Title: Physiotherapy Rehabilitation for Osteoporotic Vertebral Fracture (PROVE)

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Chief Investigator:	**Dr Karen Barker**
Investigators:	Prof Sallie Lamb, University of Oxford, Prof Cyrus Cooper, University of Oxford, Dr Kassim Javaid, University of Oxford, Prof Nigel Stallard, University of Warwick Mrs Meredith Newman, Oxford University Hospitals NHS Trust Dr Helen Campbell, University of Oxford Dr Catherine Minns Lowe, Oxford University Hospitals NHS Trust

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Signatures:	**Signed by Dr Karen Barker, Chief Investigator for PROVE**

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
3	3	4/1/2013	Dr Karen Barker	Participant consent and information leaflets reviewed and approved.
6	4	28/3/2014	Dr Karen Barker	Participant Information leaflet, Re-consent form, Letter to participants – updated PIS
7	5	10/09/2014	Dr Karen Barker	letter to participants from GPs updated and additional sites added to improve recruitment
8	6	22 Apr 2015	Dr Karen Barker	Protocol updated to include reply slip 2, advert 1&2. Also reflects updated recruitment closing date.

Trial Manager
Varsha Gandhi
NDORMS
Oxford University Hospitals NHS Trust
Windmill Road
Oxford OX3 7HE
Tel: 01865 223489
Email: varsha.gandhi@ndorms.ox.ac.uk

Sponsor
Dr Heather House
Research & Development Joint Office
University of Oxford
Oxford OX3
Tel: 01865 572245
Email: heather.house@admin.ox.ac.uk

Chief Investigator
Dr Karen Barker
Nuffield Orthopaedic Centre / NDORMS
Oxford University Hospitals NHS Trust
Windmill Road
Oxford OX3 7HE
Tel: 01865 738080
Email: karen.barker@ouh.nhs.uk

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National Institute of Health Research
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Co-applicants
Professor Sallie Lamb
Chair of Trauma Rehabilitation, Kadoorie Critical Care Research Centre
University of Oxford
Oxford OX3 7HE
s.lamb@warwick.ac.uk

Professor Cyrus Cooper
Norman Collinson Chair Musculoskeletal
NDORMS
University of Oxford
Cyrus.cooper@ndorms.ox.ac.uk

Dr Kassim Javaid
Consultant in Metabolic Medicine
The Nuffield Orthopaedic Centre
kassim.javaid@ndorms.ox.ac.uk

Professor Nigel Stallard
Professor Medical Statistics
Warwick Medical School
n.stallard@warwick.ac.uk

Mrs Meredith Newman
Senior Research Physiotherapist
The Nuffield Orthopaedic Centre
Oxford University Hospitals NHS Trust
Windmill Road, Headington
meredith.newman@ouh.nhs.uk

Mrs Helen Campbell
Health Economics Research Centre
Department Primary Care
University of Oxford
Helen.campbell@dpc.ox.ac.uk

Dr Catherine Minns Lowe
Research Physiotherapist
Physiotherapy Research Unit,
Oxford University Hospitals NHS Trust
Windmill Road, Headington
catherine.minnslowe@ouh.nhs.uk

Independent Trial Steering committee	
Chair: Professor Maria Stokes Professor of Musculoskeletal Rehabilitation University of Southampton Highfield Campus Southampton SO17 1BJ M.Stokes@soton.ac.uk	Dr Victoria Allgar Senior Lecturer in Medical Statistics Hull York Medical School University of York Y010 5DD Victoria.allgar@hyms.ac.uk
Dr Jane Simmonds Principal Lecturer in Physiotherapy School of Health and Emergency Professions University of Hertfordshire AL10 9AB j.1.simmonds@herts.ac.uk	Dr Alison Rushton Senior Lecturer in Physiotherapy School of Health and Population Sciences College of Medical and Dental Sciences 52 Pritchatts Road University of Birmingham Birmingham B15 2TT Tel: 0121 415 8597 Email: a.b.rushton@bham.ac.uk
Dr Fiona Cramp Associate Professor in Musculoskeletal Health Faculty of Health and Applied Sciences University of West of England Glenside Campus Bristol BS16 1DD Telephone: 0117 3288501 Email: Fiona.Cramp@uwe.ac.uk	Mrs Jane Aldridge Patient and Public Involvement representative
Independent Data Monitoring Committee	
Professor David Torgerson Professor and Director York Trials Unit University of York, Heslington, York Y010 5DD David.torgeson@york.ac.uk	Professor Susan Todd Professor of Medical Statistics University of Reading Room 302E, Philip Lye Building, Whitenights Campus, Reading RG6 6UR s.c.todd@reading.ac.uk.
Professor Helen Dawes Professor of Rehabilitation Department of Sport and Health Sciences Oxford Brookes University, Gypsy	

Lane, Oxford OX3 0BP hdawes@brookes.ac.uk	

2. SYNOPSIS

Study Title	Physiotherapy Rehabilitation for Osteoporotic Vertebral Fracture (PROVE)
Project ID	1078633
Study Design	A definitive prospective assessor-blinded multi-centre 3 arm randomised controlled trial with a nested qualitative study and incorporating an adaptive design approach.
Study Participants	Men and women with primary vertebral osteoporosis with a least one painful vertebral fracture sustained previously.
Planned Sample Size	RCT n= 600 participants Qualitative study n=15.
Follow-up duration	One year.
Planned Study Period	4 years.
Primary Objective	To assess the effects of a physiotherapy intervention based on exercise or manual therapy principles on clinical outcomes for people with vertebral osteoporosis.
Secondary Objectives	To evaluate acceptability and adherence to the physiotherapy programmes for patients and therapists. To conduct a parallel health economic analysis to assess the cost effectiveness of the different treatment strategies from an NHS and societal perspective.
Primary Endpoint	12 months.
Secondary Endpoints	Study 3: Interim analysis at16 weeks for first 210 patients (70 per group).
Intervention (s)	For the main trial the 3 intervention arms will be: A: Usual Care/ Control – A single education session. B: Manual Therapy - 7 physiotherapy sessions over 16 weeks C: Exercise Therapy - 7 physiotherapy sessions over 16 weeks

Objectives	Outcome Measures/Endpoints
Primary Objective To assess the effects of physiotherapy intervention based on exercise or manual therapy and to compare the two to usual care for people with symptomatic vertebral osteoporosis.	The - QUALEFFO 41(a quality of life questionnaire in patients with vertebral fractures) will be used as an outcome measure to achieve the primary objective. The QUALEFFO 41 is a disease specific measure applicable to patients with established vertebral osteoporosis, independently of whether or not they have back pain and is designed to be used as an evaluative instrument in clinical trials. - The Timed Loaded Standing (TLS) test to assess back extensor muscle endurance. This will be used to assess the change in physical function between the interventions.
Secondary Objectives 1.To compare, if appropriate, the effects of manual therapy with exercise therapy. 2.To assess the safety of and identify any significant side effects associated with the treatment programmes. 3.To investigate the acceptability and adherence to the physiotherapy programmes for patients and therapists. 4.To conduct a parallel health economic analysis to assess the cost effectiveness of the different treatment strategies from an NHS and societal perspective. 5.To conduct a nested qualitative study to explore the experiences and views of people with osteoporosis regarding their participation in the treatment interventions, their perceptions regarding the appropriateness and acceptability of the interventions and to explore the factors influencing adherence to the intervention programmes.	The following outcome measures will be used to measure balance, mobility and physical activity to achieve the secondary objectives, - The Short Performance Physical Battery will be used to assess lower extremity physical function. - The Functional Reach Test (FRT) will be used to specifically evaluate standing balance and to act as a predictor of falls risk. - 6 minute walk test at self-selected speed will be used to measure exercise endurance; an important parameter of functional, community mobility. - Physical Activity Scale for the Elderly (PASE) will be used to assess physical activity in the past week. - The EQ-5D-5L (EuroQoL Group 1990) is a short, generic measure of health outcomes and will also be completed to assist comparison with other conditions and assessment of health economics. - Pain will be assessed using the 10 point VAS visual analog scale. In addition to these outcome measures patients will be asked to complete and log home programmes to assess adherence to physiotherapy programmes.

3. **BACKGROUND AND RATIONALE**

Osteoporosis and vertebral fracture can have a considerable impact on an individual's health related quality of life (HRQoL) due to pain, limitations in activity and social participation and altered mood [1, 2]. Quality of life (QoL) has been reported to decline progressively as the number of vertebral fractures increases and is an important outcome in evaluating any intervention for vertebral osteoporosis [1, 2]. Vertebral fractures are closely related to increased thoracic kyphosis. In turn, thoracic kyphosis with a loss of lumbar lordosis (hyperkyphotic posture) is linked to increased spinal loading, back extensor muscle weakness with a significantly increased risk of further fracture, most commonly anterior vertebral wedge fracture [3, 4]. It is also associated with increased back pain and balance disturbance with a subsequent increased risk of falls and fractures as a result of falling [5, 6]. There is increasing evidence that physical therapies including manual techniques and exercise interventions that address pain and physical impairments may have an important role in improving QoL and reducing fracture risk in people with osteoporotic vertebral fractures.

Evidence for manual therapies

Traditionally, physiotherapists use manual mobilisation in the management of back pain to increase spinal range of movement. However, evidence for the effectiveness and safety of manual mobilisations in the management of thoracic hyperkyphosis in elderly people is limited, and physiotherapy guidelines caution against using spinal mobilisation in individuals with osteoporosis. High velocity spinal manipulation techniques are contraindicated [7] and concerns about the use of low velocity spinal mobilisation techniques have been expressed, but recent practice surveys, case reports and two RCT's show these techniques can be used safely [8-11]. No serious adverse events are reported in either RCT using low velocity spinal mobilisation. In each case the sample sizes are small and mobilisation is combined with exercise and other techniques making it difficult to determine its effectiveness [8, 9].

Manual techniques such as postural taping provide increased proprioceptive feedback about postural alignment and aim to improve thoracic extension, reduce pain and facilitate postural muscle activity and balance [6, 8, 9, 12]. In 2008 a small RCT of 15 osteoporotic women with vertebral fractures reported that a single session of postural taping significantly reduced thoracic kyphosis but had no immediate effects on balance or trunk muscle activity[12]. A later RCT investigated the effects of thoracic spine rehabilitation on the severity of thoracic kyphosis, pain and QoL in 37 elderly women with osteoporosis some of whom had vertebral fracture [9]. The rehabilitation group (n=21) took part in 3 months of manual mobilisations, postural taping and a 20 minute daily home exercise programme, the control group (n=16) were assigned to a physiotherapy waiting list. The rehabilitation group had a significantly reduced thoracic kyphosis but no difference in pain or QoL was demonstrated although an adverse event of minor skin irritation was reported with postural taping. In 2010 a second RCT of 20 patients investigated a 10 week package of physiotherapy treatment that included manual mobilisations, postural taping, soft tissue massage and daily home exercises. At 11 weeks the intervention group (n=11) had significantly improved QoL, pain and back strength compared to the control (n=9) group [8]. In each of these RCTs sample sizes are small, and no long term outcomes were published, so the sustainability of the effects is unknown.

Evidence for exercise interventions

A number of systematic reviews and meta-analyses report the positive effects of exercise on bone mineral density (BMD), muscle strength, QoL, falls and fractures in men and women [13-17]. A systematic review by De Kam et al (2009) [14] included patients with low BMD or diagnosed osteoporosis They concluded that exercise for individuals with low BMD could be effective in reducing the total number of falls and fractures due to improvements in balance, lower limb and back extensor muscle strength. They also found that strengthening the back extensor muscles might reduce the thoracic kyphosis but evidence suggesting that exercise could reduce the prevalence of vertebral fractures was more limited. Another review on post-menopausal osteoporotic women concluded that both impact or weight-bearing exercise and non-impact strength training exercise could prevent bone loss in the lumbar spine in postmenopausal women [17]. Nikander et al (2010) carried out a systematic review and meta-analysis to evaluate the effects of long term exercise in older adults. It also included studies on male and female adults and children [16]. They concluded that programmes that combined progressive resistance (strengthening) exercise with low intensity weight-bearing exercise such as walking and stair climbing were the most effective for preserving bone strength in the lumbar spine and femoral neck. A systematic review that looked at the effects of exercise on QoL in participants with osteoporosis found a greater improvement in all QoL domains with exercise [15]. Improvement was seen in physical function even in studies with shorter exercise programmes (3 months or less), but more improvement in pain was seen in longer interventions. These findings suggest group exercise might be better than home exercise in improving QoL, due to the benefits of shared social interactions, support and information. However, only one home-exercise study is included in their review of 4 studies so the strength of this recommendation is questionable [15] and other researchers in the fall prevention field have found that many older people do not like the idea of groups and this can be a barrier to their attendance.

Osteoporosis guidelines recommend combining strength training and weight-bearing exercise and that the exercise should be site specific, targeted to load muscle and bone at affected sites optimally and progressed [13]. Illustrating this, Sinaki et al (2002) considered the long term outcomes of 50 healthy postmenopausal women randomised to a 2 year home programme of back extensor exercise using a weighted backpack 5 days per week with progression every 4 weeks [4]. At 8 years the intervention group had significant higher BMD, back muscle strength and a lower incidence of vertebral fracture. Winters-Stone and Snow (2006) [18] studied the response of bone at specific skeletal sites to either class based lower body exercise alone or this class with the addition of upper body exercise in pre-menopausal women (n=35). After the exclusion of those with low compliance they concluded that a combined upper and lower body exercise programme to load both the hip and spine lead to significantly increased BMD at these sites.

The systematic review by de Kam et al (2009) [14] recommended that exercise interventions include balance training. It is known that an osteoporosis vertebral fracture leads to axial posture deformity which can increase both the fear of falling and the actual risk of falling. Thus, the incidence of falls is an important outcome in any treatment programme [5, 6, 19, 20]. A RCT of 1479 healthy elderly women found that a combined balance and progressive strength training programme produced the best results in terms of maintaining leg strength, balance, BMD and physical function compared to balance or strength training alone. The

intervention groups trained three times a week for 12 months [21]. Another RCT in 98 osteopenic women investigated a 20 week twice weekly class programme of weight-bearing exercise combined with balance training. Following the intervention significant improvements were seen in balance and strength of hip and back extensors and there was a non-significant trend towards improved bone density in the intervention group [22]. A further RCT in 33 osteoporotic women reported improved postural control, balance and strength after 8 weeks of two sessions per week of walking, balance and lower limb strength exercises [23].

RCTs of exercise interventions in people with vertebral osteoporosis also report benefits of reduced pain and improved QoL, strength and balance [24-30]. Interventions range from simple back extension exercises to a varied mix of general weight-bearing exercise, balance activities, stretches and combined upper, trunk and lower limb strengthening. The interventions have been delivered in class format [28-30] as a home programme [25, 27] or as a combination of physiotherapist led and home exercise programmes [30].

A RCT by Malmros et al (1998) investigated the effects of a 10 week, twice weekly physiotherapy class in 53 osteoporotic women with at least one vertebral fracture [29]. The training included balance, muscle strengthening and spinal stabilisation exercises. Pain, function and QoL improved significantly in the intervention group immediately post-treatment but when the active training stopped improvements in function and pain had reduced at 6 months. A further RCT of 60 women with osteoporosis, including some with vertebral fracture, who completed balance training classes that included stretches and walking once a week for 40 weeks showed significant improvements in balance, mobility and the frequency of falling in the intervention group [28]. Another RCT evaluated the effect of a 3 month course of exercise and education in 89 osteoporotic women with vertebral fracture [24]. The exercise component was a progressive, supervised programme for 1 hour, twice a week for 12 weeks, and involved aerobic and balance work and stretches. Significant improvements in walking, pain, and QoL were demonstrated post treatment and at the 12 month follow-up. A larger RCT of 185 osteoporotic women with vertebral fractures found a 6 month weekly programme of 3 strengthening and stretching exercise classes improved trunk extension strength and psychological symptoms [26].

Unfortunately adherence to home exercise regimes can present a challenge. One RCT reported low rates of compliance with home exercise in a group of 28 postmenopausal women following a single session of exercise and advice [31]. However, programmes with higher levels of support, that combine more frequent attendance at physiotherapy with home exercise report higher compliance and better outcomes [25].

Overall, there is evidence that both manual therapy and exercise interventions can be beneficial for this patient group. Whilst a limited number of studies provide strong support for the use of manual therapies, these are inadequately powered. Some higher quality evidence is available to support exercise prescription for individuals with osteoporosis, but fewer studies of exercise have been completed in osteoporotic populations with vertebral fracture and only a small number of these use interventions that combine weight-bearing, strength and balance activities. To date, none include men with osteoporotic vertebral fracture. There are questions about patient compliance with the exercise programmes and

whether a positive effect can be seen at levels of intervention intensity that are deliverable within current NHS resources. Whether exercise therapy is more effective than manual therapy is not known and further information is needed about the longer term outcomes of either intervention to understand whether any benefits are maintained. These factors make exercise therapy and manual therapy strong candidate interventions for inclusion in a RCT exploring the potential benefits of physiotherapy for people with osteoporotic vertebral fracture. We believe that there is sufficient evidence and experience in the clinical setting to be able to plan and undertake a definitive trial.

4. STUDY OBJECTIVES

The primary objective of the trial to assess the effects of a physiotherapy intervention based on exercise or manual therapy principles compared to normal care for people with symptomatic vertebral osteoporosis.

The secondary objectives are:

1. To compare, if appropriate, the effects of manual therapy with exercise therapy.
2. To assess the safety of and identify any significant side effects associated with the treatment programmes.
3. To investigate the acceptability and adherence to the physiotherapy programmes for patients and therapists.
4. To conduct a parallel health economic analysis to assess the cost effectiveness of the different treatment strategies from an NHS and societal perspective.
5. To conduct a nested qualitative study to explore the experiences and views of people with osteoporosis regarding their participation in the treatment interventions, their perceptions regarding the appropriateness and acceptability of the interventions and to explore the factors influencing adherence to the intervention programmes.

5. TRIAL DESIGN

The trial will be a prospective, multi-centre assessor-blinded three-arm randomised controlled trial with a nested qualitative study and an adaptive design. Patients will be randomised between three arms: usual care- a control group (A), manual therapy (B) and exercise therapy (C). Those in the usual care arm will receive a single session of education and advice, those in the active treatment arms (B + C) will be offered 7 individual physiotherapy sessions over 16 weeks. Assessments will be performed at baseline (week 0), at approximately16 weeks and 12 months; with additional postal questionnaires about quality of life administered at 6 and 9 months. An interim analysis will be conducted once 75 participants have been recruited at each arm and have completed a 16 week follow-up. Following this interim analysis the study may be adapted. If both intervention arms are promising and sufficiently similar, recruitment will continue into both intervention arms. If one arm, manual therapy or exercise therapy, is not promising relative to control this arm will be dropped from the study and the study will continue as a two arm RCT with participants randomised between the control and remaining intervention arm. If neither arm is superior to control the trial will be stopped.

5.1 Primary and Secondary Endpoints/Outcome Measure

- **Primary outcomes**

There are two primary measures for this study: one of quality of life and one measure of physical function.

1. The QUALEFFO 41 is a disease specific measure of health related quality of life (QoL) applicable to patients with established vertebral osteoporosis, independently of whether or not they have back pain and is designed to be used as an evaluative instrument in clinical trials. 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. All scores are expressed as a normalised score from 0-100, where higher scores represent worse QoL. It is validated and reliable and has been shown to be responsive in clinical trials of physiotherapy treatment
2. The Timed Loaded Standing (TLS) test to assess back extensor muscle endurance. Based upon previous literature [9] a 2.6 second change in the TLS test would be clinically significant.

The study sample size gives adequate power to detect a treatment effect in both the QUALEFFO 41 and TLS.

- **Secondary outcomes**

Information about relevant physical characteristics, namely age, height, weight, number and site of vertebral fractures and other fractures will be collected at baseline.

The Functional Co-morbidities Index will be also be completed as other diseases are likely to be present in this older population which might affect physical outcomes [32].

Thoracic kyphosis will be measured using a flexicurve ruler; the ruler is gently moulded to the countour of the spine and a tracing made to calculate an index and angle of kyphosis [33].

Other outcomes include measures of balance, mobility and physical activity. These are all areas affected by osteoporotic verebral fracture. Each test is reliable and valid, has been used with older, community dwelling adults and shown to be responsive in previous rehabilitation studies.

The Short Performance Physical Battery will be used to assess lower extremity physical function [35]. It combines tests of the ability to stand from a chair, of 4 metre walking speed and standing balance [35] and takes up to 10 minutes to complete. Poor performance is predictive of future disability, hospitalisation and care needs.

The Functional Reach Test (FRT) will be used to specifically evaluate standing balance and to act as a predictor of falls risk [36].

A 6 minute walk at self-selected speed (resting as required) will be used to measure exercise endurance; an important parameter of functional, community mobility [37].

Participants will also be asked to complete the Physical Activity Scale for the Elderly (PASE). This is a short, self-administered questionnaire to assess activity in the past week [38].

The EQ-5D-5L (EuroQoL Group 1990) is a short, generic measure of HRQoL and will also be completed to assist comparison with other conditions and assessment of health economics.

Pain - participants will be asked to specifically rate back pain on activity and at rest using a 10 point VAS.

Table 1. outcome measures and timepoints
Participants of the three groups will undergo the following measures.

TESTS	Administered by	Week 0	Month 4	Month 6	Month 9	Month 12
Functional Co-morbidities Index	Self	✓				
QUALEFFO 41	Self	✓	✓	By post	By post	✓
EQ5D-5L	Self	✓	✓	By post	By post	✓
PASE	Self	✓	✓	By post	By post	✓
Timed Loaded Stand	Assessing Therapist	✓	✓			✓
Flexicurve ruler	Assessing Therapist	✓	✓			✓
The Short Performance Physical Battery	Assessing Therapist	✓	✓			✓
The Functional Reach test	Assessing Therapist	✓	✓			✓
6 Minute walk test	Assessing Therapist	✓	✓			✓
10 point Visual Analogue Scale (VAS)	Self	✓	✓			✓

Participant diaries will be used to record the use of healthcare (including visits to a GP, consultant, complimentry medicine etc), use of aids, analgaesia, and any adverse event. Information about fractures (including vertebral fractures) and falls will be collected precisely using a prospective participant completed event calendar. These will be handed to the participants during each assessment with the clinician as well as mailed at 6 and 9 months. Participants will be requested to mail these back to the study co-ordinator. In the event they are not filled or returned, follow-up phone calls will be made by the local clinicians as necessary to promote adherence and to check this information is captured precisely [39].

5.2 Participants

600 patients will be recruited from 10-20 centres across the UK. Men and women with osteoporosis who have had a least one symptomatic vertebral fracture will be eligible for inclusion if they meet the following criteria:

Inclusion Criteria

1. Participant is willing and able to give informed consent for participation in the study.
2. A diagnosis of primary osteoporosis is confirmed by radiograph or DEXA scan (T score -2.5 SD below young adult mean) at lowest lumbar level with at least one painful vertebral fracture sustained previously.
   A vertebral fracture will be defined by a semi-quantitative method to existing radiographs, MRI or DEXA scans. A painful fracture is defined as patient reported back pain lasting for 24hrs or longer in the past 12 months (Visual analogue scale 3 or more). Individuals at different times post fracture and with different numbers and sites of fracture will be eligible.
3. Men and women aged 18 years or above will be eligible. Female participants will need to be postmenopausal as defined by the date of their last period which should be more than 2 years previously.
4. All participants will have had appropriate fracture prevention therapy (under NICE TA 161 guidelines)
5. All should be able to walk independently with or without an aid at least 10 metres and be able to understand and participate in a physiotherapy programme.

Exclusion Criteria

Individuals may not enter the study if they have any condition which might make participating in physiotherapy or exercise unsafe or confound results. This will include people with:

1. Severe unstable cardiovascular or pulmonary disease and significant psychiatric or neurological conditions.
2. Bone loss secondary to metabolic bone disorders or other disease will be also be excluded e.g.; rheumatiod arthritis, cancer, osteomalacia .
3. Primary problem is back pain with radiating pain into the lower limb
4. Individuals who have had vertebroplasty, facet joint injection or physical therapy e.g.; chiropractic, osteopathy or physiotherapy treatment for back pain in the previous 12 weeks. However, individuals who have had back pain and any of these treatments prior to this period will be eligible.

6. TRIAL PROCEDURES

6.1 Recruitment

Patients will be ideally be recruited over a 30 month period, but there is also a contingency period incorporated in to the project design (see Gantt chart). Participants will be identified for recruitment via the members of the Fracture Reduction in South Central Policy Network (FRISCy) – this includes all hospitals in the South Central region and associated General Practices. The trial will initially recruit from three centres for three months and after checking for and addressing any feasibility issues, will then gradually open recruitment to all sites. It is anticipated that 15-20 patients per month at each site will need to be screened, with an estimated take up rate of 50% of those eligible to achieve target recruitment rates. The trial team intends requesting assistance from the Musculoskeletal Thames Valley CLRN for their assistance to identify potential participants to approach to participate in the study (should GP practices request this form of support) and to assist trial recruitment (outlined

below). In addition to this, and subject to the necessary REC and R&D approvals, the lead clinician at each study site will identify potential participants from referrals for DXA scans and referrals to physiotherapy departments. The Nuffield Orthopaedic Centre will be the primary centre, with additional centres at Portsmouth, Southampton, Basingstoke, Reading, Stoke Mandeville, Milton Keynes, Winchester, High Wycombe and Slough. The participation of each centre has been agreed through the South Central Regional Physiotherapy Managers Network.

Recruitment via publicity in local media
The study will be advertised in local magazines and newspapers to further increase the recruitment potential. When a potential participant contacts the local PROVE research member through adverts, the study will be explained over the phone and contact details obtained to mailout the study information sheet along with a reply slip. The PROVE research member will emphasize that they may be able to participate only after the study eligibility criteria has been established through medical records. Written consent will be obtained via the reply slip (reply slip 2) to use their NHS number to establish diagnosis of osteoporosis and a vertebral fracture if they are local to the participating site. If they are not local to the participating site the potential participant will be requested to obtain their medical records from their GP to establish the same. Once the study eligibility is established using the NHS number by the research member the participant will then be contacted by phone to arrange a baseline assessment visit during which the main study consent will be taken. For participants who have obtained medical records from their GPs, an appointment will be made for them to come in to ensure eligibility requirements are met after which they will be enrolled into the study.

Recruitment Contingency. Recruitment rates will be monitored and discussed at all TSC meetings. Should the recruitment rate fall below projection, there is an additional contingency to extend the trial to centres outside of the FRISCy network and we have identified reserve sites at Birmingham & Swansea, through the Trauma and Orthopaedic Research Network.

Recruitment Rate. It is planned that each site will recruit for 12 months with a target to recruit 600 patients overall. That allows for the 10-20 centres participating to each recruit 5 patients / month. The target / centre / month will be moderated according to the size of the centre and the phase of the trial. The centres will be launched in stages, aiming to recruit from three centres for the first three months and then aiming to launch 3 sites per month. It is recognised that it is an ambitious target to launch centres so quickly. However the team have the capacity to allocate experienced researchers working on other projects to this activity during this busy phase, if necessary.

Table 1: recruitment targets

Target	**Trial Recruitment Period Month**														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
If 10 sites															
Sites	1	3	6	9	10	10	10	10	10	10	10	10	9	7	6

Monthly	5	15	30	45	50	50	50	50	50	50	50	50	45	35	30
Cumulative	5	20	50	95	145	195	245	295	345	395	445	495	540	575	605

Revised target to recruit upto 1st July 2016

Target	**Trial Recruitment Period Month Extended for 15 months beyond 31st March 2015**														
	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
20 sites															
Sites	15	15	17	17	20	20	20	20	20	20	20	20	20	20	20
Monthly	20	25	25	25	20	25	30	25	20	25	25	25	25	25	25
Cumulative	256	281	306	331	351	376	406	431	451	476	501	526	551	576	601

6.2 Approaching patients

Potential participants will be approached by clinicians at each study site during routine attendance for care. Clinicians treating/assessing potentially eligible participants for the study will introduce the study, hand out an invitation pack and obtain verbal consent for a PROVE / CLRN trained researcher to contact them. A screening log will be used by the clinicians. The study will be discussed with potential participants and informed consent sought for eligible participants.

6.3 Informed Consent

All potential participants will have had at least 48 hours to consider participating in the study prior to being contacted by a PROVE/CLRN researcher to discuss the trial and, if the person is eligible and agrees, to book a research visit. Informed consent will be sought at this visit by PROVE trial research clinician prior to any study interventions being provided.
Sites where the consenting and assessment locations are different, potential participants will be given study information pack during their routine visit and consent to be contacted by a research clinician to discuss the study further will be obtained. The participant will then be contacted by the PROVE/CLRN researcher via phone. Once the study is discussed and participant eligibility established an initial appointment will be made for them to come in to sign the informed consent in front of a GCP trained PROVE team member. The contact details of the participants who have signed the consent form will then be given to the assessing site PROVE team, who will then contact the patient for an appointment to come for a baseline assessment.
Additional informed consent will be sought for potential participants of the qualitative study; at least 48 hours will be given to consider participation. Research clinicians will explain the trial/study and answer any questions potential participants might have before seeking informed consent. All research clinicians will be trained in informed consent (CLRN group training, plus one-to-one training by a co-applicant of the trial team, plus practice) and be up-to-date in their GCP training. Competency will be assessed on a person by person basis and further training provided if/as appropriate: for example, in the unusual event of a research clinician being inexperienced in seeking informed consent, additional practice, plus

supervision of initial assessments will occur until competency is demonstrated to the trial team.

Participants consenting to participate in the study will undergo baseline assessment at their local trial site, following this assessment the assessor will telephone the independent randomisation centre.

6.4 Randomisation, blinding and allocation concealment

Randomisation will be performed by an independent statistician and implemented by the central telephone registration and randomisation service at the Warwick Clinical Trials Unit. Recruitment staff will register patients after confirming eligibility and consent, thus ensuring allocation concealment.
Baseline and follow up assessments will be performed by a blinded research physiotherapist to ensure investigator blinding at these points. These staff will not be involved in delivering the treatment interventions. Data will be entered by a data entry assistant to ensure the research physiotherapists remain blind to treatment assignment (for example treatment logs and patient diaries). All study personnel involved in data entry, management and analysis will be blinded until the final analysis is complete. Outcome assessors will be asked to guess the allocation assignment of each participant at each follow up assessment to determine the robustness of the blinding [40]. Additionally participants will be briefed prior to all assessments and asked not to reveal which treatment they have received. By virtue of the design it is not possible to blind the participants or the physiotherapists providing the treatment interventions.

After randomisation the Clinical Trials Unit will inform the lead clinician at each site regarding a participant's treatment allocation. The lead clinician will ensure that the referral is passed onto the appropriate clinician to provide the participant's intended group allocation.

6.5 Interventions

The interventions will be delivered by UK Health Care Professions Council registered physiotherapists with experience of musculoskeletal rehabilitation and each intervention will come within the scope of normal practice. Although the treatments are standardised it is considered important to allow therapists to personalise treatments as appropriate. For example, therapists will be able to omit or adjust the intensity of any technique or exercise to reflect an individual's capabilities and their progress.

Best practice usual care

Currently, relatively few patients are referred to formal physiotherapy for an osteoporotic vertebral fracture. Therefore, a single education session will form the usual care arm. The education will be general advice about osteoporosis, and lifestyle choices to promote bone health in line with the information available from the National Osteoporosis Society and NICE TA 161 [44]. Information will be provided in a single sheet tear off 'prescription pad' format to help make it accessible.

Active Interventions:

Participants in each active intervention group will be offered 7 individual physiotherapy sessions over 16 weeks; the initial session will last 60 minutes with subsequent sessions of 30 minutes. A 16 week programme was chosen to allow time to progress treatment intensity and achieve any gains in strength and mobility due to exercise and stretching [9, 29]. This pragmatic regime allocates equivalent physiotherapist contact time to participants in each intervention group and broadly reflects current outpatient physiotherapy resources within the NHS. Alongside individual sessions participants in each intervention group will receive education about osteoporosis and general advice about exercise.

Manual therapy intervention: Manual therapies will include low velocity spinal mobilisation performed without discomfort [8-10] and soft tissue mobilisation to erector spinae, rhomboids and upper trapezius muscles [9]. Postural taping will be used once weekly and it will be worn continuously for 3 days for the first 4 weeks if tolerated. It will be applied to create gentle skin traction and sensory feedback about posture when the individual moves into flexion [8, 9, 12]. The home programme will be a passive stretch that promotes thoracic extension for 15 minutes per day [4].

Exercise therapy intervention: The exercise programme will include active stretches, progressive balance and strength training and low to moderate intensity weight-bearing aerobic activity e.g.; walking. Participants will be trained to exercise safely and effectively e.g.; minimising the risk of falls, considering comfort, posture and spinal alignment. Exercises will be practised in the treatment sessions and continued in the home programme. The Rating of Perceived Exertion (RPE) scale will be used to set the initial load of strength exercises and walking duration elements at a self-perceived moderate level of effort, to facilitate monitoring and allow structured progression [45]. Participants will be asked to include short sessions of exercise within daily life, aiming to achieve a total of 60 minutes of exercise per day, 3 to 5 times a week depending on ability e.g.; a 30 minute walk along with 30 minutes of stretches, balance and strengthening exercises [30]. Stretches will promote spinal extension, shoulder flexion, hip extension and ankle dorsiflexion [30, 34]. Specific trunk extension and lumbar stabilisation exercises will be included. These will include prone trunk extension to neutral against gravity [4, 31, 32], there will also be upper body and lower body strengthening exercises including shoulder flexion in supine and bridging [24, 30, 34]. Specific balance exercises such as single leg standing will be included [26, 29] and wherever possible exercises will use body weight and gravity to provide resistance. To increase proprioceptive balance related cues e.g. sit to stand rather than knee extension using a weight will be encouraged [22]. We will use a series of educational and motivational strategies to foster compliance: clinician-patient goal setting, the provision of an exercise diary with a log sheet to record sessions, along with 2 scheduled telephone calls to support practice [46]. The 7 sessions in group C are frontloaded, most will take place towards the start of the 12 week intervention period (to teach and check exercise) and these two phone calls are intended to support the participant towards the end of the intervention period. The timing of these telephone calls will be at the clincian's discretion. Completion of home practice will be monitored through exercise diaries and compliance will be defined as 60% practice completion [30]. Participants undergoing interventions will be encouraged to continue their home exercises at the end of the active phase of the trial.

A member of the PROVE team will check each site's trial master form and meet with researchers and clinicians from each site on an annual basis (or more frequently should this be necessary). During these meeting, feedback will be sought re: trial procedures and (for the clinicians) the perceived acceptability of the intervention. Feedback will be documented and a copy of the minutes of the meeting will be returned to each site. Feedback will be discussed and actioned (if appropriate) at the Trial Management Group (TMG) and Trial Steering Group (TSC).

6.6 Adherence

Compliance with treatment will be defined as attending at least 4 sessions. The number of physiotherapy visits and content of treatment sessions will be recorded using both therapist completed treatment logs and patient exercise and participation diaries.

7. RESEARCH GOVERNANCE

Sponsor : The trial will be sponsored by the University of Oxford, who may also monitor or audit this study. The following groups will assume clear roles to support the trial and ensure appropriate good governance.
Trial Management Group (TMG) – The TMG will oversee the conduct of the trial and will consist of the PI, trial manager, service user and statistician. They will meet monthly. The TMG will ensure overall efficacy of the trial, compliance with protocols, ensure welfare of all participants and ensure the trial is appropriately reported and disseminated.
Trial Steering Group (TSC) – will consist of the PI, trial manager and statistician. It will appoint an independent chair from a centre not involved with the trial and independent clinical experts in both osteoporosis and rehabilitation. The TSC will have a minimum of 3 independent members. In addition, the committee will have a lay member with experience of osteoporosis. Observers from the HTA will be invited to all TSC meetings.
Data Monitoring Committee (DMC) – this will be convened with an independent statistician, clinician and chairperson. They will be tasked with reviewing the aggregated and comparative efficacy, safety and compliance data.

8. QUALITY MONITORING

Following the initial training provided to all PROVE trial assessors and clinicians involved in providing the intervention at all sites, the additional following procedures are in place to promote consistency and high quality trial procedures across all sites:

1. A member of the PROVE team will observe each assessor perform one of their first assessments to ensure assessments take place as per protocol. Repeat visits will be undertaken should any concerns arise until reliable and valid assessments take place.
2. Copies of all assessment forms will be sent to the trial co-ordinator on a monthly basis, who will check each one upon receipt to identify any issues re: missing data or poorly completed forms. The trial co-ordinator will contact individual assessors to discuss any arising issues/concerns.
3. A member of the PROVE team will observe each clinician perform one of their first treatments to ensure treatments adhere to the protocol.

4. Clinicians will be asked to complete a treatment log for each attendance by a trial participant – providing an approximate estimation of the time spent on key intervention components and detailing and explaining any deviations from the protocol.
5. A member of the PROVE team will check each site's trial master form and meet with researchers and clinicians from each site on an annual basis (or more frequently should this be necessary). During these meeting, feedback will be sought re: trial procedures and (for the clinicians) the perceived acceptability of the intervention. Feedback will be documented and a copy of the minutes of the meeting will be returned to each site. Feedback will be discussed and actioned (if appropriate) at the TMG and TSC.

9. QUALITATIVE STUDY

A subsection of trial participants will be invited to participate in a qualitative study. Participants will be made aware of this part of the trial and initial informed consent will be obtained as part of the main informed consent form. A subsection of participants will be sent letters inviting them to take part in the qualitative part of the study after they have completed the initial 16 weeks of the main trial intervention. Further informed consent will be obtained using a separate consent form upon receipt of a positive response.
Design: Qualitative study using Smith's experiential approach of interpretative phenomenological analysis (IPA) [41]. IPA is considered highly appropriate for this study since it aims to understand lived experience from the perspective of the individual. IPA explores how participants themselves make sense of their experiences and the meanings which those experiences hold for the participants.
Sample: Purposive sampling will be used to achieve a sample which includes; female and male patients, thoracic and lumbar single/multiple vertebral fracture patients and patients of varying activity levels. Fracture site, number of fractures and activity levels are known to influence outcome and, since the majority of research regarding osteoporotic patients' QoL has previously been undertaken with women, it is considered important to capture the views of male patients within the current study. 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 [42]. IPA recommends involving small numbers to gain a rich and in-depth account [41]. It is likely that 5 participants from each group (approximately 15 in total) will provide a rich insight into the experience of the intervention.
Methods: Trial participants will be invited to participate in in-depth semi-structured interviews following the intervention. While some questions have been prepared as part of a conversational guide, these will not be used as a rigid guide: follow up questions and probes will be used to help the interview flow, ensuring that relevant areas are covered and that participants can introduce new areas of discussion that they believe to be relevant [43]. Interviews will be held at a convenient time and location for each patient, from previous experience locally this is most likely to be at patient's homes. The first three patient interviews will be considered a preliminary phase; these interviews and their findings will be discussed between experienced qualitative researchers before further data collection continues. Interviews will be digitally recorded and fully transcribed. Field notes and memos

will be recorded using a digital notepad. IPA acknowledges that conducting and writing research are not neutral/objective acts and that interpretation of data is influenced by the researcher's own conceptions and processes of interpretative activity. Participants will be offered the opportunity to check their transcript, providing an opportunity for them to remove anything with which they do not feel comfortable (member checking). This will be done by post, with the option to also discuss the interview on the telephone if they prefer.

10. SAFETY REPORTING

Definition of Serious Adverse Events
A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Procedures for Serious Adverse Events
Any serious adverse event (SAE) occurring to participant/s during the study will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form. A copy should be sent to the Sponsor and appropriate Trust R&D office.

A serious adverse event is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

11. STATISTICS

11.1 Sample Size

The initial sample size calculation is based on a traditional approach to a 3 arm trial. We wish to detect a standardised effect of 0.4 in the QUALEFFO; at 80% power and an alpha of 0.05 we would require 180-200 participants in each arm or 540 to 600 people (we will use 600 people as the upper limit).

A simulation study was conducted to estimate the power of the probabilities of different outcomes at the interim analysis for a range of values for the standardised effects of the intervention arms relative to the control. In the simulation study, it was assumed that an intervention arm would be dropped at the interim analysis if the estimate of the mean effect for that arm was not more than 0.1 standard deviations greater than that for the control arm (corresponding to the planned critical difference of 0.5 points for a standard deviation of 5 points, as suggested by Bennell et al.2010)[9], and that the poorer-performing intervention arm would be dropped if the estimate of the mean effect was not more than 0.4 standard deviations less than that for the better-performing arm (corresponding to a difference of 2 points for a standard deviation of 5 points).
In the adaptive design of the type proposed, the power of the study may be defined to be the probability, given a truly effective intervention, that that intervention remains in the trial at the interim analysis and leads to a significant result in comparison to the control in the final analysis. The specified sample size was chosen to give 94 % power if the better of the two intervention arms has a true standardised treatment effect of 0.4.
The decision rule and sample size for the interim analysis is chosen to ensure that the power is high while the probability of continuing with an ineffective treatment is sufficiently low. If the true (unknown) treatment effect for an intervention is equal to the control, the probability of dropping that intervention at the interim analysis is approximately 73 %. If neither intervention is truly superior to the control, the probability of stopping the entire study at the interim analysis is approximately 60 %. Based on this interim analysis sample size, the standard error of the estimated difference between the intervention arms and the control arm at the interim analysis will be 0.82.

Qualitative study
IPA recommends involving small numbers to gain a rich and in-depth account [41]. It is likely that 5 participants from each group (approximately 15 in total) will provide a rich insight into the experience of the intervention

11.2 Data and Statistical Analysis

Approval for the fully specified data analysis plan, including pre-planned secondary analyses, will be obtained from the DMEC in the early stages of the trial. Data will be summarised and reported in accordance with CONSORT guidelines for randomised controlled trials. An intention-to-treat analysis approach will be used.

Treatment Effects: Hierarchical regression models will be used to estimate the treatment effects (with 95% confidence intervals) and will be adjusted for important co-variates (prior fracture history, fracture severity grade and age). The final statistical analysis will include data from patients from the control arm and intervention arm(s) continuing beyond the interim analysis from both the first and second stages of the trial. The analysis needs to allow for the adaptation made at the interim analysis in order to ensure that the probability of a type I error (false positive result) is controlled. It is proposed to use the analysis method described by Bretz et al. (2006) [47].

11.3 Interim analysis decision rules

The decision to adapt the trial following the interim analysis and whether to drop one of the treatment arms, or to continue will be made by an independent data monitoring committee, in collaboration with the trial Principal Investigator, trial statistician and a lay member. They will base their decision on the data from the interim analysis, using the rules below; together with data on any adverse events, any falls and further fracture history. An interim analysis will be conducted when the 16-week follow-up data is available for 75 patients per treatment arm. The aim of this interim analysis is to terminate either the manual therapy or exercise therapy arm if it appears to be poorly performing relative to the other intervention or to the control, or to terminate the trial completely if both intervention arms appear to be performing poorly relative to the control.

The interim analysis decision rule will be based on comparison of the estimated mean change from baseline in the QUALEFFO score for each of the three study arms.
Although the integrity of the trial in terms of type I error rate control does not require pre-specification of the decision rule to be used at the interim analysis, it is proposed to use the following rule to decide which intervention arm(s) should continue to be included along with the control arm in the second stage of the trial:

(1) If the mean change from baseline of the QUALEFFO score for an intervention arm is not more than 0.5 points greater than that for the control arm, that intervention arm will be dropped from the study. Note that under this rule both intervention arms might be dropped, in which case the study would stop due to futility.
(2) If the mean change from baseline of the QUALEFFO score for one intervention group is more than 2 points higher than for the other group, the intervention with the lower mean change from baseline will be dropped from the study.

These rules will lead to one of three outcomes:
Interim analysis outcome 1: The study may continue with a single intervention arm along with the control arm. This will occur if the observed mean change in QUALEFFO score for

one intervention arm exceeds that for the other intervention arm by at least 2 points and exceeds that for the control arm by at least 0.5 points.
Interim analysis outcome 2: The study may continue with both intervention arms along with the control arm. This will occur if the observed mean changes in QUALEFFO score for both intervention arms exceed that for the control arm by at least 0.5 points but the mean change for the better-performing intervention arm does not exceed that for the other intervention arm by more than 2 points.
Interim analysis outcome 3: The study is terminated. This will occur if the observed mean change in QUALEFFO score for neither intervention arm exceeds that for the control arm by 0.5 points.

These rules ensure that interventions only continue if they are sufficiently promising relative to the control, and that the most promising will be chosen to continue alone along with the control unless both are sufficiently promising and appear to be of similar efficacy, in which case both will continue.

Collection of QUALEFFO and EQ-5D-5L at 4, 6, 9 and 12 months will allow assessment of whether there is degradation of any treatment effect over time. This analysis will be carefully modelled alongside other potential confounding variables such as re-fracture and onset of any other co-morbidities. The modelling of serial measurements of functional outcome will assess the effectiveness of the interventions over time up to one year.

11.4 Data Analysis for the Qualitative Study

Audio recordings will be listened to and transcripts read until they become familiar. The data will be coded in accordance with IPA [41] which involves stages of coding data. Interviews will be broken down into discrete units, making concerted efforts to remain close to the data and to continually explore meaning. Units found to be conceptually similar will then be grouped together under more abstract categories and the findings written up. The process of constantly comparing data, codes and categories will occur throughout all data analyses. NVIVO 9 software will be used to assist in managing the data and presenting the findings to co-applicants during data analysis. The trustworthiness and rigour of the research will be enhanced by using memo writing, dependability and confirmability audits, a reflexive journal and peer review and these processes will be fully recorded throughout. Analysis will utilise Smith's experiential approach of interpretative phenomenological analysis (IPA) [41].

12. HEALTH ECONOMICS

A health economic evaluation is planned as an integral part of the trial design and will provide evidence on the cost-effectiveness of the intervention(s) selected for full evaluation by the adaptive trial design being adopted. The primary perspective for the analysis will be that of the NHS and Social Services. However, data collection will also be expanded to cover unpaid informal care (trial patients will be elderly and so the burden on relatives and/or friends may be substantial) and patient costs (previous studies have shown that patients suffering with back pain consult private practitioners including complimentary therapists) [54].

Costs: Information on the NHS resources required to implement the trial interventions including overheads, staff time, and equipment will be captured, and for each study participant data will be collected out to 12 months on NHS primary and secondary contacts, (including outpatient clinic attendances, hospital inpatient admissions, any additional rehabilitation, and GP and practice nurse visits), pain relief medication, provision of aids and adaptations, and admissions to nursing home facilities. Care provided by Social Services to 12 months (including home help and catering provision) will be documented and each patient will be asked about any costs they have incurred as a direct result of their vertebral fracture and about how much time friends and family have spent caring for them. Resource use will be valued using unit costs obtained from established national sources including the NHS reference costs, PSSRU costs of health and social care, and the Social Services database using SWIFT identifiers.
Outcomes: Patients in the trial will complete the EuroQol EQ-5D-5L questionnaire at baseline and at 4, 6, 9 and 12 months post-randomisation. Responses will be converted to a single index score of HRQoL using the tariff developed by Dolan et al. based on a sample of the UK general population, and used together with patient survival data, for the estimation of quality adjusted life years (QALYs) out to 12 months [50]

Cost-effectiveness analysis
Mean (and standard deviation) per patient costs and QALYs for the comparator and for the intervention(s) selected for the full 12-month evaluation through the adaptive trial design will be computed. Incremental analyses will be performed, with differences in costs and QALYs calculated, and an incremental cost(s) per QALY gained will be estimated. Results from the economic evaluation will identify the intervention with the greatest probability of being cost-effective given the NHS's willingness to pay for additional health gain.

13. DEFINITION OF END OF STUDY

The project will take 51 months to complete (See Project Timetable Gantt chart). The timetable is highly dependent upon the results of the interim analysis, which will occur once 70 participants have completed the 16 week intervention in each arm. At this point the decision will be taken to either adapt the trial to one intervention vs. control; continue with the 3 arm trial or stop the trial due to lack of evidence of effect for either treatment intervention. The timetable has allowed a contingency period, should our assumptions about the rate at which we can bring new centres into the trial and the rates they will recruit at, be overly optimistic. Extensive work has already occurred to secure the support of the Regional physiotherapy managers within South Central and we are confident that this, combined with our strong relationship with the CLRNs will allow us to proceed to plan. The projected start date of the study is 1st January 2013 and the final follow up visit for the final participant will be completed by the end of month 42 i.e. by June 2016.

Data analysis, economic analysis and report writing will be from month 45 onward. Summary results will be presented to TMG, TSC and DMC and user groups for comment. A full report will be prepared and submitted to the HTA, and other dissemination activities will be undertaken.

14. ETHICS

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and only a participants ID number will be used on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

Other Ethical Considerations

The trial will be conducted in compliance with the principles of the Declaration of Helsinki and MRC GCP guidelines [51].

Risks & Benefits: All participants will have access to usual care, and thus no treatment will be withheld from any trial participant. There is a slight risk that the treatment interventions could increase pain or may lead to an increase in further fracture rates (25% fracture rates may however be seen in the control group) and we will monitor for these carefully. A serious adverse event for this study is defined as any non-vertebral fracture or hospitalisation that occurs as a result of the treatment interventions.

A successful trial will yield substantial benefits overall, with clarification of the best treatment package to be offered for treating this difficult condition. Alternatively, the findings may demonstrate that physiotherapy interventions do not effectively treat this condition, thus allowing NHS resources to be saved and redirected to other more effective interventions.

The department's lone worker policy will be adhered to fully to ensure the safety of the qualitative interviewer.

15. DATA HANDLING AND RECORD KEEPING

All data and documentation related to the trial will be stored in accordance with applicable regulatory requirements and access to data will be restricted to authorised trial personnel. Identifiable study data will be based at the University of Oxford and will be accessed by authorised trial personnel. The Warwick Clinical Trials Unit will write a dedicated database under a clinical trials agreement, with clear rules about security of access:

- The randomisation database is separate from the trial database designed to store anonymised data. The randomisation database based at The University of Warwick will store details re: a participant's eligibility, study site, date of birth and initials (since this database serves as the central trial list of participants). This database will be password protected with access restricted to authorised trial personnel.
- All data will be double entered into the trial database.
- Participants will be identified by a study specific participants number and/or code in the trial database. The name and any other identifying detail will NOT be included in any trial data electronic file.
- A copy of the participant's consent form will be scanned into/ placed in the participant's medical notes and the originals kept, separate from any data, in site trial master files in a locked, secure environment.

In addition, to comply with the CONSORT statement, each study site will hold a screening log containing pt initials, age, gender and date approached to participate. These logs will be kept as hard copies at the site, with the site list of participants, in the site's trial master files. The screening log will be emailed to the study coordinator based at Oxford once a month by the site therapist responsible for maintaining the site master file.

The digital recordings of the audio data will have any personal details (e.g. names) that the interview inadvertently provides erased from these recordings (and therefore also erased on the electronic transcripts) by the interviewer. These anonymised files will be stored, using password protected files, using NVIVO 9 software.

16. FINANCING AND INSURANCE

This research is being funded by the NIHR Health Technology Assessment Programme ref: 10/99/01 - Physiotherapy Rehabilitation for Osteoporotic VErtebral fracture trial (PROVE). Sites will receive funding upon participant randomisation. This information is provided in Schedule 4 of the local site agreement and will be agreed upon by the Sponsor and Participating Site. The research is being Sponsored by the University of Oxford. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London, policy numbered :WD1200463). NHS indemnity operates in respect of the clinical treatment which is provided.

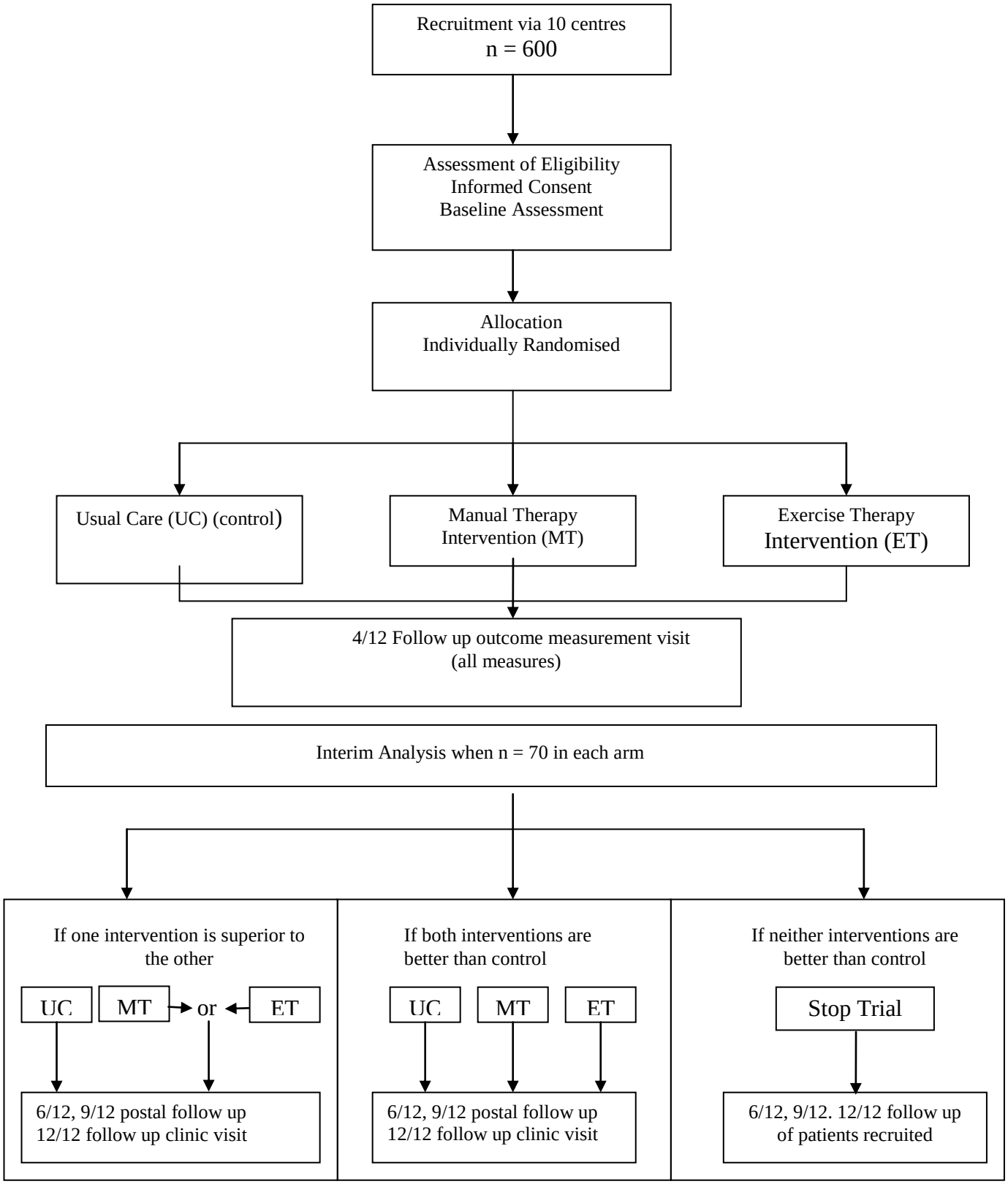
17. TIMELINE

The trial is funded to run over a period of 51 months and commenced in January 2013. The final follow up visit for the final participant is projected to be completed by the end of month 42 i.e. by June 2016. Data analysis, economic analysis and report writing will be from month 45 onwards.

Table 2: Project timetable

Project Activity	<0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
Develop educational support materials	X																					
Prepare 20 centres	X																					
Systematic review and reliability study evaluation	X																					
Site set-up/approvals	X	X																				
Train intervention providers	X	X																				
Main trial																						
Recruitment period		X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Review recruitment rates ? add sites		X	X		X		X															
Intervention treatment delivery		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
4-month follow-up			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Interim Analysis & Decision to adapt						X		x														
12-month follow-up							X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Qualitative Trial																						
Interviews patients & therapists												X	X	X	X							
Thematic Analysis												X	X	X	X							
Data analysis						X		X	X						X	X	X	X	X	X	X	X
Economic appraisal															X	X	X	X	X	X	X	X
DMC meeting		X				X			X			X		X			X			X		X
TSC meeting		X		X			X			X			X		X			X		X		X
Monitoring reports			X		X			X		X		X		X						X	X	X
HTA monograph/pubs																					X	X

FLOW CHART


Recruitment via 10 centres
n = 600
Assessment of Eligibility
Informed Consent
Baseline Assessment
Allocation
Individually Randomised
Usual Care (UC) (control)
Manual Therapy
Intervention (MT)
Exercise Therapy
Intervention (ET)
4/12 Follow up outcome measurement visit
(all measures)
Interim Analysis when n = 70 in each arm
If one intervention is superior to the other
UC
MT
or
ET
6/12, 9/12 postal follow up
12/12 follow up clinic visit
If both interventions are better than control
UC
MT
ET
6/12, 9/12 postal follow up
12/12 follow up clinic visit
If neither interventions are better than control
Stop Trial
6/12, 9/12. 12/12 follow up of patients recruited
Qualitative Study

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