BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064637
Article Type:	Protocol
Date Submitted by the Author:	13-May-2022
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Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, REHABILITATION MEDICINE

Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures: Protocol for a randomised controlled trial – the Osteoporosis Tailored exercise adherence intervention (OPTIN) study.

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Keywords

1 Physical therapy modalities; exercise, osteoporosis, spine, rehabilitation

2 Word count 3967

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ABSTRACT

Introduction: Vertebral fragility fractures affect at least 20% of the older population in the UK. Best practice guidelines recommend the use of exercise to slow the rate of bone loss, to maintain muscle strength and physical function, and to prevent falls and further fractures. However, treatment effects are often small and difficult to sustain and adherence, or the extent to which patients engage in treatment, has been identified as an important issue by many studies. Our hypothesis is that integrating adherence intervention strategies with an exercise intervention will be beneficial. We will compare physiotherapy exercise rehabilitation with adherence support versus physiotherapy exercise rehabilitation alone in terms of effects on (a) physical function, quality of life, and fear of falling and (b) exercise self-efficacy and adherence.

Methods and Analysis: A multicentre, two-arm, parallel group, superiority randomised controlled trial (RCT) with blinded assessments at baseline (0) and 4, 8, and 12 months, with a nested qualitative study and health economic analysis. 116 participants will be allocated to either (i) out-patient physiotherapy which will include a musculoskeletal assessment and treatment including balance, posture, strength training and low impact weight-bearing exercises over 16 weeks; or (ii) Opt-In intervention. This includes standard physiotherapy as above plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent 16 weeks.

Ethics and Dissemination: The study protocol was approved by West of Scotland Research Ethics Committee 4 (21/WS/0071). Trial registration number ISRCTN 14465704. The paper is based on Protocol v4.

Strengths and Limitations of this study

- The Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures (Opt-In) study is a multicentre randomised controlled trial with an embedded qualitative study and economic evaluation.
- It will recruit from at least six NHS hospitals.
- The intervention addresses adherence which is an important confounder in many trials of physiotherapy.

- The intervention was developed using current research evidence, input from expert clinicians, researchers and patient / public representatives.
- Due to the nature of the interventions the physiotherapists delivering the treatments and the participants cannot be blinded.

Introduction

Vertebral fragility fractures (VFFs) affect at least 20% of the older population in the UK and present a significant health and economic burden [1, 2]. They are associated with back pain, fatigue, low mood, restrictions in physical function and activities of daily living, and marked, persistent reductions in quality of life (QoL) [1, 2]. Without treatment, progression and functional decline are expected. Conservative treatment for osteoporosis includes bone protective medications and lifestyle adaptations. Guidelines recommend people with osteoporosis keep active and exercise to slow the rate of bone loss, to maintain muscle strength and physical function and to prevent falls and further fractures [3]. Exercise prescription with multi-component exercise programmes that include postural, balance, aerobic weight-bearing and strength exercises are recommended [1-3].

Trials evaluating exercise in people with VFFs have reported benefits across a range of outcomes [1, 2, 4-10], with a recent Cochrane review concluding there is moderate-quality evidence that exercise improves physical function [1]. However, treatment effects are often small and difficult to sustain [1, 2, 4-10]. For example, in the PROVE trial, significant, clinically relevant benefits to back muscle endurance, balance, walking capacity and physical function following physiotherapy exercise at 4 months post-randomisation did not persist at 12 months [2]. Adherence, or the extent to which patients engage in treatment, has been identified as an important issue by many studies [1, 2, 4-6, 9]. Partial adherence or non-adherence is associated with worse outcomes and conversely, higher adherence with better outcomes [1, 2, 4-10].

Multiple factors affect exercise adherence in older people with chronic health conditions including osteoporosis [11, 12]. These include low exercise self-efficacy, low motivation, depression, insufficient exercise knowledge or skill, physical ability, negative views about treatment and exercise programme design [11,12]. Considering this complexity, interventions to support adherence that recognize personal barriers and facilitators to exercise and that can draw upon multiple adherence techniques are recommended [12, 13].

Behavioural approaches can include interventions that support exercise through providing additional monitoring, interventions that aim to alter thinking patterns that contribute to non-adherence and ones that strengthen behaviours that support adherence [12]. Motivational interviewing is a collaborative process that explores potential ambivalence, obstacles and facilitators surrounding behaviour change [6]. There is evidence that additional monitoring, prompts and feedback can benefit adherence in older adults e.g., via telephone call/ text messages, wearable activity monitors or by enriching environmental cues [1]. Incorporating exercise into everyday routines can make it easier to initiate and sustain and creating 'Exercise Action Plans' that specify when, where and how exercises are undertaken can support this process [1, 13]. Using an intervention mapping approach, we developed an exercise adherence intervention underpinned theoretically by the COM-B behaviour change model [14, 15].

Aims

The aims of this study are:

- To compare physiotherapy exercise rehabilitation with adherence support with physiotherapy exercise rehabilitation alone in terms of effects on: (a) physical function, quality of life, and fear of falling and (b) exercise self-efficacy and adherence.
- To explore patient and physiotherapist views of the intervention and of adhering to exercise.
- To understand if physiotherapy exercise rehabilitation with adherence support is cost-effective.

METHODS AND ANALYSES

Study design

A multicentre, two-arm, parallel group, superiority randomised controlled trial (RCT) with blinded assessments at baseline (0) and 4, 8, and 12 months following randomisation, with a nested qualitative study and health economic analysis. Participants will be allocated to either (i) outpatient

physiotherapy which will include a musculoskeletal assessment and 6 treatment sessions over 16 weeks based on the current best practice guidance from the Royal Osteoporosis Society; or (ii) the Opt-In intervention. This includes outpatient physiotherapy as described above, plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent treatment period of 16 weeks as prescribed by the physiotherapist in collaboration with the participant. Sessions in both arms can be in-person or virtually via video-call/ telephone as agreed between participant and therapist **(Figure 1)**.

Setting

At least six National Health Service (NHS) hospitals and their related physiotherapy services.

Study Participants

Adults aged 55 years or over who have a diagnosis of at least one previous osteoporotic vertebral fracture and back pain.

Eligibility

Inclusion Criteria

Participants may enter the study if they meet ALL the following criteria:

- Men and women ≥ 55 years: all women must be at least 1 year post-menopausal.
- One or more VFFs confirmed by radiography, X-Ray, MRI, CT or DEXA scan, people with VFF of any severity and at any time-point post-fracture are eligible.
- They must have had an episode of back pain in the previous 12 months.
- All must be able to walk at least 10 metres independently with or without a walking aid.

Exclusion Criteria

Participants may not enter the study if ANY of the following apply:

- Current conditions that would make participating in physiotherapy or exercise unsafe or confound results. This includes those with significant neurological and psychiatric conditions, severe unstable cardiovascular or pulmonary disease.
- Bone loss secondary to other metabolic disorders, diseases or medication e.g., rheumatoid arthritis, anorexia, cancer, coeliac disease, steroid use.
- Individuals whose primary problem is back pain that involves pain radiating into the lower limbs.
- Vertebroplasty, facet joint injection or physiotherapy within past 12 weeks.

Recruitment

A member of the patient's direct care team will identify potential participants with VFFs via clinic lists and electronic medical records from relevant metabolic bone clinics, radiology clinics (DEXA), physiotherapy referral lists, and from Rheumatology clinics.

Screening and eligibility assessment

Potential participants, who respond to an invitation letter will be contacted by telephone to discuss the study further, to check eligibility and to answer any questions. Patients who do not meet the eligibility criteria or who do not wish to participate will receive standard NHS treatment. We will record the age and gender of these patients to assess the generalisability of those recruited.

Consent

Participants who are eligible and willing to proceed will be approached for informed consent.; they and the researcher will sign and date a consent form. For participants who are recruited to the additional nested qualitative study and interviewed on-line or via telephone, informed consent will

be obtained verbally before the interview. The researcher taking consent will read, and fill out, the consent form on behalf of the participant and then sign the form.

Randomisation

Consented participants will be randomised 1:1 using a computer-generated randomisation schedule prepared by the trial statistician (RK). Individual randomisation will be stratified by recruitment centre and permuted blocks of varying undisclosed sizes will be used. The randomisation schedule will be concealed in sequentially numbered, opaque, sealed envelopes for each site. A study administrator who has no interaction with blinded study staff will manage these envelopes. The administrator will open the randomisation envelope, and then communicate with the local site who will make the participant aware of their allocated group and refer for physiotherapy; making sure that participants are allocated to physiotherapists delivering the treatment for their allocated arm.

Blinding

Physiotherapists delivering the interventions and participants will be told the treatment allocation. Initial baseline assessment will occur prior to randomisation and the researcher undertaking assessments will not be involved in any part of the randomisation procedure to ensure that they are not able to bias the group allocation. The researcher conducting follow-up measures and the research team personnel entering data will also not be informed of allocated group and participants will be asked and reminded not to disclose their treatment group to the researcher at follow-up appointments.

Interventions

Training and monitoring

Sessions in both arms can be delivered in-person or virtually via video-call/ telephone as agreed between participant and therapist; to allow flexibility and resilience as COVID restrictions on physical attendance vary. Treatments were standardised and manualised and the study team provided training in the multi-component exercise therapy treatments (delivered to all participants) to all treating physiotherapists. Training in the behavioural adherence support intervention which comprised assessment and a set of 9 behavioural interventions (the Opt-In toolkit) was delivered separately to the therapists in the Opt-In arm. Treating physiotherapists will record the delivery and content of each treatment session in adherence logs for each participant. Regular site visits will be carried out to monitor intervention fidelity.

Standard Care

Participants will be offered a 1-hour physiotherapy assessment and six individual outpatient physiotherapy sessions spread over 16 weeks [2]. The physiotherapy will include a musculoskeletal assessment and treatment including a multi-component, progressed balance, posture, strength training and low impact weight-bearing exercise [3]. Exercise intensity will be assessed using the 10-point Rating of Perceived Exertion scale (CR10-RPE), so participants work a moderately hard to hard (RPE 4-6) intensity. Although current practice may vary, the package agreed as the standard care is based on consensus, best practice guidelines and successful delivery in the PROVE trial exercise arm [2] and aims to be a credible representation of current best practice treatment across the NHS. Treating therapists will receive prior training on prescription of the exercises [2].

Opt -In

Participants allocated to Opt-In will receive the standard package described above, plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent treatment period of 16 weeks in an individualised pattern as required by the participant.

Participants in the Opt-In arm will complete the Personalized Exercise Questionnaire (PEQ). The PEQ was developed in Canada to support patient-centred exercise prescription for people with osteoporosis and covers topics such as barriers to exercise and goals of treatment [16]. Treating physiotherapists will have a collaborative discussion with the participant using a motivational interviewing approach drawing upon PEQ responses and considering goals, motivators, facilitators, and barriers surrounding exercise. It aims to provide physiotherapists with a deeper understanding of patient motivations and circumstances, to strengthen the therapeutic alliance and the patient's own motivations for adopting exercise [12]. Using their assessment findings, the questionnaire and collaborative interview the physiotherapist will assess a participant's exercise capability (C), opportunity (O) and motivation (M) to carry out exercise behaviour and select an adherence technique from the Opt-In toolkit in response [14]. Techniques can include education about osteoporosis and exercises, education about and practice of fall prevention strategies, , Exercise Action Plans, , , a contact telephone call, and self-monitoring and feedback strategies such as, exercise confidence rating scales or using an exercise diary. Techniques are linked to COM-B domains to facilitate physiotherapist decision-making e.g., Education improves capability and motivation (C, M) and a diagrammatic decision aid was developed to facilitate rapid decision-making during treatment. Each Opt-In arm treating physiotherapist received a toolkit and training by the study team about techniques and how to use them. Physiotherapists were asked to prescribe at least 3 adherence techniques from the Opt-In toolkit over 16 weeks but could use more, the exact techniques selected were personalised to the patient as was the pattern and spread of the 60-minute adherence support time. Participants in the intervention arm were given a folder that included their exercises and selected adherence materials e.g., exercise diary, education leaflet, action plan record.

Concomitant care

Other aspects of health and social care will continue as usual. Analgesia and other medication use will be collected by self-report diary. Additional treatments sourced outside of the trial including contact with general practitioners and other health care professionals will be recorded in self-report health utilisation diaries in which participants will asked to record their use of health and social care across the study e.g., GP, nurse, other physio, hospital admissions, home carer visits in standardised study diaries. Diaries will be from 0-4, 4 to 8 and 8 to 12 months [17].

Outcome Measures

The primary outcome measure will be the Timed Up and Go (TUG) at 12 months. The TUG is a test of balance, lower limb strength and walking ability with established reliability and validity. It records the time a person takes to stand up from a chair, walk 3 metres at a self-selected speed, turn and walk back and sit down [18].

Secondary outcome measures are:

- QUALEFFO 41: a disease specific measure of health-related quality of life (QoL) applicable to patients with osteoporosis and vertebral fractures. It is a self-administered questionnaire that provides scores on five domains: pain, physical function, social function, general health perception, mental performance, and a total score. [19].

- Timed Loaded Standing (TLS): an assessment of shoulder and back muscle endurance for people with VFF(s). [20].

- Thoracic kyphosis angle: measured non-radiographically using a flexicurve ruler, allowing an angle of kyphosis to be calculated which is approximated to radiological measures of kyphosis (Cobb angle) using a standardised formula [21].

- Back pain: measured with a 10-point Numeric Pain Rating Scale (NPRS): [2].

- Functional Reach (FR) test: a measure of dynamic standing balance developed for older adults. T, the test has been used in people with VFF and performance is predictive of falls risk [22].

- Six-minute walk (6MW) test: a measure of functional walking capacity and aerobic cardio-respiratory fitness [23].

- Falls Efficacy Scale International (FES-I): a 16 item (3 minute) self-report measure of fear or concern about falling during activities. [24].

- Grip Strength: is the maximum force the hand and forearm muscles can generate measured with an isometric hand dynamometer in kilograms; maximum strength is the mean of three trials (3 seconds each) and measured for both hands [25].

- Self-efficacy for exercise (SEE) scale: a brief (<5 minute) 9-item scale that asks participants to rate how confident they would be that they would engage in exercise on a 10-point scale (not confident to very confident) under different situations e.g., if they were tired. SEE ratings are predictive of exercise behaviour [26].

- Adherence. This will be measured in two ways

a. Attendance records via clinician completed treatment logs, including a checkbox to log whether adherence techniques have been prescribed (intervention group only).

b. Exercise adherence rating scale (EARS): a brief 6-item scale that asks participants to describe how they do their recommended exercises on a 5-point scale [27].

- Falls: documented on the CRF and prospectively using participant completed event diaries. These will be collected in blocks from 0-4 months, 4 to 8 months, and 8 to 12 months during the study. Incidence and severity formation will be recorded e.g., nature of the fall, its outcome (no-harm, fracture etc) and any treatment required [2].

- EQ-5D-5L is a short, generic measure of health related QoL and will be completed to assist assessment of health economics [28].

- Global Rating Change (GRC) scale: a patient's perspective of change based on a 7-point ordinal scale (much worse, moderately worse, a little worse, no change, a little better, moderately better, much better) [29].

A summary of outcome measures and timepoints is shown in Table 1 **(Table 1)**.

Time Point	Measurement	Enrolment	allocation	Baseline	4 months	8 months	12 months
Screening Log		X					
Eligibility confirmed		x					
Informed Consent		x					
Randomisation			x				
Demographic	Age, gender, weight, ethnicity,			x			
Primary OM	Timed Up & Go			x	x	x	x
Quality of Life	Qualeffo 41			X	X	X	X
Fear Falling	FES-I			X	X	X	X
Back Pain Intensity	NRS-P			X	X	X	X
Back strength / endurance	TLS			X	X	X	X
Walking	6MWT			X	X	X	X
Balance	Functional Reach Test			X	X	X	X
Kyphosis	Flexicurve			X	X	X	X
Exercise Self Efficacy	SEE			X	X	X	X
Exercise adherence	EARS			X	X	X	X
Exercise adherence	Sessions attended				x	x	x

Table 1: Time Points at which outcomes will be assessed.

Adverse events

Foreseeable adverse events (AE) occurring because of the trial interventions will be recorded. Participants will receive information on potential AEs resulting from the exercises and what they should do if they experience an AE, as would be part of standard NHS procedure. Adverse symptoms in response to treatment and any adverse events will be monitored by clinicians regularly and in line

with local departmental procedures and captured on adverse event forms, and via questions on the CRF.

A Serious AE (SAE) is any untoward medical occurrence related to the trial interventions that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. SAEs are likely to be rare and are unlikely to occur as a result of the exercise programmes delivered in this study.

Any reports of SAE will be reported to the trial office within 24 hours of the local research team becoming aware of the event. They will be reviewed by an independent medically qualified assessor within 3 days.

Statistics and analysis

Sample Size

The primary outcome is the Timed Up & Go (TUG) test. This is the most widely used physical function measure in RCTs of exercise for people with VFF [4]. The minimal clinically important difference (MCID) for the TUG has not been established in people with VFF(s), but a MCID of 1.4s is reported for similar older populations with chronic musculoskeletal disorders [30]. The study requires 104 participants (52 per arm) to be 80% powered to detect a 1.4s difference in TUG score between groups at a 5% significance level (two-sided) assuming that the standard deviation is 2.5s. Similar trials have had loss to follow-up rates of 10% at 12 months [2]. To account for this the sample size has been inflated to 116 participants (58 per arm).

Statistical Analysis

The study will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement utilising the nonpharmacological and patient-reported outcome extensions [31,32]. Standard descriptive statistics will be used to describe the characteristics of the two groups at

baseline. Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) as appropriate will be used for continuous variables, and numbers and percentages will be used for binary and categorical variables.

Compliance with the intervention will be defined as participating in the extended interview and prescription of at least 3 adherence support techniques. This will be recorded on treatment logs. Details of the number of physiotherapy sessions attended will also be summarised by treatment group. The number and proportion of participants who withdraw will be summarised along with reasons for these. Deaths are not anticipated in this study, but details of any that do occur will also be summarised by treatment arm.

Summary statistics will be presented for all comparative outcomes, and effect estimates will be reported together with 95% confidence intervals with all tests carried out at a 5% two-sided significance level.

At 12 months post-randomisation the two treatment groups will be compared on the TUG measure using a multivariate linear regression model adjusting for recruiting centre (stratification factor), age and baseline TUG score. An unadjusted t-test will also be undertaken. The TUG is also recorded at 4, and 8 months after randomisation, and an additional analysis utilising all time points, using multi-level modelling and including a treatment by time interaction if appropriate will be undertaken. For each of these models, the assumption of approximate normality will be assessed by examining the residuals. If this assumption is not met the first approach will be to consider a transformation to achieve normality. If this is not possible, the two groups will be compared using non-parametric methods (e.g., Mann-Whitney U-test). This analysis will be unadjusted and will consider each time point separately.

Similar analyses will be performed for secondary outcomes which can be considered approximately continuous (QUALEFFO-41, FES-1, NPRS, TLS, Grip strength, 6MW, FRT, Thoracic kyphosis, SEE and

EARS) at 4-, 8- and 12-months post-randomisation. The appropriateness of the assumption of approximate normality will also be considered and transformation to normality or non-parametric methods used as appropriate. It is not anticipated that the number of falls will be approximately normal, therefore, this will be summarised by treatment group using medians and IQRs and compared using non-parametric methods. The number and proportion of participants experiencing an AE during follow-up will be summarised by treatment group and a logistic regression model adjusted for recruiting centre will be used to compare the rates in the two groups. Severity of AEs will also be summarised by treatment group.

In addition, since previous work suggests that change in thoracic kyphosis at follow-up is closely related to baseline values, a subgroup analysis of thoracic kyphosis at follow-up will be completed dependent on whether the participant was kyphotic at baseline [33].

All analyses will be performed for the intention to treat (ITT) population. This will include all randomised participants with available data who will be analysed according to their allocated intervention regardless of the treatment they received.

In addition, analysis of the primary outcome (TUG at 12 months) will be repeated for the per protocol (PP) population which will include only those participants who received their allocated treatment. Participants with other major protocol deviations (e.g., recruited and later found to be ineligible) will also be excluded from this population.

Health Economic Analysis

The relative efficiency of the intervention will be assessed by within-trial cost-utility and cost-consequences analyses [34]. The evaluation will take an NHS and personal social services

perspective. Resource use for the delivery of Opt-In and at participant level will be combined with unit cost from standard national sources to estimate average total costs. We will estimate the incremental cost per QALY (from EQ-5D-5L) and present the different cost components and multiple benefits of Opt-In in a 'balance sheet' in the cost-consequences analysis.

Embedded Qualitative study

As part of the main study a nested qualitative study will take place. The qualitative element of this study will involve a subset (12-15) of patients who undertake the Opt-In intervention who will be invited to take part in 4 short (15-20 minute) interviews about their experiences and views about exercise adherence and the adherence intervention at the following time points: i) following assessment ii) during treatment (after 3 sessions), iii) post-treatment (after 4 months), and iv) at 12 months. The interviews may occur online via video-call or face-to-face in the person's home or at a local clinic, depending on participant preference. The interviews will be audio recorded and transcribed verbatim. Participants will be given an opportunity to check the interview transcript.

Focus groups will be conducted with physiotherapists who undertake the Opt-In intervention, asking them to share their views about promoting exercise adherence and the Opt-In intervention, these will be audio-recorded with a Dictaphone.

Purposive sampling will be used to achieve a sample which includes female and male patients, patients of varying activity levels and patients of different ages and disease severity (pain/ number of fractures). These factors may influence the ability to engage with an exercise programme. Since most research regarding adherence in osteoporosis has previously been undertaken with women, it also considered important to capture the views of male patients within the current study and to capture the experiences of people with differing physical activity levels prior to the programme. The quality of a qualitative study is not dependent on its sample size; however, the sample size needs to be sufficiently large to enable relevant data to be obtained, without being so overly large that

detailed analysis is subsequently prevented [35]. Information about physiotherapists views of delivering the adherence interventions will also be sought. All those who deliver the adherence techniques will be invited to participate in a focus group.

Audio recordings will be listened to, and transcripts read until they become familiar. Data from the interviews with physiotherapists and participants will be analysed separately to understand the perspectives of each group. We will use collaborative methods to ensure a strong voice from PPI members and research rigour. We will use thematic analysis, using the six steps proposed by Braun and Clarke [36].

Patient and Public Involvement

The study funding application, intervention development and study materials preparation were supported by our patient and public involvement members who will be involved across the course of the study.

ETHICS AND DISEMMINATION.

The study protocol was approved by West of Scotland Research Ethics Committee 4 (Reference 21/WS/0071). The University of Oxford is the sponsor. The trial is registered with the International Standard Randomised Controlled Trials database ISRCTN reference number 14465704.

The protocol has been reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [37]. Results will be published reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines [38]. The Template for Intervention Description and Replication (TIDieR) statement will be used to report the intervention ensuring replication is possible [39]. Results will be published in a peer reviewed journal with authorship eligibility according to International Committee of Medical Journal Editors (ICJME) criteria. Participants will be asked if they wish to have the results shared with them prior to publication and we will share with those who request this.

TRIAL STATUS

The first patient was randomised to the trial on 1st September 2021. Recruitment is ongoing.

Contributions of Authors:

Karen L Barker: Chief Investigator, Conceived and designed the study, was awarded the funding and had overall responsibility for the study design and delivery and drafted the manuscript. She is the guarantor.

Jonathan Room: contributed to study design and provided specific content and edited manuscript. Qualitative lead.

Erin Hannink: contributed to study design and provided specific content and edited manuscript

Ruth Knight (statistical co-applicant) performed the sample size calculation, prepared randomisation schedules, planned statistical analysis methods

Meredith Newman (Trial Manager), trial design, intervention development, manualisation, training, supervision, writing and reviewing report.

Funding

The study is supported by an independent grant from the Chartered Society of Physiotherapy Charitable Trust (RP/19/01).

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, other than funding arrangements for the trial described in body of the text; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency

The lead author (KLB) affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

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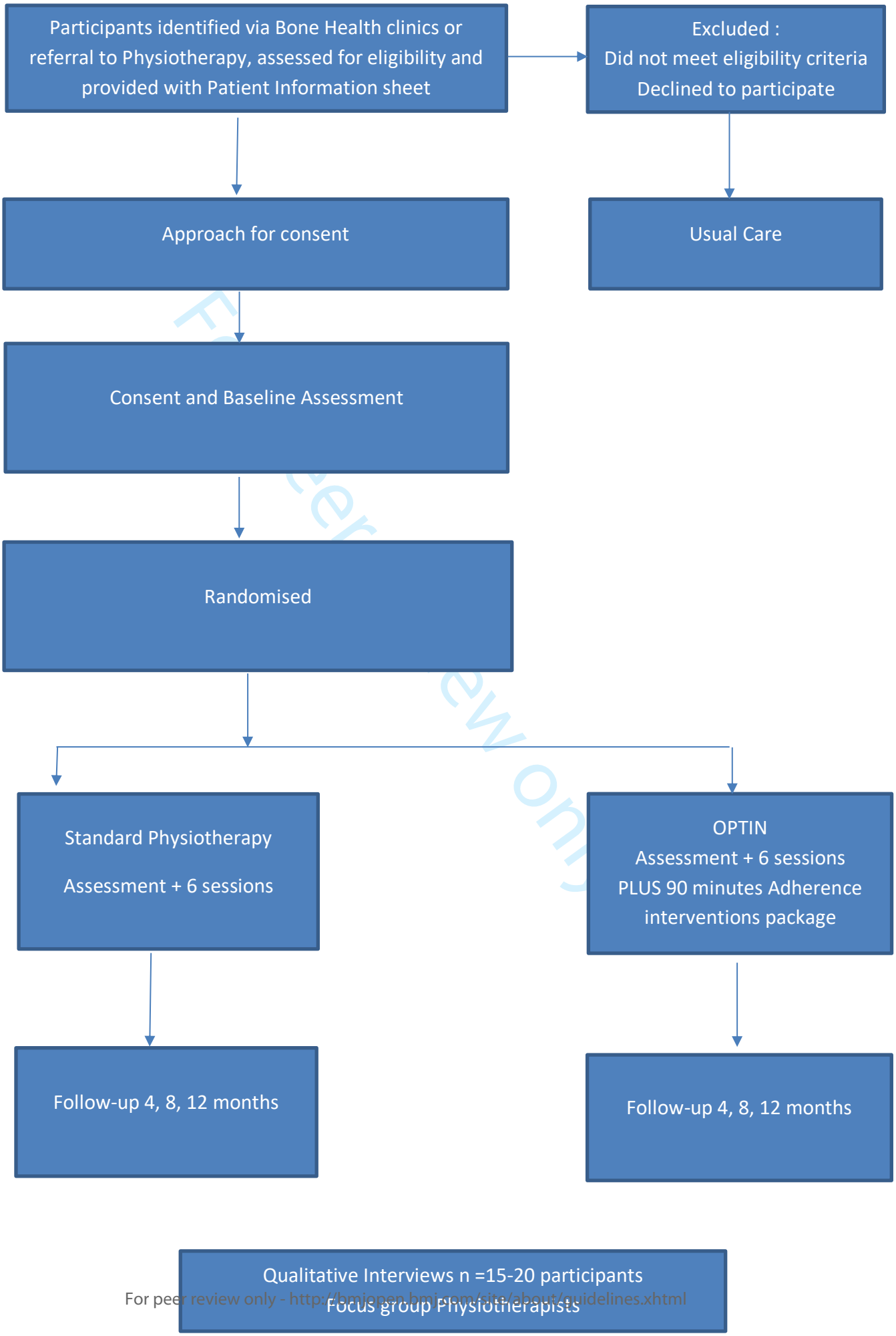

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Title Page Lines 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 3 Line 21
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Page 3 Line 22
Funding	4	Sources and types of financial, material, and other support Page 23 lines 9/10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Title page and Page 22/23
	5b	Name and contact information for the trial sponsor Page 19 Line 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention P5-6
	6b	Explanation for choice of comparators P6
Objectives	7	Specific objectives or hypotheses P6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) P6 L22-3
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained P7 L10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) p10/11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial p12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended p12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations P15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P8
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions P9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assignedp9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial n/a
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocolp10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol P15-6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) P15-17

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct P14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approvalP22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) P 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation n/a

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions P19
	31b	Authorship eligibility guidelines and any intended use of professional writers P19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures: Protocol for a randomised controlled trial – the Osteoporosis Tailored exercise adherence intervention (OPTIN) study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064637.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Aug-2022
Complete List of Authors:	Barker, Karen L.; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Room, Jonathan; Oxford University Hospitals NHS Foundation Trust, Physiotherapy Research Unit Knight, Ruth; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Hannink , Erin ; Oxford University Hospitals NHS Foundation Trust, Physiotherapy Research Unit Newman, Meredith; Oxford University Hospitals NHS Foundation Trust, Physiotherapy Research Unit
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, REHABILITATION MEDICINE

Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures: Protocol for a randomised controlled trial – the Osteoporosis Tailored exercise adherence intervention (OPTIN) study.

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Keywords: Physical therapy modalities; exercise, osteoporosis, spine, rehabilitation

1 Word count 4011.

ABSTRACT

Introduction: Vertebral fragility fractures affect at least 20% of the older population in the UK. Best practice guidelines recommend the use of exercise to slow the rate of bone loss, to maintain muscle strength and physical function, and to prevent falls and further fractures. However, treatment effects are often small and difficult to sustain and adherence, or the extent to which patients engage in treatment, has been identified as an important issue by many studies. Our hypothesis is that integrating adherence intervention strategies with an exercise intervention will be beneficial. We will compare physiotherapy exercise rehabilitation with adherence support versus physiotherapy exercise rehabilitation alone in terms of effects on (a) physical function, quality of life, and fear of falling and (b) exercise self-efficacy and adherence.

Methods and Analysis: A multicentre, two-arm, parallel group, superiority randomised controlled trial (RCT) with blinded assessments at baseline (0) and 4, 8, and 12 months, with a nested qualitative study and health economic analysis. 116 participants will be allocated to either (i) out-patient physiotherapy which will include a musculoskeletal assessment and treatment including balance, posture, strength training and low impact weight-bearing exercises over 16 weeks; or (ii) Opt-In intervention. This includes standard physiotherapy as above plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent 16 weeks.

Ethics and Dissemination: The study protocol was approved by West of Scotland Research Ethics Committee 4 (21/WS/0071). Trial registration number ISRCTN 14465704. The paper is based on Protocol v4.

Strengths and Limitations of this study

- The Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures (Opt-In) study is a multicentre randomised controlled trial with an embedded qualitative study and economic evaluation.
- It will recruit from at least six NHS hospitals.
- The intervention addresses adherence which is an important confounder in many trials of physiotherapy.
- The intervention was developed using current research evidence, input from expert clinicians, researchers and patient / public representatives.
- Due to the nature of the interventions the physiotherapists delivering the treatments and the participants cannot be blinded.

Introduction

Vertebral fragility fractures (VFFs) affect at least 20% of the older population in the UK and present a significant health and economic burden [1, 2]. They are associated with back pain, fatigue, low mood, restrictions in physical function and activities of daily living, and marked, persistent reductions in quality of life (QoL) [1, 2]. Without treatment, progression and functional decline are expected. Conservative treatment for osteoporosis includes bone protective medications and lifestyle adaptations. Guidelines recommend people with osteoporosis keep active and exercise to slow the rate of bone loss, to maintain muscle strength and physical function and to prevent falls and further fractures [3,4]. Exercise prescription with multi-component exercise programmes that include postural, balance, aerobic weight-bearing and strength exercises are recommended [1-3].

Trials evaluating exercise in people with VFFs have reported benefits across a range of outcomes [1, 2, 5-10], with a recent Cochrane review concluding there is moderate-quality evidence that exercise improves physical function [1]. However, treatment effects are often small and difficult to sustain [1, 2, 5-10]. For example, in the PROVE trial, significant, clinically relevant benefits to back muscle endurance, balance, walking capacity and physical function following physiotherapy exercise at 4 months post-randomisation did not persist at 12 months [2]. Adherence, or the extent to which patients engage in treatment, has been identified as an important issue by many studies [1, 2, 5-6, 9]. Partial adherence or non-adherence is associated with worse outcomes and conversely, higher adherence with better outcomes [1, 2, 5-10].

Multiple factors affect exercise adherence in older people with chronic health conditions including osteoporosis [11, 12]. These include low exercise self-efficacy, low motivation, depression, insufficient exercise knowledge or skill, physical ability, negative views about treatment and exercise programme design [11,12]. Considering this complexity, interventions to support adherence that recognize personal barriers and facilitators to exercise and that can draw upon multiple adherence techniques are recommended [12, 13].

Behavioural approaches can include interventions that support exercise through providing additional monitoring, interventions that aim to alter thinking patterns that contribute to non-adherence and ones that strengthen behaviours that support adherence [12]. Motivational interviewing is a collaborative process that explores potential ambivalence, obstacles and facilitators surrounding behaviour change [6]. There is evidence that additional monitoring, prompts and feedback can benefit adherence in older adults e.g., via telephone call/ text messages, wearable activity monitors or by enriching environmental cues [1]. Incorporating exercise into everyday routines can make it easier to initiate and sustain and creating 'Exercise Action Plans' that specify when, where and how exercises are undertaken can support this process [1, 13]. Using an intervention mapping approach, we developed an exercise adherence intervention underpinned theoretically by the Capability, Opportunity, Motivation - Behaviour (COM-B) behaviour change model [14, 15].

Aims

The aims of this study are:

- To compare physiotherapy exercise rehabilitation with adherence support with physiotherapy exercise rehabilitation alone in terms of effects on: (a) physical function, quality of life, and fear of falling and (b) exercise self-efficacy and adherence.
- To explore patient and physiotherapist views of the intervention and of adhering to exercise.
- To understand if physiotherapy exercise rehabilitation with adherence support is cost-effective.

METHODS AND ANALYSES

Study design

A multicentre, two-arm, parallel group, superiority randomised controlled trial (RCT) with blinded assessments at baseline (0) and 4, 8, and 12 months following randomisation, with a nested qualitative study and health economic analysis. Participants will be allocated to either (i) outpatient

physiotherapy which will include a musculoskeletal assessment and 6 treatment sessions over 16 weeks based on the current best practice guidance from the Royal Osteoporosis Society; or (ii) the Opt-In intervention. This includes outpatient physiotherapy as described above, plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent treatment period of 16 weeks as prescribed by the physiotherapist in collaboration with the participant. Sessions in both arms can be in-person or virtually via video-call/ telephone as agreed between participant and therapist **(Figure 1)**.

The trial started recruitment of patients in August 2021 and will continue recruiting until June 2023.

Setting

At least six National Health Service (NHS) hospitals and their related physiotherapy services.

Study Participants

Adults aged 55 years or over who have a diagnosis of at least one previous osteoporotic vertebral fracture and back pain.

Eligibility

Inclusion Criteria

Participants may enter the study if they meet ALL the following criteria:

- Men and women ≥ 55 years: all women must be at least 1 year post-menopausal.
- One or more VFFs confirmed by radiography, X-Ray, MRI, CT or DEXA scan, people with VFF of any severity and at any time-point post-fracture are eligible.
- They must have had an episode of back pain in the previous 12 months.
- All must be able to walk at least 10 metres independently with or without a walking aid.

Exclusion Criteria

Participants may not enter the study if ANY of the following apply:

- Current conditions that would make participating in physiotherapy or exercise unsafe or confound results. This includes those with significant neurological and psychiatric conditions, severe unstable cardiovascular or pulmonary disease.
- Bone loss secondary to other metabolic disorders, diseases or medication e.g., rheumatoid arthritis, anorexia, cancer, coeliac disease, steroid use.
- Individuals whose primary problem is back pain that involves pain radiating into the lower limbs.
- Vertebroplasty, facet joint injection or physiotherapy within past 12 weeks.

Recruitment

A member of the patient's direct care team will identify potential participants with VFFs via clinic lists and electronic medical records from relevant metabolic bone clinics, radiology clinics (DEXA), physiotherapy referral lists, and from Rheumatology clinics.

Screening and eligibility assessment

Potential participants, who respond to an invitation letter will be contacted by telephone to discuss the study further, to check eligibility and to answer any questions. Patients who do not meet the eligibility criteria or who do not wish to participate will receive standard NHS treatment. We will record the age and gender of these patients to assess the generalisability of those recruited.

Consent

Participants who are eligible and willing to proceed will be approached for informed consent.; they and the researcher will sign and date a consent form. For participants who are recruited to the

additional nested qualitative study and interviewed on-line or via telephone, informed consent will be obtained verbally before the interview. The researcher taking consent will read, and fill out, the consent form on behalf of the participant and then sign the form.

Randomisation

Consented participants will be randomised 1:1 using a computer-generated randomisation schedule prepared by the trial statistician (RK). Individual randomisation will be stratified by recruitment centre and permuted blocks of varying undisclosed sizes will be used. The randomisation schedule will be concealed in sequentially numbered, opaque, sealed envelopes for each site. A study administrator who has no interaction with blinded study staff will manage these envelopes. The administrator will open the randomisation envelope, and then communicate with the local site who will make the participant aware of their allocated group and refer for physiotherapy; making sure that participants are allocated to physiotherapists delivering the treatment for their allocated arm.

Blinding

Physiotherapists delivering the interventions and participants will be told the treatment allocation. Initial baseline assessment will occur prior to randomisation and the researcher undertaking assessments will not be involved in any part of the randomisation procedure to ensure that they are not able to bias the group allocation. The researcher conducting follow-up measures and the research team personnel entering data will also not be informed of allocated group and participants will be asked and reminded not to disclose their treatment group to the researcher at follow-up appointments.

Interventions

Training and monitoring

Sessions in both arms can be delivered in-person or virtually via video-call/ telephone as agreed between participant and therapist; to allow flexibility and resilience as COVID restrictions on physical attendance vary. Treatments were standardised and manualised and the study team provided training in the multi-component exercise therapy treatments (delivered to all participants) to all treating physiotherapists. Training in the behavioural adherence support intervention which comprised assessment and a set of 9 behavioural interventions (the Opt-In toolkit) was delivered separately to the therapists in the Opt-In arm. Treating physiotherapists will record the delivery and content of each treatment session in adherence logs for each participant. Regular site visits will be carried out to monitor intervention fidelity.

Standard Care

Participants will be offered a 1-hour physiotherapy assessment and six individual outpatient physiotherapy sessions spread over 16 weeks [2]. The physiotherapy will include a musculoskeletal assessment and treatment including a multi-component, progressed balance, posture, strength training and low impact weight-bearing exercise [3]. Exercise intensity will be assessed using the 10-point Rating of Perceived Exertion scale (CR10-RPE), so participants work at a moderately hard to hard (RPE 4-6) intensity. Although current practice may vary, the package agreed as the standard care is based on consensus, best practice guidelines and successful delivery in the PROVE trial exercise arm [2] and aims to be a credible representation of current best practice treatment across the NHS. Treating therapists will receive prior training on prescription of the exercises [2].

Opt -In

Participants allocated to Opt-In will receive the standard package described above, plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent treatment period of 16 weeks in an individualised pattern as required by the participant.

Participants in the Opt-In arm will complete the Personalized Exercise Questionnaire (PEQ). The PEQ was developed in Canada to support patient-centred exercise prescription for people with osteoporosis and covers topics such as barriers to exercise and goals of treatment [16]. Treating physiotherapists will have a collaborative discussion with the participant using a motivational interviewing approach drawing upon PEQ responses and considering goals, motivators, facilitators, and barriers surrounding exercise. It aims to provide physiotherapists with a deeper understanding of patient motivations and circumstances, to strengthen the therapeutic alliance and the patient's own motivations for adopting exercise [12]. Using their assessment findings, the questionnaire and collaborative interview the physiotherapist will assess a participant's exercise capability (C), opportunity (O) and motivation (M) to carry out exercise behaviour (B) (COM-B) and select an adherence technique from the Opt-In toolkit in response [14]. Techniques can include education about osteoporosis and exercises, education about and practice of fall prevention strategies, Exercise Action Plans, a contact telephone call, and self-monitoring and feedback strategies such as, exercise confidence rating scales or using an exercise diary. Techniques are linked to COM-B domains to facilitate physiotherapist decision-making e.g., Education improves capability and motivation (C, M) and a diagrammatic decision aid was developed to facilitate rapid decision-making during treatment. Each Opt-In arm treating physiotherapist received a toolkit and training by the study team about techniques and how to use them. Physiotherapists were asked to prescribe at least 3 adherence techniques from the Opt-In toolkit over 16 weeks but could use more. The exact techniques selected were personalised to the patient as was the pattern and spread of the 60-minute adherence support time. Participants in the intervention arm were given a folder that included their exercises and selected adherence materials e.g., exercise diary, education leaflet, action plan record. Figure 2 summarises the intervention in a logic model.

Concomitant care

Other aspects of health and social care will continue as usual. Analgesia and other medication use will be collected by self-report diary. Additional treatments sourced outside of the trial including contact with general practitioners and other health care professionals will be recorded in self-report health utilisation diaries in which participants will asked to record their use of health and social care services across the study e.g., GP, nurse, other physio, hospital admissions, home carer visits in standardised study diaries. Diaries will be from 0-4, 4 to 8 and 8 to 12 months [17].

Outcome Measures

The primary outcome measure will be the Timed Up and Go (TUG) at 12 months. The TUG is a test of balance, lower limb strength and walking ability with established reliability and validity. It records the time a person takes to stand up from a chair, walk 3 metres at a self-selected speed, turn, walk back and sit down [18].

Secondary outcome measures are:

- QUALEFFO 41: a disease specific measure of health-related quality of life (QoL) applicable to patients with osteoporosis and vertebral fractures. It is a self-administered questionnaire that provides scores on five domains: pain, physical function, social function, general health perception, mental performance, and a total score. [19].

- Timed Loaded Standing (TLS): an assessment of shoulder and back muscle endurance for people with VFF(s). [20].

- Thoracic kyphosis angle: measured non-radiographically using a flexicurve ruler, allowing an angle of kyphosis to be calculated which is approximated to radiological measures of kyphosis (Cobb angle) using a standardised formula [21].

- Back pain: measured with a 10-point Numeric Pain Rating Scale (NPRS) [22].

- Functional Reach (FR) test: a measure of dynamic standing balance developed for older adults. T, the test has been used in people with VFF and performance is predictive of falls risk [23].

- Six-minute walk (6MW) test: a measure of functional walking capacity and aerobic cardio-respiratory fitness [24].

- Falls Efficacy Scale International (FES-I): a 16 item (3 minute) self-report measure of fear or concern about falling during activities [25].

- Grip Strength: is the maximum force the hand and forearm muscles can generate measured with an isometric hand dynamometer in kilograms; maximum strength is the mean of three trials (3 seconds each) and measured for both hands [26].

- Self-efficacy for exercise (SEE) scale: a brief (<5 minute) 9-item scale that asks participants to rate how confident they would be that they would engage in exercise on a 10-point scale (not confident to very confident) under different situations e.g., if they were tired. SEE ratings are predictive of exercise behaviour [27].

- Adherence. This will be measured in two ways:

a. Attendance records via clinician completed treatment logs, including a checkbox to log whether adherence techniques have been prescribed (intervention group only).

b. Exercise adherence rating scale (EARS): a brief 6-item scale that asks participants to describe how they do their recommended exercises on a 5-point scale [28].

- Falls: documented on the CRF and prospectively using participant completed event diaries. These will be collected in blocks from 0-4 months, 4 to 8 months, and 8 to 12 months during the study. Incidence and severity formation will be recorded e.g., nature of the fall, its outcome (no-harm, fracture etc) and any treatment required [2].

- EQ-5D-5L is a short, generic measure of health related QoL and will be completed to assist assessment of health economics [29].

A summary of outcome measures and timepoints is shown in Table 1 **(Table 1)**.

Time Point	Measurement	Enrolment	allocation	Baseline	4 months	8 months	12 months
Screening Log		X					
Eligibility confirmed		x					
Informed Consent		x					
Randomisation			x				
Demographic	Age, gender, weight, ethnicity,			x			
Primary OM	Timed Up & Go			x	x	x	x
Quality of Life	QUALEFFO 41			X	X	X	X
Fear Falling	FES-I			X	X	X	X
Back Pain Intensity	NRS-P			X	X	X	X
Back strength / endurance	TLS			X	X	X	X
Walking	6MWT			X	X	X	X
Balance	Functional Reach Test			X	X	X	X
Kyphosis	Flexicurve			X	X	X	X
Grip Strength	Dynamometer			x	x	x	x
EQ-5D-5L	Health economics			x	x	x	x
Falls	Number of reported falls. Nature; outcome of falls.				x	x	x
Exercise Self Efficacy	SEE			X	X	X	X
Exercise adherence	EARS			X	X	X	X
Exercise adherence	Sessions attended				x	x	x

Table 1: Time Points at which outcomes will be assessed.

Adverse events

Adverse events (AE) occurring because of the trial interventions will be recorded. Participants will receive information on potential AEs resulting from the exercises and what they should do if they

experience an AE, as would be part of standard NHS procedure. Adverse symptoms in response to treatment and any adverse events will be monitored by clinicians regularly and in line with local departmental procedures and captured on adverse event forms, and via questions on the CRF.

A Serious AE (SAE) is any untoward medical occurrence related to the trial interventions that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. SAEs are likely to be rare and are unlikely to occur as a result of the exercise programmes delivered in this study.

Any reports of SAE will be reported to the trial office within 24 hours of the local research team becoming aware of the event. They will be reviewed by an independent medically qualified assessor within 3 days.

Statistics and analysis

Sample Size

The primary outcome is the Timed Up & Go (TUG) test. This is the most widely used physical function measure in RCTs of exercise for people with VFF [4]. The minimal clinically important difference (MCID) for the TUG has not been established in people with VFF(s), but a MCID of 1.4s is reported for similar older populations with chronic musculoskeletal disorders [30]. The study requires 104 participants (52 per arm) to be 80% powered to detect a 1.4s difference in TUG score between groups at a 5% significance level (two-sided) assuming that the standard deviation is 2.5s. Similar trials have had loss to follow-up rates of 10% at 12 months [2]. To account for this the sample size has been inflated to 116 participants (58 per arm).

Statistical Analysis

The study will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement utilising the nonpharmacological and patient-reported outcome extensions [31,32].

Standard descriptive statistics will be used to describe the characteristics of the two groups at baseline. Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) as appropriate will be used for continuous variables, and numbers and percentages will be used for binary and categorical variables.

Compliance with the intervention will be defined as participating in the extended interview and prescription of at least 3 adherence support techniques. This will be recorded on treatment logs. Details of the number of physiotherapy sessions attended will also be summarised by treatment group. The number and proportion of participants who withdraw will be summarised along with reasons for these. Deaths are not anticipated in this study, but details of any that do occur will also be summarised by treatment arm.

Summary statistics will be presented for all comparative outcomes, and effect estimates will be reported together with 95% confidence intervals with all tests carried out at a 5% two-sided significance level.

At 12 months post-randomisation the two treatment groups will be compared on the TUG measure using a multivariate linear regression model adjusting for recruiting centre (stratification factor), age and baseline TUG score. An unadjusted t-test will also be undertaken. The TUG is also recorded at 4, and 8 months after randomisation, and an additional analysis utilising all time points, using multi-level modelling and including a treatment by time interaction if appropriate will be undertaken. For each of these models, the assumption of approximate normality will be assessed by examining the residuals. If this assumption is not met the first approach will be to consider a transformation to achieve normality. If this is not possible, the two groups will be compared using non-parametric methods (e.g., Mann-Whitney U-test). This analysis will be unadjusted and will consider each time point separately.

Similar analyses will be performed for secondary outcomes which can be considered approximately continuous (QUALEFFO-41, FES-1, NPRS, TLS, Grip strength, 6MW, FRT, Thoracic kyphosis, SEE and EARS) at 4-, 8- and 12-months post-randomisation. The appropriateness of the assumption of approximate normality will also be considered and transformation to normality or non-parametric methods used as appropriate. It is not anticipated that the number of falls will be approximately normal, therefore, this will be summarised by treatment group using medians and IQRs and compared using non-parametric methods. The number and proportion of participants experiencing an AE during follow-up will be summarised by treatment group and a logistic regression model adjusted for recruiting centre will be used to compare the rates in the two groups. Severity of AEs will also be summarised by treatment group.

In addition, since previous work suggests that change in thoracic kyphosis at follow-up is closely related to baseline values, a subgroup analysis of thoracic kyphosis at follow-up will be completed dependent on whether the participant was kyphotic at baseline [33].

All analyses will be performed for the intention to treat (ITT) population. This will include all randomised participants with available data who will be analysed according to their allocated intervention regardless of the treatment they received.

In addition, analysis of the primary outcome (TUG at 12 months) will be repeated for the per protocol (PP) population which will include only those participants who received their allocated treatment. Participants with other major protocol deviations (e.g., recruited and later found to be ineligible) will also be excluded from this population.

Health Economic Analysis

The relative efficiency of the intervention will be assessed by within-trial cost-utility and cost-consequences analyses [34]. The evaluation will take an NHS and personal social services perspective. Resource use for the delivery of Opt-In and at participant level will be combined with

unit cost from standard national sources to estimate average total costs. We will estimate the incremental cost per quality-adjusted life year (QALY) (from EQ-5D-5L) and present the different cost components and multiple benefits of Opt-In in a 'balance sheet' in the cost-consequences analysis.

Embedded Qualitative study

As part of the main study a nested qualitative study will take place. The qualitative element of this study will involve a subset (12-15) of patients who undertake the Opt-In intervention who will be invited to take part in 4 short (15-20 minute) interviews about their experiences and views about exercise adherence and the adherence intervention at the following time points: i) following assessment ii) during treatment (after 3 sessions), iii) post-treatment (after 4 months), and iv) at 12 months. The interviews may occur online via video-call or face-to-face in the person's home or at a local clinic, depending on participant preference. The interviews will be audio recorded and transcribed verbatim. Participants will be given an opportunity to check the interview transcript.

Focus groups will be conducted with physiotherapists who undertake the Opt-In intervention, asking them to share their views about promoting exercise adherence and the Opt-In intervention, these will be audio-recorded with a Dictaphone.

Purposive sampling will be used to achieve a sample which includes men and women, patients of varying activity levels and patients of different ages and disease severity (pain/ number of fractures). These factors may influence the ability to engage with an exercise programme. Since most research regarding adherence in osteoporosis has previously been undertaken with women, it also considered important to capture the views of men within the current study and to capture the experiences of people with differing physical activity levels prior to the programme. The quality of a qualitative study is not dependent on its sample size; however, the sample size needs to be sufficiently large to enable relevant data to be obtained, without being so overly large that detailed analysis is subsequently prevented [35]. Information about physiotherapists views of delivering the

adherence interventions will also be sought. All those who deliver the adherence techniques will be invited to participate in a focus group.

Audio recordings will be listened to, and transcripts read until they become familiar. Data from the interviews with physiotherapists and participants will be analysed separately to understand the perspectives of each group. We will use collaborative methods to ensure a strong voice from PPI members and research rigour. We will use thematic analysis, using the six steps proposed by Braun and Clarke [36].

Patient and Public Involvement

The study funding application, intervention development and study materials preparation were supported by our patient and public involvement members who will be involved across the course of the study.

ETHICS AND DISEMMINATION.

The study protocol was approved by West of Scotland Research Ethics Committee 4 (Reference 21/WS/0071). The University of Oxford is the sponsor. The trial is registered with the International Standard Randomised Controlled Trials database ISRCTN reference number 14465704.

The protocol has been reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [37]. Results will be published reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines [38]. The Template for Intervention Description and Replication (TIDieR) statement will be used to report the intervention ensuring replication is possible [39]. Results will be published in a peer reviewed journal with authorship eligibility according to International Committee of Medical Journal Editors (ICJME) criteria. Participants will be asked if they wish to have the results shared with them prior to publication and we will share with those who request this. We plan to publish results in an

international peer-reviewed journal and at international rehabilitation and bone health focussed conferences.

Contributions of Authors:

Karen L Barker: Chief Investigator, Conceived and designed the study, was awarded the funding and had overall responsibility for the study design and delivery and drafted the manuscript. She is the guarantor.

Jonathan Room: contributed to study design and provided specific content and edited manuscript. Qualitative lead.

Erin Hannink: contributed to study design and provided specific content and edited manuscript

Ruth Knight (statistical co-applicant) performed the sample size calculation, prepared randomisation schedules, planned statistical analysis methods

Meredith Newman (Trial Manager), trial design, intervention development, manualisation, training, supervision, writing and reviewing report.

Funding

The study is supported by an independent grant from the Chartered Society of Physiotherapy Charitable Trust (RP/19/01).

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, other than funding arrangements for the trial described in body of the text; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency

The lead author (KLB) affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

Figure Legends

Figure 1: Study Flow Diagram

Figure 2: Logic Model for intervention

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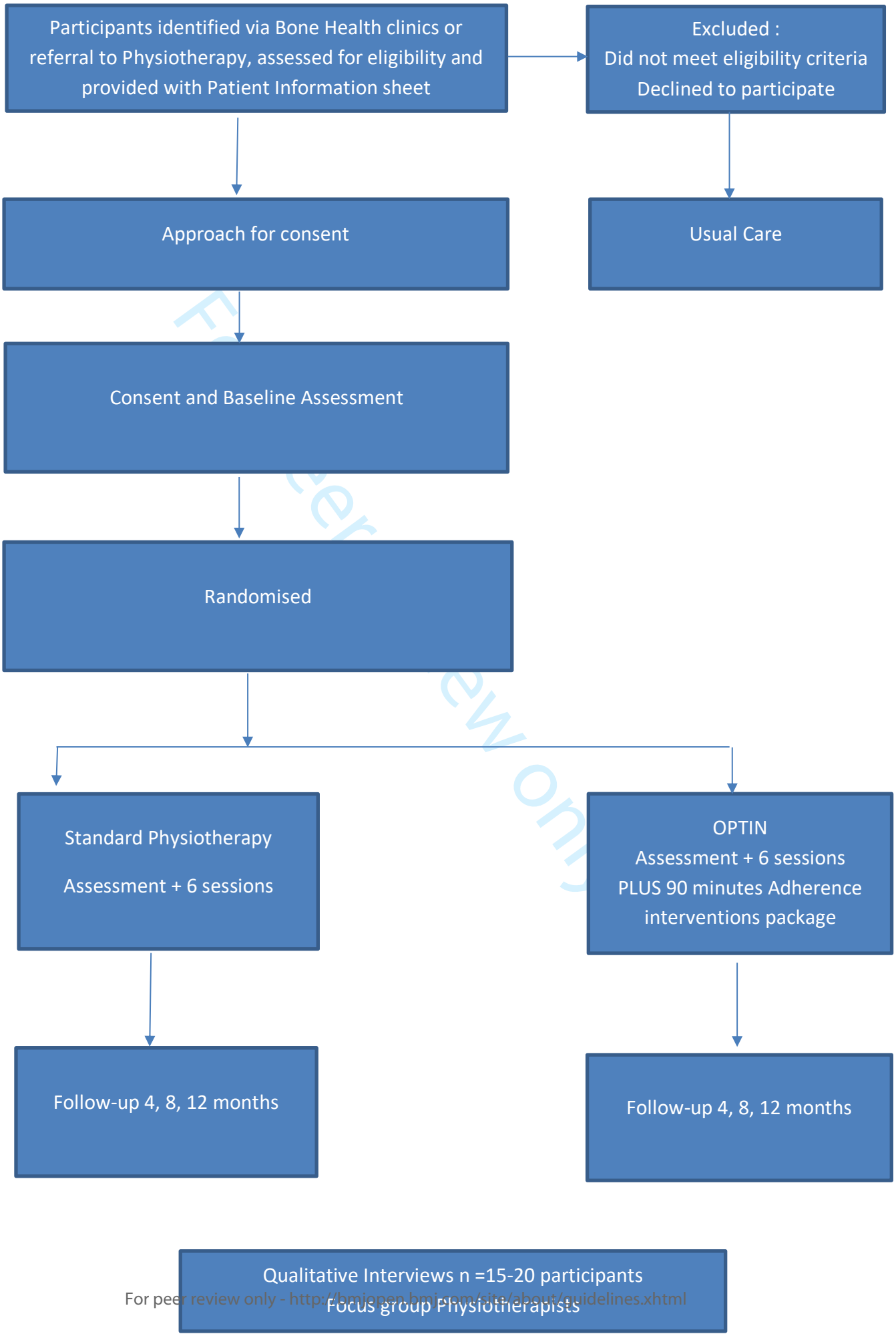

Situation: Multiple factors affect exercise adherence in older people with chronic health conditions including osteoporosis. Limited adherence diminishes the potential benefits of exercise rehabilitation

Inputs

Physiotherapist Training
- Osteoporotic vertebral fractures and exercise
- Theoretical models
- Adherence approaches

OPTIN Intervention
Assessment (90min):
- Physical status
- Capability, Opportunities/ Barriers, Motivators for Ex

Treatment
- 6 x 30min sessions &
- 6 x 10min adherence support points

Toolkit of teaching and support materials

Mechanisms of Effect

Theoretically and evidence-based interventions
Tailored to individual via assessment
Co-produced, reviewed and progressed

Holistic, integrated exercise + adherence programme

Exercise	Strength training Postural Ex	Balance training	Aerobic Weight-bearing Ex
Adherence	Educational approaches	Behavioural approaches	

Short-term Outcomes

Enhanced capability, opportunity and motivation to increase behaviour:
- Exercise adherence
- Exercise dose
- Exercise self-efficacy

Medium to Long-term Outcomes

Individual	Improvements in:	
	Functions/Structure: • Muscle endurance • Spinal posture • Standing Balance • Pain • Fear-of-falling	Activities/Participation Physical function Walking capacity Quality of Life
	No excess adverse events: falls, fractures etc	
Group	Increased efficiency: in terms of cost components and cost-benefits from an NHS and personal social services perspective	

Impacts

Improved health for people with OVF

Decreased societal health and care costs
Efficient physiotherapy

Generalisable to other chronic conditions

Evidence for guidelines and teaching

OPTIN Logic Diagram

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Title Page Lines 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 3 Line 21
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Page 3 Line 22
Funding	4	Sources and types of financial, material, and other support Page 23 lines 9/10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Title page and Page 22/23
	5b	Name and contact information for the trial sponsor Page 19 Line 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention P5-6
	6b	Explanation for choice of comparators P6
Objectives	7	Specific objectives or hypotheses P6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) P6 L22-3

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained P7 L10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) p10/11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial p12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended p12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations P15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P8

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions P9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assignedp9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial n/a
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocolp10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol P15-6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) P15-17

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct P14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approvalP22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) P 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation n/a

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions P19
	31b	Authorship eligibility guidelines and any intended use of professional writers P19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures: Protocol for a randomised controlled trial – the Osteoporosis Tailored exercise adherence intervention (OPTIN) study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-064637.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Aug-2022
Complete List of Authors:	Barker, Karen L.; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Room, Jonathan; Oxford University Hospitals NHS Foundation Trust, Physiotherapy Research Unit Knight, Ruth; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Hannink , Erin ; Oxford University Hospitals NHS Foundation Trust, Physiotherapy Research Unit Newman, Meredith; Oxford University Hospitals NHS Foundation Trust, Physiotherapy Research Unit
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, REHABILITATION MEDICINE

Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures: Protocol for a randomised controlled trial – the Osteoporosis Tailored exercise adherence intervention (OPTIN) study.

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Keywords: Physical therapy modalities; exercise, osteoporosis, spine, rehabilitation

1 Word count 4011.

ABSTRACT

Introduction: Vertebral fragility fractures affect at least 20% of the older population in the UK. Best practice guidelines recommend the use of exercise to slow the rate of bone loss, to maintain muscle strength and physical function, and to prevent falls and further fractures. However, treatment effects are often small and difficult to sustain and adherence, or the extent to which patients engage in treatment, has been identified as an important issue by many studies. Our hypothesis is that integrating adherence intervention strategies with an exercise intervention will be beneficial. We will compare physiotherapy exercise rehabilitation with adherence support versus physiotherapy exercise rehabilitation alone in terms of effects on (a) physical function, quality of life, and fear of falling and (b) exercise self-efficacy and adherence.

Methods and Analysis: A multicentre, two-arm, parallel group, superiority randomised controlled trial (RCT) with blinded assessments at baseline (0) and 4, 8, and 12 months, with a nested qualitative study and health economic analysis. 116 participants will be allocated to either (i) out-patient physiotherapy which will include a musculoskeletal assessment and treatment including balance, posture, strength training and low impact weight-bearing exercises over 16 weeks; or (ii) Opt-In intervention. This includes standard physiotherapy as above plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent 16 weeks.

Ethics and Dissemination: The study protocol was approved by West of Scotland Research Ethics Committee 4 (21/WS/0071). Trial registration number ISRCTN 14465704. The paper is based on Protocol v4.

Strengths and Limitations of this study

- The Physiotherapy exercise rehabilitation with tailored exercise adherence support for people with osteoporosis and vertebral fractures (Opt-In) study is a multicentre randomised controlled trial with an embedded qualitative study and economic evaluation.
- It will recruit from at least six NHS hospitals.
- The intervention addresses adherence which is an important confounder in many trials of physiotherapy.
- The intervention was developed using current research evidence, input from expert clinicians, researchers and patient / public representatives.
- Due to the nature of the interventions the physiotherapists delivering the treatments and the participants cannot be blinded.

Introduction

Vertebral fragility fractures (VFFs) affect at least 20% of the older population in the UK and present a significant health and economic burden [1, 2]. They are associated with back pain, fatigue, low mood, restrictions in physical function and activities of daily living, and marked, persistent reductions in quality of life (QoL) [1, 2]. Without treatment, progression and functional decline are expected. Conservative treatment for osteoporosis includes bone protective medications and lifestyle adaptations. Guidelines recommend people with osteoporosis keep active and exercise to slow the rate of bone loss, to maintain muscle strength and physical function and to prevent falls and further fractures [3,4]. Exercise prescription with multi-component exercise programmes that include postural, balance, aerobic weight-bearing and strength exercises are recommended [1-3].

Trials evaluating exercise in people with VFFs have reported benefits across a range of outcomes [1, 2, 5-10], with a recent Cochrane review concluding there is moderate-quality evidence that exercise improves physical function [1]. However, treatment effects are often small and difficult to sustain [1, 2, 5-10]. For example, in the PROVE trial, significant, clinically relevant benefits to back muscle endurance, balance, walking capacity and physical function following physiotherapy exercise at 4 months post-randomisation did not persist at 12 months [2]. Adherence, or the extent to which patients engage in treatment, has been identified as an important issue by many studies [1, 2, 5-6, 9]. Partial adherence or non-adherence is associated with worse outcomes and conversely, higher adherence with better outcomes [1, 2, 5-10].

Multiple factors affect exercise adherence in older people with chronic health conditions including osteoporosis [11, 12]. These include low exercise self-efficacy, low motivation, depression, insufficient exercise knowledge or skill, physical ability, negative views about treatment and exercise programme design [11,12]. Considering this complexity, interventions to support adherence that recognize personal barriers and facilitators to exercise and that can draw upon multiple adherence techniques are recommended [12, 13].

Behavioural approaches can include interventions that support exercise through providing additional monitoring, interventions that aim to alter thinking patterns that contribute to non-adherence and ones that strengthen behaviours that support adherence [12]. Motivational interviewing is a collaborative process that explores potential ambivalence, obstacles and facilitators surrounding behaviour change [6]. There is evidence that additional monitoring, prompts and feedback can benefit adherence in older adults e.g., via telephone call/ text messages, wearable activity monitors or by enriching environmental cues [1]. Incorporating exercise into everyday routines can make it easier to initiate and sustain and creating 'Exercise Action Plans' that specify when, where and how exercises are undertaken can support this process [1, 13]. Using an intervention mapping approach, we developed an exercise adherence intervention underpinned theoretically by the Capability, Opportunity, Motivation - Behaviour (COM-B) behaviour change model [14, 15].

Aims

The aims of this study are:

- To compare physiotherapy exercise rehabilitation with adherence support with physiotherapy exercise rehabilitation alone in terms of effects on: (a) physical function, quality of life, and fear of falling and (b) exercise self-efficacy and adherence.
- To explore patient and physiotherapist views of the intervention and of adhering to exercise.
- To understand if physiotherapy exercise rehabilitation with adherence support is cost-effective.

METHODS AND ANALYSES

Study design

A multicentre, two-arm, parallel group, superiority randomised controlled trial (RCT) with blinded assessments at baseline (0) and 4, 8, and 12 months following randomisation, with a nested qualitative study and health economic analysis. Participants will be allocated to either (i) outpatient

physiotherapy which will include a musculoskeletal assessment and 6 treatment sessions over 16 weeks based on the current best practice guidance from the Royal Osteoporosis Society; or (ii) the Opt-In intervention. This includes outpatient physiotherapy as described above, plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent treatment period of 16 weeks as prescribed by the physiotherapist in collaboration with the participant. Sessions in both arms can be in-person or virtually via video-call/ telephone as agreed between participant and therapist **(Figure 1)**.

The trial started recruitment of patients in August 2021 and will continue recruiting until June 2023.

Setting

At least six National Health Service (NHS) hospitals and their related physiotherapy services.

Study Participants

Adults aged 55 years or over who have a diagnosis of at least one previous osteoporotic vertebral fracture and back pain.

Eligibility

Inclusion Criteria

Participants may enter the study if they meet ALL the following criteria:

- Men and women ≥ 55 years: all women must be at least 1 year post-menopausal.
- One or more VFFs confirmed by radiography, X-Ray, MRI, CT or DEXA scan, people with VFF of any severity and at any time-point post-fracture are eligible.
- They must have had an episode of back pain in the previous 12 months.
- All must be able to walk at least 10 metres independently with or without a walking aid.

Exclusion Criteria

Participants may not enter the study if ANY of the following apply:

- Current conditions that would make participating in physiotherapy or exercise unsafe or confound results. This includes those with significant neurological and psychiatric conditions, severe unstable cardiovascular or pulmonary disease.
- Bone loss secondary to other metabolic disorders, diseases or medication e.g., rheumatoid arthritis, anorexia, cancer, coeliac disease, steroid use.
- Individuals whose primary problem is back pain that involves pain radiating into the lower limbs.
- Vertebroplasty, facet joint injection or physiotherapy within past 12 weeks.

Recruitment

A member of the patient's direct care team will identify potential participants with VFFs via clinic lists and electronic medical records from relevant metabolic bone clinics, radiology clinics (DEXA), physiotherapy referral lists, and from Rheumatology clinics.

Screening and eligibility assessment

Potential participants, who respond to an invitation letter will be contacted by telephone to discuss the study further, to check eligibility and to answer any questions. Patients who do not meet the eligibility criteria or who do not wish to participate will receive standard NHS treatment. We will record the age and gender of these patients to assess the generalisability of those recruited.

Consent

Participants who are eligible and willing to proceed will be approached for informed consent.; they and the researcher will sign and date a consent form. For participants who are recruited to the

additional nested qualitative study and interviewed on-line or via telephone, informed consent will be obtained verbally before the interview. The researcher taking consent will read, and fill out, the consent form on behalf of the participant and then sign the form [Supplementary file].

Randomisation

Consented participants will be randomised 1:1 using a computer-generated randomisation schedule prepared by the trial statistician (RK). Individual randomisation will be stratified by recruitment centre and permuted blocks of varying undisclosed sizes will be used. The randomisation schedule will be concealed in sequentially numbered, opaque, sealed envelopes for each site. A study administrator who has no interaction with blinded study staff will manage these envelopes. The administrator will open the randomisation envelope, and then communicate with the local site who will make the participant aware of their allocated group and refer for physiotherapy; making sure that participants are allocated to physiotherapists delivering the treatment for their allocated arm.

Blinding

Physiotherapists delivering the interventions and participants will be told the treatment allocation. Initial baseline assessment will occur prior to randomisation and the researcher undertaking assessments will not be involved in any part of the randomisation procedure to ensure that they are not able to bias the group allocation. The researcher conducting follow-up measures and the research team personnel entering data will also not be informed of allocated group and participants will be asked and reminded not to disclose their treatment group to the researcher at follow-up appointments.

Interventions

Training and monitoring

Sessions in both arms can be delivered in-person or virtually via video-call/ telephone as agreed between participant and therapist; to allow flexibility and resilience as COVID restrictions on physical attendance vary. Treatments were standardised and manualised and the study team provided training in the multi-component exercise therapy treatments (delivered to all participants) to all treating physiotherapists. Training in the behavioural adherence support intervention which comprised assessment and a set of 9 behavioural interventions (the Opt-In toolkit) was delivered separately to the therapists in the Opt-In arm. Treating physiotherapists will record the delivery and content of each treatment session in adherence logs for each participant. Regular site visits will be carried out to monitor intervention fidelity.

Standard Care

Participants will be offered a 1-hour physiotherapy assessment and six individual outpatient physiotherapy sessions spread over 16 weeks [2]. The physiotherapy will include a musculoskeletal assessment and treatment including a multi-component, progressed balance, posture, strength training and low impact weight-bearing exercise [3]. Exercise intensity will be assessed using the 10-point Rating of Perceived Exertion scale (CR10-RPE), so participants work at a moderately hard to hard (RPE 4-6) intensity. Although current practice may vary, the package agreed as the standard care is based on consensus, best practice guidelines and successful delivery in the PROVE trial exercise arm [2] and aims to be a credible representation of current best practice treatment across the NHS. Treating therapists will receive prior training on prescription of the exercises [2].

Opt -In

Participants allocated to Opt-In will receive the standard package described above, plus an additional, integrated assessment interview (30mins) and 60 minutes of adherence support spread over the subsequent treatment period of 16 weeks in an individualised pattern as required by the participant.

Participants in the Opt-In arm will complete the Personalized Exercise Questionnaire (PEQ). The PEQ was developed in Canada to support patient-centred exercise prescription for people with osteoporosis and covers topics such as barriers to exercise and goals of treatment [16]. Treating physiotherapists will have a collaborative discussion with the participant using a motivational interviewing approach drawing upon PEQ responses and considering goals, motivators, facilitators, and barriers surrounding exercise. It aims to provide physiotherapists with a deeper understanding of patient motivations and circumstances, to strengthen the therapeutic alliance and the patient's own motivations for adopting exercise [12]. Using their assessment findings, the questionnaire and collaborative interview the physiotherapist will assess a participant's exercise capability (C), opportunity (O) and motivation (M) to carry out exercise behaviour (B) (COM-B) and select an adherence technique from the Opt-In toolkit in response [14]. Techniques can include education about osteoporosis and exercises, education about and practice of fall prevention strategies, Exercise Action Plans, a contact telephone call, and self-monitoring and feedback strategies such as, exercise confidence rating scales or using an exercise diary. Techniques are linked to COM-B domains to facilitate physiotherapist decision-making e.g., Education improves capability and motivation (C, M) and a diagrammatic decision aid was developed to facilitate rapid decision-making during treatment. Each Opt-In arm treating physiotherapist received a toolkit and training by the study team about techniques and how to use them. Physiotherapists were asked to prescribe at least 3 adherence techniques from the Opt-In toolkit over 16 weeks but could use more. The exact techniques selected were personalised to the patient as was the pattern and spread of the 60-minute adherence support time. Participants in the intervention arm were given a folder that included their exercises and selected adherence materials e.g., exercise diary, education leaflet, action plan record. Figure 2 summarises the intervention in a logic model.

Concomitant care

Other aspects of health and social care will continue as usual. Analgesia and other medication use will be collected by self-report diary. Additional treatments sourced outside of the trial including contact with general practitioners and other health care professionals will be recorded in self-report health utilisation diaries in which participants will asked to record their use of health and social care services across the study e.g., GP, nurse, other physio, hospital admissions, home carer visits in standardised study diaries. Diaries will be from 0-4, 4 to 8 and 8 to 12 months [17].

Outcome Measures

The primary outcome measure will be the Timed Up and Go (TUG) at 12 months. The TUG is a test of balance, lower limb strength and walking ability with established reliability and validity. It records the time a person takes to stand up from a chair, walk 3 metres at a self-selected speed, turn, walk back and sit down [18].

Secondary outcome measures are:

- QUALEFFO 41: a disease specific measure of health-related quality of life (QoL) applicable to patients with osteoporosis and vertebral fractures. It is a self-administered questionnaire that provides scores on five domains: pain, physical function, social function, general health perception, mental performance, and a total score. [19].

- Timed Loaded Standing (TLS): an assessment of shoulder and back muscle endurance for people with VFF(s). [20].

- Thoracic kyphosis angle: measured non-radiographically using a flexicurve ruler, allowing an angle of kyphosis to be calculated which is approximated to radiological measures of kyphosis (Cobb angle) using a standardised formula [21].

- Back pain: measured with a 10-point Numeric Pain Rating Scale (NPRS) [22].

- Functional Reach (FR) test: a measure of dynamic standing balance developed for older adults. T, the test has been used in people with VFF and performance is predictive of falls risk [23].

- Six-minute walk (6MW) test: a measure of functional walking capacity and aerobic cardio-respiratory fitness [24].

- Falls Efficacy Scale International (FES-I): a 16 item (3 minute) self-report measure of fear or concern about falling during activities [25].

- Grip Strength: is the maximum force the hand and forearm muscles can generate measured with an isometric hand dynamometer in kilograms; maximum strength is the mean of three trials (3 seconds each) and measured for both hands [26].

- Self-efficacy for exercise (SEE) scale: a brief (<5 minute) 9-item scale that asks participants to rate how confident they would be that they would engage in exercise on a 10-point scale (not confident to very confident) under different situations e.g., if they were tired. SEE ratings are predictive of exercise behaviour [27].

- Adherence. This will be measured in two ways:

a. Attendance records via clinician completed treatment logs, including a checkbox to log whether adherence techniques have been prescribed (intervention group only).

b. Exercise adherence rating scale (EARS): a brief 6-item scale that asks participants to describe how they do their recommended exercises on a 5-point scale [28].

- Falls: documented on the CRF and prospectively using participant completed event diaries. These will be collected in blocks from 0-4 months, 4 to 8 months, and 8 to 12 months during the study. Incidence and severity formation will be recorded e.g., nature of the fall, its outcome (no-harm, fracture etc) and any treatment required [2].

- EQ-5D-5L is a short, generic measure of health related QoL and will be completed to assist assessment of health economics [29].

A summary of outcome measures and timepoints is shown in Table 1 **(Table 1)**.

Time Point	Measurement	Enrolment	allocation	Baseline	4 months	8 months	12 months
Screening Log		X					
Eligibility confirmed		x					
Informed Consent		x					
Randomisation			x				
Demographic	Age, gender, weight, ethnicity,			x			
Primary OM	Timed Up & Go			x	x	x	x
Quality of Life	QUALEFFO 41			X	X	X	X
Fear Falling	FES-I			X	X	X	X
Back Pain Intensity	NRS-P			X	X	X	X
Back strength / endurance	TLS			X	X	X	X
Walking	6MWT			X	X	X	X
Balance	Functional Reach Test			X	X	X	X
Kyphosis	Flexicurve			X	X	X	X
Grip Strength	Dynamometer			x	x	x	x
EQ-5D-5L	Health economics			x	x	x	x
Falls	Number of reported falls. Nature; outcome of falls.				x	x	x
Exercise Self Efficacy	SEE			X	X	X	X
Exercise adherence	EARS			X	X	X	X
Exercise adherence	Sessions attended				x	x	x

Table 1: Time Points at which outcomes will be assessed.

Adverse events

Adverse events (AE) occurring because of the trial interventions will be recorded. Participants will receive information on potential AEs resulting from the exercises and what they should do if they

experience an AE, as would be part of standard NHS procedure. Adverse symptoms in response to treatment and any adverse events will be monitored by clinicians regularly and in line with local departmental procedures and captured on adverse event forms, and via questions on the CRF.

A Serious AE (SAE) is any untoward medical occurrence related to the trial interventions that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. SAEs are likely to be rare and are unlikely to occur as a result of the exercise programmes delivered in this study.

Any reports of SAE will be reported to the trial office within 24 hours of the local research team becoming aware of the event. They will be reviewed by an independent medically qualified assessor within 3 days.

Statistics and analysis

Sample Size

The primary outcome is the Timed Up & Go (TUG) test. This is the most widely used physical function measure in RCTs of exercise for people with VFF [4]. The minimal clinically important difference (MCID) for the TUG has not been established in people with VFF(s), but a MCID of 1.4s is reported for similar older populations with chronic musculoskeletal disorders [30]. The study requires 104 participants (52 per arm) to be 80% powered to detect a 1.4s difference in TUG score between groups at a 5% significance level (two-sided) assuming that the standard deviation is 2.5s. Similar trials have had loss to follow-up rates of 10% at 12 months [2]. To account for this the sample size has been inflated to 116 participants (58 per arm).

Statistical Analysis

The study will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement utilising the nonpharmacological and patient-reported outcome extensions [31,32].

Standard descriptive statistics will be used to describe the characteristics of the two groups at baseline. Means and standard deviations (SDs) or medians and interquartile ranges (IQRs) as appropriate will be used for continuous variables, and numbers and percentages will be used for binary and categorical variables.

Compliance with the intervention will be defined as participating in the extended interview and prescription of at least 3 adherence support techniques. This will be recorded on treatment logs. Details of the number of physiotherapy sessions attended will also be summarised by treatment group. The number and proportion of participants who withdraw will be summarised along with reasons for these. Deaths are not anticipated in this study, but details of any that do occur will also be summarised by treatment arm.

Summary statistics will be presented for all comparative outcomes, and effect estimates will be reported together with 95% confidence intervals with all tests carried out at a 5% two-sided significance level.

At 12 months post-randomisation the two treatment groups will be compared on the TUG measure using a multivariate linear regression model adjusting for recruiting centre (stratification factor), age and baseline TUG score. An unadjusted t-test will also be undertaken. The TUG is also recorded at 4, and 8 months after randomisation, and an additional analysis utilising all time points, using multi-level modelling and including a treatment by time interaction if appropriate will be undertaken. For each of these models, the assumption of approximate normality will be assessed by examining the residuals. If this assumption is not met the first approach will be to consider a transformation to achieve normality. If this is not possible, the two groups will be compared using non-parametric methods (e.g., Mann-Whitney U-test). This analysis will be unadjusted and will consider each time point separately.

Similar analyses will be performed for secondary outcomes which can be considered approximately continuous (QUALEFFO-41, FES-1, NPRS, TLS, Grip strength, 6MW, FRT, Thoracic kyphosis, SEE and EARS) at 4-, 8- and 12-months post-randomisation. The appropriateness of the assumption of approximate normality will also be considered and transformation to normality or non-parametric methods used as appropriate. It is not anticipated that the number of falls will be approximately normal, therefore, this will be summarised by treatment group using medians and IQRs and compared using non-parametric methods. The number and proportion of participants experiencing an AE during follow-up will be summarised by treatment group and a logistic regression model adjusted for recruiting centre will be used to compare the rates in the two groups. Severity of AEs will also be summarised by treatment group.

In addition, since previous work suggests that change in thoracic kyphosis at follow-up is closely related to baseline values, a subgroup analysis of thoracic kyphosis at follow-up will be completed dependent on whether the participant was kyphotic at baseline [33].

All analyses will be performed for the intention to treat (ITT) population. This will include all randomised participants with available data who will be analysed according to their allocated intervention regardless of the treatment they received.

In addition, analysis of the primary outcome (TUG at 12 months) will be repeated for the per protocol (PP) population which will include only those participants who received their allocated treatment. Participants with other major protocol deviations (e.g., recruited and later found to be ineligible) will also be excluded from this population.

Health Economic Analysis

The relative efficiency of the intervention will be assessed by within-trial cost-utility and cost-consequences analyses [34]. The evaluation will take an NHS and personal social services perspective. Resource use for the delivery of Opt-In and at participant level will be combined with

unit cost from standard national sources to estimate average total costs. We will estimate the incremental cost per quality-adjusted life year (QALY) (from EQ-5D-5L) and present the different cost components and multiple benefits of Opt-In in a 'balance sheet' in the cost-consequences analysis.

Embedded Qualitative study

As part of the main study a nested qualitative study will take place. The qualitative element of this study will involve a subset (12-15) of patients who undertake the Opt-In intervention who will be invited to take part in 4 short (15-20 minute) interviews about their experiences and views about exercise adherence and the adherence intervention at the following time points: i) following assessment ii) during treatment (after 3 sessions), iii) post-treatment (after 4 months), and iv) at 12 months. The interviews may occur online via video-call or face-to-face in the person's home or at a local clinic, depending on participant preference. The interviews will be audio recorded and transcribed verbatim. Participants will be given an opportunity to check the interview transcript.

Focus groups will be conducted with physiotherapists who undertake the Opt-In intervention, asking them to share their views about promoting exercise adherence and the Opt-In intervention, these will be audio-recorded with a Dictaphone.

Purposive sampling will be used to achieve a sample which includes men and women, patients of varying activity levels and patients of different ages and disease severity (pain/ number of fractures). These factors may influence the ability to engage with an exercise programme. Since most research regarding adherence in osteoporosis has previously been undertaken with women, it also considered important to capture the views of men within the current study and to capture the experiences of people with differing physical activity levels prior to the programme. The quality of a qualitative study is not dependent on its sample size; however, the sample size needs to be sufficiently large to enable relevant data to be obtained, without being so overly large that detailed analysis is subsequently prevented [35]. Information about physiotherapists views of delivering the

adherence interventions will also be sought. All those who deliver the adherence techniques will be invited to participate in a focus group.

Audio recordings will be listened to, and transcripts read until they become familiar. Data from the interviews with physiotherapists and participants will be analysed separately to understand the perspectives of each group. We will use collaborative methods to ensure a strong voice from PPI members and research rigour. We will use thematic analysis, using the six steps proposed by Braun and Clarke [36].

Patient and Public Involvement

The study funding application, intervention development and study materials preparation were supported by our patient and public involvement members who will be involved across the course of the study.

ETHICS AND DISEMMINATION.

The study protocol was approved by West of Scotland Research Ethics Committee 4 (Reference 21/WS/0071). The University of Oxford is the sponsor. The trial is registered with the International Standard Randomised Controlled Trials database ISRCTN reference number 14465704.

The protocol has been reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [37]. Results will be published reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines [38]. The Template for Intervention Description and Replication (TIDieR) statement will be used to report the intervention ensuring replication is possible [39]. Results will be published in a peer reviewed journal with authorship eligibility according to International Committee of Medical Journal Editors (ICJME) criteria. Participants will be asked if they wish to have the results shared with them prior to publication and we will share with those who request this. We plan to publish results in an

international peer-reviewed journal and at international rehabilitation and bone health focussed conferences.

Contributions of Authors:

Karen L Barker: Chief Investigator, Conceived and designed the study, was awarded the funding and had overall responsibility for the study design and delivery and drafted the manuscript. She is the guarantor.

Jonathan Room: contributed to study design and provided specific content and edited manuscript. Qualitative lead.

Erin Hannink: contributed to study design and provided specific content and edited manuscript

Ruth Knight (statistical co-applicant) performed the sample size calculation, prepared randomisation schedules, planned statistical analysis methods

Meredith Newman (Trial Manager), trial design, intervention development, manualisation, training, supervision, writing and reviewing report.

Funding

The study is supported by an independent grant from the Chartered Society of Physiotherapy Charitable Trust (RP/19/01).

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work, other than funding arrangements for the trial described in body of the text; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency

The lead author (KLB) affirms that the manuscript is an honest, accurate and transparent account of the study being reported.

Figure Legends

Figure 1: Study Flow Diagram

Figure 2: Logic Model for intervention

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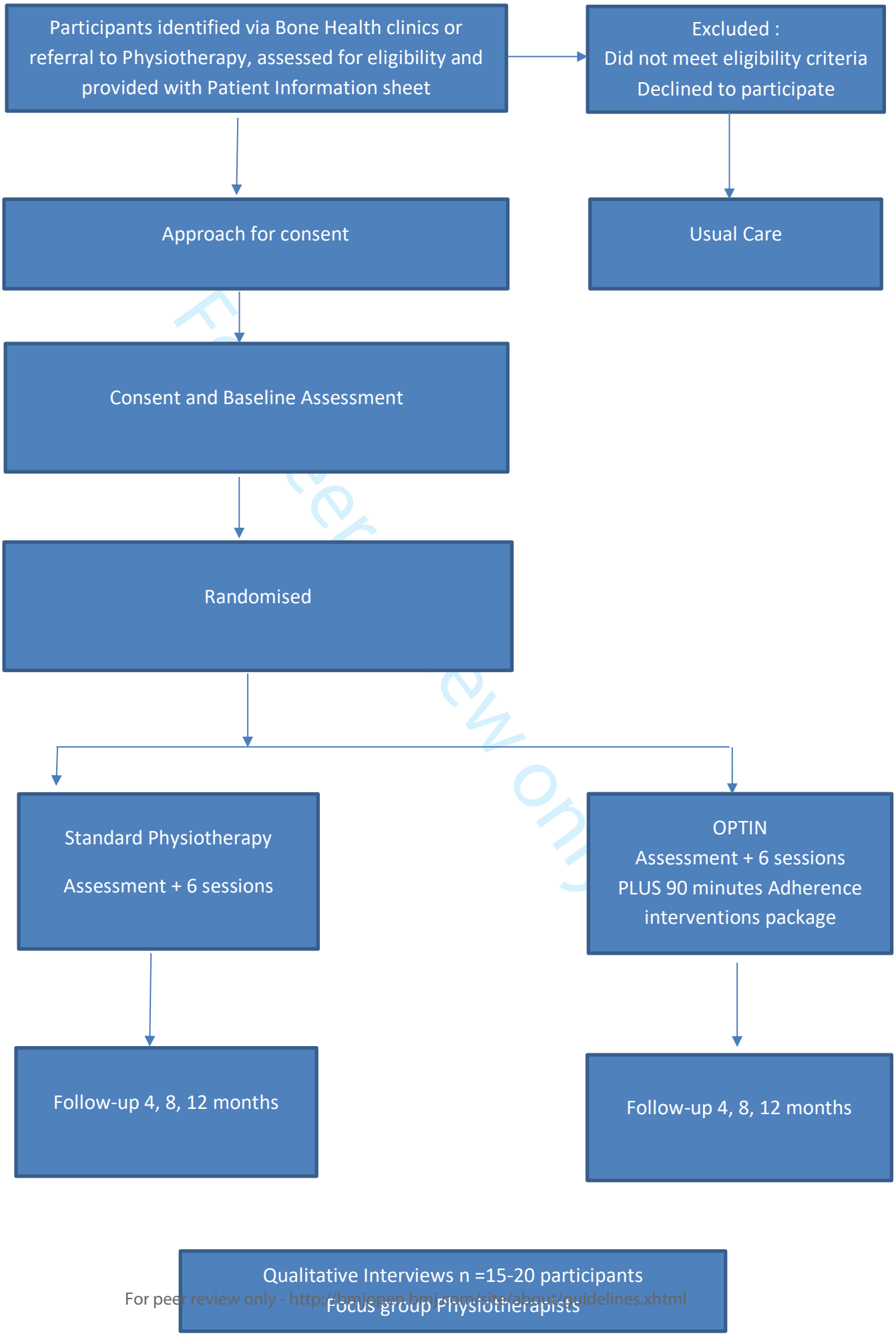

Situation: Multiple factors affect exercise adherence in older people with chronic health conditions including osteoporosis. Limited adherence diminishes the potential benefits of exercise rehabilitation

Inputs

Physiotherapist Training
- Osteoporotic vertebral fractures and exercise
- Theoretical models
- Adherence approaches

OPTIN Intervention
Assessment (90min):
- Physical status
- Capability, Opportunities/ Barriers, Motivators for Ex

Treatment
- 6 x 30min sessions &
- 6 x 10min adherence support points

Toolkit of teaching and support materials

Mechanisms of Effect

Theoretically and evidence-based interventions
Tailored to individual via assessment
Co-produced, reviewed and progressed

Holistic, integrated exercise + adherence programme

Exercise	Strength training Postural Ex	Balance training	Aerobic Weight-bearing Ex
Adherence	Educational approaches	Behavioural approaches	

Short-term Outcomes

Enhanced capability, opportunity and motivation to increase behaviour:
- Exercise adherence
- Exercise dose
- Exercise self-efficacy

Medium to Long-term Outcomes

Individual	Improvements in:	
	Functions/Structure: • Muscle endurance • Spinal posture • Standing Balance • Pain • Fear-of-falling	Activities/Participation Physical function Walking capacity Quality of Life
	No excess adverse events: falls, fractures etc	
Group	Increased efficiency: in terms of cost components and cost-benefits from an NHS and personal social services perspective	

Impacts

Improved health for people with OVF

Decreased societal health and care costs
Efficient physiotherapy

Generalisable to other chronic conditions

Evidence for guidelines and teaching

OPTIN Logic Diagram

TRUST LOGO (if applicable), or a placeholder, 'local logo/letterhead'

Chief Investigator: Professor Karen Barker

Principal Investigator: <<PI name here>>
<<Local hospital address here>>

Study code	*Site code*	*Participant number*
O P T		

CONSENT FORM – Main study

OsteoPorosis Tailored exercise adherence INtervention (Opt-In)

	If you agree, please initial each box
1. I confirm that I have read the information sheet dated..... (version.....) for this study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Oxford, from regulatory authorities and from the NHS Trust(s), where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to my General Practitioner being informed of my participation in the study.	
5. I understand I may be contacted for the option to participate in qualitative interview or focus group related to the study.	
6. I agree to take part in this study.	

_____	_____	_____
Name of Participant	*Date*	*Signature*
_____	_____	_____
Name of Person taking Consent	*Date*	*Signature*

**1 copy for participant; 1 copy for local researcher site file; 1 (original) to be kept in medical notes* (if participant is a patient).

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Title Page Lines 1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Page 3 Line 21
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier Page 3 Line 22
Funding	4	Sources and types of financial, material, and other support Page 23 lines 9/10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Title page and Page 22/23
	5b	Name and contact information for the trial sponsor Page 19 Line 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention P5-6
	6b	Explanation for choice of comparators P6
Objectives	7	Specific objectives or hypotheses P6

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) P6 L22-3
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained P7 L10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) P7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) p10/11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial p12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended p12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations P15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P8
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions P9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assignedp9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial n/a
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocolp10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol P15-6
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) n/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) P15-17

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct P14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approvalP22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) P 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation n/a

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions P19
	31b	Authorship eligibility guidelines and any intended use of professional writers P19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.