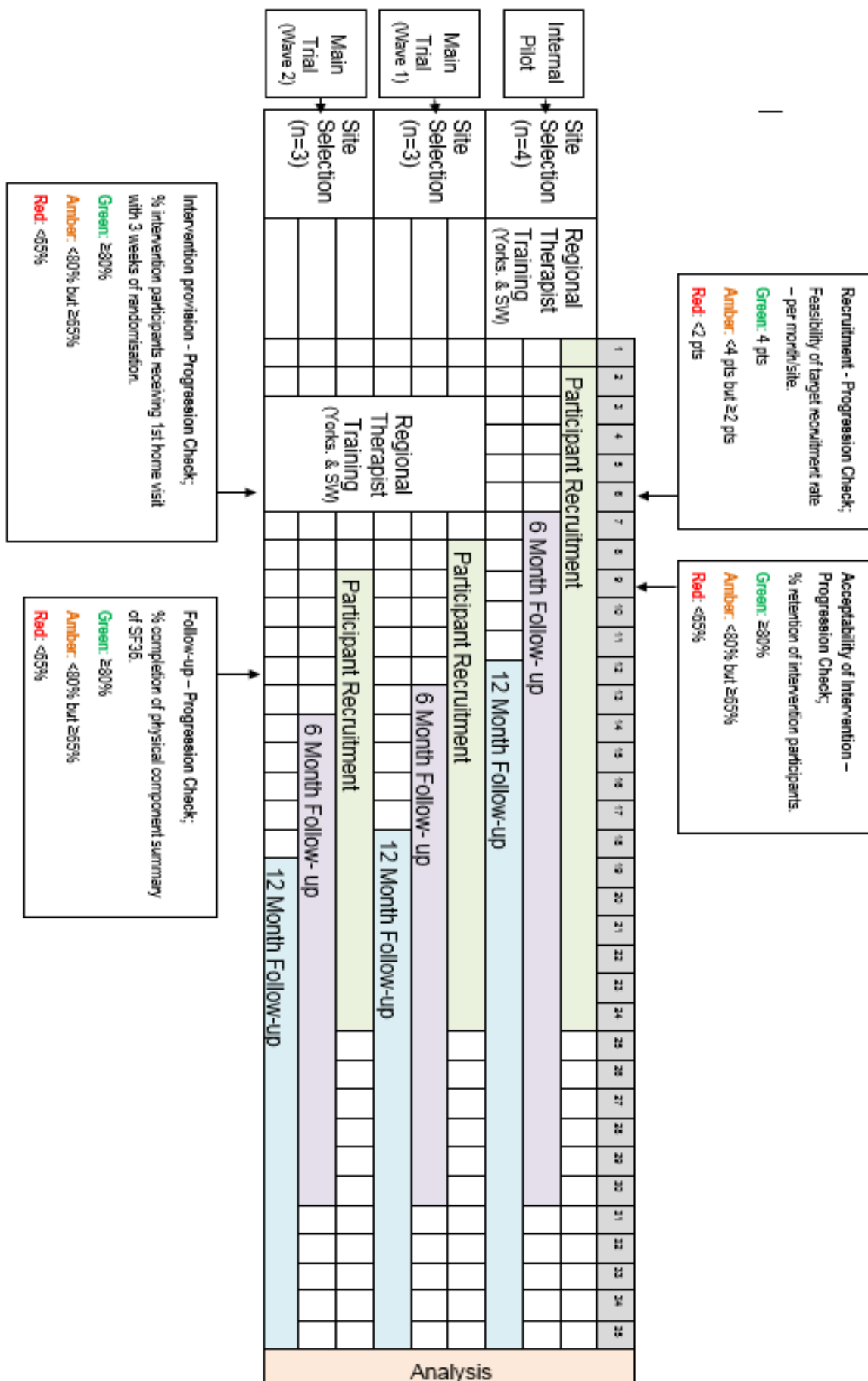
AE	Adverse Event
CA	Competent Authority
CI	Chief Investigator
CFS	Clinical Frailty Scale
CRF	Case Report Form
EC	European Commission
EHR	Electronic Health Records
EU	European Union
EQ5D 5L	EuroQol 5-Dimension Health Questionnaire 5-Level
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MCS	Mental Component Summary
NEADL	Nottingham Extended Activities of Daily Living Index
NHS R&D	National Health Service Research & Development
ONS	Office for National Statistics
PCS	Physical Component Summary
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REF	Research Excellence Framework
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF6D	Short-Form health survey 6 Dimension score
SF36	Short-Form 36 Item Health Questionnaire
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
TIDieR	Template for Intervention Description and Replication

5. FLOW Diagrams

5.1. Flow Diagram 1 – Patient Pathway

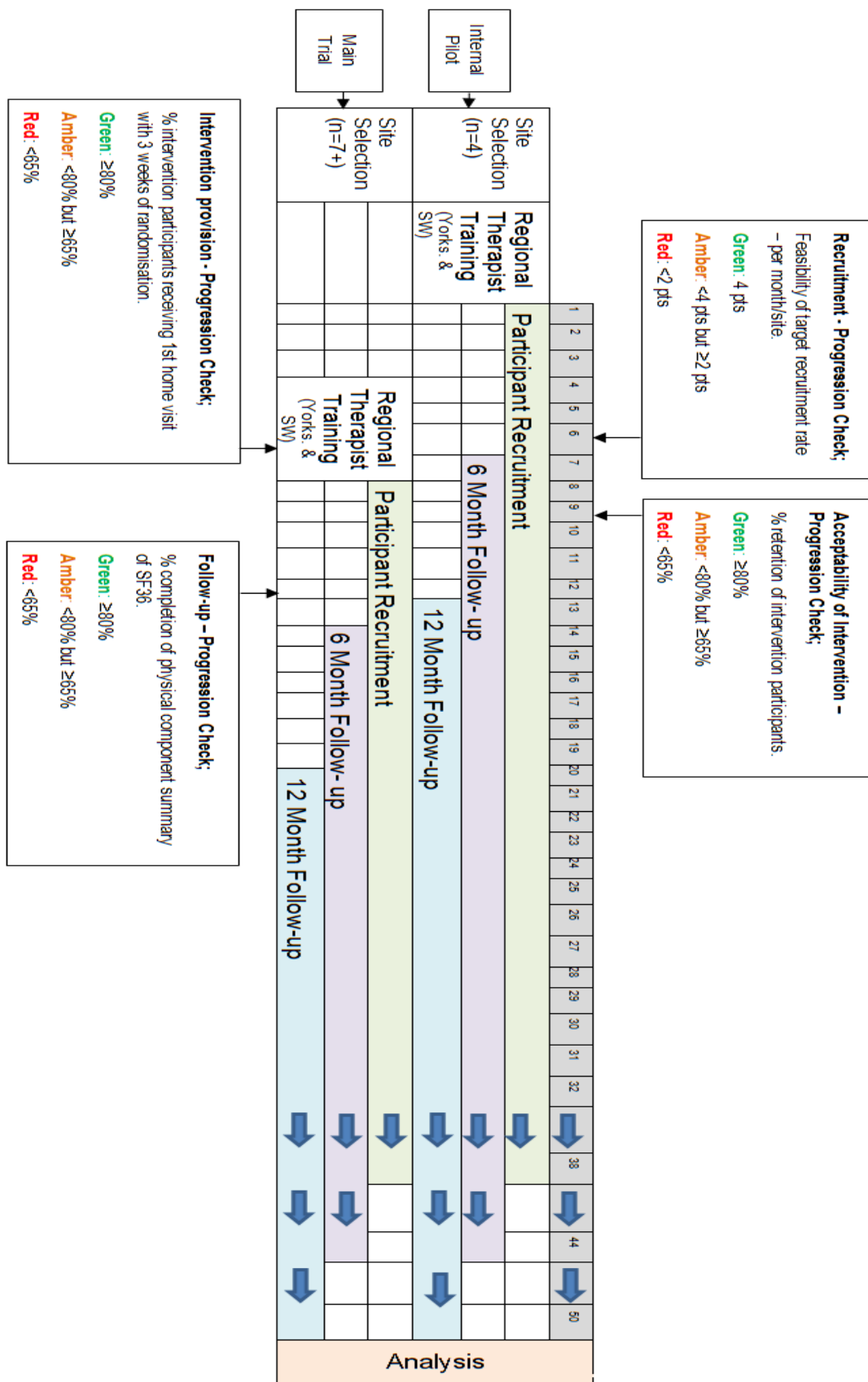


5.2. Flow Diagram 2a – Study Progression

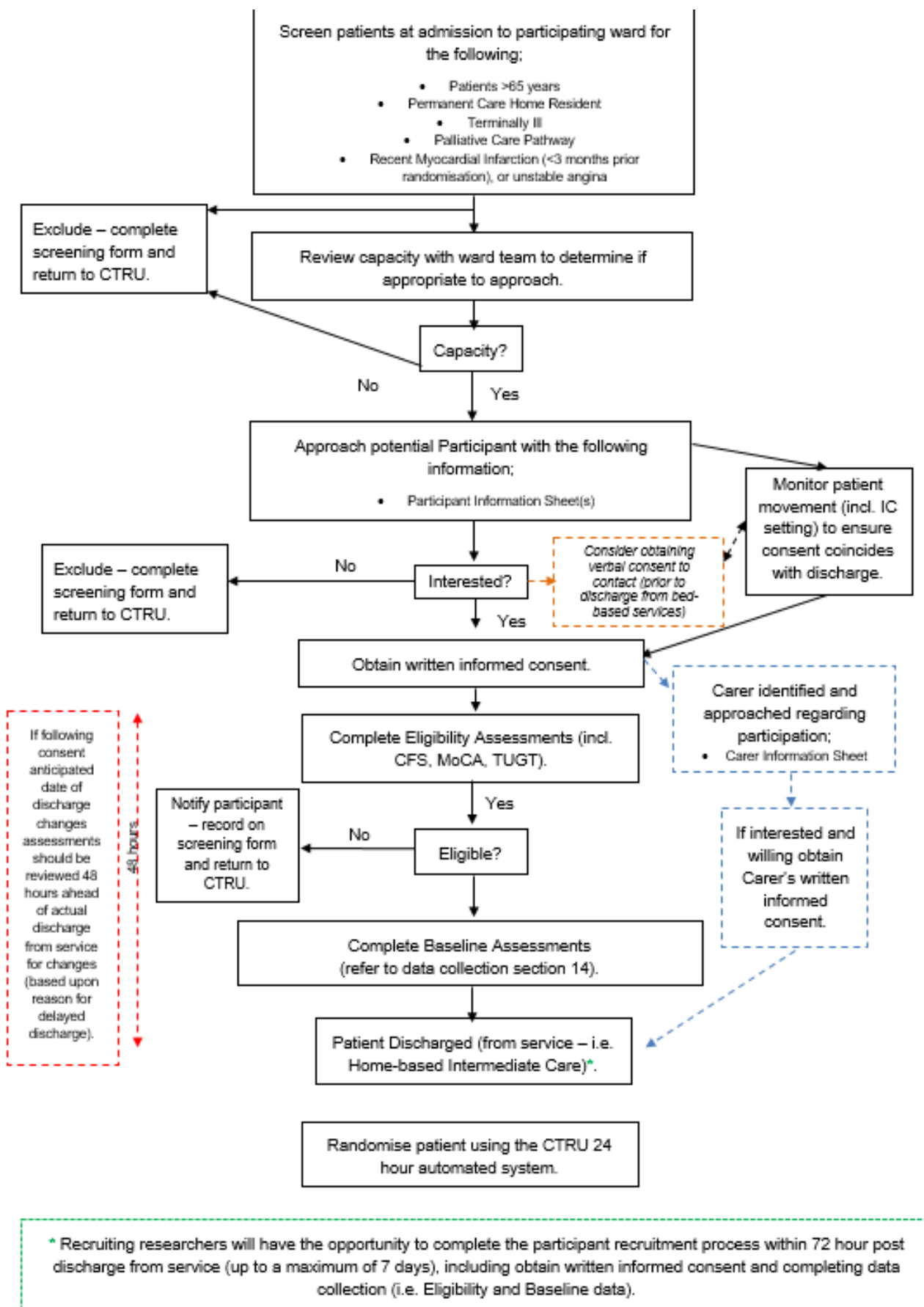


5.3. Flow Diagram 2b – Revised (Extended) Study Progression

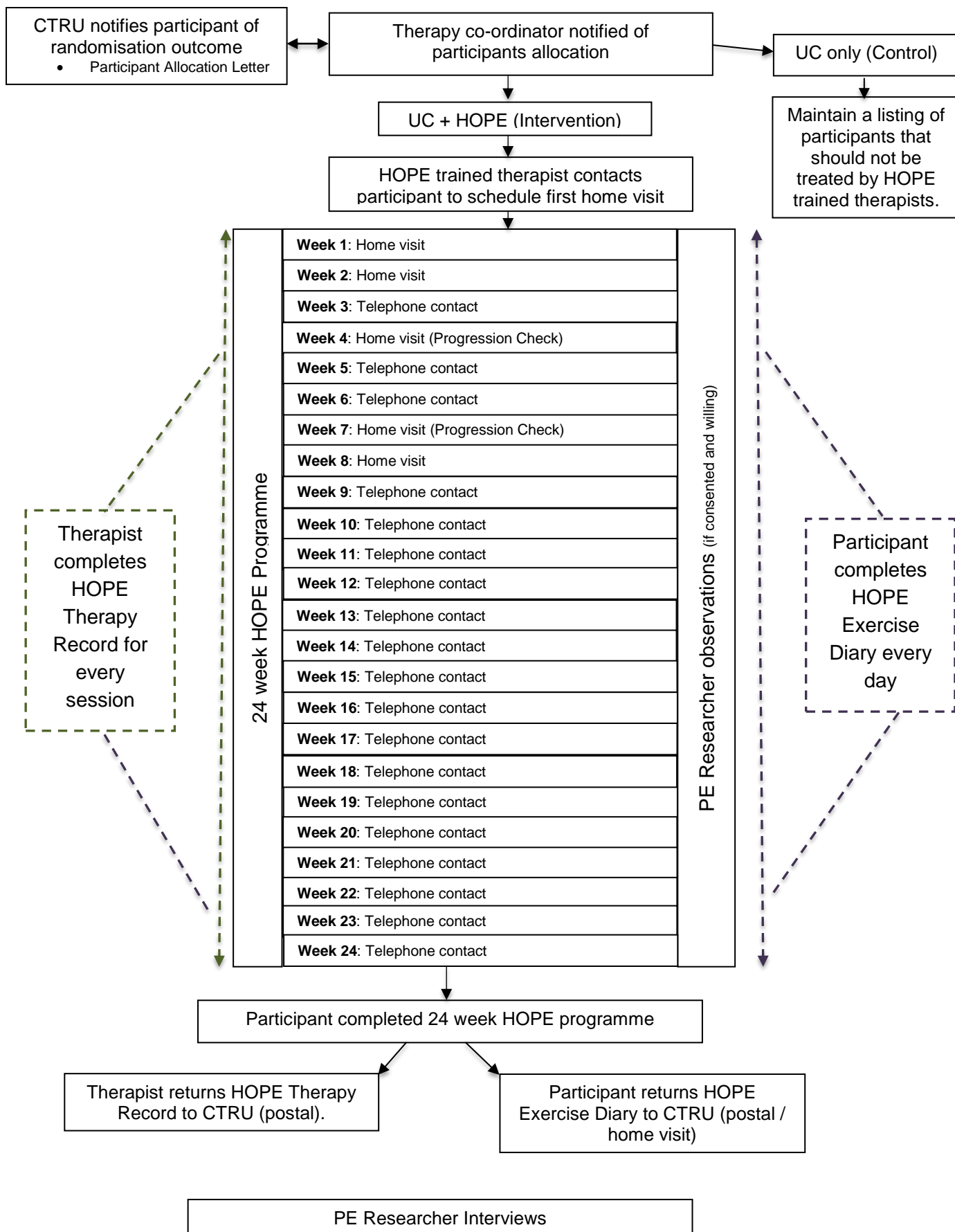
Timelines have been revised with Protocol v5.0 to extend the recruitment phase of the trial.



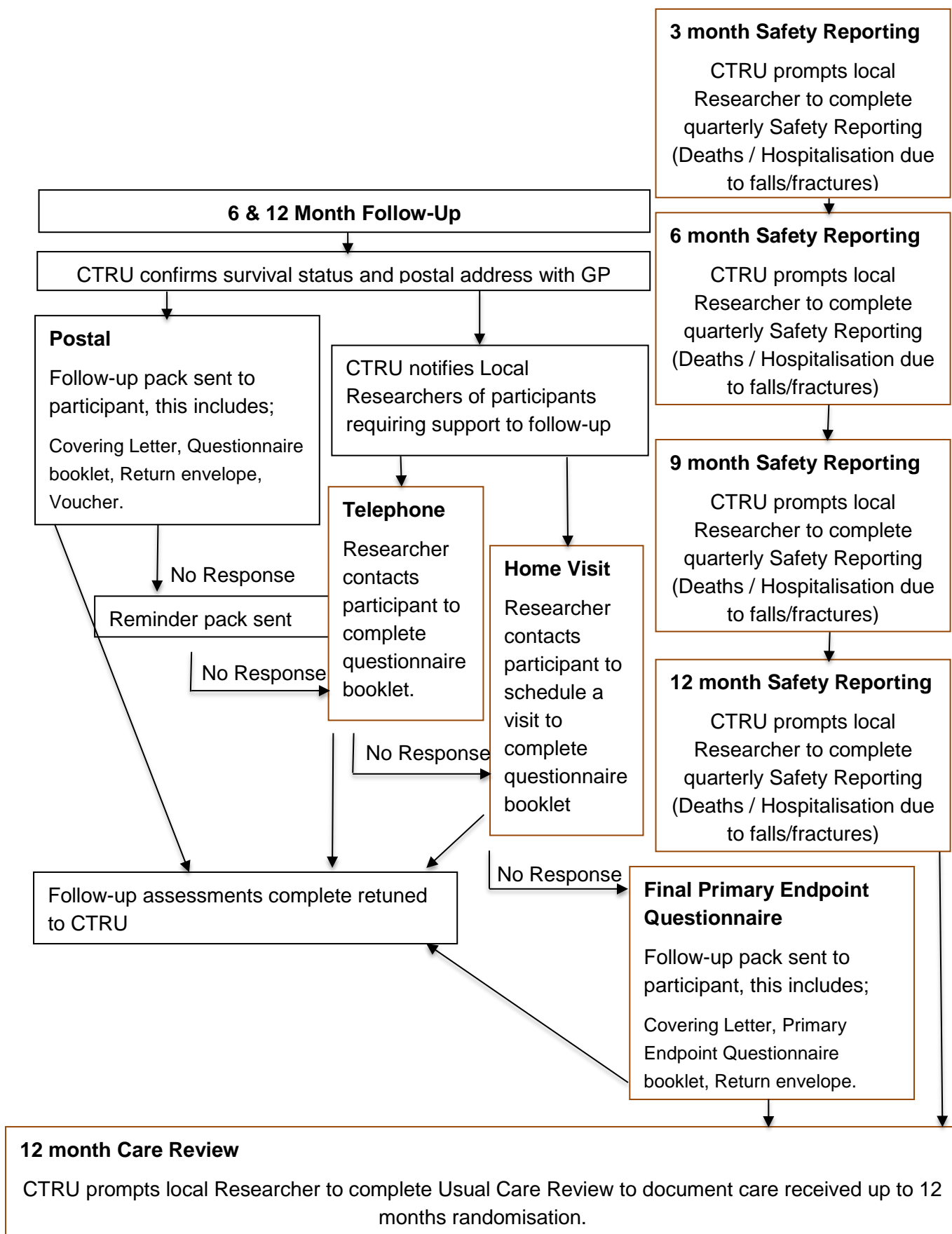
5.4. Flow Diagram 3 - Participant Recruitment



5.5. Flow Diagram 4 – Intervention Delivery



5.6. Flow Diagram 5 – Follow-up



6. STUDY PROTOCOL

Individually randomised controlled multi-centre study to determine the clinical and cost effectiveness of a home-based exercise intervention for older people with frailty as extended rehabilitation following acute illness or injury, including embedded process evaluation.

6.1 Background

Frailty is a condition characterised by reduced biological reserves and increased vulnerability to adverse outcomes including falls, disability, hospitalisation and care home admission [1]. It develops as a consequence of an age-related decline in several physiological systems, which collectively results in a vulnerability to sudden health status changes triggered by relatively minor stressor events. The majority of older people (>65 years) in hospital have frailty and are at increased risk of readmission or death following discharge home [2, 3].

Sarcopenia (loss of muscle mass and strength) is a core component of frailty [4, 5] and periods of immobility in older age, such as that experienced during an acute illness or injury, can accelerate loss of skeletal muscle function [6]. Furthermore, the inflammatory response that is commonly associated with acute illness or injury can lead to catabolism of muscle protein for generation of energy and immune proteins, which can further accelerate loss of muscle mass and strength [1]. This is especially problematic in frailty because accelerated loss of skeletal muscle function can compromise the capability to perform activities of daily living (e.g. walking, dressing, toileting, climbing stairs), jeopardising successful functioning in the home environment, which may lead to a requirement for increased home care, or admission to long-term care residence.

Following admission to hospital with acute illness or injury, approximately 1/3 of frail older people are likely to be discharged home after a brief period of rehabilitation on an inpatient ward [7] but are at high risk of readmission [3]. Around 1/3 are likely to be admitted from/discharged to a care home, or die during admission. A further 1/3 are referred to intermediate care (IC), which is a range of community rehabilitation services predominantly for older people with frailty to promote recovery and reduce premature need for long-term care [8]. IC is provided in two general forms: bed based (e.g. community hospital) and home-based (e.g. hospital at home) services. National guidelines for both bed-based and home-based IC recommend only a brief contact (two to six weeks) with services [8]. Findings from the 2014 UK National Audit of Intermediate Care [1] identified that many recipients of IC did not feel ready to leave the service, indicating the possibility of incomplete recovery. Although reduced early readmission to hospital (<30 days) has been reported in five studies of IC [9], no difference in re-admissions between 60 days and six months has been identified, indicating that the early benefits of IC may not be sustained [10]. A simple, generalisable intervention that can address more directly the abnormal health state of frailty and so augment usual NHS rehabilitation care provided to older people admitted to hospital following an acute illness or injury is required. A programme of progressive physical exercise is a candidate intervention [11].

Exercise has positive physiological effects on skeletal muscle, the brain and the endocrine system [1]. Additionally, observational studies have identified a consistent inverse dose-response relationship between physical activity and inflammation [12], which may be especially relevant following acute illness or injury. RCT evidence indicates that exercise can down-regulate inflammation in older people, and that the benefit is most pronounced in older people at greatest risk of disability and loss of independence [13]. Systematic reviews of exercise interventions for older people with frailty have reported evidence for improvements in mobility and activities of daily living, but few studies measured effects on quality of life and no studies reported on cost-effectiveness [11, 14]. This evidence for positive physiological, mobility and functional benefits of exercise in frailty supports our proposal for a home-based exercise intervention to extend the rehabilitation period for older people with frailty following acute illness or injury.

6.2 Evidence explaining why this research is needed now

The majority of older people in hospital have frailty and are at risk of accelerated decline in skeletal muscle function [1, 2, 6] with increased risk of early readmission or death following discharge [6]. Contact with an intermediate care service is recommended as national policy to enhance recovery after hospital admission for an acute illness or injury but people frequently do not feel ready to return home, and are at risk of subsequent readmission [1, 10]. Indeed, the benefits of rehabilitation in intermediate care are attenuated over time [15]. There is preliminary evidence from systematic reviews to indicate that exercise interventions can improve mobility and function for frail older people and slow progression to disability but few studies have used well-validated frailty tools or reported on health related quality of life and no studies have reported on cost-effectiveness [11, 14, 16, 17]. Exercise programmes based on progressive strength training were important for functional improvement.

In keeping with the MRC framework, we have developed and tested in a pilot RCT, a home-based exercise intervention for older people with frailty (Home-based Older People's Exercise (HOPE) programme). This is a 12 week graded, progressive exercise intervention aimed at improving strength, endurance and balance that is presented to participants in an exercise manual and delivered by community-based physiotherapists and therapy assistants. Participants in the HOPE programme receive weekly support through five face-to-face home visits and seven telephone sessions and we will extend the programme with weekly telephone calls for a further 12 weeks to ensure that participants are well positioned for on-going self-management following completion of the programme. The manualised nature of the intervention and use of face-to-face and telephone support is consistent with evidence-based strategies to promote physical activity behaviour change, and intervention adherence [18, 19].

In the pilot RCT of the HOPE programme 474 potential participants (community-dwelling frail older people) were contacted; 154 (32%) did not respond to GP invitation letter. 320 were assessed against the full eligibility criteria and, of these, 57 (18%) were ineligible; 179 (56%) declined to participate; 84 (26%) were recruited and randomised (18). Different methods of participant approach were piloted; 31% of potentially eligible participants were recruited when the initial approach was made face-to-face by a member of the clinical team. The programme was delivered by NHS staff in the pilot study and participants received a mean of 3.7 home visits and 3.5 telephone sessions. 67% of participants recorded acceptable adherence of 1 to 3 times per day on 5 days each week. Feasibility was demonstrated, with potential for a positive clinically important intervention effect on mobility (mean between group difference in timed-up-and-go test (TUGT) 28.6s, 95% CI -8.5 to 65.9s) 14 weeks post-randomisation without adverse outcomes. 75% of participants received the first intervention visit in an acceptable timeframe (<3 weeks).

7. AIMS AND OBJECTIVES

The aim is to establish whether the HOPE programme plus usual care is a clinically and cost effective extended rehabilitation programme for older people with frailty discharged home from hospital or from intermediate care services after acute illness or injury, when compared with usual care alone.

7.1 Primary objective

To establish whether a home-based exercise intervention plus usual care as extended rehabilitation for older people with frailty improves health-related quality of life, measured using the Physical Component Summary (PCS) of the Short-Form 36 Item Health Questionnaire (SF36) 12 months after randomisation.

7.2 Secondary objectives

1. To establish whether the intervention reduces hospital readmission, care home admission rates, hospitalisation due to falls, mortality and overall health and social care resource use at six and twelve months post-randomisation.
2. To establish whether the intervention improves the PCS at six months.
3. To establish whether the intervention improves mental health, measured using the Mental Component Summary (MCS) of the SF36 at six and twelve months
4. To establish whether the intervention improves activities of daily living, measured using the Barthel index, and Nottingham Extended Activities of Daily Living (NEADL) scale at six and twelve months.
5. To establish whether the intervention is cost-effective, measured using differences in cost of service use between groups and the incremental cost effectiveness ratios (ICERs) using quality-adjusted life years (QALYs) derived from the EuroQol 5 dimension health questionnaire, 5 level (EQ-5D-5L) and the Short-form 6 dimension health index (SF6D) at six and twelve months.
6. To understand how the intervention is experienced and understood by providers and recipients, and explore the organisational implications of embedding and sustaining the intervention in preparation for wider NHS roll-out.

7.3 Internal pilot objectives

1. To assess whether the provision and acceptability of the intervention meet the pre-defined progression criteria thresholds, via the proportion of participants receiving their first home visit within three weeks and retention of intervention participants respectively.
2. To assess whether study recruitment and six-month follow-up rates meet the pre-defined progression criteria thresholds.

8. STUDY DESIGN

HERO is a pragmatic, multi-centre individually randomised controlled trial with a two-level, partially nested hierarchical design, internal pilot with clear progression criteria and an embedded process evaluation.

The study aims to recruit 718 participants (318 control and 400 intervention) from general / elderly medicine, trauma and orthopaedics wards in approximately 10 UK hospitals and from linked intermediate care (IC) services. Sample size adjusted in Protocol v5.0 to 742 (325 control and 417 intervention), please see detail below in 8.1 Important changes to methods after trial commencement, and 20.1 Sample Size Calculation. Recruitment will take place across two geographical hubs (Yorkshire and South West England). The intervention will be delivered in the participant's home by community-based physiotherapists and therapy assistants, and will consist of the HOPE programme in addition to usual care. Participants in the control arm are to receive unrestricted usual care provided by primary, community and social services. This approach has been taken to demonstrate it is feasible to provide our intervention (HOPE programme) as part of routine care across the wider NHS, if benefit is demonstrated.

Participants will be allocated to the treatment groups using the CTRU automated randomisation service. The allocation programme will individually randomise with a 1.25:1 ratio (HOPE extended rehabilitation programme and usual care: usual care) using minimisation incorporating a random element, stratified by: site; discharge setting (hospital, bed-based IC, or home-based IC); intended level of HOPE programme (level 1, 2 or 3); and reason for admission (acute illness or injury). Individual randomisation is appropriate as risk of contamination between HOPE extended rehabilitation and usual care is low because the planned intervention is a bespoke, home-based exercise intervention for older people that is unlikely to be replicated by existing community therapy services.

The primary outcome for the study is whether use of the HOPE programme, alongside usual care, improves health-related quality of life for older people with frailty. This outcome will be measured using the PCS of the SF36 at 12 months after randomisation. The outcome data will be collected using self-report postal questionnaires at six and 12 months, by telephone assessment if physical disability prevents written communication, or by face-to-face assessment for participants with mild dementia who live alone. Data will be collected at the care provider (therapist) and participant (self-complete diary) level to assess adherence to the intervention. Health care resource use, mortality, hospital admissions with falls, new care home placement and hospital readmission will be collected by participant self-report questionnaires and informed by routine data (such as hospital episode statistics and GP usage) where appropriate and used to define usual care.

Participants and personnel delivering the intervention will not be blind to the treatment allocation. Outcome assessment using self-report methods is planned to reduce the risk of detection bias. Telephone follow-up and face-to-face assessments will be performed blinded to treatment allocation to reduce the risk of detection bias, where possible, for study participants requiring these methods.

8.1. Important changes to methods after trial commencement

Revision of sample size

The sample size has increased from 718 to 742 (325 control, 417 intervention). The assumptions informing the sample size calculations were updated at the time of requesting an extension to recruitment in August 2019.

The original sample size calculations required 718 participants (318 control, 400 intervention). This provided 90% power to detect the specified effect size of 0.317 (minimum difference of 3 points on SF36 PCS; SD 9.47). Utilising all available information at that time, the calculations incorporated the following assumptions:

- ICC of 0.03
- 20 therapists
- average of 20 patients per therapist (cluster size)
- coefficient of variation of cluster size no greater than 0.23 (allows for some variability in number of patients seen by each therapist, without compromising power)
- loss to follow-up of 25%

The revised sample size calculations incorporate updated assumptions, based on data collected at the time of recruitment extension, predicting final numbers of trained therapists and numbers of patients per therapist and ensuring loss to follow-up is minimised as far as possible. No change was made to the original ICC estimate of 0.03.

- Increase number of trained therapists to a maximum of 60
- Reduce average cluster size to 7 patients per therapist (increases power)
- Increase coefficient of variation of cluster size to 0.7 (this reflects the anticipated greater variability in the number of patients seen by each therapist, compared to originally estimated, but reduces power)
- Increase loss to follow-up to 35% (reduces power)
- Thus the revised sample size to achieve 90% power requires 742 participants (417 intervention, 325 control).

9. STUDY INTERVENTION

For a full definition of the intervention in accordance with TIDiER principles please refer to the working example in Appendix 2.

HOPE programme (+ usual care):

The HOPE programme is a 12-week home-based manualised, graded, progressive exercise intervention aimed at improving strength, endurance and balance, delivered by community therapy staff. The manual consists of five sections: 1) information; 2) safety tips; 3) good posture; 4) exercises and 5) staying on track. The core constituents of the HOPE programme are strengthening exercises for the muscle groups required for basic mobility skills like getting out of bed, standing up from a chair, walking a short distance and getting off the toilet [20]. Maintenance of these mobility skills is critical for older people with frailty because impairment increases risk of immobility, causing further loss of muscle mass, activity limitation and potential dependence on others for care. The exercises require no special equipment and can be performed without professional supervision. The programme incorporates relevant behaviour change techniques [21] based predominantly on social cognitive theory and control theory, including providing information on benefits of exercise; setting graded tasks; goal setting; prompting self-monitoring.

The HOPE programme is graded into three levels to account for the spectrum of frailty. To start the programme, participants are stratified to the appropriate level using their performance on the timed-up-and-go test (TUGT) as part of the randomisation process.

Participants will be allocated to intervention level by;

- HOPE Level 1: Participants completing the TUGT in >30 seconds, who are more likely to require assistance with walking, climbing the stairs and leaving the house.
- HOPE Level 2: Participants completing the test in 20-29 seconds demonstrate greater variability in mobility, balance and functional ability.
- HOPE Level 3: Participants who complete the test in less than 20 seconds tend to be able to get in and out of a chair without assistance and climb stairs.

At the beginning of the intervention participants are requested to perform five repetitions of each exercise in the routine. This progresses to 10 and then 15 repetitions as performance improves. The exercise routine takes less than 15 minutes to complete, and participants are requested to complete the routine 3 times a day on 5 days of the week. Progression is by increasing repetitions, introducing new exercises or advancing to the next HOPE programme level.

Following the 12-week programme participants will receive a further 12 weeks of telephone-based support for intervention sustainability.

In accordance with the pragmatic study design, and to best reflect clinical practice, the study protocol does not restrict access/referral to usual care services. Additional interventions during study participation will be documented as part of the usual care review. Any deviations from the HOPE programme will be documented by therapists and participants.

9.1 Therapist identification

Physiotherapists and therapy assistants who are familiar with delivering community rehabilitation programmes to older people will be identified to deliver the intervention. Identification of therapists (and therapy assistants) to deliver the HOPE programme will vary by site dependent upon the size of the rehabilitation service and therapist capacity. However, it is anticipated that a minimum of two therapists will be trained at each site to accommodate caseload based on anticipated recruitment and randomisation schedule. Details on the therapist experience, ability and clinical role will be documented for accurate reporting as per the TIDieR checklist [22].

9.2 Therapist Training

To minimise inter-therapist variation and enhance fidelity, physiotherapists and therapy assistants will receive detailed intervention training in interactive workshops. Training will be delivered in local standardised site training (Yorkshire and South West) sessions by members of the study team with relevant experience in the HOPE programme. Training is limited to a single workshop as the programme is readily learned by trained NHS physiotherapists and therapy assistants who are familiar with delivering community rehabilitation programmes to older people. Ongoing training and support will be provided as required, and will be documented.

Intervention training will include clinical reasoning for the HOPE programme exercises, strategies and practical delivery of the programme including intervention progression, and the importance of avoiding contamination of intervention principles to control participants (usual care). Participants will receive personalised graded HOPE manuals which will provide details of principles to support rehabilitation, exercises, monitoring, and progression, which HOPE trained therapists will support the implementation of. Supervision of therapy staff will be by usual NHS line management. Adherence to the HOPE manual will be documented in Therapy records, and discussions with therapy staff as part of the Process Evaluation.

Details of training provision, including content, attendance, duration, and training providers will be documented. Intervention therapists will have access to training materials to support intervention delivery. Access to training materials will be available via the CTRU website for those with relevant permissions (i.e. HOPE trained therapists) and access to materials will be monitored during the study.

9.3 Delivery of the intervention

Following randomisation, the therapy co-ordinator(s) at site will be notified of participant treatment allocation, including level of intervention (via email/telephone/fax) to make appropriate arrangements to support intervention delivery. Participants will be informed of their treatment allocation, and subsequent arrangements for ongoing involvement (i.e. intervention delivery, follow-up assessments) with a treatment allocation letter sent by CTRU (to maintain researcher blinding). Participants should commence treatment within 3 weeks of randomisation (at discharge). The importance of intervention delivery timelines will be reiterated in treatment allocation notifications.

The intervention will be delivered in the participant's home. Participants will be notified of their treatment allocation by letter following randomisation after discharge from hospital. Intervention participants will receive a copy of their personalised graded HOPE manual with this allocation letter, but will be instructed not to commence exercises until their first visit from a HOPE trained therapist. Intervention participants will then be contacted by a member of the therapy team following discharge from hospital or intermediate care services to schedule the first home visit within 3 weeks of discharge. The first session will constitute a home visit from a HOPE trained therapist and will include an introduction to the HOPE manual, demonstration of exercises (based on allocated HOPE level determined from TUGT), establishing goals and summarising how to complete the daily exercise diary. Participants will keep a copy of their HOPE manual which includes their exercise diary to support completion of the exercise programme.

Participants will receive weekly support from physiotherapists and/or therapy assistants through five face-to-face home visits (weeks 1, 2, 4, 7 and 8) and seven telephone sessions across 12 weeks during the intervention period. Following the 12 week intervention period a further 12 weeks of telephone-based support for intervention sustainability will be provided. The telephone sessions will be used to progress exercises and incorporate strategies to motivate and encourage participants to promote adherence to the exercise programme.

Data will be captured on, for example, the number of contacts and sessions, date and duration of sessions, mode of delivery, location and type of session, and progression using a Therapy Record.

Participants will also complete an exercise diary to document how many times each exercises were completed and on which days of the week. Participant diaries will be returned to CTRU by post upon

completion of the HOPE programme (i.e. 24 weeks). Diaries will be collected in a staged process to minimise the risk of lost data, with diaries collected; 1. Therapist collection at the final Home Visit (anticipated week 8), 2. Participant return at the end of HOPE programme (supported by a reminder letter from CTRU).

Participants receiving the HOPE programme who are readmitted to hospital will be reassessed and continue the intervention from the most appropriate point based on their reassessment. Participants deemed unable to continue with the HOPE programme will discontinue the programme and the reason for this will be documented. Participation in the study will continue unless the participant withdraws consent for further study participation.

9.4 Usual care

Usual care is defined as 'The wide range of care that is provided in a community whether it is adequate or not, without a normative judgment' [23]. Usual care will be provided by primary care, secondary care, community and social services and will be available to both intervention and control participants.

To increase external validity and relevance of study findings to clinical practice, the study protocol does not restrict access to usual care, in line with our pragmatic study design [24] and the possibility for heterogeneity of usual care treatments available for older people with frailty. For example, usual care at a personal level will depend on individual frailty, level of independence and social predicaments. It is likely to include GP care (GP appointments for medical problems; home visits for housebound patients); district nurse input (wound management; catheter/continence care; medication support); home care packages (day to day assistance with personal cares e.g. washing, dressing, toileting), but usual care may also include use of voluntary sector services, day centres, and respite care. Use of services will be recorded at baseline and follow-up assessments in both intervention and control groups.

9.5 Contamination

The HOPE programme is a bespoke, manualised, home-based exercise intervention for older people, using core exercises routinely utilised in current NHS practice. There is therefore potential for contamination following training, so we plan to limit access to the HOPE manual to only those attending training as an essential step in minimising risk of contamination of usual care participants. During therapist training the importance of minimising contamination, and mechanisms to limit contamination will be stressed.

To limit potential therapist contamination HOPE-trained therapists should not treat control participants referred to community rehabilitation services during the study period where feasible. Therapy teams will be notified of all participants recruited following randomisation, with a list of control participants maintained. Referrals to therapy services will be recorded in both intervention and control arms to monitor provision of usual care, and included as covariates in the statistical analysis.

It is possible that behaviour change in control participants, their carers and health and social care practitioners may be induced by study information, including knowledge of allocation status. Participants will be provided with general study information and informed about allocation group status. Control group participants will not be provided with detailed information about the intervention.

Sources of contamination will be explored further during the pilot study and, if identified, appropriate strategies will be rolled out to minimise contamination.

10. SITE IDENTIFICATION AND ELIGIBILITY

Clinical leads for elderly care and therapy services at NHS Acute Trust sites in Yorkshire and the South West will be approached by the Hub lead to determine if they wish to take part in the study. Sites expressing an interest in the study will be invited to complete a feasibility questionnaire to determine that appropriate services are available to support recruitment and delivery of the intervention. The feasibility questionnaire will include details to support site set-up (e.g. current services, patient pathways and commissioning), data collection, and a review of current services. A summary of participating centres, including screening, and reasons for non-selection, will be maintained by the CTRU.

Potential centres will be screened to confirm eligibility based on the following:

Inclusion criteria:

- Elderly medicine / trauma and orthopaedics services provided at acute hospital site.
- Availability of bed-based and home-based intermediate care services that routinely receive patients transferred from the acute hospital site.
- Agreement by community therapy services manager that site recruitment targets are feasible and acceptable for the service to support intervention delivery.

Exclusion criteria

- Existing provision of routine extended rehabilitation service (>6 weeks) for older people with frailty following discharge home from hospital or from intermediate care.

Participating centres will be required to have obtained local management approvals and undertake appropriate training in the intervention and study procedures prior to the start of recruitment into the study.

11. PARTICIPANT ELIGIBILITY AND IDENTIFICATION

The target population for this study is older people (aged >65) with frailty admitted to hospital following acute illness or injury then discharged home directly from hospital or from intermediate care services.

Participant recruitment will vary by centre dependent upon service infrastructure and patient pathways. These will be established during site set-up and strategies will be put in place to maximise identification and recruitment of potential patients. We plan to recruit older people with frailty and their carers from the following clinical sites: 1) Elderly care wards; 2) Trauma and orthopaedic wards and 3) Linked intermediate care services (bed-based and home-based). Recruiting participants across these sites will ensure that our study design is closely aligned with current usual NHS rehabilitation pathways for older people with frailty following acute illness or injury.

Inclusion criteria:

Patients meeting **all** of the following criteria (and none of the exclusion criteria) at screening **will be** eligible to take part in the study;

- Age >65 years.
- Admitted to general medicine / elderly medicine or trauma & orthopaedics wards following acute illness or injury then discharged home from hospital or from intermediate care*.
- Mild, moderate or severe frailty, defined as a score of 5-7 on the 9-item Clinical Frailty Scale (CFS).
- Ability to complete the TUGT without additional external support (other than usual walking aids).
- Willing and able to give informed consent to participate in the study.
- Able to comply with intervention delivery (consideration of audio-visual impairments)

* Intermediate care services are provided to patients after leaving hospital. The aim is to provide rehabilitation to maximise independence after a stay in hospital. These services can be provided, for example, in a community hospital, commissioned residential home beds or in people's own homes. A variety of different professionals can deliver this type of specialised care. The person or team providing the care plan will depend on the individual's needs at the time [25].

Exclusion criteria

Patients meeting **any** of the following criteria **will not** be eligible to take part in the study;

- Permanent care home residents (but not those occupying temporary rehabilitation beds within a care home as part of intermediate care services).
- Moderate/severe dementia at baseline* (defined as Montreal Cognitive Assessment test <20).
- Recent (<3 months prior randomisation) myocardial infarction, or unstable angina.
- Another household member in the study.
- Very severe frailty (defined as score of 8 on CFS).
- Terminally ill (defined as score of 9 on CFS).
- Receiving palliative care.
- Referral at discharge for condition-specific rehabilitation (e.g. pulmonary rehabilitation, stroke rehabilitation, falls prevention programme).
- Currently participating in HERO or another contraindicated study[†]

** Baseline assessments should be completed within 2 days of consent ahead of participant randomisation at discharge.*

+ Patients can only be enrolled into the HERO study once. Participation in another study will not necessarily exclude a patient from participation. CTRU should be notified of any potential conflicting studies to facilitate a review of the feasibility of co-enrolment by the Chief Investigator and Trial Management Group. The review will consider methodological impact and participant burden.

To compensate for the variations in discharge planning across services, and to minimise patient burden at a critical transition of care, recruiting researchers will have the opportunity to complete the participant recruitment process within 72 hours post discharge from service (up to a maximum of 7 days), including obtain written informed consent and completing data collection (i.e. Eligibility and Baseline data). Verbal consent to contact the participant will be obtained during the participants stay within inpatient services. Management of recruitment timelines, and permitted deviations should be reviewed with CTRU in advance of randomisation.

Eligibility waivers to inclusion and exclusion criteria are not permitted.

Carer Recruitment

Carers for **all** eligible participants will be approached to participate in the project following written informed consent from the participant.

In this study a carer is defined as anyone who cares, unpaid, for a friend or family member who due to illness, disability or a mental health problem cannot cope without their support.

Carer participation may entail observations of interactions during delivery of the intervention (dependent upon participant allocation) and semi-structured interviews as part of the Process Evaluation (PE). A purposive sample of carers will be selected to take part in PE activities, therefore carers may not be required to undertake any additional activity other than baseline demographics as part of the study. Confirmation of ongoing consent will be sought ahead of participation in observations / interviews. This will be clearly outlined in study information sheets for carers and during the consent process.

If carers are interested in participating in the process evaluation (observations and interviews) CRN/local research staff will discuss what involvement may entail, and obtain written consent for a researcher to observe their involvement with their relative/friend's participation in the exercise programme. A sample of carers will then be contacted ahead of interviews to confirm willingness to participate in these elements with formal written consent obtained to support this activity.

Inclusion criteria:

Carers meeting **all** of the following criteria (and none of the exclusion criteria) at screening **will be** eligible to take part in the study;

- Anticipated to provide support following the participants discharge from hospital.
- Anticipated to be available to support HOPE programme sessions (if randomly allocated to intervention).

Exclusion criteria

Carers meeting **any** of the following criteria **will not** be eligible to take part in the study;

- Unable to provide written informed consent.

11.1 Screening

Participating research sites will be required to complete a Screening Form for all patients aged >65 years following admission to the relevant ward / service with acute illness or injury. Screening forms will be completed by experienced and appropriately trained CRN or local research staff. Initial screening based on discussions with ward staff will screen out clearly ineligible participants (age ≤65; care home residents; receiving palliative care; recent MI, lacking capacity to provide informed consent).

Screening forms should be returned to the CTRU on a monthly basis. Anonymised information will be collected including: age, gender, ethnicity and whether the patient is randomised or not randomised.

Screened patients who are not randomised because they are ineligible or because they decline participation will also have the following information recorded: the reason not eligible for study participation OR the reason eligible but declined.

Documented reasons for ineligibility or declining participation will be closely monitored by the Research team as part of a regular review of recruitment progress. This information will also allow for generalisation of study results in accordance with CONSORT reporting guidelines. This information will also be used to highlight any issues in the identification or recruitment of patients during the internal pilot.

CRN/local Research staff will monitor potential participants throughout their admission, including transfer to intermediate care services and Intensive Care, and seek informed consent approximately 48 hours prior to discharge home from hospital or from intermediate care (bed-based and home-based).

12. INFORMED CONSENT

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

Informed Consent should be timed to coincide with discharge planning and consideration of information and associated data collection linked to recruitment at a critical transition of care. An average of 48 hours' notice of discharge acts as a guide at site; staff will be best placed to judge the timing of informed consent and completion of data collection.

The right of a participant to refuse participation without giving reasons must be accepted. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and has been provided with a contact point where he/she may obtain further information about the study.

The CRN/local Research staff will approach potentially eligible participants and raise the possibility of study participation verbally. Potential participants who express an interest will be given verbal and written information and will be provided with an opportunity to have family members or an supporting carer present for further discussion (if wished). The initial discussion and explanation will also include an assessment of capacity. During the initial approach the researcher will determine if the potential participant has a carer, and will provide additional information regarding carer involvement if appropriate.

Potential participants will have a period of time to decide whether they wish to take part in the study. This period of time will depend on the duration of stay in hospital or intermediate care, with consideration of time required to support study procedures (i.e. participant recruitment / data collection). Informed consent will be sought prior to discharge with sufficient time (approximately 48 hours) for eligibility assessments and, if applicable, baseline data collection, to be performed prior to discharge (or within an appropriate timeframe post discharge). If the participant has a carer, consent for carer participation will be sought after participant consent and eligibility assessments, ahead of the participants discharge from hospital.

Participants able to give informed consent will sign, or make a mark on the study consent form. Where a participant is unable to sign, or make a mark, s/he will be asked to indicate his/her consent verbally. This will be witnessed by an independent observer (staff member, family member or friend, immediate carer) and recorded on the consent form. The original consent form will be retained in the investigator site file. A copy of the consent form will be given to the patient, and to the CTRU.

If the potential participant has capacity and chooses to consent, eligibility assessments will be undertaken and, if appropriate the baseline assessments will be completed ahead of randomising the participant to their treatment allocation. Participants found to be ineligible will not be randomised and will be informed by the recruiting Researcher.

12.1 Changes in capacity

Considering the study population, there is potential for participant's capacity to change during the course of the study.

Although the majority of participants will complete postal questionnaires at follow-up, which precludes routine assessment of capacity at follow-up, we have incorporated a strategy that considers potential for changes in capacity. If participants fail to respond to postal questionnaires or the hub researchers become

aware of any concern regarding capacity, a member of the hub research team will attempt to establish contact with the participant via telephone. If, during conversation, researchers identify concerns regarding capacity a home visit will be scheduled to establish capacity, willingness to continue participation supported by appropriate consent, and support ongoing data collection. This will include seeking advice from a Personal consultee regarding continued participation in the study.

If any changes in capacity are noted during intervention delivery the supporting Therapist will determine the participant's willingness and ability to continue, in accordance with routine clinical judgements. If the participant is no longer willing to continue this will be documented as a withdrawal from treatment, with involvement in additional activities to be reviewed by the researcher at follow-up.

Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU. The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

13. RANDOMISATION

Participants will be randomised after confirmation of eligibility, informed consent and collection of baseline data is complete following confirmation of discharge. Informed written consent for entry into the study **must** be obtained prior to randomisation.

Randomisation will be performed using the CTRU automated 24-hour randomisation service, which will provide each participant with a unique Study ID. Usernames/authorisation codes and PINs, provided by the CTRU when all site specific approvals are in place, and used by CRN staff / local researchers, will be required to access the randomisation service.

Participants will be individually randomised in a 1.25:1 allocation ratio (HOPE extended rehabilitation programme + usual care: usual care) to ensure the study is powered for the primary objective while accounting for the partially nested design of the study. The increased proportion of participants allocated to the intervention arm accounts for a greater level of correlation anticipated in the outcomes for those receiving the HOPE programme, as a result of participants treated by the same community therapy staff.

Allocation will use a computer-generated minimisation programme incorporating a random element, stratified by: site; discharge setting (hospital, bed-based intermediate care, or home-based intermediate care); intended level of HOPE programme (level 1, 2 or 3) based upon TUGT; reason for admission (acute illness or injury).

The following details will be required at randomisation:

- Participant Screening Number;
- Participant identifiers: initials, date of birth, NHS/Hospital ID;
- Location (site code);
- Date of discharge;
- Confirmation of eligibility;
- Confirmation of informed consent;
- Confirmation of baseline assessments;
- Stratification factors

Web address for 24-hour randomisation service: <https://lictr.leeds.ac.uk/webrand/>

Telephone line for 24-hour randomisation service: 0113 343 2290

Following successful randomisation the researcher completing the randomisation process and the PI at that site will receive an automated email confirmation of randomisation, omitting details regarding allocation. Therapy co-ordinators will receive an automated email outlining participant details, date of discharge (from hospital or intermediate care), and allocation highlighting subsequent tasks required (i.e. scheduling home visit). Participants will be notified of their random allocation via letter, with details of subsequent actions (i.e. Therapist home visit, follow-up assessments), this information provision will be supported by an info-graphic

detailing timelines for intervention provision and follow-up assessments. Confirmation of study participation will also be forwarded via letter to the participant's GP (as outlined in the relevant consent form).

14. DATA COLLECTION

Required data, assessment tools, collection time points and processes are described in detail in sections below and summarised in Table 1.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with standard routine care at the participating site.

Assessments will either be administered by CRN / local researchers, or self-completed. Completion of assessments can also be supported by participant's family and friends, where appropriate. Proxy completion of questionnaires is not permitted. Clinical staff will also be consulted for completion of relevant assessments and additional information will be obtained from a review of medical notes.

CRN and local researchers will receive training on the completion of all study specific assessments to ensure standardised completion as part of study initiation. If any assessments are completed as part of standard care, and are within the appropriate eligibility window, they should not be repeated to minimise participant burden and potential for recall bias.

The assessments will be ordered within the questionnaire booklet to prioritise primary outcome data. Researchers (CRN / local researcher) will consider participant fatigue during data collection, and offer participants the opportunity to complete assessments over additional days if required. This will be at the discretion of the researcher and will be documented.

Participating centres will be expected to maintain a file of essential study documentation (Investigator Site File), which will be provided by CTRU, and to retain copies of all completed Case Report forms (CRFs) and questionnaires for the study as appropriate.

Table 1 – Summary of Assessments

Assessment	Type	Method of Completion	Timeline			
			Screening	Baseline	6 Months	12 Months
Patient / Carer Screening (Demographics)	CRF	Researcher	X			
Consent (Participant & Carer)	Consent Form	Self-completion (Witnessed)	X			
Participant Eligibility (CFS / MoCA/TUGT)	CRF / Questionnaire Booklet	Researcher / Self-completion	X			
Carer Eligibility	CRF	Researcher	X			
Participant Contact Details (Address/Telephone/GP Details)	CRF	Researcher		X		
Participant Demographics (Age / Gender /Home circumstances / Reason for admission / Length of Hospital stay)	CRF	Researcher		X		
Carer Contact Details (Address/Telephone)	CRF	Researcher		X		
Carer Demographics (Age / Gender / Relationship to participant / Care responsibilities)	CRF	Researcher		X		
SF36 (Short Form 36 Item Health questionnaire)	Questionnaire Booklet	Researcher / Self-completion		X	X	X
NEADL (Nottingham Extended Activities of Daily Life)	Questionnaire Booklet	Researcher / Self-completion		X	X	X
Barthel Index of activities of daily living	Questionnaire Booklet	Researcher / Self-completion		X	X	X
EQ 5D 5L (EuroQol 5-Dimension health questionnaire 5 Level)	Questionnaire Booklet	Researcher / Self-completion		X	X	X
Health Care Resource Use (Informal care/ social care/ voluntary sector)	Questionnaire Booklet	Researcher / Self-completion		X	X	X
Falls Questionnaire	Questionnaire Booklet	Researcher / Self-completion			X	X
Comorbidities (Charlson Index)	Questionnaire Booklet	Researcher		X		
Usual Care Data (GP Care / District Nurse input / Home care packages)	CRF	Researcher		X	X	X
Safety Reporting	CRF	Researcher		Ongoing (3-monthly following Randomisation)		
Primary and Secondary Care Data (Routine data sources)	CRF	GP / CTRU		X	X	X

Intervention Data				
Assessment	Type	Method of Completion	Training	Intervention Period (Week 1 – 24)
HOPE Training Attendance	CRF	HOPE Trainer	X	
Therapist Questionnaire	Questionnaire	Therapist	X	
HOPE Therapy Record	Manual	Therapist		Completed at each contact (weekly)
Participant Exercise Diary	Diary	Participant		Completed daily for 24 weeks

14.1 Eligibility Assessments

The following information will be completed following informed consent to confirm participant's eligibility:

- Confirmation of informed consent
- Date of Birth (age)
- Confirmation of Frailty via completion of CFS (Clinical Frailty Scale) with clinical team
- Confirmation of dementia status/severity via completion of MoCA (Montreal Cognitive Assessment) via patient assessment
- Confirmation of completion of TUGT (Timed-Up-and-Go Test) via patient assessment

Eligibility assessments should be completed immediately following consent to confirm participation. If the patient is deemed to be ineligible the CRN/local researcher should inform the participant, update the screening form documenting the reason for ineligibility, and securely destroy study specific assessments. Eligibility should be confirmed ahead of randomisation, in the event of delays in discharge, assessments should be reviewed and repeated, where applicable (i.e. discharge delayed due to deterioration in condition).

14.2 Baseline Assessments

For participants that provide informed consent and are confirmed to meet the eligibility criteria the following information will be completed;

- NHS number
- Date of admission
- Location of admission
- Route of admission (i.e. not a permanent care home resident)
- Presenting problem requiring admission
- Movements pre-admission
- Date and location of discharge (from hospital/intermediate care services)
- Length of hospital stay
- Living arrangement
- Carer arrangements
- Contact details (i.e. address, telephone number, preferred method of contact)
- GP details
- SF36
- NEADL (review abilities pre-admission)
- Barthel Index
- EQ-5D-5L
- Healthcare Resource Use (including use of informal and formal care services (i.e. community rehabilitation programmes), district nursing support 30 days pre-admission)
- Comorbidities (Charlson Index)

Baseline assessments should be completed in the 48 hours prior to discharge, or within sufficient time frame if recruited post discharge, and ahead of randomisation. In the event of delays in discharge, assessments should be reviewed and repeated, where applicable.

14.3 Participant Data – 6 and 12 month Follow-up Assessments

Follow-up assessments will be completed at six and 12 months post randomisation. Assessments can be completed by post, telephone, and face-to-face dependent upon the participant's needs. CTRU will coordinate follow-up assessments, confirming survival status and address, and determining the appropriate method of contact. Participants that require telephone or face-to-face contact will be highlighted to the recruiting team (CRN/local researcher) to ensure continuity of care. Follow-up assessments will be completed by a blinded researcher (where relevant), with the method of data collection and the researcher completing information (where applicable) documented on data collection forms.

Participants will receive a small unconditional monetary incentive (£10 gift voucher) to support all methods of follow-up at 6 and 12 months, with circulation of incentives dependent upon method of completion.

Researchers (CRN / local researcher) will consider participant fatigue during data collection, and offer participants the opportunity to complete assessments over 2 days, if required, for those methods completed by a researcher.

The following data will be collected from participants at 6 and 12 months:

- SF36
- Barthel Index of activities of daily living
- Nottingham extended activities of daily living index (NEADL)
- EQ5D-5L
- Healthcare resource use (including health, informal care, social care and voluntary sector (i.e. community rehabilitation programmes) resource use)

14.4 Usual Care Data

Data on “usual care” will be obtained from GP practices (with potential for centralised access via routine datasets) and CRN / local Researchers will collect data for all participants regarding all hospital attendances from the time of randomisation to 12 months post-randomisation from Hospital Records. This data will supplement other methods (e.g. routine data / Healthcare Resource Use) to define “usual care” within the study population. This data will be collected 12 months post-randomisation to minimise researcher burden.

14.5 Carer Data

Data from carer's will be collected following informed consent and eligibility assessments for the study participant. Information will include confirmation of eligibility, contact details, and demographics of the carer to inform purposive sampling for the PE.

14.6 Intervention Data

Intervention data will be recorded in the HOPE Therapy Record by therapists and will include details of each session (including date, duration of sessions, mode of delivery, what was delivered) and assessment of progress. Participants will also complete a diary to record the number of times each exercise was performed each week. These diaries will be reviewed by the therapist at relevant sessions to review compliance to the HOPE manual with support tailored accordingly.

Therapy records, and participant diaries will be returned to CTRU by post. If patients are unable to return diaries by post, alternative methods of collection will be considered (e.g. home visit). Therapy records should be reviewed by site staff to remove any personal identifiers ahead of returning to CTRU.

14.7 Routine Data Sets

Information obtained from routine data sets will be used to define “usual care” within the study population, support economic evaluation, and supplement safety data.

14.7.1 Primary Care

Where possible, data on primary care use for each participant will be obtained from sites via Electronic Health Records (EHR). The type of system (e.g. SystmOne / EMISWeb / Vision) in each locality will be established during site set-up and procedures will be put in place to obtain data from the EHR. Approvals to access EHR will be sought dependent upon GP practices required based upon participant recruitment. EHR data will be collected using a combination of approaches, including direct access from the system

provider or obtaining from individual GP practices. Data will be collected to include the period from time of randomisation to 12 months post randomisation.

14.7.2 Secondary Care

Where possible, data regarding secondary care use for each participant will be obtained via NHS Digital Hospital Episode Statistics (HES) data. This will include hospital attendances - including A&E, outpatient appointments and admissions due to falls (if possible). Date and cause of death will be obtained via NHS Digital from the Office for National Statistics mortality dataset. Data will be collected to include the period from time of randomisation to 12 months post randomisation.

15. BLINDING

Participants and personnel delivering the home-based exercise intervention as extended rehabilitation will not be blind to allocation group. We have considered how knowledge of allocation status could influence participant and clinician behaviour change in relation to usual care, and have incorporated measures to limit these possibilities. We plan to interview a sample of intervention and control group participants to better understand provision of usual care across sites in the process evaluation, including whether knowledge of allocation status may have influenced participant behaviour.

Our study design incorporates measures to reduce the risk of detection bias. Six and 12-month follow-up will be by postal assessment where possible. A member of the research team who is blind to allocation group will offer telephone follow-up to participants who are unable to complete postal forms due to physical disability preventing writing (e.g. severe arthritis) and a face-to-face assessment for participants with mild dementia who live alone. Participants receiving telephone or face-to-face assessments will be sent clear, easy to understand written information prior to the follow-up assessment that explains the importance of maintaining blinding.

Although GPs will be informed about study participation, they will not be informed about allocation status, reducing the risk of inducing GP behaviour change based on this knowledge. The wider health and social care team will not be informed about study participation or allocation status.

15.1 Unblinding

Researchers collecting outcome measures will be blind to participant allocation, with every effort made to maintain blinding throughout the study. In the event a Researcher becomes unblinded to a participant's allocation they must document the event and report to CTRU as soon as possible following unblinding. CTRU and oversight committees will monitor instances of unblinding to review for systematic errors that could impact upon study integrity. Where feasible, additional and subsequent data collection will be completed by an alternative researcher who is blinded to allocation.

16. WITHDRAWAL CRITERIA

Participants will be free to withdraw consent and leave the study at any time without giving reasons and without affecting their care. If a patient withdraws consent to participate, clarification will be sought on whether withdrawal is from, for example, participation in the intervention, questionnaire completion or access to health and social care records. Previously collected anonymised data will still be used in the analyses.

Individual assessments will not be carried out where the participant appears reluctant to participate (i.e. no response to postal questionnaires, telephone contacts), even if they have consented. However, outcome data that do not involve participant contact (e.g. from medical or healthcare records) will continue to be collected in these cases.

17. ASSESSMENT INSTRUMENTS

Modified Short-Form 36 item health questionnaire (SF36) [26]

The SF36 is a valid, reliable, responsive and feasible measure that has been extensively tested. The eight individual scales that comprise the SF36 incorporate the aspects of health and well-being that are relevant for quality of life in older age.

SF36 Physical Component Summary (PCS) [27]

The PCS score incorporates physical functioning; role-physical; bodily pain and general health scales, so has face validity for capturing the important effects of a home-based exercise intervention as extended rehabilitation for older people with frailty. PCS scores range from 0-100, with higher values indicating better health.

SF36 Mental Component Summary (MCS)

The MCS score incorporates vitality; social functioning; role-emotional and mental health scales. It therefore has good face validity for capturing the non-specific benefits of rehabilitation.

Short-Form health survey 6 Dimension score (SF6D) [28]

The SF6D is a preference-based health utility index can be derived from the SF36 for health economic analysis.

Timed Up-and-Go Test (TUGT) [29]

This measures, in seconds, the time taken to stand up from a standard chair, walk a distance of 3 metres, turn, walk back to the chair and sit down. The TUGT was developed as a basic mobility test for older people [29]. The original TUGT validation study identified that those who complete the test in 30 seconds or more are likely to require assistance with walking, climbing the stairs and leaving the house.

Clinical Frailty Scale (CFS) [30, 31]

The CFS is a well-established ordinal measure of frailty that been validated for use in the hospital setting, with higher scores indicating more severe frailty [30, 31]. On the basis of nine individual categories it enables identification of older people who are very fit (category 1), through to those with mild (category 5), moderate (category 6) and severe (category 7) frailty. Those with very severe frailty (category 8) and terminal illness (category 9) are also identified. The CFS is a simple tool that can be used by clinical and research staff, so is feasible for routine use. It is a stable test that provides information about an older person's pre-admission health. This is in contrast with most performance-based frailty measures (e.g. gait speed, grip strength), which conflate illness severity and sudden changes in mobility with frailty, so are unsuitable for use in the context of acute illness or injury. For example, a previously fit older person with an acute illness or injury is likely to have a slow gait speed; weak grip strength, etc.

Montreal Cognitive Assessment (MoCA) [32]

The MoCA is a rapid screening instrument for mild cognitive dysfunction [32]. It assesses different cognitive domains: attention and concentration, executive function, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Total possible score is 30 points; a score of 27 or above is considered normal.

Barthel Index of activities of daily living [33]

The Barthel index assesses functional status on a 20 point scale by recording ability to complete ten basic activities of daily living, including bathing; dressing; mobility; stairs; toilet use. Higher scores indicate greater independence.

Charlson Index [34]

The Charlson comorbidity index is a validated measure used to combine the risk from age, and the risk from comorbid disease into a single variable estimating the risk of death. Higher scores indicate greater comorbidity burden.

Nottingham Extended Activities of Daily Living (NEADL) [35]

The NEADL measures help needed with instrumental activities of daily living, including walking around outside; doing the housework; using the telephone. Scores are from 0 to 66, with higher values indicating greater independence.

EuroQol 5-Dimension Health Questionnaire (5 Levels) (EQ5D-5L) [28]

The EQ-5D-5L is a measure of health utility (quality of life) comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems; slight

problems; moderate problems; severe problems; unable. Scores are combined and converted into a summary index (0 for dead, 1 for perfect health and negative values for states worse than death).

Healthcare Resource Use

In addition to use of routine datasets we will use an adapted version of the Health Resource Use data collection form we developed for the NIHR Prevention of Falls Injury Trial (PreFit; <https://www.journalslibrary.nihr.ac.uk/projects/081441/#/>). The form will include health, informal care, social care and voluntary sector resource.

18. PROCESS EVALUATION

18.1 Design

We plan an embedded mixed-methods process evaluation, informed by the MRC guidance for process evaluation of complex interventions [37]. We will use a range of methods including documentary analysis, non-participant observation, and semi-structured interviews to explore and understand the implementation of the intervention across the two hubs (Yorkshire and SW) and how it is experienced and understood by providers and recipients.

18.2 Objectives

The process evaluation will:

- Observe the training workshops, focusing on both the content of the training and staff engagement in the workshops; the questions staff have regarding the intervention and how it is to be delivered and monitored.
- Observe and engage in informal discussion with therapists and therapy assistants in their base location in the early and late intervention periods to understand how they plan the delivery of the intervention and how it is managed in the context of their usual workload. These observations will contribute to understanding how the organisational and professional contexts impact on the provision of rehabilitation-focused services to the participant group.
- Observe the delivery of the home-based exercise intervention during the face-to-face home visits including staff and patient and family member/carer (where present) interaction and informal discussion regarding use of the exercise manual and exercise diaries. Use of services by participants will be recorded at baseline. We will also use this data to sample and observe some of the services accessed by participants to help understanding of the range of activity reported as usual care.
- Interview staff on what constitutes usual care across sites will form part of the data collected. These views will be discussed 2- 4 weeks prior to HOPE programme training with the lead physiotherapist in each service via standardised telephone interview (N~10).
- Interview a purposive sample of staff who deliver the intervention (N~12).
- Interview intervention participants, including those who did and did not engage with the intervention, and control participants (N~20). Family members will be invited to participate in the semi-structured interviews where it is apparent they have some involvement in supporting participants with the intervention, and/or continued usual care at a place and time convenient for them.
- Evaluate intervention adherence using data from participant exercise diaries and therapy records completed by participating therapists.

The wider organisational implications of embedding and sustaining the intervention will be explored as part of the above.

18.3 Sampling

We will purposively sample approximately 40 participants and their carers, in both the Yorkshire and South west hub, and approximately 12 therapists delivering the 24 week home based exercise programme (and control group equivalents). We will also interview service managers to define staff perceptions of usual care.

18.3.1 Eligibility and Recruitment

Therapy Leads/Managers

Therapy leads at each participating site will be eligible for telephone interview and will be provided with relevant information during study set up. Written informed consent will be obtained prior to telephone interview.

HOPE Programme Therapists

All therapy staff participating in training workshops will be eligible for non-participant observations. Therapy staff who have completed intervention training and who have delivered the 24 week home-based exercise programme to five or more participants will be eligible for individual interviews. Therapy staff sampling will be refined using additional details recorded as part of the information collected as part of staff identification for completion of the TiDIER checklist (e.g. experience, ability, clinical role). Therapy staff will be provided with study information and informed consent will be obtained for non-participant observation and interviews prior to training workshop sessions. Follow up contact regarding participation in interviews will be made with a purposive sample of therapists with additional information provided and written consent obtained before interviews are conducted.

Intervention Participants

Study participants who give informed consent for a researcher to attend therapy home visit sessions and/or observation of telephone calls as part of the study consent process will be purposively sampled for participant observations, dependent upon treating therapist consent (as summarised above).

Participants and Carers

Study participants, and their carers, who give informed consent to take part in an interview with a PE researcher will be purposively sampled for a home visit to participate in a semi-structured interview.

Participant consent for follow up contact regarding participation in an interview will be obtained as part of the study consent process, with additional information provision and informed consent obtained from participants ahead of a request for participation in interviews.

Carer consent for researcher observations of their involvement with their relative/friend's participation in the exercise programme, and for further contact regarding additional involvement, will be obtained as part of the study consent process. Additional information and informed consent will be obtained from carers ahead of any request for carer participation in interviews.

Ongoing confirmation of participant and carer involvement in observations and interviews will also be confirmed verbally prior to commencing these activities.

18.4 Data collection and storage

Interviews will be audio recorded, following agreement from the interviewee, using a digital audio recording device and will be professionally transcribed. During transcription, any potentially identifying information that may be contained in the interview discussions will be anonymised or removed. Only the research team and the transcriber will listen to the interview audio files. Audio files will be securely transferred in encrypted format, and securely stored at AUECR, accessible to only those members of the study team requiring such access. Fieldnotes from observations and interviews will also be stored at AUECR.

18.5 Analysis

Normalisation Process Theory (NPT) will provide the theoretical framework for the process evaluation. NPT focuses on the work staff undertake to introduce and implement complex interventions into practice settings. The four elements of NPT provide a focus for the data collection and contribute to focusing within the data analysis. Data will be managed using NVivo 10 (QSR International, 2014). Quantitative and qualitative data to evaluate fidelity (e.g. therapy logs, exercise diaries) will be collected from therapists and participants across all sites and analysed using descriptive statistics and content analysis. Fieldnotes and interview data will be analysed using a thematic approach [38].

19. SAFETY REPORTING PROCEDURES

19.1 Definitions

Term	Definition
Adverse Event (AE)	An adverse event is; <ul style="list-style-type: none"> any unintentional, unfavourable clinical sign or symptom any new illness or disease or the deterioration of existing disease or illness
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: <ul style="list-style-type: none"> results in death is life-threatening requires inpatient hospitalisation or prolongation of existing hospitalisation results in persistent or significant disability/incapacity consists of a congenital anomaly or birth defect <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the 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.</p>
Related Unexpected Serious Adverse Event (RUSAE)	The National Research Ethics Service (NRES) defines related and unexpected SAEs as follows: <ul style="list-style-type: none"> 'Related' – that is, it resulted from administration of any research procedures; and 'Unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence.

19.2 Operational definitions

19.2.1 Expected Adverse Events/ Serious Adverse Events (non-reportable)

Events such as falls and musculoskeletal injury represent an inherent consequence of an active rehabilitation process and therefore cannot be entirely avoided. Similarly, in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected. In recognition of this, events fulfilling the definition of an AE or SAE will not be reportable in this study unless they are specified in the section below or fulfil the definition of a Related and Unexpected Serious Adverse Event (RUSAE).

19.2.2 Expected serious adverse events – standard reporting

The following events are expected within the study population and will be collected from date of consent until 12 months post-randomisation as follows:

- Death– researcher reported, via ongoing (quarterly) checks of survival status and obtaining ONS data at the end of the study
- Falls/fractures resulting in hospitalisation – researcher reported via quarterly checking of hospitalisation (recruiting site only) and obtaining HES data at the end of the study.

As these events are expected within the study population they will not be subject to expedited reporting to the main Research Ethics Committee (REC), but will be reported annually to the REC (in routine annual progress reports) and reviewed by relevant study oversight committees in accordance with the Trial Monitoring plan.

19.2.3 Related and Unexpected SAEs – expedited reporting

All Related/Unexpected SAEs occurring from the date of consent up to 12 months post randomisation must be recorded on the Related/Unexpected Serious Adverse Event (RUSAE) Form and faxed to the CTRU within 24 hours of the clinical research staff becoming aware of the event.

For each Related/Unexpected SAE the following information will be collected:

- date of SAE
- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome

Any follow-up information should be faxed to CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. The original RUSAE Form(s) should be retained by site until the event has reached a final outcome and all queries have been resolved (as determined by CTRU). When requested, please return original (wet-ink) initial and follow-up reports to CTRU.

**CTRU FAX NUMBER FOR REPORTING RELATED/UNEXPECTED SERIOUS
ADVERSE EVENTS: 0113 343 1471**

All Related/Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the Sponsor and the main REC by the CTRU on behalf of the Chief Investigator within 15 days.

19.2.4 Reporting to External Bodies

Safety issues will be reported to the REC in the annual progress report. A summary of all events will also be reported to the Trial Steering Committee (TSC) and Sponsor.

Expedited reporting of events to REC and the Sponsor will be subject to current NRES guidance, CTRU SOPs and Sponsor requirements.

19.3 Responsibilities

Chief Investigator (CI):

The (CI) is responsible for reviewing all events assessed as Related / Unexpected in the opinion of the Principal Investigator / Site staff. In the event of disagreement between local assessment and the CI, the local assessment may be upgraded or downgraded by the CI prior to reporting to the main REC. The CI is also responsible for reviewing reported deaths and falls/fractures on a monthly basis.

CTRU:

The CTRU are responsible for:

- Expedited reporting of RUSAEs to the REC and Sponsor within required timelines.
- Flagging and reviewing deaths with the CI on a monthly basis, and escalating these to the TSC if deemed necessary
- Preparing annual safety reports to main REC and safety reports to the TSC.

Trial Steering Committee (TSC):

The TSC are responsible for:

- Periodically reviewing safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.
- Consideration of study continuation in light of safety concerns, and taking appropriate action to escalate issues of concern.

20. STATISTICAL CONSIDERATIONS

A detailed Statistical Analysis Plan (SAP) will be drafted in accordance with current CTRU standard operating procedures and will be finalised and agreed by the appropriate members of the research team before any analyses are undertaken. Following analysis of the progression criteria from the internal pilot no formal interim analyses are planned. A single final analysis is planned after the study is closed to recruitment and follow-up and when the full database has been cleaned and locked.

20.1 Sample size calculation

Sample size adjusted in Protocol v5.0 to 742 (325 control and 417 intervention), please see detail above in 8.1 Important changes to methods after trial commencement. Outlined below is the original sample size calculation.

718 participants (318 control, 400 intervention) will be randomised, at the point of discharge from hospital or from intermediate care, to receive either the HOPE extended rehabilitation programme (+ usual care) or usual care only. This sample size will provide 90% power to detect a minimum clinically important difference of 3 points on the 12 month primary outcome, the Short-Form 36 item health questionnaire (SF36) physical component summary (PCS) score (SD 9.47) at the 2-sided 5% significance level. The calculations account for 25% loss to follow-up, clustering in the intervention arm only (10 sites, 40 participants per intervention site, harmonic mean of 5 therapists (clusters) per site (range 2 to 8), 0.03 ICC, an average of 8 participants per therapist, 0.47 coefficient of variation to account for varying number of participants per therapist), and an allocation ratio of 1.25:1 (HOPE extended rehabilitation programme + usual care: usual care).

For community-dwelling older people, a mean PCS score of 30 (SD=9.47) has been reported [39]. The smallest detectable difference of 2.8 points has been reported for the PCS in a population of older people receiving rehabilitation for lower limb osteoarthritis [40]. Hence, our sample size is powered to detect a minimum clinically important difference of 3 points, as this is both a clinically relevant and detectable difference for this intervention, and is consistent with a moderate effect size of 0.3. Hence it is clinically meaningful for both patients and commissioners of rehabilitation services. In the pilot study 15% of participants were lost to follow-up but for the purposes of this study we have assumed a higher rate of no greater than 25% due to longer follow-up; recruitment in a population more likely to be readmitted to hospital; and a primary outcome measured primarily through postal questionnaires which have a lower completion rate than researcher-administered outcomes.

In partially nested designs, there is a different ICC in the two arms since there is a therapist effect in the intervention arm, not present in the control arm. This results in unequal variation in the patient outcomes between the two arms, which reduces power [41, 42]. For this study, clustering will only exist in the intervention arm to account for between-therapist effects for those delivering the HOPE programme to participants. An intra-cluster correlation coefficient (ICC) of 0.03 has been assumed, given that standardised training and manuals for delivering the intervention will minimise the ICC. A review of similar HTA trials supports an assumption of an ICC no greater than 0.03; for example, an RCT (08/14/51) of rehabilitation for improving outdoor mobility for people after stroke assumed an ICC of 0.02 in design and observed a therapist effect ICC of 0.005 [43] whilst the ProACT65 RCT (06/36/14) of exercise programmes for adults over 65 years assumed an ICC of 0.01 in design and observed an ICC of 0.009 [44].

20.2 Planned recruitment rate

The original sample size of 718 required sites to recruit 72 participants per site, an average recruitment rate of 4 to 5 participants per site per month. This target will compensate for embedding trial procedures during the initial stages of recruitment.

The revised recruitment target is 742 participants across 10 sites over a revised total of 38 months (see flow diagram 2b). Site set-up will be staggered to accommodate six months recruitment in the internal pilot (4 sites) and intervention training, giving a range of 30 – 38 months for recruitment. Data from participants in the internal pilot will be included in the main study analysis.

The sample size requires varying recruiting site targets, dependent upon when a site commences recruitment in accordance with study timelines. Internal pilot sites (4 sites) will recruit for up to 38 months, other main trial sites will recruit for up to 30 months from initiation of the trial at site. Original site targets supported an average recruitment rate of 4 to 5 participants per site per month, once recruitment rates stabilise allowing for embedding of study procedures during the initial stages of recruitment.

Following admission to hospital with acute illness or injury, it is anticipated that around 1/3 of frail older people will be discharged from **elderly medicine wards** or **trauma/orthopaedic wards** after a short period of rehabilitation. A further 1/3 of frail older people will require transfer to **intermediate care** for an additional relatively brief period of rehabilitation (usually less than two weeks). It is expected that the remaining 1/3 of frail older people will be admitted from/discharged to a care home, so will be ineligible, or will have died during admission. Therefore, recruiting participants across these sites will ensure that the study design is closely aligned with current usual NHS rehabilitation pathways for frail older people following acute illness or injury.

Original recruitment calculation was based on pilot work, in which 84 participants were recruited over a 16 month period in a single-site (approximately 5 per month). This monthly recruitment rate ensured feasibility of intervention delivery by NHS therapy staff as part of routine care. For a medium sized district general hospital (DGH), estimates of hospital frailty prevalence, national audit of intermediate care data and NHS secondary care data indicate that around 60 participants will be available to recruit per month per site. For a small DGH, around 40 participants will be available to recruit per month. Informed by our pilot study, on the basis of a 30% recruitment rate we feel that our recruitment estimates are therefore achievable, realistic, based on therapist and researcher workload, and that we anticipate will be feasible for intervention delivery across participating sites.

Recruitment across trial sites has been variable between sites and across time. We monitor recruitment and work with sites to maximise recruitment towards targets and account for changing circumstance. For the extended recruitment window, projections have been made to calculate the additional time required to recruit to the trial sample size. In order to achieve the sample size, the monthly target nationally is 26 participants per month on average. Projections were based on review of observed recruitment in 2019 at individual sites, current site resource, and knowledge of planned changes at sites.

20.3 Primary outcome analysis

The primary analysis will compare mean SF36 PCS scores at 12 months between arms using a linear mixed-effects heteroscedastic model to account for clustering of outcomes in the intervention arm due to therapist effects [45]. The model will be adjusted for the stratified design factors (site, discharge setting, intended level of HOPE programme and reason for admission), age, gender, baseline measures (SF36), and participant previous engagement or referral to community rehabilitation services. The analysis will be undertaken on the intention to treat (ITT) population, which includes all randomised participants in their allocated treatment group, regardless of the level of treatment adherence. Corresponding 95% confidence interval and p-values will be reported as well as the ICC for the intervention arm. Model diagnostics will be used to check that the underlying assumptions are not violated in the analysis.

Missing outcomes, especially those due to death, may not be missing at random, hence first we will explore and summarise the missing data patterns and reasons for missingness to guide the appropriate analytical strategy. If this work confirms that it is reasonable to assume data are missing at random (MAR), the primary analysis will use multiple imputation to deal with missing data. We will include a wide range of variables in the imputation models, including all variables in the substantive analysis, plus, as far as computationally feasible, all variables predictive of the missing values themselves (including potentially time of death) and all variables influencing the process causing the missing data, even if they are not of interest in the substantive analysis.

If the initial work does not confirm MAR, we will explore the use of other more complex methods for the primary analysis taking account of data missing not at random (MNAR), such as pattern mixture modelling.

To assess the impact of death on our potential treatment effect, we will then undertake a sensitivity analysis by repeating the primary analysis modelling but exclude those participants who have died.

A per protocol analysis of the primary outcome will also be conducted based on pre-defined criteria associated with intervention adherence.

20.4 Secondary outcome analysis

Secondary outcomes of SF36 MCS score, Barthel Index, NEADL scores, EQ-5D-5L summary index, and A&E or hospital admissions due to falls will be analysed using the same methods as described for the primary outcome and adjusted for the same stratification and participant level covariates. The analysis of the SF36 MCS score will additionally adjust for the baseline SF36 PCS score.

The binary secondary outcomes of new care home placement, hospital readmission, composite of new care home placement or hospital readmission and mortality will be compared between arms using logistic generalised estimating equations or random intercept models to account for heteroscedasticity [28], adjusted for stratification factors and age.

20.5 Intervention summaries

Intervention delivery will be assessed by summarising the number and timing of home visits and telephone sessions received by participants in the intervention arm. In addition, protocol compliance of the therapists will be summarised using the written therapy records from each session delivered. Participant adherence to the intervention will be evaluated using data from exercise diaries, which detail the number of exercise repetitions completed on each day of the week. Participant drop-out rates will be calculated and the reasons for drop-out will be summarised.

20.6 Interim analysis and criteria for the premature termination of the study

No formal interim analyses are planned for the primary or secondary outcomes. A single final analysis is planned after the study is closed to recruitment and follow-up and when the full database has been cleaned and locked.

Descriptive statistics only will be used to evaluate the progression criteria for the four internal pilot sites. The progression criteria assess the level of recruitment for each site, follow-up rates, as well as provision and acceptability of the intervention. This analysis will inform study continuation beyond the internal pilot phase. The internal pilot recruitment will last a period of 6 months. The progression criteria will be assessed, based on a traffic light system of green (go), amber (review) and red (stop), as follows:

- **Provision of intervention** (Assessed at 6 months after start of internal pilot recruitment)
Green: $\geq 80\%$ of intervention participants receiving their first home visit within 3 weeks
Amber: $< 80\%$ but $\geq 65\%$ of intervention participants receiving their first home visit within 3 weeks
Red: $< 65\%$ of intervention participants receiving their first home visit within 3 weeks
- **Acceptability of intervention** (Assessed at 9 months after start of internal pilot recruitment)
Green: $\geq 80\%$ retention of intervention participants
Amber: $< 80\%$ but $\geq 65\%$ retention of intervention participants
Red: $< 65\%$ retention of intervention participants
- **Recruitment** (Assessed at 6 months after start of internal pilot recruitment)
Green: ≥ 4 patients/month/site (measured in months 4-6 to allow time for recruitment to stabilise)
Amber: < 4 but ≥ 2 patients/month/site
Red: < 2 patients/month/site
- **Six month follow-up** (Assessed at 12 months after start of internal pilot recruitment)
Green: $\geq 80\%$ completion of the SF-36 physical component summary
Amber: $< 80\%$ but $\geq 65\%$ completion of the SF-36 physical component summary
Red: $< 65\%$ completion of the SF-36 physical component summary

If any criteria are graded as amber, a rescue plan will be developed outlining steps to be taken to improve intervention provision, recruitment, retention and/or follow-up (as appropriate), and will be approved by the TSC before submission to the HTA. If the progression criteria are failed (red), then the internal pilot will not progress to the definitive study. If the progression criteria are met by the end of the internal pilot then the study will continue and outcome data from participants in the internal pilot will be included in the main study analysis.

21. ECONOMIC EVALUATION

We will carry out within-trial and long-term cost effectiveness analyses. Analyses will report differences in cost of service use between groups and the incremental cost effectiveness ratios using QALYs derived from EQ-5D-5L [46].

The primary within-trial analysis will compare direct costs and 12 month outcomes of patients randomised to the HOPE programme (+ usual care) as extended rehabilitation for older people with frailty after acute illness or injury versus control (usual care alone). The perspective adopted will be that of the NHS and Public Social Services. Resource utilisation will be captured using routine GP and HES data and a patient questionnaire suitable for self-report. The design of the patient questionnaire will build upon the work undertaken by the Health Economics Unit at Leeds on previous studies within similar populations. Administered at 6 and 12

months, the questionnaire will ask participants to recall resource use over the prior 3 months. This will be extrapolated to the six months period. 2013-14 unit costs for health and social care resources will be derived from local and national sources [47, 48]. Given the time period no discounting is required. Secondary analyses will adopt a societal perspective taking account of productivity costs and out-of-pocket expenditures incurred by participants. These data will be captured using routine GP and HES data and the patient questionnaires.

As highlighted previously, data will be collected at baseline, six and 12 months to estimate incremental cost-effectiveness ratios (ICERs) comparing the intervention with the control group. Mortality and quality of life (derived from the EQ-5D-5L) over the study period will be used to generate quality-adjusted life-years (QALYs) [49]. Parameter uncertainty will be quantified using non-parametric bootstrapping techniques. Outputs will be presented as ICERs, cost effectiveness acceptability curves and expected net benefit. As well as identifying the most cost-effective means of achieving a QALY, the NICE threshold of £20,000 per QALY will be applied when considering prophylaxis [50]. The impact of missing data will be examined using imputation methods. Sensitivity analyses will consider key cost drivers and factors that might affect the outcomes measured to explore uncertainty in the conclusions drawn [51]. Utility values derived from the SF36 will be included as a sensitivity analysis.

The long term cost effectiveness model will compare effectiveness of the HOPE programme (+ usual care) as extended rehabilitation for older people with frailty after acute illness or injury versus control (usual care alone). The long-term model will take the perspective of the health and social care providers. The decision analytic cost effectiveness analysis model will use a lifetime time horizon to capture the full impact of any mortality differences on the long term cost effectiveness. It is likely that the model will be a Markov or semi-Markov state model. As far as possible the transition rates for the model will be estimated from the clinical study data. Model parameters for which data could not be collected within the study, for example, the long-term costs and outcomes of hospital readmission/care home placement, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature.

The primary outcome measure will be the QALY. Utility weights will be taken from the UK General Population tariff for the EQ-5D-5L [52]. Unit costs will be taken from national databases including NHS reference costs and the PSSRU costs of health and social care. Probabilistic sensitivity analyses will be undertaken using Monte Carlo simulation techniques. The outputs reported from the analysis will be the same as for the within study analysis.

22. MONITORING, AUDIT & INSPECTION

22.1 General Consideration

Our research involves older people with frailty, who may have a range of health problems and social predicaments, including cognitive impairment, visual impairment, and social isolation. A key ethical issue for consideration is recruitment of participants with cognitive impairment, who may lack capacity to provide informed consent. We have considered this possibility in detail as part of our planned recruitment strategy.

The Mental Capacity Act 2005 (MCA) provides a framework for the assessment of the capacity of an individual to make informed decisions. All members of the research team will receive training in the MCA and its application in the research setting. We will include the opportunity to have family members or supporting carers present to help support the capacity assessment. We will obtain formal written consent to participate from participants who have capacity to provide informed consent. It will be made clear that the participant can withdraw consent at any stage, and that no intervention or assessment will be undertaken where the participant appears reluctant, even if they have previously consented. Potential participants who lack capacity to consent to join the study will not be recruited.

22.2 Trial Monitoring

A Trial Monitoring plan will be developed and agreed by the Trial Management Group (TMG) and Trial Steering Committee (TSC). This will be informed by a Trial Risk Assessment which will consider the safety or physical or mental integrity of the study participants and the scientific value of the research (including the potential risk associated with the implementation of the intervention and recruitment which can, if not monitored and mitigated, affect the integrity and smooth running of this study). This monitoring plan will detail the timing and content of reports to monitor study conduct and implementation and adherence with the Consolidated Standards of Reporting Trials (CONSORT). This monitoring plan may also include site monitoring.

For a study of this nature, a separate Data Monitoring and Ethics Committee (DMEC) is not required. Rather, the TSC will adopt a safety monitoring role, with the constitution of a sub-committee to review safety issues where this becomes necessary.

As deaths are expected within the study population they will not be subject to expedited reporting to the REC, unless the TSC advises that the frequency of deaths observed within the study population is significantly higher than that expected in this population.

22.3 Data Monitoring

Data will be monitored for quality and completeness by the CTRU, using established verification, validation and checking processes. Missing data, except individual data items collected via the postal questionnaires, will be chased until they are received, confirmed as not available, or when the study is at analysis. Reminders will be sent to participants if postal questionnaires are not returned on time. Hub researchers will also be offered telephone and face-to-face visits to facilitate data completion where appropriate.

The CTRU/Sponsor reserve the right to conduct intermittent source data verification on a sample of participants. Source data verification will involve direct access to patient notes at the participating hospitals, and other relevant investigation reports.

22.4 Clinical Governance Issues

The Sponsor for the study is Bradford Teaching Hospitals NHS Foundation Trust. The Sponsor will ensure responsibility and accountability for study conduct and procedures associated with the protocol.

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and where applicable to individual NHS Trusts.

23. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

23.1 Quality Assurance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical studies, as applicable under UK regulations, the NHS Research Governance Framework (RGF), and through adherence to CTRU SOPs and study specific guidance implemented to ensure delivery of the study in accordance with this protocol.

23.1.1 Serious Breaches

Investigators are required to promptly notify the CTRU if a serious breach occurs (as defined in the latest version of the NRES SOP). This is defined as a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree the safety or physical or mental integrity of the study subjects, or the scientific value of the research.

In the event of doubt or for further information, the Investigator should contact the Chief Investigator.

23.2 Ethical Considerations

23.2.1 Consent

Those approached to participate in the study will have the right to refuse consent without having to provide a reason. Those who consent to take part in the study will be free to withdraw at any time without having to provide a reason. If participants of the proposed study withdraw consent from further participation their data will be included in the final study analysis unless they specifically withdraw consent for their data to be used. This will be made clear at the time of consent and when they withdraw from the study.

23.2.2 Potentially vulnerable adults

It is likely that some of the participants will be people who may be considered vulnerable. The researcher will consult with the clinical team to review capacity, and if appropriate, will engage with the participant and their friends and family member(s) to determine whether they are able to give informed consent. The study complies with the MCA (2005).

23.2.3 Safeguarding of adults

It is possible that, during discussions, participants may disclose information to the research team (CRN / local Researcher), or they may have concerns that the individual may be experiencing abuse, or is at risk of abuse. In such circumstances the researcher will follow their NHS Trusts' Safeguarding Adults policy (or equivalent document).

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996. Informed written consent will be obtained from the patient prior to randomisation into the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main REC and the appropriate Site Specific Assessor for each participating centre prior to entering into the study. The CTRU and / or CI will provide the main REC with a copy of the final protocol, information sheets, consent forms and all other relevant study documentation.

24. CONFIDENTIALITY

All information, especially personal information (name, address, telephone number, date of birth) collected during the course of the study will be kept strictly confidential. Information from the main study will be held securely on paper and electronically at CTRU in Leeds.

Data collection forms that are transferred to or from the CTRU will be coded with a study number and will include two identifiers, usually their initials and date of birth. Appropriate storage, restricted access and disposal arrangements personal and clinical details will be put in place.

The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- consent from participants (and carers) to record personal details including name, date of birth, address and telephone number, NHS number, hospital number, GP name and address
- appropriate storage, restricted access and disposal arrangements for personal and clinical details of participants
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation.
- consent from participants to access information held and maintained by centralised sources (i.e. NHS Digital – HES/ONS data, EHR – e.g. SystmOne / EMIS / Vision)
- consent from participants for the data collected for the study to be used to evaluate safety and develop new research.
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.
- transcripts, data collected through observations (field notes and observational records, summaries of documentary analysis), and reflective reports will be anonymised.

All data collected as part of the Process Evaluation will be transferred and stored securely at the AUECR in accordance with the Data Protection Act 2018. Recordings of semi-structured interviews will be transcribed verbatim. This may be conducted by a UK-based third party with an appropriate confidentiality and data security agreement.

25. STATEMENT OF INDEMNITY

This study is sponsored by the Bradford Teaching Hospitals NHS Foundation Trust and the NHS indemnity scheme will apply to meet the potential legal liability of the sponsor for negligent harm caused harm to participants arising from the management of the research. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a research study, and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

26. STUDY ORGANISATIONAL STRUCTURE

26.1 Responsibilities

Detailed responsibilities are outlined in relevant Organisational sub-contracts, below provides a summary of general responsibilities.

Sponsor

The Sponsor is responsible for study initiation management and financing of the study as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the study contract.

Chief Investigator (CI)

As defined by the NHS RGF, the CI is responsible for the design, management and reporting of this study.

Academic Unit of Elderly Care and Rehabilitation (AUECR)

The AUECR will be responsible for day-to-day management of the study, collaborating with the CTRU to develop study related documentation including the protocol and recruitment materials, MREC and R&D submissions. They will also be responsible for; 1. Promotion of the study and identification of suitable services, including feasibility assessment and facilitating discussions with commissioners and local collaborators, 2. All aspects of the intervention including development, training and delivery will be the responsibility of the AUECR, as will the management and overall supervision of the performance and conduct of the research team, 3. All aspects of the process evaluation, including development, observation materials, interviews, and analysis.

Clinical Trials Research Unit (CTRU)

The CTRU will provide set-up, implementation and monitoring of study conduct to CTRU SOPs and MRC GCP standards including study design, protocol development, randomisation design and implementation, database development and provision, CRF design, monitoring schedule and statistical analysis and reporting. In addition, the CTRU will support main REC and Research and Development (R&D) submissions, and site set-up and on-going management including non-clinical training, monitoring reports and promotion of the study. The CTRU will be responsible for the database administrative functions, data management including postal follow-up and telephone reminders, safety reporting, and all statistical analyses.

University of Exeter

The University of Exeter (South West Hub Lead) will be responsible for promotion of the study and identification of suitable services, including feasibility assessment and facilitating discussions with commissioners and local collaborators. The will also be responsible for management and overall supervision of the performance and conduct of the research team.

Academic Unit of Health Economics (AUHE)

The AUHE at the University of Leeds will be responsible for the selection and design of the resource use questionnaire and development of the Health Economics sections of the protocol, the calculation of indicative costs and cost-effectiveness, and the presentation of these results.

Principal Investigator

Overall responsibly for conduct of the study at the participating site, including (but not limited to) assessment of eligibility, informed consent and patient safety.

Site Staff

Site research staff are responsible for the conduct of the study in accordance with the study protocol and terms of the statement of activities for the study. Site therapists are responsible for delivering the intervention in accordance with the study protocol, the HOPE manuals and terms of the statement of activities for the study.

26.2 Oversight / Trial Monitoring Groups

Trial Steering Committee (TSC)

The TSC, with an independent Chair, will provide overall supervision of the study, in particular monitor study progress, and provide public, clinical, and professional advice, with pre-agreed terms of reference

including completion of the pilot study according to pre-defined success criteria. It will include an Independent Chair, not less than two other independent members and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

For a study of this nature, a separate Data Monitoring and Ethics Committee is not required. Rather, the TSC will adopt a safety function, with the constitution of a sub-committee to review safety issues, where this becomes necessary.

Trial Management Group (TMG)

The TMG, comprising the CI, key co-applicants, CTRU delivery team, other key external members of staff involved in the study will be assigned responsibility for the clinical set-up, on-going management, promotion of the study, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and HRA approval and supporting applications for local capability / capacity assessments, (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the TSC, (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment and follow-up procedures, (viii) auditing consent procedures, data collection, study end-point validation and database development. The TMG team will meet quarterly as a minimum, dependent upon the phase of the study and the input required as determined by the team.

27. PUBLICATION / DISSEMINATION POLICY

The study will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the study depends upon the collaboration of all participants. For this reason, credit will be given to those who have collaborated through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content;
- and final approval of the version to be published;
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, Co-Applicants, and relevant senior CTRU and AUECR staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main study publication, giving details of roles in planning, conducting and reporting the study.

27.1 Dissemination Policy

The TMG / TSC will oversee the publication plan and will be consulted prior to release or publication of any study data.

Individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the study until the main results of the study have been published. Local collaborators may not have access to study data until after publication of the main study results.

NIHR Health Technology Assessment

The NIHR must be notified of all outputs (i.e. publications). A copy of any outputs and any information pertaining to it must be sent to NIHR at the same time as submission or at least 28 days before the date intended for publication, or it being placed in the public domain, whichever is earlier.

All publications must acknowledge NIHR HTA as the study's funding source and include an appropriate disclaimer regarding expressed views and opinions (example text is provided on the HTA website).

27.2 Authorship Guidelines

The agreed first author of abstracts is responsible for circulating these to the other members of the TMG for review at least 15 days prior to the deadline for submission.

The agreed first author of manuscripts is responsible for ensuring:

- timely circulation of all drafts to all co-authors during manuscript development and prior to submission
- timely (and appropriate) circulation of reviewers' comments to all co-authors
- incorporation of comments into subsequent drafts
- communication with the TSC (i.e. ensuring submission is in line with TSC publication plan, and ensuring TSC receive the final draft prior to submission)

The first author is responsible for submission of the publication and must keep the TMG and all authors informed of the abstract's or manuscript's status. The TSC will be kept informed of rejections and publications as these occur. On publication, the first author should send copies of the abstract or manuscript to the TSC, the TMG, the Sponsor and to all co-authors, and ensure communication with the NIHR.

27.3 Access to the final study dataset

To maintain the scientific integrity of the study, data will not be released prior to the end of the study, either for study publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigator or CTRU. In addition, individual collaborators must not publish data concerning their patients which is directly relevant to the questions posed in the study until the main results of the study have been published.

27.4 Data source

Data from the CTRU main study database in Leeds must be used for data analyses for all abstracts and publications relating to the questions posed within the study protocol, with the exception of additional Process Evaluation data. Furthermore, the statistical team at the CTRU must perform all such analyses.

27.5 Data release

To maintain the scientific integrity of the study, data will not be released prior to the first publication of the results of the study, either for study publication or oral presentation purposes, without the permission of the TSC.

28. END OF STUDY / ARCHIVING

28.1 End of study

The end of the study is defined as the date of the last participant's last data item (i.e. the date of the 12 month follow-up of the last participant randomised).

28.2 Archiving

At the end of the study, data will be securely archived for a minimum of 10 years. Arrangements for confidential destruction will then be made. No records may be destroyed without first obtaining written permission from the Sponsor.

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30. APPENDICIES

30.1 Appendix 1 – Contacts

Trial Funder

NIHR HTA Programme

Evaluation, Trials and Studies Coordinating Centre, University of Southampton, Alpha House, Enterprise Road, Southampton, SO16 7NS

Telephone: 02380595586

Email: info@netscc.ac.uk

Co-applicants

Andrew Clegg (CI)

Clinical Senior Lecturer & Honorary Consultant Geriatrician, Academic Unit of Elderly Care and Rehabilitation, University of Leeds, Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford, BD9 6RJ

David Clarke

Associate Professor in Stroke Care, Academic Unit of Elderly Care and Rehabilitation, University of Leeds, Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford, BD9 6RJ

Bonnie Cundill

Principal Statistician, Clinical Trials Research Unit (CTRU), Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, LS2 9JT

Amanda Farrin

Professor of Clinical Trials & Evaluation of Complex Interventions, Clinical Trials Research Unit (CTRU), University of Leeds, Leeds, LS2 9JT

Anne Forster

Professor of Stroke Rehabilitation and Head of AUECR, Academic Unit of Elderly Care and Rehabilitation, University of Leeds, Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford, BD9 6RJ

Victoria Goodwin

Senior Research Fellow, University of Exeter, 2.26 South Cloisters, St Luke's Campus, Magdalen Road, Exeter, EX1 2LU

Suzanne Hartley

Head of Trial Management – Complex Interventions Division, Clinical Trials Research Unit (CTRU), Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, LS2 9JT

Claire Hulme

Professor of Health Economics, Academic Unit of Health Economics, Leeds Institute for Health Sciences, University of Leeds, Leeds, LS2 9JT

Phil Wright

Therapy Co-ordinator - Older People, Community and Intermediate Care. Therapy Services, Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Ln, Bradford BD9 6RJ

John Young

Professor of Elderly Care Medicine, Academic Unit of Elderly Care and Rehabilitation, University of Leeds, Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Duckworth Lane, Bradford, BD9 6RJ

30.2 Appendix 2 – TIDieR checklist



Template for Intervention
Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

N°	What	Details
1	Name	The Home-based Older People's Exercise (HOPE) programme
2	Why: Rationale, theory, goal	<p>Sarcopenia (loss of muscle mass and strength) is a core component of frailty and periods of immobility in older age, such as that experienced during an acute illness or injury, can accelerate loss of skeletal muscle function. This is especially problematic in frailty because accelerated loss of skeletal muscle function can compromise the capability to perform activities of daily living (e.g. walking, dressing, toileting, climbing stairs), jeopardising successful functioning in the home environment, which may lead to a requirement for increased home care, or admission to long-term care residence. Systematic reviews of exercise interventions for older people with frailty have reported evidence for improvements in mobility and activities of daily living, but few trials have measured effects on quality of life and no trials have reported on cost-effectiveness.</p> <p>This evidence for positive physiological, mobility and functional benefits of exercise in frailty provides the rationale for a home-based exercise programme to extend the rehabilitation period for older people with frailty following acute illness or injury.</p> <p>The HOPE programme is graded into three levels to account for the spectrum of frailty. To start the programme, participants are stratified to the appropriate level using their performance on the timed-up-and-go test (TUGT).</p> <p>Participants are allocated to intervention level by;</p> <ul style="list-style-type: none"> - HOPE Level 1: Participants completing the TUGT in >30 seconds, who are more likely to require assistance with walking, climbing the stairs and leaving the house. - HOPE Level 2: Participants completing the test in 20-29 seconds, who demonstrate greater variability in mobility, balance and functional ability. - HOPE Level 3: Participants who complete the test in less than 20 seconds, who tend to be able to get in and out of a chair without assistance and climb stairs. <p>The programme incorporates relevant behaviour change techniques based predominantly on social cognitive theory and control theory, including providing information on benefits of exercise; setting graded tasks; goal setting; prompting self-monitoring.</p> <p>The primary goal of the HOPE programme is to improve health-related quality of life for older people with frailty after acute illness or injury. Secondary goals include improvements in activities of daily living, mental</p>

		health, and reduced hospitalisation and care home admission.
3	What Materials	<p><u>HOPE Manual</u>: The HOPE manual consist of 5 sections; 1. Information, 2. Safety Tips, 3. Good Posture, 4. Exercises, 5. Staying on track. It contains photographs and simple descriptions of the individual exercises to instruct participants. The HOPE manual also contains an exercise diary to monitor intervention adherence.</p> <p><u>Therapy Record</u>: The therapy record is based on standard records used by therapy staff as part of clinical practice. It includes participant information (e.g. demographic details, comorbidities, medications) and individual pages so that therapy staff can record a narrative description of each participant contact (home visits and telephone calls). The therapy record also enables recording of information required to calculate costs for intervention delivery, including travel time/distance.</p>
4	What Procedures	<ul style="list-style-type: none"> • 24 weeks (12 initial weeks incorporating five home visits and seven telephone calls and 12 additional weeks of telephone support. • The core constituents of the HOPE programme are strengthening exercises for the muscle groups required for basic mobility skills like getting out of bed, standing up from a chair, walking a short distance and getting off the toilet. • The HOPE programme is graded into three levels to account for the spectrum of frailty; The exercises are taught to participants by a HOPE-trained therapist, require no special equipment and can be performed without ongoing professional supervision. • Intervention delivery is initiated by the HOPE-trained therapist, who makes telephone contact with the participant to schedule the initial home visit. <ul style="list-style-type: none"> ○ Weeks 1, 2, 4, 7, and 8 are face-to-face home visits with a therapist. • Weeks 3, 5, 6, 9, 10, 11, and 12 are telephone calls with a therapist.
5	Who provided	<ul style="list-style-type: none"> • Suitably trained physiotherapists and therapy assistants who are familiar with delivering community rehabilitation programmes to older people. • Physiotherapists and therapy assistants will receive detailed intervention training in interactive workshops delivered by clinicians experienced in HOPE programme. • Intervention training will include rationale, theory and goals of the HOPE programme; description of intervention materials and procedures; along with strategies and practical delivery of the programme. • Supervision of therapy staff will be by usual NHS line management. • Intervention adherence will be recorded in an exercise adherence diary included as part of the exercise manual, therapy records.. • Access to training materials will require relevant permissions and will be monitored during the study.
6	How: mechanisms of delivery	The HOPE programme is delivered by a trained therapist in five face-to-face home visits and 19 telephone calls for ongoing support.

7	Where: location of delivery	Participants will be recruited from hospital and intermediate care rehabilitation sites and randomised at the point of discharge home. The HOPE programme will be delivered in the participant's own home by the HOPE-trained therapist, with no specialist equipment required.
8	When and how much	<ul style="list-style-type: none"> • The HOPE programme is delivered over a 24 week schedule, with 5 Home visits and 19 Telephone contacts • The exercise routine takes less than 15 minutes to complete, and participants are requested to complete the routine 3 times a day on 5 days of the week. • At the beginning of the intervention participants are requested to perform five repetitions of each exercise in the routine. This progresses to 10 and then 15 repetitions as performance improves. • Progression is by increasing repetitions, introducing new exercises or advancing to the next HOPE programme level and is reviewed at weeks 4 and 7 as per the HOPE manual. • Participants document activities completed in HOPE participant diary.
9	Tailoring	<ul style="list-style-type: none"> • The HOPE Programme level (level 1, 2 or 3) is tailored to individual participants because it is dependent upon initial assessment of mobility based on the TUGT score. • Intervention progression is tailored to individual participant response to intervention.
10*	Modifications	On-going
11	How well (planned)	<ul style="list-style-type: none"> • Intervention data collection (7 months post randomisation - Intervention duration: 24 weeks) <ul style="list-style-type: none"> ○ Data will be captured on, for example, the number of contacts and sessions, date and duration of sessions, mode of delivery, location and type of session, and progression using a Therapy Case Report Form. ○ Participants will also complete an exercise diary to document how many times each exercises were completed and on which days of the week. • Process Evaluation Staff Interviews (early and late intervention periods)
12*	How well (actual)	On-going