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The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: The protocol for a semi-randomised controlled trial of targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass

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ABSTRACT

Introduction

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training and impact loading program in comparison to a supervised machine-based isometric exercise training program using the bioDensity™ system in older men with low bone mass. We will also determine the safety and acceptability of each exercise training mode. Intervention group responses will be compared with those of a self-selected, non-randomised control sample of sex- and age-matched men who will follow their usual lifestyle activities for eight months.

Methods and analysis

Apparently-healthy men over fifty years with low bone mass, screened for medical conditions and medications known to adversely affect bone health, will be recruited. Eligible participants will be randomly allocated to eight months of either exercise program with block randomisation based on presence or absence of osteoporosis medications. A twice-weekly, thirty-minute, supervised exercise program will be conducted for both groups. The primary outcome will be change in femoral neck areal bone mineral density determined by Dual-energy X-ray Absorptiometry (DXA). Secondary outcomes, assessed at baseline and eight months, will include: DXA-derived whole body, bilateral proximal femur and lumbar spine areal bone mineral density; proximal femur bone geometry and volumetric density extracted using 3D hip analysis software; anthropometry; body composition; kyphosis; vertebral fracture assessment; physical function; safety (adverse events and injuries); and compliance. Intention-to-treat and per-protocol analyses will be conducted.

Discussion

Whether a high-load, low-repetition progressive resistance training plus impact loading program or a machine-based isometric exercise program can improve determinants of fracture risk, without causing injury, has not been examined in men. Determination of the efficacy, safety and acceptability of such programs will facilitate formulation of future exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who have previously been underrepresented.

Ethics and dissemination

Participant confidentiality will be maintained with publication of results. The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC).

Trial registration number

Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)

ANZCTR12616000344493; Pre-results.

Date and version identifier

Original protocol manuscript for submission (Version 1): November 2016.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised high intensity, progressive resistance training and impact loading program on several determinants of fracture risk for older men with low bone mass, compared with a machine-based isometric exercise program using the bioDensity™ system.
- Owing to the higher prevalence of osteoporosis and associated fracture in women, there are few investigations into the effects of exercise on musculoskeletal health in older men. The current unique focus on older men with poor bone health will therefore address a notable gap in the literature.
- The engagement of a non-randomised control group of demographically-matched men who have elected not to exercise for eight months is a design limitation that was implemented for pragmatic reasons. Our pilot testing demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of male study volunteers to adhere to a control requirement to refrain exercise for eight months when they volunteered under the expectation to participate in exercise. We argue that there are also ethical issues of withholding exercise under those conditions.
- Our study sample will include largely healthy older men, so our findings may not be applicable to men with comorbidities or other exclusion characteristics.

INTRODUCTION

Epidemiological data indicates the global prevalence of osteoporosis to be over 200 million,[1] with around 1.2 million Australians,[2] 10.2 million Americans [3] and 15 million European men and women over fifty years of age being effected.[4] It has been suggested that 285,000 Australian men aged over fifty will be diagnosed as osteoporotic, and a further 2.48 million older men diagnosed as osteopenic by 2022.[5] With the aging of the population, there will undoubtedly be a corresponding increasing prevalence of low bone mass and consequent increase in the incidence of low trauma fracture.[6]

It is widely accepted that bone adapts to the mechanical loads it habitually experiences. Experimental data from animal models has revealed the most influential loading characteristics for osteogenesis are magnitude,[7,8] rate [9] and frequency [10-12] of the engendered strain. Evidence also indicates dynamic loading is more osteogenic than static loading.[13] The optimal exercise prescription for the prevention and management of osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads, applied at a rapid rate. High-load resistance training with high-impact jumping, the combination of which will elicit high strains and strain rates in bone, is thus theoretically the optimal exercise protocol for bone. Although such exercise is considered safe for healthy individuals with normal bone mass, it is unclear whether it will be safe for individuals with reduced bone mass who are at increased risk of fracture. Previous therapeutic exercise recommendations for individuals with low bone mass, particularly those who have experienced a low trauma fracture, have been conservative; focussing largely on low intensity fall prevention training (i.e. balance and mobility exercises).[14,15] Such low to moderate intensity exercise programs impart a sub-optimal osteogenic stimulus, as they incur negligible strain in bone.

Recently a bone-targeted, high intensity, progressive resistance training and impact loading (HiPRT/Impact) exercise program was undertaken with postmenopausal women with low to very low bone mass at the hip or spine - the LIFTMOR (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation) trial. Preliminary results revealed the HiPRT/Impact protocol to be both safe and effective, reporting positive changes to musculoskeletal health in this population at increased risk of fragility fracture.[16] In light of the fact that osteoporosis affects men as well as women, it was necessary to replicate the protocol in older men to determine if it will be similarly effective.

Separately, but simultaneously with the LIFTMOR trial, an isometric device (the bioDensity™ system, Performance Health Systems, Northbrook, IL, USA) was developed in the USA to facilitate near-maximal isometric contractions against instrumented external resistance, with a goal to increase bone mass. The developers are currently marketing the device on the grounds that short-duration, low-volume, high-load bioDensity™ training can enhance bone mass in individuals with osteoporosis, however, concrete evidence is lacking. The Griffith University Bone Densitometry Research Laboratory has acquired a bioDensity™ device for the purposes of examining safety and efficacy alongside the HiPRT/Impact protocol in a semi-randomised controlled trial design.

METHODS AND ANALYSES

Ethics and dissemination

The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC), and all research activities will be conducted in accordance with the *Declaration of Helsinki*. The study is also registered with the Australian New Zealand Clinical Trials Registry (Trial number ANZCTR12616000344493). Written informed consent will be obtained from all participants prior to testing by the investigator performing baseline assessments.

Pilot men's data and the LIFTMOR for women trial provide evidence of an extremely low risk of injuries from the current exercise protocols, with no severe injuries reported from a total of 7300 training sessions. Early termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety Monitoring Board was not engaged. Instead, data will be monitored via annual progress reports to the Griffith University Human Research Ethics Committee. Any adverse events which occur between annual reports will be reported independently to the Griffith University Human Research Ethics Committee, in compliance with the *Australian Code for the Responsible Conduct of Research* developed by the National Health and Medical Research Council, and the University *Code for the Responsible Conduct of Research*. For participants who are unaccustomed to physical activity it is likely they will experience some degree of muscle soreness following any change in exercise exposure. In the unlikely event that a participant experiences significant intervention-related muscle soreness, or an injury occurs during the study period, consultations with a qualified Physiotherapist (external to the trial) at the Griffith University Allied Health Clinic will be available. If further treatment is required they will be referred to an appropriate healthcare professional.

All participants will be supplied with a full summary of individual and overall study results to encourage retention for the duration of the study, and to comply with ethical requirements.

The usual scientific reporting practices will take place, including presentations at discipline meetings and publication in peer reviewed journals. Community and clinical talks will also be given as appropriate. Participant confidentiality will be maintained with publication of results.

Study aims

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training plus impact loading (HiPRT/Impact) program in comparison to supervised bioDensity™ machine-based isometric exercise training, or no intervention (control), for improving femoral neck (FN) bone mineral density (BMD) in older men with low bone mass. The primary outcome measure was selected according to clinical relevance, in light of the large personal and economic impact of hip fracture. It is hypothesised that eight months of twice-weekly HiPRT/Impact training will improve FN BMD more than bioDensity™ training or control, and similar benefit will be observed in secondary outcome measures. Furthermore, we hypothesise that there will not be a higher rate of adverse events during eight months of HiPRT/Impact compared with bioDensity™ training or control.

Study design

The current project is a three-arm, eight-month, semi-randomised, controlled exercise intervention trial. Proposed participant flow is outlined in Figure 1. The eight-month exercise intervention period has been chosen as the minimum time frame in which notable changes in bone mass are likely to be detected from densitometry.[17] Eligible volunteers to the intervention arm will be randomly assigned to one of two exercise programs; either supervised HiPRT/Impact or bioDensity™ training. The third arm will be a non-randomised

control group of sex- and age-matched participants with lower than average bone mass recruited from the same community. The control group will follow their usual lifestyle for eight months, but undergo identical testing to the two exercise intervention groups at baseline and follow-up. We acknowledge the somewhat unorthodox semi-randomised design does not constitute the most rigorous clinical trial practice, but adopt it out of necessity. Pilot testing conducted in our laboratory revealed that male study volunteers who expect to participate in an exercise trial, but are randomised to a conventional inactive control group, refuse to adhere to the requirement to refrain from exercise for eight months. We also believe that it is unethical to withhold access to a potentially beneficial bone-targeted exercise program for older men at increased risk of fragility fracture who are specifically seeking exercise therapy. For pragmatic reasons then, we will independently recruit a demographically-matched sample of men who, for a variety of reasons (not including functional capacity), elect to remain sedentary for a minimum of eight months.

Sample size

There have been no published reports of men's studies comparing the effects of heavy progressive resistance training and machine-based isometric training using the bioDensity™ system on FN BMD, thus estimates of sample size were based on the reported rate of annual loss. For men over the age of fifty, longitudinal studies have reported an annual loss of 0.42 to 0.45 % FN BMD per year.[18,19] Thus, to detect a significant difference in FN BMD change, from a two-tailed test with a power of 80 % and $\alpha = 0.05$, approximately 32 participants per group will be required. Allowing for a 20 % dropout, a total of 38 participants per group is required. The 20 % dropout rate reflects those reported in previous bone-targeted exercise interventions in men,[20-22] and the dropout rate of randomised controlled intervention trials in adults (20.9 %).[23] Recruitment for this study started in May 2016, and will continue until the planned sample size is achieved.

Setting and recruitment

Baseline and follow-up assessments, and supervised training, will be conducted at Griffith University, Gold Coast, Queensland, Australia. Methods of recruitment include local media outlets (print media and radio), social media, official website (www.liftmor.org), word of mouth, and notice board flyer advertisement at local lawn bowls clubs, golf clubs and senior citizens clubs.

Eligibility and screening

Apparently healthy, able-bodied men over fifty years of age will be recruited. Volunteers are to be excluded if they have any of the following: uncontrolled cardiovascular or respiratory disease; disclosure of musculoskeletal or neurological conditions likely to affect their ability to perform exercise; medications known to affect bone metabolism (e.g. corticosteroids, thyroxine, antiepileptic, and antiretroviral agents); medical conditions known to affect musculoskeletal health (e.g. Paget's disease, hyperparathyroidism, and thyrotoxicosis); current participation in high-load resistance or impact-type exercise; metal implants (e.g. joint prostheses); recent radiation therapy or radiographic investigations; recent fracture or lower extremity surgery; or malignancy. Further exclusion for the exercise arm will be based on an inability or unwillingness to take part in eight months of twice-weekly exercise training due to motivation, travel or work commitments. No upper age limit is stipulated. Potential participants who contact the investigator will initially undergo a preliminary phone screening for inclusion and exclusion criteria. If eligibility is established, prospective participants will be invited to attend the University research facility for BMD screening and, when relevant, to undergo baseline assessments. Potential exercise intervention participants and self-selected age-matched men will then undergo preliminary Dual-energy X-ray Absorptiometry (DXA) scans. If osteopenia (T-score between -1.0 and -2.5) or osteoporosis (T-score < -2.5)

is detected at the lumbar spine and/or proximal femur, the individual will be eligible for inclusion and the full suite of scans. Participants will be discontinued if they: 1) withdraw consent, 2) cease to attend training sessions for longer than three weeks, 3) initiate or discontinue osteoporosis medications, or initiate medications known to effect bone metabolism, 4) become injured and unable to participate, 5) perform additional forms of exercise such as resistance training or impact-type exercise external to the trial, and 6) are advised by their general practitioner to cease training.

Randomisation and allocation

Allocation of eligible participants to the supervised HiPRT/Impact and bioDensity™ training groups will be achieved via block randomisation, stratified by the presence (more than twelve months exposure) or absence (lack of exposure) of osteoporosis medications, using a computer-generated randomisation sequence (www.randomization.com, accessed 17th May 2016). To ensure concealment, the allocation sequence will be prepared in advance by an external source, and filed in sequentially-numbered, sealed, opaque envelopes. Upon completion of baseline testing those identified as eligible will be randomly allocated to their exercise group and their supervised exercise training sessions will be scheduled.

Exercise interventions

Progressive resistance training and impact loading exercise program

The HiPRT/Impact group will perform approximately thirty minutes of supervised, high-load, free weight training and impact loading, twice-weekly, on non-consecutive days. During the initial two weeks, participants will perform low-load variants of each exercise focussing on technique. Following this familiarisation period, sessions will comprise three fundamental compound movement exercises (deadlift, squat and overhead press) at five sets of five

repetitions, corresponding to greater than 80 to 85 % of one repetition maximum. Load magnitude will be progressively increased in increments of 2.5 kg over the course of the intervention when they are able to easily complete seven repetitions at their current weight. In addition, five sets of five repetitions of jumping chin-ups (interspersed with rest) with a firm, flat-footed landing will be performed each session. Impact intensity will be gradually increased by moving towards achieving a stiff-legged landing as tolerated. Participants will provide a Rating of Perceived Exertion (RPE) with the aid of the 6-20 point Borg scale [24] at completion of each training session. Training will be fully supervised by a qualified exercise scientist. Weight progressions and RPE will be recorded in training diaries.

Machine-based isometric exercise program

The supervised bioDensity™ group will exercise twice-weekly, on non-consecutive days to match the HiPRT/Impact group protocol. Four exercises will be performed; chest press, leg press, core pull, and vertical lift. The chest press and leg press closely mirror conventional strength training equipment, the core pull movement combines an abdominal crunch with an underhand chin-up, and the vertical lift simulates a high-hang deadlift position. One self-initiated near-maximal five-second isometric contraction will be performed for each of the four exercises (per manufacturer's recommendations), with integrated monitors providing real-time peak muscle force production feedback. Participants will provide an RPE with the aid of the 6-20 point Borg scale [24] for each exercise. They will be instructed to achieve a near-maximal five second isometric contraction at an intensity corresponding to greater than 80 to 85 % of one repetition maximum, translating to an RPE of greater than sixteen on the 6-20 point Borg scale.[25] A single qualified trainer will supervise all sessions to operate the bioDensity™ system, and ensure the exercises are performed correctly and safely. Peak force, average force and RPE will be recorded in participant training diaries.

Control group activities

The sex- and age-matched control group will be encouraged to maintain their customary physical activity and dietary patterns over the eight month duration of the study. To monitor deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to list variations to their physical activity level and diet on a fortnightly basis. Space is also provided to record any illness, injuries other than muscle soreness, falls, fractures, changes to their medical conditions and medications (inclusive of over the counter medications). Diaries are to be returned at follow-up. Fortnightly emails will act as reminders to complete diary entries, with a monthly email requiring a reply to the investigator to prompt recording of any relevant changes. To detect change in bone-relevant physical activity or dietary calcium intake over the course of the eight-month study, participants will complete questionnaires (described below) at baseline and follow-up.

Outcome measures

All outcome measures will be performed at baseline and eight-month follow-up by a single investigator, using identical facilities, procedures and equipment. A summary of outcome measures is presented in Table 1.

Primary outcome

The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink, France).

Secondary outcomes

Secondary outcomes (described in more detail below) will include: changes in anthropometrics, as well as in whole body and regional measures of bone, muscle and fat. Kyphosis will be examined in order to track angular changes of the spine with exercise exposure. Vertebral fracture assessment using the Genant semiquantitative approach [26]

from lateral thoracolumbar spine imaging will be conducted pre- and post-intervention by DXA. A series of commonly utilised performance tasks will be employed to examine changes in lower extremity muscle force and power, dynamic balance, and maximal trunk extensor strength in keeping with standard protocols. Standardised instructions will be provided for all performance tasks, with the best performance of three trials to be included in the analyses. Previously validated questionnaires will be used to estimate dietary calcium consumption, current and past bone-relevant physical activity, quality of life and exercise appeal. Participant safety (adverse events and injuries) and compliance will be monitored across the intervention period using training diaries.

Bone strength indices

Whole body, bilateral proximal femur (trochanter and total hip regions), and lumbar spine areal BMD, bone mineral content and bone area will also be determined by DXA. Parameters of proximal femur (femoral neck and total hip regions) trabecular and cortical bone geometry and volumetric density will be extracted from standard DXA scans using 3D hip analysis software (DMS Group, Mauguio, France). Quantitative Ultrasonography will be used to evaluate changes in calcaneal bone quality (QUS; Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA). Volumetric BMD and geometric parameters contributing to bone strength at the tibia (4 %, 14 %, 38 % and 66 % sites) and radius (4 % and 66 % sites) will be determined from peripheral Quantitative Computed Tomography scans of the forearm and leg (pQCT; XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). pQCT-derived bone parameters will include: total content, density and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, density, cross-sectional area and thickness; periosteal and endocortical circumference; and biomechanical strength indices calculated from density and area (total and trabecular bone strength indices, polar section modulus, and polar strength strain index).

Anthropometrics and body composition

Height will be measured via the stretch stature method with a wall-mounted stadiometer Model 216; Seca, Hamburg, Germany). Weight will be measured using a mechanical beam scale without shoes and in light clothing (Model 700; Seca, Hamburg, Germany). Body mass index will be determined per the accepted method (Body Mass Index = weight/height^2; kg·m^{-2}). Waist circumference, a predictor of visceral abdominal adiposity, will be measured using a steel tape following National Institute of Health guidelines (Model W606PM; Lufkin Executive Thinline, Apex, USA).[27] Briefly, the tape will be positioned on the horizontal plane at the level of the iliac crests on bare skin, and recorded at the end of gentle expiration. Body composition parameters inclusive of lean mass, fat mass, appendicular lean mass and percentage body fat will be derived from whole body DXA. Muscle cross-sectional area, an index of muscle size, and muscle density, an index of intramuscular fat, will be determined from pQCT scans of the forearm and leg at the 66 % site.

Thoracic kyphosis and vertebral fracture assessment

Thoracic kyphosis will be assessed in relaxed standing (neutral posture) and standing 'at attention' using a gravity-referenced inclinometer, following a procedure similar to MacIntyre and colleagues (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia).[28] The inclinometer will be zeroed at the twelfth thoracic to first lumbar intervertebral space, and the angle at the seventh cervical to first thoracic intervertebral space recorded. Lateral thoracolumbar spine DXA will be performed in the lateral decubitus position to calculate Cobb angle via two methods: 1) vertebral body endplates, and 2) anterior vertebral body margins. The superior endplate of the forth thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra will be manually digitized, perpendicular lines extended and the angle at their intersection measured.[29] To account for endplate angulation and tilt due to vertebral irregularity, the anterior margins will be digitized and the angle at their intersection measured.[30] In addition, lateral thoracolumbar spine DXA allows vertebral fracture identification using the Genant method.[26] The anterior, medial and posterior heights of the

vertebral body are used to grade (mild, moderate or severe) wedge, biconcave or crush deformity.

Timed up-and-go

The timed up-and-go test is a measure of functional mobility, and dynamic balance.[31] Participants will be instructed to rise from a seated position without using their hands for assistance, walk at a brisk pace to a mark on the floor a distance of three meters away, pivot, and return to assume the start position. Participants will be timed from the point at which their back no longer makes contact with the chair, to when they return to the start and adopt the correct seated position.

Five-times sit-to-stand

The five-times sit-to-stand is a reliable assessment of the ability to rise unassisted from a seated position, with relevance to functional mobility, dynamic balance and lower extremity muscle strength.[32] Participants will be asked to move from a sitting to standing position, without the use of their arms, for five repetitions following the recommendations of Bohannon and colleagues for assessing older adults.[33]

Functional reach

A modified version of the original functional reach test (that incorporated a yardstick) will be used to assess dynamic balance, which has been identified as an important component of falls risk.[34] Participants will stand with shoulders perpendicular to a Perspex board marked with vertical measurement lines, dominant arm extended so the shoulder is flexed 90 °, and hand forming a fist. The participant will be instructed to reach forward by flexing the trunk at the hip, maintaining a fixed base of support, without stepping or losing balance. The start and finish positions of the third metacarpal in respect to the measurement lines will be recorded to determine displacement.

Muscle power

Lower extremity muscle power will be assessed by a countermovement vertical jump test. Participants will be instructed to perform a jump for maximum height, without arm swing, whilst positioned on a floor-mounted 900 mm x 600 mm load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA). Impulse and impulse relative to body weight will be calculated from the vertical component of the ground reaction force of the loading and take-off phase according to the method described by Linthorne.[35]

Isometric muscle strength

Maximal isometric force of the lower extremity will be estimated using a leg strength platform dynamometer (TTM Muscle Meter, Tokyo, Japan). The participant will stand on the dynamometer platform assuming a semi-squat position with knees flexed 65 º (knee angle of 115 º), trunk extended and back flat against the wall. A straight bar handle is affixed to the dynamometer by a chain at a length so the arms are fully extended to grip it. After ensuring the chain is taut, the dynamometer is manually zeroed. Participants will be instructed to attempt to straighten their legs, whilst keeping their back fully in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.84$, $p < 0.001$; test-retest reliability $r = 0.97$, $p < 0.001$). (Little A, Harding AT, Weeks BK, Horan SA, Watson SL, and Beck BR, 2016; unpublished data; conference abstract)

Maximal isometric back extensor muscle strength will be assessed in erect standing using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA). The participant will be positioned midway between two vertical wall-mounted anchor rails, with an inelastic belt fastened horizontally around the hips in order to restrain the pelvis. The padded transducer pressure plate will be positioned over the seventh thoracic vertebral spinous process. Participants will be instructed to push back into the wall with their shoulders,

ensuring their feet remain flat with their heels in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.85$, $p < 0.001$; test-retest reliability $r = 0.93$, $p < 0.001$). (Harding AT, Weeks BK, Horan SA, Little A, Watson SL, and Beck BR, 2016; Unpublished data; conference abstract)

Dietary calcium intake

Calcium intake will be assessed using the AusCal, a calcium-focused food frequency questionnaire designed and validated for the Australian diet.[36] Frequency of consumption per day, week or month, and approximate serving size will be recorded for each of the listed calcium-rich food and beverage items over the previous year. The AusCal will be investigator-administered. Questionnaire responses will be entered into customised FoodWorks analysis software to generate average daily calcium intake (Version 7, Xyris Software, Brisbane, Australia).

Bone-specific physical activity

The Bone-specific Physical Activity Questionnaire (BPAQ) [37] will be used to quantify current and historical physical activity of relevance to bone. Respondents will list all regular, structured physical activity and years of participation, with a minimum of investigator assistance. BPAQ scores will be calculated using an on-line, custom-designed analysis program (http://www.fithdysign.com/BPAQ/). Mathematical algorithms in the calculator were developed using load ratings from vertical ground reaction forces of each activity, participation frequency, years of involvement and an age-weighting factor. High loading ratings represent high-impact activities, whilst the age-weighting factor reflects higher mechanosensitivity to physical activity during youth. Previous research has found BPAQ scores are predictive of variance in DXA-derived bone strength parameters at clinically

relevant sites in healthy middle-aged and older men.[38] This instrument has high reliability, with intra-class correlation coefficients of 0.92 to 0.97.[39]

Exercise appeal

The Physical Activity Enjoyment Scale (PACES), designed by Mullen and colleagues,[40] is a self-reported eight-item questionnaire which uses a seven-point Likert scale for each item. The respondent is required to circle the number corresponding to their current thoughts about physical activity. Higher PACES scores indicate a greater level of exercise appeal. Inclusion of this instrument was based on physical activity enjoyment being identified as a potential determinant of exercise adherence.[41]

Quality of life

The World Health Organisation Quality of Life questionnaire was developed to assess four quality of life domains using a five-point Likert interval scale.[42] Higher scores are indicative of higher quality of life. Participants will self-complete the questionnaire. Internal consistency across a large heterogeneous population from a field trial during its development showed each domain to have moderate to high Cronbach's α levels; physical health (α = 0.82), psychological health (α = 0.81), social relationships (α = 0.68), and environment (α = 0.80).[43]

Safety and compliance

Prior to each training session participants will rate their level of muscle soreness on a ten-point visual analogue scale, and note alterations to their diet, physical activity, health or medications since their previous session. Injuries other than muscle soreness, illness, falls and fractures will be documented. Attendance will be entered to determine program compliance, with 100 % being defined as completion of seventy sessions over the course of eight months. Adverse events will be fully documented by investigators, and monitored across the intervention period.

Table 1. Summary of outcome measures

Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Medix DR, Medilink, France)
Secondary outcome measures	
Other bone outcomes	
Whole body aBMD, BMC and bone area; lumbar spine aBMD, BMC and bone area; and proximal femur (trochanter and total hip regions) aBMD, BMC and bone area	DXA scans (Medix DR, Medilink, France)
Femoral neck (trabecular, cortical and total) BMC, vBMD and volume; total hip (trabecular, cortical and total) BMC, vBMD and volume	Proximal femur DXA scan (Medix DR, Medilink, France), 3D hip software (DMS Group, Mauguio, France)
Calcaneal broadband ultrasound attenuation, speed of sound and stiffness index	Calcaneal QUS (Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA)
Total content, vBMD and cross-sectional area; trabecular content, density, and cross-sectional area; cortical content, vBMD, cross-sectional area and thickness; periosteal and endocortical circumference; total and trabecular bone strength indices; polar section modulus; polar strength strain index	Forearm 4 % and 66 % sites, and leg 4 %, 14 %, 38 % and 66 % sites pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)
Anthropometry	
Height	Wall mounted stadiometer (Model 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model 700; Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lufkin Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix DR, Medilink, France)
Muscle cross-sectional area and muscle density	Forearm 66 % site and leg 66 % site pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)

Thoracic kyphosis	Plurimeter gravity referenced inclinometer (Australasian Medical & Therapeutic Instruments, Australia) Lateral thoracolumbar spine DXA (Medix DR, Medilink, France)
Vertebral fracture assessment	Lateral thoracolumbar spine DXA (Medix DR, Medilink, France)
Functional performance	
Timed up-and-go	Digital stopwatch (Fisher Scientific, USA)
Five-times sit-to-stand	Digital stopwatch (Fisher Scientific, USA)
Functional reach	Perspex board with measurement grid-lines
Muscle power	
Countermovement vertical jump	Load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA)
Isometric muscle strength	
Lower extremity strength	Leg platform dynamometer (TTM Muscle Meter, Tokyo, Japan)
Back extensor strength	Dynamometer (Lafayette Manual Muscle Testing Systems, USA)
Dietary calcium intake	AusCal questionnaire
Bone-specific physical activity	Bone-specific Physical Activity Questionnaire (BPAQ)
Exercise appeal	Physical Activity Enjoyment Scale (PACES) questionnaire
Quality of Life	World Health Organisation Quality of Life (WHOQOL) questionnaire
Safety (adverse events and injuries) and compliance	Purpose designed lifestyle diaries and training diaries Trainer records

aBMD, areal bone mineral density; BMC, bone mineral content; BPAQ, Bone-specific Physical Activity Questionnaire; DXA, Dual-energy X-Ray Absorptiometry; PACES, Physical Activity Enjoyment Scale; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density; WHOQOL, World Health Organisation Quality of Life.

Data integrity

Participants will be allocated a unique study ID and data will be de-identified for analysis. After final data collection and cleaning, the data will be locked before analysis. Paper records will be stored securely at Griffith University in a laboratory with restricted swipe card access, and retained for a minimum of fifteen years. Electronic data will be stored securely on password-protected University computers. Management, storage and retention of research data will be in line with Griffith University policy, the *Griffith University Code for the Responsible Conduct of Research*. There will be no contractual agreements limiting data set access. De-identified data will be shared for meta-analyses or other collaborations on a case by case basis.

Blinding

The study will be single-blind; participants in the two exercise groups will only be aware of the details of their allocated exercise protocol. They will train separately, and will not be apprised of study hypotheses. The investigator performing baseline assessments will be blinded to the allocation sequence, which will be revealed to both investigator and participant only after baseline testing. As the assessor will also be training the participants, in order to maintain the highest level of test-retest reliability, follow-up testing will not be assessor blinded. The study is an unfunded PhD student project.

Data analyses

Statistical analyses will be undertaken using SPSS Version 23.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics of participant characteristics, biometric and dependent variables will be presented as means ± standard deviations and frequencies where appropriate. Comparisons at baseline will be evaluated using independent sample *t*-tests (two-tailed) for normally distributed continuous data, and Chi-Square for categorical data. Between-group

comparisons for outcome measures will be examined using repeated measures Analysis of Covariance for time and group-by-time interaction effects, controlling for age, height, weight, baseline values, calcium intake and training program compliance. In accordance with the principles of a classic intention-to-treat approach, all randomised participants will be included in the final analyses, regardless of withdrawal or compliance. In the case of missing data, mean imputation will be used. Per-protocol exploratory analyses will be performed comparing outcome measures between the HiPRT/Impact, bioDensity™ and control groups for those with training program compliance of greater than 70 % to examine maximum treatment efficacy. Multiple linear regression analyses will be employed to examine the relative influence of certain variables on the bone response. Statistical significance will be set at $p \leq 0.05$.

DISCUSSION

To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised HiPRT/Impact exercise program on determinants of fracture risk for older men with low bone mass, compared with supervised bioDensity™ training or control. To date, exercise prescription recommendations for individuals with osteoporosis have stipulated low to moderate intensity exercise,[14,15] which does not provide an adequate stimulus to elicit osteogenic adaptation. Both the HiPRT/Impact and bioDensity™ exercise programs are designed around key loading characteristics known to be osteogenic in animal models, and adhere to the principle of progressive overload. The execution of the current trial is warranted in order to progress exercise recommendations for older men with who are at increased risk of fracture. Trials that have implemented higher intensity (> 80 % of one repetition maximum) compound movement resistance training exercises in older adults have demonstrated such exercise can be safely performed (no adverse events were reported), with positive effects on bone mass and muscle strength [16,44] but little is known about the response in men with low to very low bone mass. The original high-load LIFTMOR trial [16] was implemented in postmenopausal women with low to very low bone mass. Maddalozzo and Snow [44] included older men and postmenopausal women of unknown bone health status (no baseline T-scores were reported) in their study. Evidence confirming the ability of high-load bioDensity™ training to improve bone health in older men with osteopenia or osteoporosis is also lacking. It is intended that the findings of our unique trial will provide further insight into exercise recommendations for the prevention and rehabilitation of osteoporosis in men.

Acknowledgements

The authors wish to acknowledge Ms Lisa Weis for her pivotal role in developing the original heavy resistance training program implemented in the LIFTMOR trial.

Author Contributions

Conception and design of the study: ATH, BKW, SLW, BRB; Obtained the equipment award brokered by Osteoporosis Australia: BRB; Manuscript preparation and editing the final paper for submission: ATH, BKW, SLW, BRB; Preparation of Information Sheets, Consent Forms, and Case Report Forms: ATH, BKW, SLW, BRB; Participant recruitment and data collection: ATH; Principle investigator: BRB.

Competing Interests

The Authors declare that there is no conflict of interest in preparing this article.

Funding Acknowledgements

This work was supported by Performance Health Systems (Northbrook, IL, USA) with the supply and installation of the bioDensity™ system through an equipment award (no grant number available) brokered by Osteoporosis Australia (Glebe, NSW, Australia). These funding sources have no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit the results.

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Ethics Approval

The trial has received ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC), and has been prospectively registered with the Australian New Zealand Clinical Trials Registry (#ANZCTR12616000344493).

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Figure legend

Figure 1. Proposed participant flow (CONSORT diagram)

bioDensity™, machine-based isometric exercise using the bioDensity™ system; DXA, Dual-energy X-Ray Absorptiometry; HiPRT/Impact, high-load progressive resistance training plus impact loading; ITT, intention-to-treat; RT, resistance training.

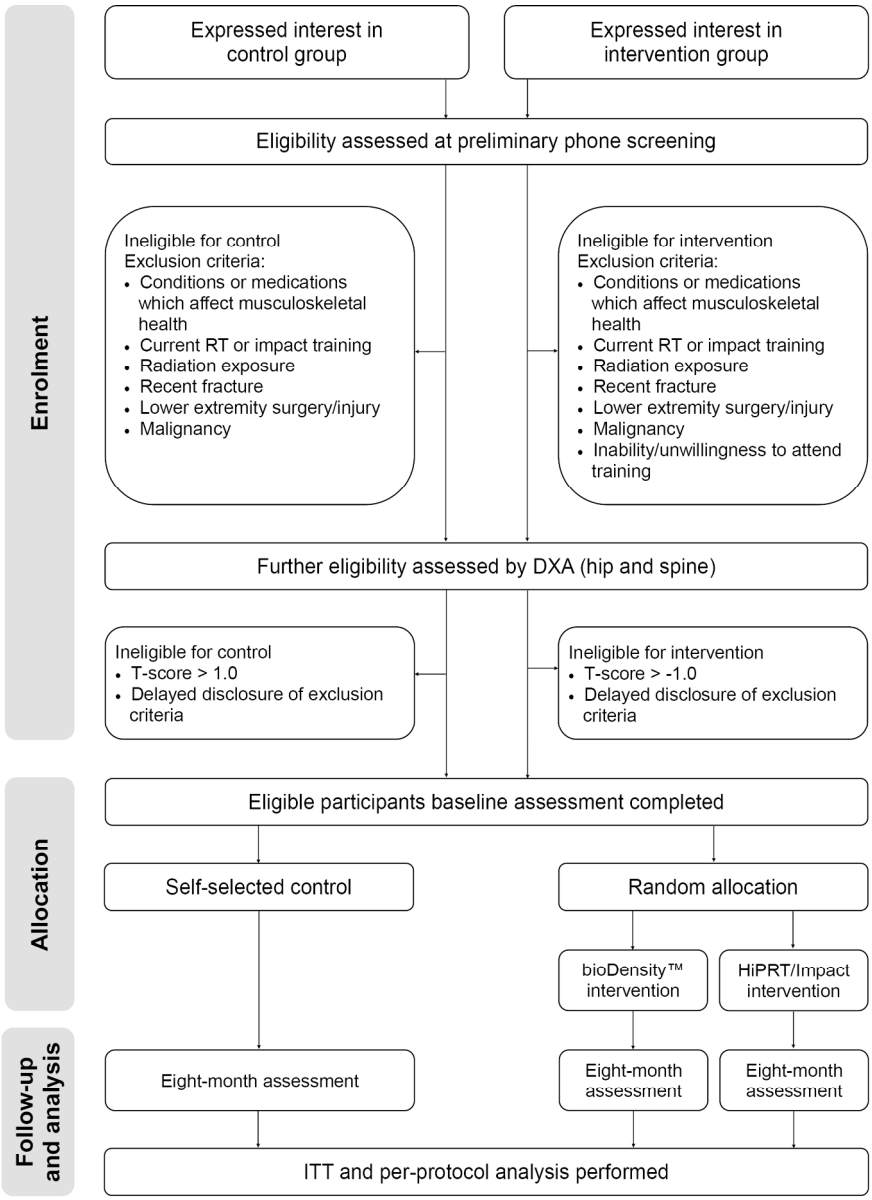

Figure 1. Proposed participant flow (CONSORT diagram)‼ ┼ ‼ ┼
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173x233mm (300 x 300 DPI)

INFORMATION SHEET

Project Title

"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"

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Background

As a person ages there is a gradual reduction in bone health and an increased risk of falling which, when combined, increases the risk of fractures. This study will help to determine if one or both of two different types of heavy resistance training safely and effectively improve bone strength, muscle and fat, and physical function in older men with low bone mass.

Method

Who:

- Healthy men over 50 years of age with low bone mass

What:

- You will be *randomly* assigned to either a high-load resistance training program, or a machine-based isometric exercise program, or you will choose to be in a no-exercise control group.
- Training for the resistance and machine-based exercise programs will occur twice a week for 8 months.
- If you are a control, all we require is your attendance at two testing sessions, 8 months apart.
- Before and after the 8-month exercise period you will be asked to complete:
  - Questionnaires regarding your health, diet and the amount of exercise you undertake
  - Some simple physical tasks including: standing jump, reaching, back and leg strength tests, and walking
  - Body composition scans using a dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and a peripheral quantitative computed tomographer (pQCT). Those tests are painless and non-invasive but involve either sitting beside or lying still on special scanners for between 3-10 minutes per scan.
- The total time for each testing session will be approximately 2 hours.
- In the final month of your training program you may be asked to attend a 30 minute interview to discuss your experiences throughout the training period
- We may video or photograph some activities, but you may opt out of those if you would prefer.

Where:

- Testing will take place at Griffith University Gold Coast campus (Southport) in the School of Allied Health Sciences.
- Both heavy resistance training and machine-based training will take place at Griffith University Gold Coast campus (Southport).

Inclusion Criteria

You may be eligible to participate in this study if you are over the age of 50 and have low bone mass (we can tell you if you do) and are willing to undertake an 8-month exercise program comprised of two exercise sessions per week, or merely attend Griffith University for two testing sessions 8 months apart (no new exercise for 8 months).

Exclusion Criteria

You may be excluded if any of the following apply to you:

- Any reason why you cannot safely participate in vigorous physical activity (i.e. uncontrolled cardiovascular disease, certain musculoskeletal conditions, etc.)
- Metal implants (e.g. staples, joint replacement) or foreign bodies (e.g. shrapnel)

- More than two x-ray examinations in the past year or radiation treatment
- Malignancy
- Cognitive impairment
- Certain kinds of current physical activity
- Medications and/or conditions know to influence bone health (e.g. Paget's Disease)

Risks

The risks associated with the project are relatively minor. For those unaccustomed to physical activity, it is likely that you will experience muscle soreness following any change in exercise exposure. There is also a risk of injury during exercise. Such injuries are uncommon but may include low back pain, joint sprains, or muscle strains. All physical testing and both exercise training programs will be closely supervised by the investigators to help reduce those risks. If you have low bone mass, you are at greater risk of fracture during heavy lifting exercises than people with higher bone mass. It will be important to perform the exercises as instructed by your trainer to make sure you are doing them safely. Should an injury occur during a study training session, an initial consult and one follow-up consultation will be available free of charge at the Griffith University *Physiotherapy and Active Health Centre*. If further treatment is required, investigators can refer you to an appropriate healthcare professional. The *Physiotherapy and Active Health Centre* has undertaken to provide discounted rates to physiotherapy patients referred by study investigators.

There are also slight risks associated with some of our tests. DXA and pQCT scans are non-invasive and painless, but they do involve exposure to small quantities of ionising radiation. The amount of radiation exposure during a chest x-ray is 8 times greater than that for either pQCT or DXA tests. The radiation exposure for DXA and pQCT scans is less than 0.01 mSv. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year. The exposure to radiation during plane travel is approximately 0.005 mSv per hour, thus a 14 hour international flight from Australia to Los Angeles would expose an individual to approximately 0.07 mSv, or 28 times the radiation from a single DXA scan.

Benefits

- Each participant will receive free bone, muscle and fat scans and an estimate of calcium consumption.
- Participants assigned to the exercise groups will receive a free 8-month exercise training program.
- Your involvement in this study will help contribute to the understanding of exercise as a treatment strategy for bone health, which will help countless individuals suffering from osteoporosis.

Confidentiality

Results will be kept as confidential as is possible by law and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375.

Use of video recordings and photography

You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password protected computer for a minimum of 5 years.

Contacting the Investigators

We are happy to answer any questions you may have. For general inquiries please contact Miss Amy Harding (student researcher), at amy.harding@griffithuni.edu.au or on 0410 616 596. If you have any concerns with the study, please do not hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, or Prof Belinda Beck on (07) 5552 8793.

Feedback

Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if you're interested, the overall study findings.

Voluntary Participation

Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to participate, you are free to withdraw your consent and discontinue your involvement at any time.

Complaints Mechanism

The University requires that all participants be informed that if they have any complaints concerning the manner in which a research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, Research Ethics, Office for Research, Room 4.25, Science, Engineering and Architecture (G11), Griffith University, Gold Coast campus, Q 4222, Phone: 373 54375 or research-ethics@griffith.edu.au.

Please retain this document for your information.

CONSENT FORM

Project Title

"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"

Investigators

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Consent Statement

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that will I be *randomly* assigned to a high-load resistance training program, or a machine-based isometric exercise program, or I can choose to be in the no exercise group
- If I am assigned to an exercise group I understand that I will be asked to undertake an 8-month training program, consisting of 2 roughly 30 min sessions per week.
- I understand that there will be a testing session approximately 2 hours in duration both before and after the 8-month exercise period;
- I understand that I will undergo dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and peripheral quantitative computed tomographer (pQCT) scans and measurement of height, weight and waist circumference, to determine body composition;
- I understand that I will be asked to complete several questionnaires relating to physical activity, quality of life, evaluation of the exercise program and diet;
- I understand that I will be asked to perform a series of physical tasks including: standing jump, walking, back and leg strength tests, and reaching tasks;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand the benefits of my participation in this research;
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without comment or penalty;
- I understand that I can contact the Manager, Research Ethics, on 373 54375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

_____	_____	_____
(Participant)	(Participant signature)	(Date)

Optional video and photography consent:

☐ I agree to be video recorded while performing the physical activities to be used during presentations, media coverage and publication of research findings.

☐ I agree to be photographed while performing the physical activities to be used during presentations, media coverage and publication of research findings.

Public title

The LIFTMOR for Men trial: Is heavy resistance training or a machine-based isometric exercise program more effective at reducing risk of fracture in older men with reduced bone mass?

Scientific title

A randomised controlled trial to determine the effectiveness of heavy progressive resistance training versus high load machine-based isometric resistance training to reduce the risk of osteoporotic fracture in older men with low bone mass

Secondary ID

Nil known

Universal Trial Number

N/A

Trial acronym

LIFTMOR (for Men): Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

Private notes (not publicly viewable)

Nil

Health condition

Osteopenia, osteoporosis, vertebral fracture, kyphosis, hip fracture

Condition category & condition code

Musculoskeletal health- osteoporosis

Injuries and accidents: Fracture

Study type

Interventional

Intervention code

Rehabilitation: 'Treatment: other' and/or 'Prevention'

Description of intervention(s)/exposure

The study is a three-arm, semi-randomised controlled exercise intervention trial. Eligible volunteers will be randomly allocated to one of two eight month, twice-weekly, 30-minute exercise programs; either supervised heavy progressive resistance training and impact loading, or machined-based isometric resistance training using the bioDensity system.

Arm 1 – supervised heavy progressive resistance training and weight-bearing impact loading.

Three compound movement exercises (deadlift, overhead press, and back squat) using olympic weights will be completed. For each exercise, 5 sets of 5 repetitions, corresponding to an intensity of 80-85 % of 1 repetition maximum will be performed. 5 sets of 5 repetitions of weight-bearing impact loading exercises (i.e. drop jumps) will also be performed, with height of the jump progressively increasing across the intervention period.

Arm 2 – supervised high-load isometric exercise using the bioDensity system.

A single set of four isometric exercises (chest press, leg press, core and arm pull, and vertical lift) will be performed according to bioDensity device specifications. For each exercise, one repetition of a self-initiated 75%-maximum contraction will be held for 5 seconds.

Sessions are supervised by a single qualified trainer (Bachelor of Exercise Science graduate, Certificate III in Fitness, Level 1 Sports Trainer Sports Medicine Australia). The training is also certified in First Aid and Cardiopulmonary Resuscitation.

Training diaries will be used to record participant attendance at training sessions, and completion of each element of the training session. Compliance will be determined as the number of sessions attended as a percentage of total possible sessions.

Comparator/control treatment

Arm 3 – the comparator will be a non-randomised sample of men, recruited independently but sex- and age-matched to the exercise arms. They will simply continue with their usual activities for 8 months, but will undergo the identical testing protocol at baseline and follow-up as the two randomised arms. Weekly email contact will be maintained to approximate investigator exposure and track alterations to habitual diet or physical activity levels over the 8 month period.

Diaries will be provided and all participants will be encouraged to record any changes to medication, medical conditions and general health.

Primary outcomes

1) Whole body, bilateral proximal femur (femoral neck, trochanter and total hip regions of interest) and lumbar spine bone mineral density determined by Dual-energy X-ray Absorptiometry. All participants, pre (baseline) and post-intervention (8 months).

Secondary outcomes

1) Indices of bone and muscle strength of the forearm and leg determined from peripheral Quantitative Computed Tomography. All participants, pre (baseline) and post-intervention (8 months).
2) Heel bone quality determined by Quantitative Ultrasonometry. All participants, pre (baseline) and post-intervention (8 months).
3) Body composition (lean mass, fat mass, appendicular lean mass and percentage body fat) from whole body Dual-energy X-ray Absorptiometry. All participants, pre (baseline) and post-intervention (8 months).
4) Muscle strength, physical function and balance will be measured using previously validated techniques. All participants, pre (baseline) and post-intervention (8 months).
5) Kyphosis will be measured using inclinometer
6) Daily average calcium intake, quality of life and bone-specific physical activity using validated questionnaires. All participants, pre (baseline) and post-intervention (8 months).
7) Safety (adverse events and injuries) and compliance from training diaries across the whole exercise intervention period.

Control group

Usual activities

Recruitment country

Australia

Recruitment site location state

Queensland

Recruitment status

Imminent

Anticipated date of first participant enrolment

Ethics application status

Approved

Brief summary

Recent work undertaken at Griffith University (the LIFTMOR trial) has revealed that brief exposure to a bone-targeted heavy progressive resistance training program is both safe, and effective for enhancing musculoskeletal health and function, in postmenopausal women with low to very low bone mass. Similar claims have been made by the developers of the bioDensity system, designed around the premise that low volume machine-based isometric resistance training produces beneficial effects on balance, physical function, muscle strength and bone mass. Whether dynamic or isometric resistance training will be more effective in men over the age of 50 with reduced bone mass at the hip and spine remains to be seen.

Key inclusion criteria

Men

Apparently healthy

With low bone mineral density (hip or spine BMD T-score less than or equal to -1.0)

Not currently or recently participating in regular resistance training or impact-type exercise

Minimum age

50 years

Maximum age

No limit

Gender

Males

Can healthy volunteers participate?

No; as participants have low bone mineral density. They are in fact 'apparently-healthy'.

Key exclusion criteria

Current participation in resistance training or exercise with an impact-loading component

Uncontrolled cardiovascular disease/respiratory conditions

Neurological conditions which might limit an individual's ability to perform resistance training

Malignancy

Hernia

Medications know to adversely affect musculoskeletal health such as corticosteroids, anti-convulsants

Medical conditions known to effect musculoskeletal health such as hyperparathyroidism, Paget's disease, diabetes

Purpose of the study

Prevention of age-related musculoskeletal deterioration

Allocation to treatment

Semi-randomised controlled trial

Enrolment procedure

Block randomisation to exercise will occur after participants are stratified for the presence or absence of medications for osteoporosis. The allocation sequence will be generated by a person independent of the trial and filed in sealed opaque envelopes.

Random order generated by computer program

Open trial (not masked)

Intervention assignment parallel

Phase not applicable

Time of endpoints efficacy

Recruitment

Anticipated start date May 2016

Anticipated date of last participant enrolled Nov 2017

Target sample size 150

Not yet recruiting

Funding & sponsors

Osteoporosis Australia Equipment award (bioDensity device supplied and installed by Performance Health Systems)

Osteoporosis Australia National Office

Postal: PO Box 550, Broadway, NSW, Australia 2007

Street: Level 2, 255 Broadway, Glebe, NSW, Australia 2037

research@osteoporosis.org.au

Phone: 02 9518 8140

Fax: 02 9518 6306

Secondary Funding & sponsors

Performance Health Systems

International head office:

401 Huehl Road, Suite 2A,

Northbrook, Illinois, 60062

United States of America

Ethical approval

Approved Griffith University Human Research Ethics Committee

170 Kessels Road Nathan, QLD 4111 Australia AHS/07/14/HREC

Submitted for approval for the initial LIFTMOR (for women) trial: 1st April 2014

Approval date of variations for the 3-arm trial LIFTMOR for Men: 18th January 2016

Approval expires: 17th Feb 2018

Contact details – Primary sponsor

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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	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	ANZCTR trial registry (online)/Supplementary file
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	26
	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	26

	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)	_8, 23, 26_____
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	___6-7_____
	6b	Explanation for choice of comparators	__9-10_____
Objectives	7	Specific objectives or hypotheses	____9_____
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)	__9-10_____
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	_____11_____
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)	___11-12_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	___12-14_____
	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)	_11-12_____

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14 (Controls) 13 (Exercise interventions) 8 (Dissemination of results)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8, 12 _____
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	____14-22_____
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)	CONSORT (Figure 1) 9-10_____
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	___10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___11_____
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	___12_____
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 assigned	___12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___12_____

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___23_____
	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 protocol	_14-22_____
	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	_____8_____ Data analyses ITT approach 23-24
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	__23_____
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	23-24_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	23-24_____
	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)	23-24_____
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	____8_____

	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	____8-9_____
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	____8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____8_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__8_____
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)	__N/A_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__8_____
	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	_9, 23_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__26_____
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	__23_____
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	__8_____

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	__8, 9_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__8, 9_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file_____
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	_N/A_____

*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

The LIFTMOR-M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: A protocol to determine if a semi-randomised controlled trial of supervised targeted exercise reduces risk of osteoporotic fracture in older men with low bone mass

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Impact, Isometric exercise, Osteoporosis, Resistance training, Men

Study Protocol (Rehabilitation Medicine)

Title:

The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: A protocol to determine if a semi-randomised controlled trial of supervised targeted exercise reduces risk of osteoporotic fracture in older men with low bone mass

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Word Count:

6542 (1 Figure; 1 Table; 56 References)

Keywords:

Impact; Isometric exercise; Men; Osteoporosis; Resistance training.

ABSTRACT

Introduction

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training and impact loading program in comparison to a supervised machine-based isometric exercise training program using the bioDensity™ system in older men with low bone mass. We will also determine the safety and acceptability of each exercise training mode. Intervention group responses will be compared with those of a self-selected, non-randomised control sample of sex- and age-matched men who will follow their usual lifestyle activities for eight months.

Methods and analysis

Apparently-healthy men over fifty years with low bone mass, screened for medical conditions and medications known to adversely affect bone health, will be recruited. Eligible participants will be randomly allocated to eight months of either exercise program with block randomisation based on presence or absence of osteoporosis medications. A twice-weekly, thirty-minute, supervised exercise program will be conducted for both groups. The primary outcome will be change in femoral neck areal bone mineral density determined by Dual-energy X-ray Absorptiometry (DXA). Secondary outcomes, assessed at baseline and eight months, will include: DXA-derived whole body, bilateral proximal femur and lumbar spine areal bone mineral density; proximal femur bone geometry and volumetric density extracted using 3D hip analysis software; anthropometry; body composition; kyphosis; vertebral fracture assessment; physical function; safety (adverse events and injuries); and compliance. Intention-to-treat and per-protocol analyses will be conducted.

Discussion

Whether a high-load, low-repetition progressive resistance training plus impact loading program or a machine-based isometric exercise program can improve determinants of fracture risk, without causing injury, has not been examined in men. Determination of the efficacy, safety and acceptability of such programs will facilitate formulation of future exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who have previously been underrepresented.

Ethics and dissemination

Participant confidentiality will be maintained with publication of results. The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC).

Trial registration number

Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)

ANZCTR12616000344493; Pre-results.

Date and version identifier

Original protocol manuscript for submission (Version 1): November 2016.

Protocol manuscript for submission (Version 2) with revisions from peer review: December 2016

Authors: ATH, BKW, SLW, BRB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised high intensity, progressive resistance training and impact loading program on several determinants of fracture risk for older men with low bone mass, compared with a machine-based isometric exercise program using the bioDensity™ system.
- There are few investigations into the effects of exercise on musculoskeletal health in older men, thus the current unique focus on older men with poor bone health will address a notable gap in the literature.
- The engagement of a non-randomised control group of demographically-matched men who have elected not to exercise for eight months is a design limitation that was implemented for pragmatic reasons.
- Our study sample will include largely healthy older men, so our findings may not be applicable to men with comorbidities or other exclusion characteristics.

INTRODUCTION

Epidemiological data indicates the global prevalence of osteoporosis to be over 200 million,[1] with around 1.2 million Australians,[2] 10.2 million Americans [3] and 15 million European men and women over fifty years of age being affected.[4] It has been suggested that 285,000 Australian men aged over fifty will be diagnosed as osteoporotic, and a further 2.48 million older men diagnosed as osteopenic by 2022.[5] With the aging of the population, there will undoubtedly be a corresponding increasing prevalence of low bone mass and consequent increase in the incidence of low trauma fracture.[6]

It is widely accepted that bone adapts to the mechanical loads it habitually experiences. Experimental data from animal models has revealed the most influential loading characteristics for osteogenesis are magnitude,[7,8] rate [9] and frequency [10-12] of the engendered strain. Evidence also indicates dynamic loading is more osteogenic than static loading.[13] The optimal exercise prescription for the prevention and management of osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads, applied at a rapid rate. High-load resistance training with high-impact jumping, the combination of which will elicit high strains and strain rates in bone, is thus theoretically the optimal exercise protocol for bone. Although such exercise is considered safe for healthy individuals with normal bone mass, it is unclear whether it will be safe for individuals with reduced bone mass who are at increased risk of fracture. Previous resistance exercise recommendations for individuals with low bone mass, particularly those who have experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate level of intensity,[14,15] based on a lack of quality evidence that high intensity resistance training is safe and effective.

Recently a bone-targeted, high intensity, progressive resistance training and impact loading (HiRIT) exercise program was undertaken with post-menopausal women with low to very low bone mass at the hip or spine - the LIFTMOR (Lifting Intervention For Training Muscle and

Osteoporosis Rehabilitation) trial. Interim results indicated the HiRIT protocol was well tolerated (no injuries sustained during supervised training sessions) and effective, exhibiting positive changes to musculoskeletal health in post-menopausal women at increased risk of fragility fracture.[16] Although the lifetime risk of fracture is greater in women over the age of fifty (one in three), than men of the same age (one in five), older men are more likely to suffer serious post-fracture consequences.[4,17] The most devastating low-trauma fracture site for older men is the hip, with mortality exceeding that of similarly aged women within the first year post-fracture.[18] In light of the fact that osteoporosis, and low-trauma fractures, affect men as well as women, it was necessary to replicate the protocol in older men to determine if it will be similarly effective.

Separately, but simultaneously with the LIFTMOR trial, an isometric device (the bioDensity™ system, Performance Health Systems, Northbrook, IL, USA) was developed in the USA to facilitate near-maximal isometric contractions against instrumented external resistance, with a goal to increase bone mass. The developers are currently marketing the device on the grounds that short-duration, low-volume, high-load bioDensity™ training can enhance bone mass in individuals with osteoporosis: however, concrete evidence is lacking. To date, four studies examining the bioDensity™ training protocol have been published,[19-22] only one of which included bone outcome measures.[22] In the latter observational study seventy post-menopausal women with low bone mass were invited by their general practitioner to take part in a six-month bioDensity™ intervention (one training session per week) for which the primary outcome was maximal isometric muscle force production. A sub-group of nine participants underwent Dual-energy X-ray Absorptiometry (DXA) examinations for bone density. Those individuals reportedly sustained increases in bone mineral density (BMD) at the hip (14.9 ± 11.5 %) and spine (16.6 ± 12.2 %) – responses that far exceed the BMD responses to previously reported exercise interventions. The lumbar spine T-score of one participant improved from -3.1 to -0.10. As considerable methodological shortcomings were evident in the latter study design, including low sample size, no monitoring of dietary calcium

intake or physical activity, lack of control group, lack of disclosure of simultaneous bone medications, and the fact that follow-up DXA scans were conducted sixty days after the intervention was completed suggests that a more rigorous examination of efficacy of bioDensity™ training is indicated.

Short-duration (thirty minute), twice-weekly therapeutic exercise programs for older men with low bone mass, such as the proposed HiRIT and bioDensity™ training protocols, provide an attractive alternative to more burdensome and time consuming programs typically recommended for osteoporosis. Indeed, trials examining the influence of progressive resistance training, hopping/jumping or multicomponent programs on bone health in men have adopted session frequencies of three,[23-28] four,[29] or even seven [30] per week. Hinton and colleagues [28] compared thrice-weekly sessions of jump training with twice-weekly sessions of periodised progressive resistance training, however, healthy physically active men aged 25 to 60 years were recruited. Whether high-load, low-volume training methods can safely improve bone strength in older men with low bone mass remains a knowledge gap. Thus, the Griffith University Bone Densitometry Research Laboratory has acquired a bioDensity™ device for the purposes of examining safety and efficacy alongside the HiRIT protocol in a semi-randomised controlled trial design.

METHODS AND ANALYSES

Ethics and dissemination

The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities will be conducted in accordance with the *Declaration of Helsinki*. The study is also registered with the Australian New Zealand Clinical Trials Registry (Trial number ANZCTR12616000344493). Written informed consent will be obtained from all participants prior to testing by the investigator performing baseline assessments.

Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial [16] (Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide evidence of an extremely low risk of injuries from the current exercise protocols, with no severe injuries reported from a total of 7300 training sessions. Similar to the current protocol, ethical approval was granted by the GUHREC for both studies, and written informed consent was obtained from all participants. Strategies were in place to reduce the risk of injuries or adverse events occurring during the aforementioned trials, and included: 1) full supervision of high-load resistance training sessions by a qualified exercise scientist; 2) small group sizes in the supervised training sessions; 3) an initial familiarisation period during which low-load exercise variants focused on proper lifting technique was implemented, and 4) weight lifted was progressively increased with training exposure. In order to monitor safety, participants were required to complete training diaries at every training session to record illnesses, falls, fractures, injuries, and muscle soreness. Early termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual progress reports to the GUHREC. Any adverse events which occur between annual reports will be reported independently to the GUHREC, in compliance with the *Australian Code for the Responsible Conduct of Research* developed by the National Health and Medical Research Council, and the University *Code for the Responsible Conduct of Research*. The

GUHREC is a registered institution with the National Health and Medical Research Council (Registration number EC00162). For participants who are unaccustomed to physical activity it is likely they will experience some degree of muscle soreness following any change in exercise exposure. In the unlikely event that a participant experiences significant intervention-related muscle soreness, or an injury occurs during the study period, consultations with a qualified Physiotherapist (external to the trial) at the Griffith University Allied Health Clinic will be available. If further treatment is required they will be referred to an appropriate healthcare professional.

All participants will be supplied with a full summary of individual and overall study results to encourage retention for the duration of the study, and to comply with ethical requirements. The usual scientific reporting practices will take place, including presentations at discipline meetings and publication in peer reviewed journals. There will be no interim analyses published prior to completion of the trial. Community and clinical talks will also be given as appropriate. Participant confidentiality will be maintained with publication of results.

Study aims

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training plus impact loading (HiRIT) program in comparison to supervised bioDensity™ machine-based isometric exercise training, or no intervention (control), for improving femoral neck (FN) bone mineral density (BMD) in older men with low bone mass. The primary outcome measure was selected according to clinical relevance, in light of the large personal and economic impact of hip fracture. It is hypothesised that eight months of twice-weekly HiRIT training will improve FN BMD more than bioDensity™ training or control, and similar benefit will be observed in secondary outcome measures. Furthermore, we hypothesise that there will not be a higher rate of adverse events during eight months of HiRIT compared with bioDensity™ training or control.

Study design

The current project is a three-arm, eight-month, semi-randomised, controlled exercise intervention trial. Proposed participant flow is outlined in Figure 1. The eight-month exercise intervention period has been chosen as the minimum time frame in which notable changes in bone mass are likely to be detected from densitometry.[31] Eligible volunteers to the intervention arm will be randomly assigned to one of two exercise programs; either supervised HiRIT or bioDensity™ training. The third arm will be a non-randomised control group of sex- and age-matched participants with lower than average bone mass recruited from the same community. The control group will follow their usual lifestyle for eight months, but undergo identical testing to the two exercise intervention groups at baseline and follow-up. We acknowledge the somewhat unorthodox semi-randomised design does not constitute the most rigorous clinical trial practice, but adopt it out of necessity. Pilot testing conducted in our laboratory revealed that male study volunteers who expect to participate in an exercise trial, but are randomised to a conventional inactive control group, refuse to adhere to the requirement to refrain from exercise for eight months. We also believe that it is unethical to withhold access to a potentially beneficial bone-targeted exercise program for older men at increased risk of fragility fracture who are specifically seeking exercise therapy. For pragmatic reasons then, we will independently recruit a demographically-matched sample of men who, for a variety of reasons (not including functional capacity), elect to remain sedentary for a minimum of eight months.

Sample size

There have been no published reports of men's studies comparing the effects of heavy progressive resistance training and machine-based isometric training using the bioDensity™ system on FN BMD, thus estimates of sample size were based on the reported rate of

annual loss. For men over the age of fifty, longitudinal studies have reported an annual loss of 0.42 to 0.45 % FN BMD per year.[32,33] Thus, to detect a significant difference in FN BMD change, from a two-tailed test with a power of 80 % and $\alpha = 0.05$, approximately 32 participants per group will be required. Allowing for a 20 % dropout, a total of 38 participants per group is required. The 20 % dropout rate reflects those reported in previous bone-targeted exercise interventions in men,[28-30] and the dropout rate of randomised controlled intervention trials in adults (20.9 %).[34] Recruitment for this study started in May 2016, and will continue until the planned sample size is achieved.

Setting and recruitment

Baseline and follow-up assessments will be conducted in the Bone Densitometry Research Laboratory, School of Allied Health Sciences, Griffith University, Gold Coast campus, Queensland, Australia. All supervised training sessions will be conducted in the Strength Training Research Facility, co-located in the School of Allied Health Sciences. Both measurements and interventions will be conducted at this single location. Methods of recruitment include local media outlets (print media and radio), social media, official website (www.liftmor.org), word of mouth, and notice board flyer advertisement at local lawn bowls clubs, golf clubs and senior citizens clubs.

Eligibility and screening

Apparently healthy, able-bodied men over fifty years of age will be recruited. Volunteers are to be excluded if they have any of the following: uncontrolled cardiovascular or respiratory disease; disclosure of musculoskeletal or neurological conditions likely to affect their ability to perform exercise; medications known to affect bone metabolism (e.g. corticosteroids, thyroxine, antiepileptic, and antiretroviral agents); medical conditions known to affect

musculoskeletal health (e.g. Paget's disease, hyperparathyroidism, and thyrotoxicosis); current participation in high-load resistance or impact-type exercise; metal implants (e.g. joint prostheses); recent radiation therapy or radiographic investigations; recent fracture or lower extremity surgery; or malignancy. Further exclusion for the exercise arm will be based on an inability or unwillingness to take part in eight months of twice-weekly exercise training due to motivation, travel or work commitments. No upper age limit is stipulated. Potential participants who contact the investigator will initially undergo a preliminary phone screening for inclusion and exclusion criteria. If eligibility is established, prospective participants will be invited to attend the University research facility for BMD screening and, when relevant, to undergo baseline assessments. Potential exercise intervention participants and self-selected age-matched men will then undergo preliminary Dual-energy X-ray Absorptiometry (DXA) scans. If osteopenia (T-score between -1.0 and -2.5) or osteoporosis (T-score < -2.5) is detected at the lumbar spine and/or proximal femur, the individual will be eligible for inclusion and the full suite of scans. Participants will be discontinued if they: 1) withdraw consent, 2) cease to attend training sessions for longer than three weeks, 3) initiate or discontinue osteoporosis medications, or initiate medications known to affect bone metabolism, 4) become injured and unable to participate, 5) perform additional forms of exercise such as resistance training or impact-type exercise external to the trial, and 6) are advised by their general practitioner to cease training.

Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity™ training groups will be achieved via block randomisation, stratified by the presence (more than twelve months exposure) or absence (lack of exposure) of osteoporosis medications, using a computer-generated randomisation sequence (www.randomization.com, accessed 17th May 2016). To ensure concealment, the allocation sequence will be prepared in advance by an

external source, and filed in sequentially-numbered, sealed, opaque envelopes. Upon completion of baseline testing those identified as eligible will be randomly allocated to their exercise group and their supervised exercise training sessions will be scheduled.

Exercise interventions

Progressive resistance training and impact loading exercise program

The HiRIT group will perform approximately thirty minutes of supervised, high-load, free weight training and impact loading, twice-weekly, on non-consecutive days. During the initial two weeks, participants will perform low-load variants of each exercise focussing on technique. Following this familiarisation period, sessions will comprise three fundamental compound movement exercises (deadlift, squat and overhead press) at five sets of five repetitions, corresponding to greater than 80 to 85 % of one repetition maximum. Load magnitude will be progressively increased in increments of 2.5 kg over the course of the intervention when they are able to easily complete seven repetitions at their current weight. In addition, five sets of five repetitions of jumping chin-ups (interspersed with rest) with a firm, flat-footed landing will be performed each session. Impact intensity will be gradually increased by moving towards achieving a stiff-legged landing as tolerated. Participants will provide a Rating of Perceived Exertion (RPE) with the aid of the 6-20 point Borg scale [35] at completion of each training session. Maximal strength testing, to determine one repetition maximum for the deadlift and squat, will be performed at weeks twelve and twenty-four. Briefly, the maximal strength test protocol will begin with a warm-up set of five to ten repetitions at a relatively light load (approximately 50 % of the heaviest weight they have previously lifted for five repetitions). After a one-minute rest they will perform one set of three to five repetitions at 60 to 80 % of their perceived maximum. Gradually the load will increase in 2.5 to 5.0 kg increments until a failed attempt (within three to six attempts), with each attempt interspersed with a two-minute rest. One repetition maximum is defined as the

heaviest weight a participant can lift once with correct lifting technique. A similar one repetition maximum testing protocol was found to be reliable for untrained middle-aged adults (intraclass correlation coefficients > 0.97).[36] Training will be fully supervised by a qualified exercise scientist. Weight progressions and RPE will be recorded in training diaries.

Machine-based isometric exercise program

The supervised bioDensity™ group will exercise twice-weekly, on non-consecutive days to match the HiRIT group protocol. Four exercises will be performed; chest press, leg press, core pull, and vertical lift. The chest press and leg press closely mirror conventional strength training equipment, the core pull movement combines an abdominal crunch with an underhand chin-up, and the vertical lift simulates a high-hang deadlift position. During the initial two weeks, participants will perform a lower intensity repetition of each exercise focussing on technique. Following this familiarisation period, one self-initiated near-maximal five-second isometric contraction will be performed for each of the four exercises (per manufacturer's recommendations). Integrated monitors provide real-time peak muscle force production feedback. Participants will provide an RPE with the aid of the 6-20 point Borg scale [35] for each exercise. They will be instructed to achieve a near-maximal five second isometric contraction at an intensity corresponding to greater than 80 to 85 % of one repetition maximum, translating to an RPE of greater than sixteen on the 6-20 point Borg scale.[37] A single qualified trainer will supervise all sessions to operate the bioDensity™ system, and ensure the exercises are performed correctly and safely. Peak force, average force and RPE will be recorded in participant training diaries.

Control group activities

The sex- and age-matched control group will be encouraged to maintain their customary physical activity and dietary patterns over the eight month duration of the study. To monitor deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to list variations to their physical activity level and diet on a fortnightly basis. Space is also provided to record any illnesses, falls, fractures, changes to their medical conditions and medications (inclusive of over the counter medications), and injuries other than muscle soreness. Diaries are to be returned at follow-up. Fortnightly emails will act as reminders to complete diary entries, with a monthly email requiring a reply to the investigator to prompt recording of any relevant changes. To detect change in bone-relevant physical activity or dietary calcium intake over the course of the eight-month study, participants will complete questionnaires (described below) at baseline and follow-up.

Outcome measures

All outcome measures will be performed at baseline and eight-month follow-up by a single investigator, using identical facilities, procedures and equipment. A summary of outcome measures is presented in Table 1.

Primary outcome

The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink, France).

Secondary outcomes

Secondary outcomes (described in more detail below) will include: changes in anthropometrics, as well as in whole body and regional measures of bone, muscle and fat. Kyphosis will be examined in order to track angular changes of the spine with exercise exposure. Vertebral fracture assessment using the Genant semiquantitative approach [38]

from lateral thoracolumbar spine imaging will be conducted pre- and post-intervention by DXA. A series of commonly utilised performance tasks will be employed to examine changes in lower extremity muscle force and power, dynamic balance, and maximal trunk extensor strength in keeping with standard protocols. Standardised instructions will be provided for all performance tasks, with the best performance of three trials to be included in the analyses. Previously validated questionnaires will be used to estimate dietary calcium consumption, current and past bone-relevant physical activity, quality of life and exercise appeal. Participant safety (adverse events and injuries) and compliance will be monitored across the intervention period using training diaries.

Bone strength indices

Whole body, bilateral proximal femur (trochanter and total hip regions), and lumbar spine areal BMD, bone mineral content and bone area will also be determined by DXA. Parameters of proximal femur (femoral neck and total hip regions) trabecular and cortical bone geometry and volumetric density will be extracted from standard DXA scans using 3D hip analysis software (DMS Group, Mauguio, France). Quantitative Ultrasonography will be used to evaluate changes in calcaneal bone quality (QUS; Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA). Volumetric BMD and geometric parameters contributing to bone strength at the tibia and radius will be determined from peripheral Quantitative Computed Tomography scans of the forearm and leg (pQCT; XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany; voxel size 0.5 mm, slice thickness 2.3 mm and scan speed 25 mm/sec). A planar scout view of the ankle joint line on the skeletally non-dominant leg will be acquired so the anatomical reference line can be adjusted to bisect the tibial endplate. A total of four image slices will be acquired at 4 %, 14 %, 38 % and 66 % sites proximal to the distal edge of the tibial endplate. A planar scout scan perpendicular to the long axis of the skeletally non-dominant forearm will be performed at the level of the ulnar head, and the reference line positioned at the distal edge of the radius. Two image

slices will be acquired at the 4 % and 66 % sites proximal to the distal endplate of the radius. pQCT-derived bone parameters will include: total content, density and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, density, cross-sectional area and thickness; periosteal and endocortical circumference; and biomechanical strength indices calculated from density and area (total and trabecular bone strength indices, polar section modulus, and polar strength strain index).

Anthropometrics and body composition

Height will be measured via the stretch stature method with a wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany). Weight will be measured using a mechanical beam scale without shoes and in light clothing (Model 700; Seca, Hamburg, Germany). Body mass index will be determined per the accepted method (Body Mass Index = weight/height^2; kg·m^{-2}). Waist circumference, a predictor of visceral abdominal adiposity, will be measured using a steel tape following National Institute of Health guidelines (Model W606PM; Lufkin Executive Thinline, Apex, USA).[39] Briefly, the tape will be positioned on the horizontal plane at the level of the iliac crests on bare skin, and recorded at the end of gentle expiration. Body composition parameters inclusive of lean mass, fat mass, appendicular lean mass and percentage body fat will be derived from whole body DXA. Muscle cross-sectional area, an index of muscle size, and muscle density, an index of intramuscular fat, will be determined from pQCT scans of the forearm and leg at the 66 % site.

Thoracic kyphosis and vertebral fracture assessment

Thoracic kyphosis will be assessed in relaxed standing (neutral posture) and standing 'at attention' using a gravity-referenced inclinometer, following a procedure similar to MacIntyre and colleagues (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia).[40] The inclinometer will be zeroed at the twelfth thoracic to first lumbar intervertebral space, and the angle at the seventh cervical to first thoracic intervertebral space recorded. Lateral

thoracolumbar spine DXA will be performed in the lateral de cubitus position to calculate Cobb angle via two methods: 1) vertebral body endplates, and 2) anterior vertebral body margins. The superior endplate of the fourth thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra will be manually digitized, perpendicular lines extended and the angle at their intersection measured.[41] To account for endplate angulation and tilt due to vertebral irregularity, the anterior margins will be digitized and the angle at their intersection measured.[42] In addition, lateral thoracolumbar spine DXA allows vertebral fracture identification using the Genant method.[38] The anterior, medial and posterior heights of the vertebral body are used to grade (mild, moderate or severe) wedge, biconcave or crush deformity.

Timed up-and-go

The timed up-and-go test is a measure of functional mobility, and dynamic balance.[43] Participants will be instructed to rise from a seated position without using their hands for assistance, walk at a brisk pace to a mark on the floor a distance of three meters away, pivot, and return to assume the start position. Participants will be timed from the point at which their back no longer makes contact with the chair, to when they return to the start and adopt the correct seated position.

Five-times sit-to-stand

The five-times sit-to-stand is a reliable assessment of the ability to rise unassisted from a seated position, with relevance to functional mobility, dynamic balance and lower extremity muscle strength.[44] Participants will be asked to move from a sitting to standing position, without the use of their arms, for five repetitions following the recommendations of Bohannon and colleagues for assessing older adults.[45]

Functional reach

A modified version of the original functional reach test (that incorporated a yardstick) will be used to assess dynamic balance, which has been identified as an important component of falls risk.[46] Participants will stand with shoulders perpendicular to a Perspex board marked with vertical measurement lines, with the dominant arm located nearest the board and extended forwards to 90 ° shoulder flexion, with the hand forming a fist. The participant will be instructed to reach forward by flexing the trunk at the hip, maintaining a fixed base of support, without stepping or losing balance. If the participant makes contact with the Perspex board, takes a step or loses balance, the trial will be repeated. The start and finish positions of the third metacarpal in respect to the measurement lines will be recorded to determine displacement.

Muscle power

Lower extremity muscle power will be assessed by a countermovement vertical jump test. Participants will be instructed to perform a jump for maximum height, without arm swing, whilst positioned on a floor-mounted 900 mm x 600 mm load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA). Impulse and impulse relative to body weight will be calculated from the vertical component of the ground reaction force of the loading and take-off phase according to the method described by Linthorne.[47]

Isometric muscle strength

Maximal isometric force of the lower extremity will be estimated using a leg strength platform dynamometer (TTM Muscle Meter, Tokyo, Japan). The participant will stand on the dynamometer platform assuming a semi-squat position with knees flexed (knee angle of 115 °, hip flexion angle of 65 °), trunk extended and back flat against the wall. A straight bar handle is affixed to the dynamometer by a chain at a length so the arms are fully extended to grip it. After ensuring the chain is taut, the dynamometer is manually zeroed. Participants will be instructed to attempt to straighten their legs, whilst keeping their back fully in contact

with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.84$, $p < 0.001$; test-retest reliability $r = 0.97$, $p < 0.001$). (Little A, Harding AT, Weeks BK, Horan SA, Watson SL, and Beck BR, 2016; unpublished data; conference abstract)

Maximal isometric back extensor muscle strength will be assessed in erect standing using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA). The participant will be positioned midway between two vertical wall-mounted anchor rails, with their back and heels against the wall. An inelastic belt between the two rails will be fastened horizontally around the hips in order to restrain the pelvis. The padded transducer pressure plate will be positioned by the investigator between the wall and the seventh thoracic vertebral spinous process, until held securely against the wall by the pressure of the participant's back. Participants will be instructed to push back into the wall with their shoulders, ensuring their feet remain flat with their heels in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.85$, $p < 0.001$; test-retest reliability $r = 0.93$, $p < 0.001$). (Harding AT, Weeks BK, Horan SA, Little A, Watson SL, and Beck BR, 2016; Unpublished data; conference abstract)

Dietary calcium intake

Calcium intake will be assessed using the AusCal, a calcium-focused food frequency questionnaire designed and validated for the Australian diet.[48] Frequency of consumption per day, week or month, and approximate serving size will be recorded for each of the listed calcium-rich food and beverage items over the previous year. The AusCal will be investigator-administered. Questionnaire responses will be entered into customised FoodWorks analysis software to generate average daily calcium intake (Version 7, Xyris Software, Brisbane, Australia).

Bone-specific physical activity

The Bone-specific Physical Activity Questionnaire (BPAQ) [49] will be used to quantify current and historical physical activity of relevance to bone. Respondents will list all regular, structured physical activity and years of participation, with a minimum of investigator assistance. BPAQ scores will be calculated using an on-line, custom-designed analysis program (http://www.fithdysign.com/BPAQ/). Mathematical algorithms in the calculator were developed using load ratings from vertical ground reaction forces of each activity, participation frequency, years of involvement and an age-weighting factor. High loading ratings represent high-impact activities, whilst the age-weighting factor reflects higher mechanosensitivity to physical activity during youth. Previous research has found BPAQ scores are predictive of variance in DXA-derived bone strength parameters at clinically relevant sites in healthy middle-aged and older men.[50] This instrument has high reliability, with intra-class correlation coefficients of 0.92 to 0.97.[51]

Barriers and facilitators

The Physical Activity Enjoyment Scale (PACES), designed by Mullen and colleagues,[52] is a self-reported eight-item questionnaire which uses a seven-point Likert scale for each item. The respondent is required to circle the number corresponding to their current thoughts about physical activity. Higher PACES scores indicate a greater level of exercise appeal. Inclusion of this instrument was based on physical activity enjoyment being identified as a potential determinant of exercise adherence.[53] Semi-structured interviews to determine exercise appeal, barriers and facilitators to participation in HiRIT or bioDensity™ training programs will be conducted within one month of completing the eight-month intervention by an independent investigator. Interviews will be tape-recorded with participant consent, and transcribed verbatim. Interview transcripts will be thematically coded using NVivo qualitative software (Version 10, QRS International Pty Ltd) to determine barriers and facilitators to participation in higher-intensity, bone-targeted exercise.

Quality of life

The World Health Organisation Quality of Life questionnaire was developed to assess four quality of life domains using a five-point Likert interval scale.[54] Higher scores are indicative of higher quality of life. Participants will self-complete the questionnaire. Internal consistency across a large heterogeneous population from a field trial during its development showed each domain to have moderate to high Cronbach's α levels; physical health (α = 0.82), psychological health (α = 0.81), social relationships (α = 0.68), and environment (α = 0.80).[55]

Safety and compliance

Prior to each training session participants will rate their level of muscle soreness on a ten-point visual analogue scale, and note alterations to their diet, physical activity, health or medications since their previous session. Illnesses, falls, fractures, and injuries other than muscle soreness will be documented. Attendance will be entered to determine program compliance, with 100 % being defined as completion of seventy sessions over the course of eight months. Adverse events will be fully documented by investigators, and monitored across the intervention period.

Table 1. Summary of outcome measures

Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Medix DR, Medilink, France)
Secondary outcome measures	
Other bone outcomes	
Whole body aBMD, BMC and bone area; lumbar spine aBMD, BMC and bone area; and proximal femur (trochanter and total hip regions) aBMD, BMC and bone area	DXA scans (Medix DR, Medilink, France)
Femoral neck (trabecular, cortical and total) BMC, vBMD and volume; total hip (trabecular, cortical and total) BMC, vBMD and volume	Proximal femur DXA scan (Medix DR, Medilink, France), 3D hip software (DMS Group, Mauguio, France)
Calcaneal broadband ultrasound attenuation, speed of sound and stiffness index	Calcaneal QUS (Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA)
Total content, vBMD and cross-sectional area; trabecular content, density, and cross-sectional area; cortical content, vBMD, cross-sectional area and thickness; periosteal and endocortical circumference; total and trabecular bone strength indices; polar section modulus; polar strength strain index	Forearm 4 % and 66 % sites, and leg 4 %, 14 %, 38 % and 66 % sites pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)
Anthropometry	
Height	Wall mounted stadiometer (Model 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model 700; Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lufkin Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix DR, Medilink, France)
Muscle cross-sectional area and muscle density	Forearm 66 % site and leg 66 % site pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)

Thoracic kyphosis	Plurimeter gravity referenced inclinometer (Australasian Medical & Therapeutic Instruments, Australia) Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Vertebral fracture assessment	Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Functional performance	
Timed up-and-go	Digital stopwatch (Fisher Scientific, USA)
Five-times sit-to-stand	Digital stopwatch (Fisher Scientific, USA)
Functional reach	Perspex board with measurement grid-lines
Muscle power	
Countermovement vertical jump	Load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA)
Isometric muscle strength	
Lower extremity strength	Leg platform dynamometer (TTM Muscle Meter, Tokyo, Japan)
Back extensor strength	Dynamometer (Lafayette Manual Muscle Testing Systems, USA)
Dietary calcium intake	AusCal questionnaire
Bone-specific physical activity	Bone-specific Physical Activity Questionnaire (BPAQ)
Barriers and facilitators	Physical Activity Enjoyment Scale (PACES) questionnaire Semi-structured interviews
Quality of Life	World Health Organisation Quality of Life (WHOQOL) questionnaire
Safety (adverse events and injuries) and compliance	Purpose designed lifestyle diaries and training diaries Trainer records

aBMD, areal bone mineral density; BMC, bone mineral content; BPAQ, Bone-specific Physical Activity Questionnaire; DXA, Dual-energy X-Ray Absorptiometry; PACES, Physical Activity Enjoyment Scale; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density; WHOQOL, World Health Organisation Quality of Life.

Data integrity

Participants will be allocated a unique study ID and data will be de-identified for analysis. After final data collection and cleaning, the data will be locked before analysis. Paper records will be stored securely at Griffith University in a laboratory with restricted swipe card access, and retained for a minimum of fifteen years. Electronic data will be stored securely on password-protected University computers. Management, storage and retention of research data will be in line with Griffith University policy, the *Griffith University Code for the Responsible Conduct of Research*. There will be no contractual agreements limiting data set access. De-identified data will be shared for meta-analyses or other collaborations on a case by case basis. De-identified data will be made available to the bioDensity™ manufacturer, Performance Health Systems, after the final study results have been published.

Blinding

The study will be single-blind; participants in the two exercise groups will only be aware of the details of their allocated exercise protocol. They will train separately, and will not be apprised of study hypotheses. The investigator performing baseline assessments will be blinded to the allocation sequence, which will be revealed to both investigator and participant only after baseline testing. As the assessor will also be training the participants, in order to maintain the highest level of test-retest reliability, follow-up testing will not be assessor blinded. The study is an unfunded PhD student project.

Data analyses

Statistical analyses will be undertaken using SPSS Version 23.0 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous outcome variables will be examined using the Kolomogorov-Smirnov test. Descriptive statistics of participant characteristics,

biometric and dependent variables will be presented as means ± standard deviations and frequencies where appropriate. Comparisons at baseline and follow-up will be evaluated using independent sample *t*-tests (two-tailed) for normally distributed continuous data, non-parametric equivalents for non-normally distributed data, and Chi-Square for categorical data. Between-group comparisons for outcome measures will be examined using repeated measures Analysis of Covariance for time and group-by-time interaction effects using percent change from baseline, adjusting for age, height, weight, baseline values, calcium intake and training program compliance. In accordance with the principles of a classic intention-to-treat approach, all randomised participants will be included in the final analyses, regardless of withdrawal or compliance. In the case of missing follow-up data due to study withdrawal, imputation of the mean percentage change value for the specific group will be employed. Per-protocol exploratory analyses will be performed comparing outcome measures between the HiRIT, bioDensity™ and control groups for those with training program compliance of greater than 70 % to examine maximum treatment efficacy. Multiple linear regression analyses of absolute change will be employed to examine the relative influence of certain variables, found to correlate with outcomes measures, on the bone response. Statistical significance will be set at $p \leq 0.05$.

DISCUSSION

To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised HiRIT exercise program on determinants of fracture risk for older men with low bone mass, compared with supervised bioDensity™ training or control. In the past, exercise prescription recommendations for individuals with osteoporosis have stipulated an emphasis on low to moderate intensity exercise,[14,15] with a goal to prevent falls; however, such exercises are unlikely to provide an adequate stimulus to elicit notable osteogenic adaptation. Both of the current HiRIT and bioDensity™ exercise programs have been designed around key loading characteristics shown to be osteogenic in animal models, and adhere to the principle of progressive overload. The execution of the current trial is warranted in order to progress exercise recommendations for older men with low to very low bone mass, who are at increased risk of fracture.

Although some knowledge exists, exercise intervention studies targeting older men with low bone mass are yet to be conducted over an adequate time period to detect changes in bone with confidence. There is, however, evidence that high intensity (> 80 to 85 % of one repetition maximum) compound movement resistance training exercises can be safely tolerated (with no significant adverse events), and elicit positive effects on bone mass and muscle strength in older adults.[16,24,26,56] Whilst the aforementioned studies suggest such exercise prescription elicits bone and muscle strength changes, little is known about the response in men with low to very low bone mass, or also individuals have sustained a low-trauma fracture. The original high-load LIFTMOR trial [16] implemented in post-menopausal women with low to very low bone mass, enhanced bone mass with a high level of safety. Maddalozzo and Snow [24] also examined the ability of high-intensity resistance training (functional standing free-weights program) to enhance bone in older men and post-menopausal women, but as no baseline T-scores were reported it is not clear if their participants were at increased risk of fracture. Kukuljan and co-workers [26] examined the influence of twelve-months progressive resistance training and weight-bearing impact on

musculoskeletal health in men over the age of fifty with normal to low bone mass. While positive changes were observed at the hip and spine, individuals with osteoporosis and/or a history of osteoporotic fracture were excluded from the intervention. A short (twelve week) trial conducted by Mosti and colleagues [56] randomly allocated post-menopausal women with osteopenia and osteoporosis to a supervised high-intensity hack squat program or control. Four sets of three to five repetitions at 85 to 90 % of one repetition maximum were performed thrice weekly. The significant increases in bone mineral content and area at the lumbar spine and femoral neck observed in the exercise group must be interpreted with caution in light of the small sample (eight women in the strength training group completed the study), and the short study duration which is not normally considered long enough to detect BMD change from densitometry.

Evidence confirming the ability of high-load, low-volume, machine-based bioDensity™ training to improve bone health in older men with osteopenia or osteoporosis is essentially absent. The study will establish preliminary efficacy of two potentially beneficial exercise interventions and provides the opportunity to examine comparative efficacy. By examining the effects of two non-traditional exercise programs on musculoskeletal health and risk factors for falls in a poorly researched population our findings will contribute evidence towards developing efficacious non-pharmacological osteoporosis therapy.

Limitations

Several limitations warrant discussion. First, due to the somewhat unorthodox semi-randomised study design, there exists the possibility of self-selection bias. Pilot testing demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of older male study volunteers to adhere to a control requirement to refrain from exercise for eight months. When volunteering under the premise of receiving an exercise program, we argue that there are also ethical issues of withholding exercise from individuals who wish to take it up. We have attempted to minimise the risk by applying uniform inclusion and exclusion criteria for all study participants, with the exception of a willingness to participant in an eight-month exercise intervention. The extent to which the self-selected control group differs from the intervention groups will be determined and reported in the course of descriptive analyses of baseline data. Any differences will be accounted for by adjusting for baseline values in the final analyses. Second, the current trial is not powered to detect significant differences in fractures as safety (adverse events and injuries) is a secondary outcome. Nevertheless, reporting adverse events and injuries is informative when determining if an exercise program can be translated to clinical practice. Third, the outcome assessor will not be blind to group allocation, will deliver the intervention, and will be responsible for documenting adverse events and reporting to the GUHREC. Participants will be instructed to report even the slightest degree of discomfort/pain/muscle soreness or injury, and a protocol is in place for independent review by a qualified Physiotherapist or General Practitioner, as required. It is also an ethical requirement to report such events to the GUHREC, and harms or unintended events must be included when reporting randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse event would contravene both Institutional and National research ethics guidelines. A blinded outcome assessor is beyond the means of this unfunded project, and therefore our current study design has been adopted out of necessity.

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Author Contributions

Conception and design of the study: ATH, BKW, SLW, BRB; Obtained the equipment award brokered by Osteoporosis Australia: BRB; Manuscript preparation and editing the final paper for submission: ATH, BKW, SLW, BRB; Preparation of Information Sheets, Consent Forms, and Case Report Forms: ATH, BKW, SLW, BRB; Participant recruitment and data collection: ATH; Principle investigator: BRB.

Competing Interests

The Authors declare that there is no conflict of interest in preparing this article.

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Ethics Approval

The trial has received ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC), and has been prospectively registered with the Australian New Zealand Clinical Trials Registry (#ANZCTR12616000344493).

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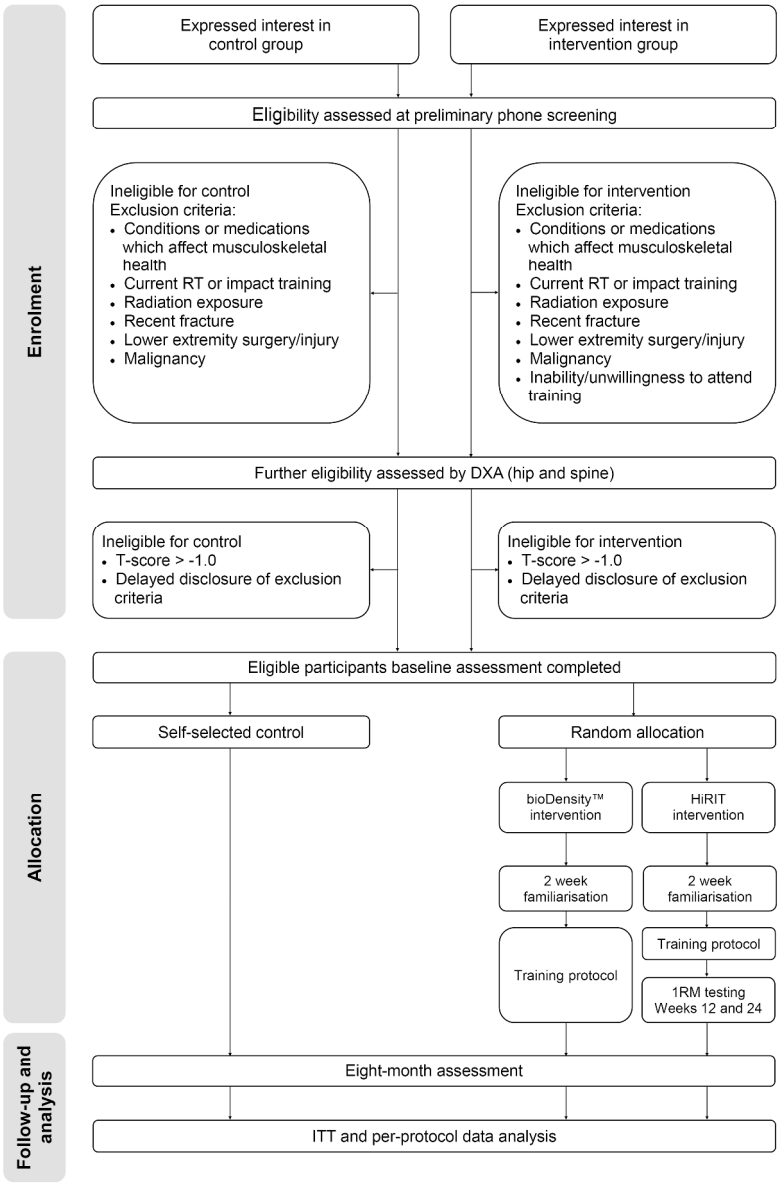
Figure legend

Figure 1. Proposed participant flow (CONSORT diagram)

bioDensity™, machine-based isometric exercise using the bioDensity™ system; DXA, Dual-energy X-Ray Absorptiometry; HiRIT, high-load progressive resistance training plus impact loading; ITT, intention-to-treat; RM, repetition maximum; RT, resistance training.



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242x367mm (300 x 300 DPI)

Public title

The LIFTMOR for Men trial: Is heavy resistance training or a machine-based isometric exercise program more effective at reducing risk of fracture in older men with reduced bone mass?

Scientific title

A randomised controlled trial to determine the effectiveness of heavy progressive resistance training versus high load machine-based isometric resistance training to reduce the risk of osteoporotic fracture in older men with low bone mass

Secondary ID

Nil known

Universal Trial Number

N/A

Trial acronym

LIFTMOR (for Men): Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

Private notes (not publicly viewable)

Nil

Health condition

Osteopenia, osteoporosis, vertebral fracture, kyphosis, hip fracture

Condition category & condition code

Musculoskeletal health- osteoporosis

Injuries and accidents: Fracture

Study type

Interventional

Intervention code

Rehabilitation: 'Treatment: other' and/or 'Prevention'

Description of intervention(s)/exposure

The study is a three-arm, semi-randomised controlled exercise intervention trial. Eligible volunteers will be randomly allocated to one of two eight month, twice-weekly, 30-minute exercise programs; either supervised heavy progressive resistance training and impact loading, or machined-based isometric resistance training using the bioDensity system.

Arm 1 – supervised heavy progressive resistance training and weight-bearing impact loading.

Three compound movement exercises (deadlift, overhead press, and back squat) using olympic weights will be completed. For each exercise, 5 sets of 5 repetitions, corresponding to an intensity of 80-85 % of 1 repetition maximum will be performed. 5 sets of 5 repetitions of weight-bearing impact loading exercises (i.e. drop jumps) will also be performed, with height of the jump progressively increasing across the intervention period.

Arm 2 – supervised high-load isometric exercise using the bioDensity system.

A single set of four isometric exercises (chest press, leg press, core and arm pull, and vertical lift) will be performed according to bioDensity device specifications. For each exercise, one repetition of a self-initiated 75%-maximum contraction will be held for 5 seconds.

Sessions are supervised by a single qualified trainer (Bachelor of Exercise Science graduate, Certificate III in Fitness, Level 1 Sports Trainer Sports Medicine Australia). The training is also certified in First Aid and Cardiopulmonary Resuscitation.

Training diaries will be used to record participant attendance at training sessions, and completion of each element of the training session. Compliance will be determined as the number of sessions attended as a percentage of total possible sessions.

Comparator/control treatment

Arm 3 – the comparator will be a non-randomised sample of men, recruited independently but sex- and age-matched to the exercise arms. They will simply continue with their usual activities for 8 months, but will undergo the identical testing protocol at baseline and follow-up as the two randomised arms. Weekly email contact will be maintained to approximate investigator exposure and track alterations to habitual diet or physical activity levels over the 8 month period.

Diaries will be provided and all participants will be encouraged to record any changes to medication, medical conditions and general health.

Primary outcomes

1) Whole body, bilateral proximal femur (femoral neck, trochanter and total hip regions of interest) and lumbar spine bone mineral density determined by Dual-energy X-ray Absorptiometry. All participants, pre (baseline) and post-intervention (8 months).

Secondary outcomes

1) Indices of bone and muscle strength of the forearm and leg determined from peripheral Quantitative Computed Tomography. All participants, pre (baseline) and post-intervention (8 months).
2) Heel bone quality determined by Quantitative Ultrasonometry. All participants, pre (baseline) and post-intervention (8 months).
3) Body composition (lean mass, fat mass, appendicular lean mass and percentage body fat) from whole body Dual-energy X-ray Absorptiometry. All participants, pre (baseline) and post-intervention (8 months).
4) Muscle strength, physical function and balance will be measured using previously validated techniques. All participants, pre (baseline) and post-intervention (8 months).
5) Kyphosis will be measured using inclinometer
6) Daily average calcium intake, quality of life and bone-specific physical activity using validated questionnaires. All participants, pre (baseline) and post-intervention (8 months).
7) Safety (adverse events and injuries) and compliance from training diaries across the whole exercise intervention period.

Control group

Usual activities

Recruitment country

Australia

Recruitment site location state

Queensland

Recruitment status

Imminent

Anticipated date of first participant enrolment

Ethics application status

Approved

Brief summary

Recent work undertaken at Griffith University (the LIFTMOR trial) has revealed that brief exposure to a bone-targeted heavy progressive resistance training program is both safe, and effective for enhancing musculoskeletal health and function, in postmenopausal women with low to very low bone mass. Similar claims have been made by the developers of the bioDensity system, designed around the premise that low volume machine-based isometric resistance training produces beneficial effects on balance, physical function, muscle strength and bone mass. Whether dynamic or isometric resistance training will be more effective in men over the age of 50 with reduced bone mass at the hip and spine remains to be seen.

Key inclusion criteria

Men

Apparently healthy

With low bone mineral density (hip or spine BMD T-score less than or equal to -1.0)

Not currently or recently participating in regular resistance training or impact-type exercise

Minimum age

50 years

Maximum age

No limit

Gender

Males

Can healthy volunteers participate?

No; as participants have low bone mineral density. They are in fact 'apparently-healthy'.

Key exclusion criteria

Current participation in resistance training or exercise with an impact-loading component

Uncontrolled cardiovascular disease/respiratory conditions

Neurological conditions which might limit an individual's ability to perform resistance training

Malignancy

Hernia

Medications know to adversely affect musculoskeletal health such as corticosteroids, anti-convulsants

Medical conditions known to effect musculoskeletal health such as hyperparathyroidism, Paget's disease, diabetes

Purpose of the study

Prevention of age-related musculoskeletal deterioration

Allocation to treatment

Semi-randomised controlled trial

Enrolment procedure

Block randomisation to exercise will occur after participants are stratified for the presence or absence of medications for osteoporosis. The allocation sequence will be generated by a person independent of the trial and filed in sealed opaque envelopes.

Random order generated by computer program

Open trial (not masked)

Intervention assignment parallel

Phase not applicable

Time of endpoints efficacy

Recruitment

Anticipated start date May 2016

Anticipated date of last participant enrolled Nov 2017

Target sample size 150

Not yet recruiting

Funding & sponsors

Osteoporosis Australia Equipment award (bioDensity device supplied and installed by Performance Health Systems)

Osteoporosis Australia National Office

Postal: PO Box 550, Broadway, NSW, Australia 2007

Street: Level 2, 255 Broadway, Glebe, NSW, Australia 2037

research@osteoporosis.org.au

Phone: 02 9518 8140

Fax: 02 9518 6306

Secondary Funding & sponsors

Performance Health Systems

International head office:

401 Huehl Road, Suite 2A,

Northbrook, Illinois, 60062

United States of America

Ethical approval

Approved Griffith University Human Research Ethics Committee

170 Kessels Road Nathan, QLD 4111 Australia AHS/07/14/HREC

Submitted for approval for the initial LIFTMOR (for women) trial: 1st April 2014

Approval date of variations for the 3-arm trial LIFTMOR for Men: 18th January 2016

Approval expires: 17th Feb 2018

Contact details – Primary sponsor

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INFORMATION SHEET

Project Title

"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"

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Background

As a person ages there is a gradual reduction in bone health and an increased risk of falling which, when combined, increases the risk of fractures. This study will help to determine if one or both of two different types of heavy resistance training safely and effectively improve bone strength, muscle and fat, and physical function in older men with low bone mass.

Method

Who:

- Healthy men over 50 years of age with low bone mass

What:

- You will be *randomly* assigned to either a high-load resistance training program, or a machine-based isometric exercise program, or you will choose to be in a no-exercise control group.
- Training for the resistance and machine-based exercise programs will occur twice a week for 8 months.
- If you are a control, all we require is your attendance at two testing sessions, 8 months apart.
- Before and after the 8-month exercise period you will be asked to complete:
  - Questionnaires regarding your health, diet and the amount of exercise you undertake
  - Some simple physical tasks including: standing jump, reaching, back and leg strength tests, and walking
  - Body composition scans using a dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and a peripheral quantitative computed tomographer (pQCT). Those tests are painless and non-invasive but involve either sitting beside or lying still on special scanners for between 3-10 minutes per scan.
- The total time for each testing session will be approximately 2 hours.
- In the final month of your training program you may be asked to attend a 30 minute interview to discuss your experiences throughout the training period
- We may video or photograph some activities, but you may opt out of those if you would prefer.

Where:

- Testing will take place at Griffith University Gold Coast campus (Southport) in the School of Allied Health Sciences.
- Both heavy resistance training and machine-based training will take place at Griffith University Gold Coast campus (Southport).

Inclusion Criteria

You may be eligible to participate in this study if you are over the age of 50 and have low bone mass (we can tell you if you do) and are willing to undertake an 8-month exercise program comprised of two exercise sessions per week, or merely attend Griffith University for two testing sessions 8 months apart (no new exercise for 8 months).

Exclusion Criteria

You may be excluded if any of the following apply to you:

- Any reason why you cannot safely participate in vigorous physical activity (i.e. uncontrolled cardiovascular disease, certain musculoskeletal conditions, etc.)
- Metal implants (e.g. staples, joint replacement) or foreign bodies (e.g. shrapnel)

- More than two x-ray examinations in the past year or radiation treatment
- Malignancy
- Cognitive impairment
- Certain kinds of current physical activity
- Medications and/or conditions know to influence bone health (e.g. Paget's Disease)

Risks

The risks associated with the project are relatively minor. For those unaccustomed to physical activity, it is likely that you will experience muscle soreness following any change in exercise exposure. There is also a risk of injury during exercise. Such injuries are uncommon but may include low back pain, joint sprains, or muscle strains. All physical testing and both exercise training programs will be closely supervised by the investigators to help reduce those risks. If you have low bone mass, you are at greater risk of fracture during heavy lifting exercises than people with higher bone mass. It will be important to perform the exercises as instructed by your trainer to make sure you are doing them safely. Should an injury occur during a study training session, an initial consult and one follow-up consultation will be available free of charge at the Griffith University *Physiotherapy and Active Health Centre*. If further treatment is required, investigators can refer you to an appropriate healthcare professional. The *Physiotherapy and Active Health Centre* has undertaken to provide discounted rates to physiotherapy patients referred by study investigators.

There are also slight risks associated with some of our tests. DXA and pQCT scans are non-invasive and painless, but they do involve exposure to small quantities of ionising radiation. The amount of radiation exposure during a chest x-ray is 8 times greater than that for either pQCT or DXA tests. The radiation exposure for DXA and pQCT scans is less than 0.01 mSv. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year. The exposure to radiation during plane travel is approximately 0.005 mSv per hour, thus a 14 hour international flight from Australia to Los Angeles would expose an individual to approximately 0.07 mSv, or 28 times the radiation from a single DXA scan.

Benefits

- Each participant will receive free bone, muscle and fat scans and an estimate of calcium consumption.
- Participants assigned to the exercise groups will receive a free 8-month exercise training program.
- Your involvement in this study will help contribute to the understanding of exercise as a treatment strategy for bone health, which will help countless individuals suffering from osteoporosis.

Confidentiality

Results will be kept as confidential as is possible by law and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375.

Use of video recordings and photography

You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password protected computer for a minimum of 5 years.

Contacting the Investigators

We are happy to answer any questions you may have. For general inquiries please contact Miss Amy Harding (student researcher), at amy.harding@griffithuni.edu.au or on 0410 616 596. If you have any concerns with the study, please do not hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, or Prof Belinda Beck on (07) 5552 8793.

Feedback

Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if you're interested, the overall study findings.

Voluntary Participation

Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to participate, you are free to withdraw your consent and discontinue your involvement at any time.

Complaints Mechanism

The University requires that all participants be informed that if they have any complaints concerning the manner in which a research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, Research Ethics, Office for Research, Room 4.25, Science, Engineering and Architecture (G11), Griffith University, Gold Coast campus, Q 4222, Phone: 373 54375 or research-ethics@griffith.edu.au.

Please retain this document for your information.

CONSENT FORM

Project Title

"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"

Investigators

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Consent Statement

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that will I be *randomly* assigned to a high-load resistance training program, or a machine-based isometric exercise program, or I can choose to be in the no exercise group
- If I am assigned to an exercise group I understand that I will be asked to undertake an 8-month training program, consisting of 2 roughly 30 min sessions per week.
- I understand that there will be a testing session approximately 2 hours in duration both before and after the 8-month exercise period;
- I understand that I will undergo dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and peripheral quantitative computed tomographer (pQCT) scans and measurement of height, weight and waist circumference, to determine body composition;
- I understand that I will be asked to complete several questionnaires relating to physical activity, quality of life, evaluation of the exercise program and diet;
- I understand that I will be asked to perform a series of physical tasks including: standing jump, walking, back and leg strength tests, and reaching tasks;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand the benefits of my participation in this research;
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without comment or penalty;
- I understand that I can contact the Manager, Research Ethics, on 373 54375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

_____	_____	_____
(Participant)	(Participant signature)	(Date)

Optional video and photography consent:

☐ I agree to be video recorded while performing the physical activities to be used during presentations, media coverage and publication of research findings.

☐ I agree to be photographed while performing the physical activities to be used during presentations, media coverage and publication of research findings.

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	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	ANZCTR trial registry (online)/Supplementary file
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	31
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Author affiliations – 1; Author contributions - 31
	5b	Name and contact information for the trial sponsor	31
	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	Data access – 26; Statement - 31

	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)	Ethics and dissemination – 9-10; Data integrity – 26; Author contributions - 31
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	Introduction - 6-8; Study aims - 10
	6b	Explanation for choice of comparators	Study design - 11
Objectives	7	Specific objectives or hypotheses	Study aims - 10
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)	Study design - 11
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	Setting - 12
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)	Inclusion/Exclusion criteria – 12-13; Trainer delivering the intervention - 14-15; Investigator performing assessments - 31
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-15

	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)	Eligibility and screening 12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16 (Controls) 14-15 (Exercise interventions) 10 (Dissemination of results to participants)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Eligibility and screening 12-13
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	Primary outcome – 16; Secondary outcomes – 16-25; Data analyses – 26-27; Explanation for clinical relevance (Introduction) – 6-7
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)	CONSORT (Figure 1); Study design - 11
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	Sample size calculation - 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Recruitment - 12

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	Randomisation and allocation – 13-14
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 assigned	Randomisation and allocation – 13-14; Blinding - 26
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Randomisation and allocation – 13-14; Blinding - 26
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Randomisation and allocation – 13-14; Blinding - 26
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Randomisation and allocation – 13-14; Blinding – 26; Study limitations - 30
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 protocol	Primary outcome – 16; Secondary outcomes – 16-25

	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	Provision of participant results summary - 10; Data analyses ITT approach 27
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	Data integrity - 26
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	Data analyses – 26-27
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Data analyses – 26-27
	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)	Data analyses – 26-27
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	Ethics and dissemination – 9-10; Data integrity – 26; Author contributions - 31
	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	Ethics and dissemination – 9-10; Data integrity – 26; Author contributions - 31

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	Ethics and dissemination – 9; Study limitations - 30
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Data integrity – 26; Statement regarding study sponsor - 31
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination – 9-10
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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Ethical clearance – 9; Informed consent - 9
	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	Ethical clearance – 9; Data integrity - 26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Competing interests and funding acknowledgements - 31

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	Statement regarding study sponsor - 31
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	Ethics and dissemination – 9-10
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	Dissemination of results – 10; Data provisions for study sponsors - 26
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Dissemination of results – 10; Data set access - 26
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
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	N/A

*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

The LIFTMOR-M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: Protocol for a semi-randomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Impact, Isometric exercise, Osteoporosis, Resistance training, Men

Study Protocol (Rehabilitation Medicine)

Title:

The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: Protocol for a semi-randomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass

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Word Count:

6542 (1 Figure; 1 Table; 56 References)

Keywords:

Impact; Isometric exercise; Men; Osteoporosis; Resistance training.

ABSTRACT

Introduction

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training and impact loading program in comparison to a supervised machine-based isometric exercise training program using the bioDensity™ system in older men with low bone mass. We will also determine the safety and acceptability of each exercise training mode. Intervention group responses will be compared with those of a self-selected, non-randomised control sample of sex- and age-matched men who will follow their usual lifestyle activities for eight months.

Methods and analysis

Apparently-healthy men over fifty years with low bone mass, screened for medical conditions and medications known to adversely affect bone health, will be recruited. Eligible participants will be randomly allocated to eight months of either exercise program with block randomisation based on presence or absence of osteoporosis medications. A twice-weekly, thirty-minute, supervised exercise program will be conducted for both groups. The primary outcome will be change in femoral neck areal bone mineral density determined by Dual-energy X-ray Absorptiometry (DXA). Secondary outcomes, assessed at baseline and eight months, will include: DXA-derived whole body, bilateral proximal femur and lumbar spine areal bone mineral density; proximal femur bone geometry and volumetric density extracted using 3D hip analysis software; anthropometry; body composition; kyphosis; vertebral fracture assessment; physical function; safety (adverse events and injuries); and compliance. Intention-to-treat and per-protocol analyses will be conducted.

Discussion

Whether a high-load, low-repetition progressive resistance training plus impact loading program or a machine-based isometric exercise program can improve determinants of fracture risk, without causing injury, has not been examined in men. Determination of the efficacy, safety and acceptability of such programs will facilitate formulation of future exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who have previously been underrepresented.

Ethics and dissemination

Participant confidentiality will be maintained with publication of results. The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC).

Trial registration number

Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)

ANZCTR12616000344493; Pre-results.

Date and version identifier

Original protocol manuscript for submission (Version 1): November 2016.

Protocol manuscript for submission (Version 2) with revisions from peer review: December 2016

Protocol manuscript for submission (Version 3) with revisions from peer review: February 2017

Authors: ATH, BKW, SLW, BRB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised high intensity, progressive resistance training and impact loading program on several determinants of fracture risk for older men with low bone mass, compared with a machine-based isometric exercise program using the bioDensity™ system.
- There are few investigations into the effects of exercise on musculoskeletal health in older men, thus the current unique focus on older men with poor bone health will address a notable gap in the literature.
- The engagement of a non-randomised control group of demographically-matched men who have elected not to exercise for eight months is a design limitation that was implemented for pragmatic reasons.
- Our study sample will include largely healthy older men, so our findings may not be applicable to men with comorbidities or other exclusion characteristics.

INTRODUCTION

Epidemiological data indicates the global prevalence of osteoporosis to be over 200 million,[1] with around 1.2 million Australians,[2] 10.2 million Americans [3] and 15 million European men and women over fifty years of age being affected.[4] It has been suggested that 285,000 Australian men aged over fifty will be diagnosed as osteoporotic, and a further 2.48 million older men diagnosed as osteopenic by 2022.[5] With the aging of the population, there will undoubtedly be a corresponding increasing prevalence of low bone mass and consequent increase in the incidence of low trauma fracture.[6]

It is widely accepted that bone adapts to the mechanical loads it habitually experiences. Experimental data from animal models has revealed the most influential loading characteristics for osteogenesis are magnitude,[7,8] rate [9] and frequency [10-12] of the engendered strain. Evidence also indicates dynamic loading is more osteogenic than static loading.[13] The optimal exercise prescription for the prevention and management of osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads, applied at a rapid rate. High-load resistance training with high-impact jumping, the combination of which will elicit high strains and strain rates in bone, is thus theoretically the optimal exercise protocol for bone. Although such exercise is considered safe for healthy individuals with normal bone mass, it is unclear whether it will be safe for individuals with reduced bone mass who are at increased risk of fracture. Previous resistance exercise recommendations for individuals with low bone mass, particularly those who have experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate level of intensity,[14,15] based on a lack of quality evidence that high intensity resistance training is safe and effective.

Recently a bone-targeted, high intensity, progressive resistance training and impact loading (HiRIT) exercise program was undertaken with post-menopausal women with low to very low bone mass at the hip or spine - the LIFTMOR (Lifting Intervention For Training Muscle and

Osteoporosis Rehabilitation) trial. Interim results indicated the HiRIT protocol was well tolerated (no injuries sustained during supervised training sessions) and effective, exhibiting positive changes to musculoskeletal health in post-menopausal women at increased risk of fragility fracture.[16] Although the lifetime risk of fracture is greater in women over the age of fifty (one in three), than men of the same age (one in five), older men are more likely to suffer serious post-fracture consequences.[4,17] The most devastating low-trauma fracture site for older men is the hip, with mortality exceeding that of similarly aged women within the first year post-fracture.[18] In light of the fact that osteoporosis, and low-trauma fractures, affect men as well as women, it was necessary to replicate the protocol in older men to determine if it will be similarly effective.

Separately, but simultaneously with the LIFTMOR trial, an isometric device (the bioDensity™ system, Performance Health Systems, Northbrook, IL, USA) was developed in the USA to facilitate near-maximal isometric contractions against instrumented external resistance, with a goal to increase bone mass. The developers are currently marketing the device on the grounds that short-duration, low-volume, high-load bioDensity™ training can enhance bone mass in individuals with osteoporosis: however, concrete evidence is lacking. To date, four studies examining the bioDensity™ training protocol have been published,[19-22] only one of which included bone outcome measures.[22] In the latter observational study seventy post-menopausal women with low bone mass were invited by their general practitioner to take part in a six-month bioDensity™ intervention (one training session per week) for which the primary outcome was maximal isometric muscle force production. A sub-group of nine participants underwent Dual-energy X-ray Absorptiometry (DXA) examinations for bone density. Those individuals reportedly sustained increases in bone mineral density (BMD) at the hip (14.9 ± 11.5 %) and spine (16.6 ± 12.2 %) – responses that far exceed the BMD responses to previously reported exercise interventions. The lumbar spine T-score of one participant improved from -3.1 to -0.10. As considerable methodological shortcomings were evident in the latter study design, including low sample size, no monitoring of dietary calcium

intake or physical activity, lack of control group, lack of disclosure of simultaneous bone medications, and the fact that follow-up DXA scans were conducted sixty days after the intervention was completed suggests that a more rigorous examination of efficacy of bioDensity™ training is indicated.

Short-duration (thirty minute), twice-weekly therapeutic exercise programs for older men with low bone mass, such as the proposed HiRIT and bioDensity™ training protocols, provide an attractive alternative to more burdensome and time consuming programs typically recommended for osteoporosis. Indeed, trials examining the influence of progressive resistance training, hopping/jumping or multicomponent programs on bone health in men have adopted session frequencies of three,[23-28] four,[29] or even seven [30] per week. Hinton and colleagues [28] compared thrice-weekly sessions of jump training with twice-weekly sessions of periodised progressive resistance training; however, healthy physically active men aged 25 to 60 years were recruited. Whether high-load, low-volume training methods can safely improve bone strength in older men with low bone mass remains a knowledge gap. Thus, the Griffith University Bone Densitometry Research Laboratory has acquired a bioDensity™ device for the purposes of examining safety and efficacy alongside the HiRIT protocol in a semi-randomised controlled trial design.

METHODS AND ANALYSES

Ethics and dissemination

The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities will be conducted in accordance with the *Declaration of Helsinki*. The study is also registered with the Australian New Zealand Clinical Trials Registry (Trial number ANZCTR12616000344493). Written informed consent will be obtained from all participants prior to testing by the investigator performing baseline assessments.

Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial [16] (Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide evidence of an extremely low risk of injuries from the current exercise protocols, with no severe injuries reported from a total of 7300 training sessions. Similar to the current protocol, ethical approval was granted by the GUHREC for both studies, and written informed consent was obtained from all participants. Strategies were in place to reduce the risk of injuries or adverse events occurring during the aforementioned trials, and included: 1) full supervision of high-load resistance training sessions by a qualified exercise scientist; 2) small group sizes in the supervised training sessions; 3) an initial familiarisation period during which low-load exercise variants focused on proper lifting technique was implemented, and 4) weight lifted was progressively increased with training exposure. In order to monitor safety, participants were required to complete training diaries at every training session to record illnesses, falls, fractures, injuries, and muscle soreness. Early termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual progress reports to the GUHREC. Any adverse events which occur between annual reports will be reported independently to the GUHREC, in compliance with the *Australian Code for the Responsible Conduct of Research* developed by the National Health and Medical Research Council, and the University *Code for the Responsible Conduct of Research*. The

GUHREC is a registered institution with the National Health and Medical Research Council (Registration number EC00162). For participants who are unaccustomed to physical activity it is likely they will experience some degree of muscle soreness following any change in exercise exposure. In the unlikely event that a participant experiences significant intervention-related muscle soreness, or an injury occurs during the study period, consultations with a qualified Physiotherapist (external to the trial) at the Griffith University Allied Health Clinic will be available. If further treatment is required they will be referred to an appropriate healthcare professional.

All participants will be supplied with a full summary of individual and overall study results to encourage retention for the duration of the study, and to comply with ethical requirements. The usual scientific reporting practices will take place, including presentations at discipline meetings and publication in peer reviewed journals. There will be no interim analyses published prior to completion of the trial. Community and clinical talks will also be given as appropriate. Participant confidentiality will be maintained with publication of results.

Study aims

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training plus impact loading (HiRIT) program in comparison to supervised bioDensity™ machine-based isometric exercise training, or no intervention (control), for improving femoral neck (FN) areal bone mineral density (BMD) in older men with low bone mass. The primary outcome measure was selected according to clinical relevance, in light of the large personal and economic impact of hip fracture. It is hypothesised that eight months of twice-weekly HiRIT training will improve FN BMD more than bioDensity™ training or control, and similar benefit will be observed in secondary outcome measures. Furthermore, we hypothesise that there will not be a higher rate of adverse events during eight months of HiRIT compared with bioDensity™ training or control.

226

227 **Study design**

228 The current project is a three-arm, eight-month, semi-randomised, controlled exercise
229 intervention trial. Proposed participant flow is outlined in Figure 1. The eight-month exercise
230 intervention period has been chosen as the minimum time frame in which notable changes in
231 bone mass are likely to be detected from densitometry.[31] Eligible volunteers to the
232 intervention arm will be randomly assigned to one of two exercise programs; either
233 supervised HiRIT or bioDensity™ training. The third arm will be a non-randomised control
234 group of sex- and age-matched participants with lower than average bone mass recruited
235 from the same community. The control group will follow their usual lifestyle for eight months,
236 but undergo identical testing to the two exercise intervention groups at baseline and follow-
237 up. We acknowledge the somewhat unorthodox semi-randomised design does not
238 constitute the most rigorous clinical trial practice, but adopt it out of necessity. Pilot testing
239 conducted in our laboratory revealed that male study volunteers who expect to participate in
240 an exercise trial, but are randomised to a conventional inactive control group, refuse to
241 adhere to the requirement to refrain from exercise for eight months. We also believe that it
242 is unethical to withhold access to a potentially beneficial bone-targeted exercise program for
243 older men at increased risk of fragility fracture who are specifically seeking exercise therapy.
244 For pragmatic reasons then, we will independently recruit a demographically-matched
245 sample of men who, for a variety of reasons (not including functional capacity), elect to
246 remain sedentary for a minimum of eight months.

247

248 **Sample size**

249 There have been no published reports of men's studies comparing the effects of heavy
250 progressive resistance training and machine-based isometric training using the bioDensity™
251 system on FN BMD, thus estimates of sample size were based on the reported rate of

annual loss. For men over the age of fifty, longitudinal studies have reported an annual loss of 0.42 to 0.45 % FN BMD per year.[32,33] Thus, to detect a significant difference in FN BMD change, from a two-tailed test with a power of 80 % and α = 0.05, approximately 32 participants per group will be required. Allowing for a 20 % dropout, a total of 38 participants per group is required. The 20 % dropout rate reflects those reported in previous bone-targeted exercise interventions in men,[28-30] and the dropout rate of randomised controlled intervention trials in adults (20.9 %).[34] Recruitment for this study started in May 2016, and will continue until the planned sample size is achieved.

Setting and recruitment

Baseline and follow-up assessments will be conducted in the Bone Densitometry Research Laboratory, School of Allied Health Sciences, Griffith University, Gold Coast campus, Queensland, Australia. All supervised training sessions will be conducted in the Strength Training Research Facility, co-located in the School of Allied Health Sciences. Both measurements and interventions will be conducted at this single location. Methods of recruitment include local media outlets (print media and radio), social media, official website (www.liftmor.org), word of mouth, and notice board flyer advertisement at local lawn bowls clubs, golf clubs and senior citizens clubs.

Eligibility and screening

Apparently healthy, able-bodied men over fifty years of age will be recruited. Volunteers are to be excluded if they have any of the following: uncontrolled cardiovascular or respiratory disease; disclosure of musculoskeletal or neurological conditions likely to affect their ability to perform exercise; medications known to affect bone metabolism (e.g. corticosteroids, thyroxine, antiepileptic, and antiretroviral agents); medical conditions known to affect

musculoskeletal health (e.g. Paget's disease, hyperparathyroidism, and thyrotoxicosis); current participation in high-load resistance or impact-type exercise; metal implants (e.g. joint prostheses); recent radiation therapy or radiographic investigations; recent fracture or lower extremity surgery; or malignancy. Further exclusion for the exercise arm will be based on an inability or unwillingness to take part in eight months of twice-weekly exercise training due to motivation, travel or work commitments. No upper age limit is stipulated. Potential participants who contact the investigator will initially undergo a preliminary phone screening for inclusion and exclusion criteria. If eligibility is established, prospective participants will be invited to attend the University research facility for BMD screening and, when relevant, to undergo baseline assessments. Potential exercise intervention participants and self-selected age-matched men will then undergo preliminary Dual-energy X-ray Absorptiometry (DXA) scans. If osteopenia (T-score between -1.0 and -2.5) or osteoporosis (T-score < -2.5) is detected at the lumbar spine and/or proximal femur, the individual will be eligible for inclusion and the full suite of scans. Participants will be discontinued if they: 1) withdraw consent, 2) cease to attend training sessions for longer than three weeks, 3) initiate or discontinue osteoporosis medications, or initiate medications known to affect bone metabolism, 4) become injured and unable to participate, 5) perform additional forms of exercise such as resistance training or impact-type exercise external to the trial, and 6) are advised by their general practitioner to cease training.

Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity™ training groups will be achieved via block randomisation, stratified by the presence (more than twelve months exposure) or absence (lack of exposure) of osteoporosis medications, using a computer-generated randomisation sequence (www.randomization.com, accessed 17th May 2016). To ensure concealment, the allocation sequence will be prepared in advance by an

external source, and filed in sequentially-numbered, sealed, opaque envelopes. Upon completion of baseline testing those identified as eligible will be randomly allocated to their exercise group and their supervised exercise training sessions will be scheduled.

Exercise interventions

Progressive resistance training and impact loading exercise program

The HiRIT group will perform approximately thirty minutes of supervised, high-load, free weight training and impact loading, twice-weekly, on non-consecutive days. Sessions will comprise three fundamental compound movement exercises (deadlift, squat and overhead press). During the initial two weeks, participants will perform low-load variants of each exercise focussing on technique for the purposes of familiarisation. During training weeks three to twelve participants will perform five sets of each exercise, lifting the maximum weight possible for five repetitions while maintaining correct form. The Rating of Perceived Exertion (RPE) scale will be used to subjectively select exercise intensity and guide weight progression prior to determining one repetition maximum. Participants will aim for a RPE ≥ 16 (6-20 point Borg scale [35]) to achieve a high intensity equivalent before one repetition maximum testing. Maximal strength testing, to determine one repetition maximum for the deadlift and squat, will be performed at weeks twelve and twenty-four. Briefly, the maximal strength test protocol will begin with a warm-up set of five to ten repetitions at a relatively light load (approximately 50 % of the heaviest weight they have previously lifted for five repetitions). After a one-minute rest they will perform one set of three to five repetitions at 60 to 80 % of their perceived maximum. Gradually the load will increase in 2.5 to 5.0 kg increments until a failed attempt (within three to six attempts), with each attempt interspersed with a two-minute rest. One repetition maximum is defined as the heaviest weight a participant can lift once with correct lifting technique. A similar one repetition maximum testing protocol was found to be reliable for untrained middle-aged adults

(intraclass correlation coefficients > 0.97).[36] From training week twelve onwards participants will perform five sets of five repetitions for each exercise, corresponding to an intensity of greater than 80 to 85 % of one repetition maximum. Load magnitude will be progressively increased in increments of 2.5 kg over the course of the intervention when they are able to easily complete seven repetitions at their current weight. In addition, five sets of five repetitions of jumping chin-ups (interspersed with rest) with a firm, flat-footed landing will be performed each session. Impact intensity will be gradually increased by moving towards achieving a stiff-legged landing as tolerated. Training will be fully supervised by a qualified exercise scientist. Weight progressions and RPE will be recorded in training diaries.

Machine-based isometric exercise program

The supervised bioDensity™ group will exercise twice-weekly, on non-consecutive days to match the HiRIT group protocol. Four exercises will be performed; chest press, leg press, core pull, and vertical lift. The chest press and leg press closely mirror conventional strength training equipment, the core pull movement combines an abdominal crunch with an underhand chin-up, and the vertical lift simulates a high-hang deadlift position. During the initial two weeks, participants will perform a lower intensity repetition of each exercise focussing on technique. Following this familiarisation period, one self-initiated near-maximal five-second isometric contraction will be performed for each of the four exercises (per manufacturer's recommendations). Integrated monitors provide real-time peak muscle force production feedback. Participants will provide an RPE with the aid of the 6-20 point Borg scale [35] for each exercise. They will be instructed to achieve a near-maximal five second isometric contraction at an intensity corresponding to greater than 80 to 85 % of one repetition maximum, translating to an RPE of greater than or equal to sixteen on the 6-20 point Borg scale.[37] A single qualified trainer will supervise all sessions to operate the

bioDensity™ system, and ensure the exercises are performed correctly and safely. Peak force, average force and RPE will be recorded in participant training diaries.

Control group activities

The sex- and age-matched control group will be encouraged to maintain their customary physical activity and dietary patterns over the eight month duration of the study. To monitor deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to list variations to their physical activity level and diet on a fortnightly basis. Space is also provided to record any illnesses, falls, fractures, changes to their medical conditions and medications (inclusive of over the counter medications), and injuries other than muscle soreness. Diaries are to be returned at follow-up. Fortnightly emails will act as reminders to complete diary entries, with a monthly email requiring a reply to the investigator to prompt recording of any relevant changes. To detect change in bone-relevant physical activity or dietary calcium intake over the course of the eight-month study, participants will complete questionnaires (described below) at baseline and follow-up.

Outcome measures

All outcome measures will be performed at baseline and eight-month follow-up by a single investigator who is not blind to group allocation, using identical facilities, procedures and equipment. A summary of outcome measures is presented in Table 1.

Primary outcome

The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink, France).

Secondary outcomes

Secondary outcomes (described in more detail below) will include: changes in anthropometrics, as well as in whole body and regional measures of bone, muscle and fat. Kyphosis will be examined in order to track angular changes of the spine with exercise exposure. Vertebral fracture assessment using the Genant semiquantitative approach [38] from lateral thoracolumbar spine imaging will be conducted pre- and post-intervention by DXA. A series of commonly utilised performance tasks will be employed to examine changes in lower extremity muscle force and power, dynamic balance, and maximal trunk extensor strength in keeping with standard protocols. Standardised instructions will be provided for all performance tasks, with the best performance of three trials to be included in the analyses. Previously validated questionnaires will be used to estimate dietary calcium consumption, current and past bone-relevant physical activity, quality of life and exercise appeal. Participant safety (adverse events and injuries) and compliance will be monitored across the intervention period using training diaries.

Bone strength indices

Whole body, bilateral proximal femur (trochanter and total hip regions), and lumbar spine areal BMD, bone mineral content and bone area will also be determined by DXA. Parameters of proximal femur (femoral neck and total hip regions) trabecular and cortical bone geometry and volumetric density will be extracted from standard DXA scans using 3D hip analysis software (DMS Group, Mauguio, France). Quantitative Ultrasonography will be used to evaluate changes in calcaneal bone quality (QUS; Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA). Volumetric BMD and geometric parameters contributing to bone strength at the tibia and radius will be determined from peripheral Quantitative Computed Tomography scans of the forearm and leg (pQCT; XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany; voxel size 0.5 mm, slice thickness 2.3 mm and scan speed 25 mm/sec). Tibial length will be measured by means of palpation as the distance from the proximal border of the medial tibial plateau to the distal tip of the medial

malleolus, and radial length measured from the proximal tip of the olecranon process to the distal tip of the ulnar styloid process. A planar scout view of the ankle joint line on the skeletally non-dominant leg will be acquired so the anatomical reference line can be adjusted to bisect the tibial endplate. A total of four image slices will be acquired at 4 %, 14 %, 38 % and 66 % sites proximal to the distal edge of the tibial endplate. For the distal tibia (4 % site) contour mode 3 at 169 mg/cm^3 and peel mode 4 at 650 mg/cm^3, with a 10 % peel, will be used to determine total and trabecular content, total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional area. At the midshaft of the tibia (38 % site) cort mode 2 at 710 mg/cm^3 will be used to define cortical content, volumetric bone mineral density, area and thickness, and periosteal and endocortical circumference. Cort mode 2 at 480 mg/cm^3 will be used to determine polar section modulus and the polar strength strain index. A planar scout scan perpendicular to the long axis of the skeletally non-dominant forearm will be performed at the level of the ulnar head, with the reference line positioned at the distal edge of the most horizontal portion of the radial cortical endplate. Two image slices will be acquired at the 4 % and 66 % sites proximal to the distal endplate of the radius. For the distal radius (4 % site) contour mode 3 at 169 mg/cm^3 and peel mode 4 at 650 mg/cm^3, with a 10 % peel, will be used to determine total and trabecular content, total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional area. At the proximal radius (66 % site) cort mode 2 at 710 mg/cm^3 will be used to define cortical content, volumetric bone mineral density, area and thickness, and periosteal and endocortical circumference. Cort mode 2 at 480 mg/cm^3 will be used to determine polar section modulus and the polar strength strain index. pQCT-derived bone parameters will include: total content, density and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, density, cross-sectional area and thickness; periosteal and endocortical circumference; and biomechanical strength indices calculated from density and area (total and trabecular bone strength indices, polar section modulus, and polar

strength strain index). All pQCT analyses will be conducted using host software Version 6.20 (Stratec Medizintechnik GmbH, Pforzheim, Germany).

Anthropometrics and body composition

Height will be measured via the stretch stature method with a wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany). Weight will be measured using a mechanical beam scale without shoes and in light clothing (Model 700; Seca, Hamburg, Germany). Body mass index will be determined per the accepted method (Body Mass Index = weight/height^2; kg·m^{-2}). Waist circumference, a predictor of visceral abdominal adiposity, will be measured using a steel tape following National Institute of Health guidelines (Model W606PM; Lufkin Executive Thinline, Apex, USA).[39] Briefly, the tape will be positioned on the horizontal plane at the level of the iliac crests on bare skin, and recorded at the end of gentle expiration. Body composition parameters inclusive of lean mass, fat mass, appendicular lean mass and percentage body fat will be derived from whole body DXA. Muscle cross-sectional area, an index of muscle size, and muscle density, an index of intramuscular fat, will be determined from pQCT scans of the forearm and leg at the 66 % site.

Thoracic kyphosis and vertebral fracture assessment

Thoracic kyphosis will be assessed in relaxed standing (neutral posture) and standing 'at attention' using a gravity-referenced inclinometer, following a procedure similar to MacIntyre and colleagues (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia).[40] The inclinometer will be zeroed at the twelfth thoracic to first lumbar intervertebral space, and the angle at the seventh cervical to first thoracic intervertebral space recorded. Lateral thoracolumbar spine DXA will be performed in the lateral de cubitus position to calculate Cobb angle via two methods: 1) vertebral body endplates, and 2) anterior vertebral body margins. The superior endplate of the fourth thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra will be manually digitized, perpendicular lines extended and the

angle at their intersection measured.[41] To account for endplate angulation and tilt due to vertebral irregularity, the anterior margins will be digitized and the angle at their intersection measured.[42] In addition, lateral thoracolumbar spine DXA allows vertebral fracture identification using the Genant method.[38] The anterior, medial and posterior heights of the vertebral body are used to grade (mild, moderate or severe) wedge, biconcave or crush deformity.

Timed up-and-go

The timed up-and-go test is a measure of functional mobility, and dynamic balance.[43] Participants will be instructed to rise from a seated position without using their hands for assistance, walk at a brisk pace to a mark on the floor a distance of three meters away, pivot, and return to assume the start position. Participants will be timed from the point at which their back no longer makes contact with the chair, to when they return to the start and adopt the correct seated position.

Five-times sit-to-stand

The five-times sit-to-stand is a reliable assessment of the ability to rise unassisted from a seated position, with relevance to functional mobility, dynamic balance and lower extremity muscle strength.[44] Participants will be asked to move from a sitting to standing position, without the use of their arms, for five repetitions following the recommendations of Bohannon and colleagues for assessing older adults.[45]

Functional reach

A modified version of the original functional reach test (that incorporated a yardstick) will be used to assess dynamic balance, which has been identified as an important component of falls risk.[46] Participants will stand with shoulders perpendicular to a Perspex board marked with vertical measurement lines, with the dominant arm located nearest the board and extended forwards to 90 ° shoulder flexion, with the hand forming a fist. The participant

will be instructed to reach forward by flexing the trunk at the hip, maintaining a fixed base of support, without stepping or losing balance. If the participant makes contact with the Perspex board, takes a step or loses balance, the trial will be repeated. The start and finish positions of the third metacarpal in respect to the measurement lines will be recorded to determine displacement.

Muscle power

Lower extremity muscle power will be assessed by a countermovement vertical jump test. Participants will be instructed to perform a jump for maximum height, without arm swing, whilst positioned on a floor-mounted 900 mm x 600 mm load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA). Impulse and impulse relative to body weight will be calculated from the vertical component of the ground reaction force of the loading and take-off phase according to the method described by Linthorne.[47]

Isometric muscle strength

Maximal isometric force of the lower extremity will be estimated using a leg strength platform dynamometer (TTM Muscle Meter, Tokyo, Japan). The participant will stand on the dynamometer platform assuming a semi-squat position with knees flexed (knee angle of 115 º, hip flexion angle of 65 º), trunk extended and back flat against the wall. A straight bar handle is affixed to the dynamometer by a chain at a length so the arms are fully extended to grip it. After ensuring the chain is taut, the dynamometer is manually zeroed. Participants will be instructed to attempt to straighten their legs, whilst keeping their back fully in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.84$, $p < 0.001$; test-retest reliability $r = 0.97$, $p < 0.001$). (Little A, Harding AT, Weeks BK, Horan SA, Watson SL, and Beck BR, 2016; unpublished data; conference abstract)

Maximal isometric back extensor muscle strength will be assessed in erect standing using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA). The participant will be positioned midway between two vertical wall-mounted anchor rails, with their back and heels against the wall. An inelastic belt between the two rails will be fastened horizontally around the hips in order to restrain the pelvis. The padded transducer pressure plate will be positioned by the investigator between the wall and the seventh thoracic vertebral spinous process, until held securely against the wall by the pressure of the participant's back. Participants will be instructed to push back into the wall with their shoulders, ensuring their feet remain flat with their heels in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.85$, $p < 0.001$; test-retest reliability $r = 0.93$, $p < 0.001$). (Harding AT, Weeks BK, Horan SA, Little A, Watson SL, and Beck BR, 2016; Unpublished data; conference abstract)

Dietary calcium intake

Calcium intake will be assessed using the AusCal, a calcium-focused food frequency questionnaire designed and validated for the Australian diet.[48] Frequency of consumption per day, week or month, and approximate serving size will be recorded for each of the listed calcium-rich food and beverage items over the previous year. The AusCal will be investigator-administered. Questionnaire responses will be entered into customised FoodWorks analysis software to generate average daily calcium intake (Version 7, Xyris Software, Brisbane, Australia).

Bone-specific physical activity

The Bone-specific Physical Activity Questionnaire (BPAQ) [49] will be used to quantify current and historical physical activity of relevance to bone. Respondents will list all regular, structured physical activity and years of participation, with a minimum of investigator

assistance. BPAQ scores will be calculated using an on-line, custom-designed analysis program (http://www.fithdysign.com/BPAQ/). Mathematical algorithms in the calculator were developed using load ratings from vertical ground reaction forces of each activity, participation frequency, years of involvement and an age-weighting factor. High loading ratings represent high-impact activities, whilst the age-weighting factor reflects higher mechanosensitivity to physical activity during youth. Previous research has found BPAQ scores are predictive of variance in DXA-derived bone strength parameters at clinically relevant sites in healthy middle-aged and older men.[50] This instrument has high reliability, with intra-class correlation coefficients of 0.92 to 0.97.[51]

Barriers and facilitators

The Physical Activity Enjoyment Scale (PACES), designed by Mullen and colleagues,[52] is a self-reported eight-item questionnaire which uses a seven-point Likert scale for each item. The respondent is required to circle the number corresponding to their current thoughts about physical activity. Higher PACES scores indicate a greater level of exercise appeal. Inclusion of this instrument was based on physical activity enjoyment being identified as a potential determinant of exercise adherence.[53] Semi-structured interviews to determine exercise appeal, barriers and facilitators to participation in HiRIT or bioDensity™ training programs will be conducted within one month of completing the eight-month intervention by an independent investigator. Interviews will be tape-recorded with participant consent, and transcribed verbatim. Interview transcripts will be thematically coded using NVivo qualitative software (Version 10, QRS International Pty Ltd) to determine barriers and facilitators to participation in higher-intensity, bone-targeted exercise.

Quality of life

The World Health Organisation Quality of Life questionnaire was developed to assess four quality of life domains using a five-point Likert interval scale.[54] Higher scores are

indicative of higher quality of life. Participants will self-complete the questionnaire. Internal consistency across a large heterogeneous population from a field trial during its development showed each domain to have moderate to high Cronbach's α levels; physical health (α = 0.82), psychological health (α = 0.81), social relationships (α = 0.68), and environment (α = 0.80).[55]

Safety and compliance

Prior to each training session participants will rate their level of muscle soreness on a ten-point visual analogue scale, and note alterations to their diet, physical activity, health or medications since their previous session. Illnesses, falls, fractures, and injuries other than muscle soreness will be documented. Attendance will be entered to determine program compliance, with 100 % being defined as completion of seventy sessions over the course of eight months. Adverse events will be fully documented by investigators, and monitored across the intervention period.

Table 1. Summary of outcome measures

Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Medix DR, Medilink, France)
Secondary outcome measures	
Other bone outcomes	
Whole body aBMD, BMC and bone area; lumbar spine aBMD, BMC and bone area; and proximal femur (trochanter and total hip regions) aBMD, BMC and bone area	DXA scans (Medix DR, Medilink, France)
Femoral neck (trabecular, cortical and total) BMC, vBMD and volume; total hip (trabecular, cortical and total) BMC, vBMD and volume	Proximal femur DXA scan (Medix DR, Medilink, France), 3D hip software (DMS Group, Mauguio, France)
Calcaneal broadband ultrasound attenuation, speed of sound and stiffness index	Calcaneal QUS (Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA)
Total content, vBMD and cross-sectional area; trabecular content, density, and cross-sectional area; cortical content, vBMD, cross-sectional area and thickness; periosteal and endocortical circumference; total and trabecular bone strength indices; polar section modulus; polar strength strain index	Forearm 4 % and 66 % sites, and leg 4 %, 14 %, 38 % and 66 % sites pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)
Anthropometry	
Height	Wall mounted stadiometer (Model 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model 700; Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lufkin Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix DR, Medilink, France)
Muscle cross-sectional area and muscle density	Forearm 66 % site and leg 66 % site pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)

Thoracic kyphosis	Plurimeter gravity referenced inclinometer (Australasian Medical & Therapeutic Instruments, Australia) Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Vertebral fracture assessment	Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Functional performance	
Timed up-and-go	Digital stopwatch (Fisher Scientific, USA)
Five-times sit-to-stand	Digital stopwatch (Fisher Scientific, USA)
Functional reach	Perspex board with measurement grid-lines
Muscle power	
Countermovement vertical jump	Load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA)
Isometric muscle strength	
Lower extremity strength	Leg platform dynamometer (TTM Muscle Meter, Tokyo, Japan)
Back extensor strength	Dynamometer (Lafayette Manual Muscle Testing Systems, USA)
Dietary calcium intake	AusCal questionnaire
Bone-specific physical activity	Bone-specific Physical Activity Questionnaire (BPAQ)
Barriers and facilitators	Physical Activity Enjoyment Scale (PACES) questionnaire Semi-structured interviews
Quality of Life	World Health Organisation Quality of Life (WHOQOL) questionnaire
Safety (adverse events and injuries) and compliance	Purpose designed lifestyle diaries and training diaries Trainer records

aBMD, areal bone mineral density; BMC, bone mineral content; BPAQ, Bone-specific Physical Activity Questionnaire; DXA, Dual-energy X-Ray Absorptiometry; PACES, Physical Activity Enjoyment Scale; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density; WHOQOL, World Health Organisation Quality of Life.

Data integrity

Participants will be allocated a unique study ID and data will be de-identified for analysis. After final data collection and cleaning, the data will be locked before analysis. Paper records will be stored securely at Griffith University in a laboratory with restricted swipe card access, and retained for a minimum of fifteen years. Electronic data will be stored securely on password-protected University computers. Management, storage and retention of research data will be in line with Griffith University policy, the *Griffith University Code for the Responsible Conduct of Research*. There will be no contractual agreements limiting data set access. De-identified data will be shared for meta-analyses or other collaborations on a case by case basis. De-identified data will be made available to the bioDensity™ manufacturer, Performance Health Systems, after the final study results have been published.

Blinding

The study will be single-blind; participants in the two exercise groups will only be aware of the details of their allocated exercise protocol. They will train separately, and will not be apprised of study hypotheses. The investigator performing baseline assessments will be blinded to the allocation sequence, which will be revealed to both investigator and participant only after baseline testing. As the assessor will also be training the participants, in order to maintain the highest level of test-retest reliability, follow-up testing will not be assessor blinded.

Data analyses

Statistical analyses will be undertaken using SPSS Version 24.0 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous outcome variables will be examined using the Kolomogorov-Smirnov test. Descriptive statistics of participant characteristics,

biometric and dependent variables will be presented as means ± standard deviations and frequencies where appropriate. Between-group comparisons of descriptive statistics at baseline will be evaluated using Analysis of Variance (ANOVA) for normally distributed continuous data, non-parametric equivalents for non-normally distributed data (Kruskal-Wallis one-way ANOVA), and Chi-Square for categorical data. Between-group comparisons for outcome measures will be examined using repeated measures Analysis of Covariance (RMANCOVA) for group, time and group-by-time interaction effects using raw baseline and follow-up data, adjusting for age, initial weight, calcium intake and baseline values.. Secondary exploratory RMANCOVA analyses adjusting for age, initial weight, calcium intake, baseline values, and training program compliance will be performed. In accordance with the principles of a classic intention-to-treat approach, all randomised participants will be included in the final analyses, regardless of withdrawal or compliance. In the case of missing follow-up data due to study withdrawal, imputation of the mean percentage change value for the specific group will be employed. Per-protocol exploratory analyses will be performed comparing outcome measures between the HiRIT, bioDensity™ and control groups for those with training program compliance of greater than 70 % to examine maximum treatment efficacy. Multiple linear regression analyses of absolute change from baseline will be employed to examine the relative influence of certain variables, found to significantly correlate with outcomes measures, on the bone response. Statistical significance will be set at $p \leq 0.05$.

DISCUSSION

To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised HiRIT exercise program on determinants of fracture risk for older men with low bone mass, compared with supervised bioDensity™ training or control. In the past, exercise prescription recommendations for individuals with osteoporosis have stipulated an emphasis on low to moderate intensity exercise,[14,15] with a goal to prevent falls; however, such exercises are unlikely to provide an adequate stimulus to elicit notable osteogenic adaptation. Both of the current HiRIT and bioDensity™ exercise programs have been designed around key loading characteristics shown to be osteogenic in animal models, and adhere to the principle of progressive overload. The execution of the current trial is warranted in order to progress exercise recommendations for older men with low to very low bone mass, who are at increased risk of fracture.

Although some knowledge exists, exercise intervention studies targeting older men with low bone mass are yet to be conducted over an adequate time period to detect changes in bone with confidence. There is, however, evidence that high intensity (> 80 to 85 % of one repetition maximum) compound movement resistance training exercises can be safely tolerated (with no significant adverse events), and elicit positive effects on bone mass and muscle strength in older adults.[16,24,26,56] While the aforementioned studies suggest such high intensity exercise prescription elicits bone and muscle strength changes, little is known about the response in men with low to very low bone mass, or men with low bone mass who have previously sustained a low-trauma fracture. The original high-load LIFTMOR trial [16] implemented in post-menopausal women with low to very low bone mass, enhanced bone mass with a high level of safety. Maddalozzo and Snow [24] also examined the ability of high-intensity resistance training (functional standing free-weights program) to enhance bone in older men and post-menopausal women, but as no baseline T-scores were reported it is not clear if their participants were at increased risk of fracture. Kukuljan and co-workers [26] examined the influence of twelve-months progressive

resistance training and weight-bearing impact on musculoskeletal health in men over the age of fifty with normal to low bone mass. While positive changes were observed at the hip and spine, individuals with osteoporosis and/or a history of osteoporotic fracture were excluded from the intervention. A short (twelve week) trial conducted by Mosti and colleagues [56] randomly allocated post-menopausal women with osteopenia and osteoporosis to a supervised high-intensity hack squat program or control. Four sets of three to five repetitions at 85 to 90 % of one repetition maximum were performed thrice weekly. The significant increases in bone mineral content and area at the lumbar spine and femoral neck observed in the exercise group must be interpreted with caution in light of the small sample (eight women in the strength training group completed the study), and the short study duration which is not normally considered long enough to detect BMD change from densitometry.

Evidence confirming the ability of high-load, low-volume, machine-based bioDensity™ training to improve bone health in older men with osteopenia or osteoporosis is essentially absent. The study will establish preliminary efficacy of two potentially beneficial exercise interventions and provides the opportunity to examine comparative efficacy. By examining the effects of two non-traditional exercise programs on musculoskeletal health and risk factors for falls in a poorly researched population our findings will contribute evidence towards developing efficacious non-pharmacological osteoporosis therapy.

Limitations

Several limitations warrant discussion. First, due to the somewhat unorthodox semi-randomised study design, there exists the possibility of self-selection bias. Pilot testing demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of older male study volunteers to adhere to a control requirement to refrain from exercise for eight months. When volunteering under the premise of receiving an exercise program, we argue that there are also ethical issues of withholding exercise from individuals who wish to take it up. We have attempted to minimise the risk by applying uniform inclusion and exclusion criteria for all study participants, with the exception of a willingness to participate in an eight-month exercise intervention. The extent to which the self-selected control group differs from the intervention groups will be determined and reported in the course of descriptive analyses of baseline data. Any differences will be accounted for by adjusting for baseline values in the final analyses. Second, the current trial is not powered to detect significant differences in fractures as safety (adverse events and injuries) is a secondary outcome. Nevertheless, reporting adverse events and injuries is informative when determining if an exercise program can be translated to clinical practice. Third, the outcome assessor will not be blind to group allocation, will deliver the intervention, and will be responsible for documenting adverse events and reporting to the GUHREC. Participants will be instructed to report even the slightest degree of discomfort/pain/muscle soreness or injury, and a protocol is in place for independent review by a qualified Physiotherapist or General Practitioner, as required. It is also an ethical requirement to report such events to the GUHREC, and harms or unintended events must be included when reporting randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse event would contravene both Institutional and National research ethics guidelines. A blinded outcome assessor is beyond the means of this unfunded project, and therefore our current study design has been adopted out of necessity.

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Author Contributions

Conception and design of the study: ATH, BKW, SLW, BRB; Obtained the equipment award brokered by Osteoporosis Australia: BRB; Manuscript preparation and editing the final paper for submission: ATH, BKW, SLW, BRB; Preparation of Information Sheets, Consent Forms, and Case Report Forms: ATH, BKW, SLW, BRB; Participant recruitment and data collection: ATH; Principle investigator: BRB.

Competing Interests

The Authors declare that there is no conflict of interest in preparing this article.

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Ethics Approval

The trial has received ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC), and has been prospectively registered with the Australian New Zealand Clinical Trials Registry (#ANZCTR12616000344493).

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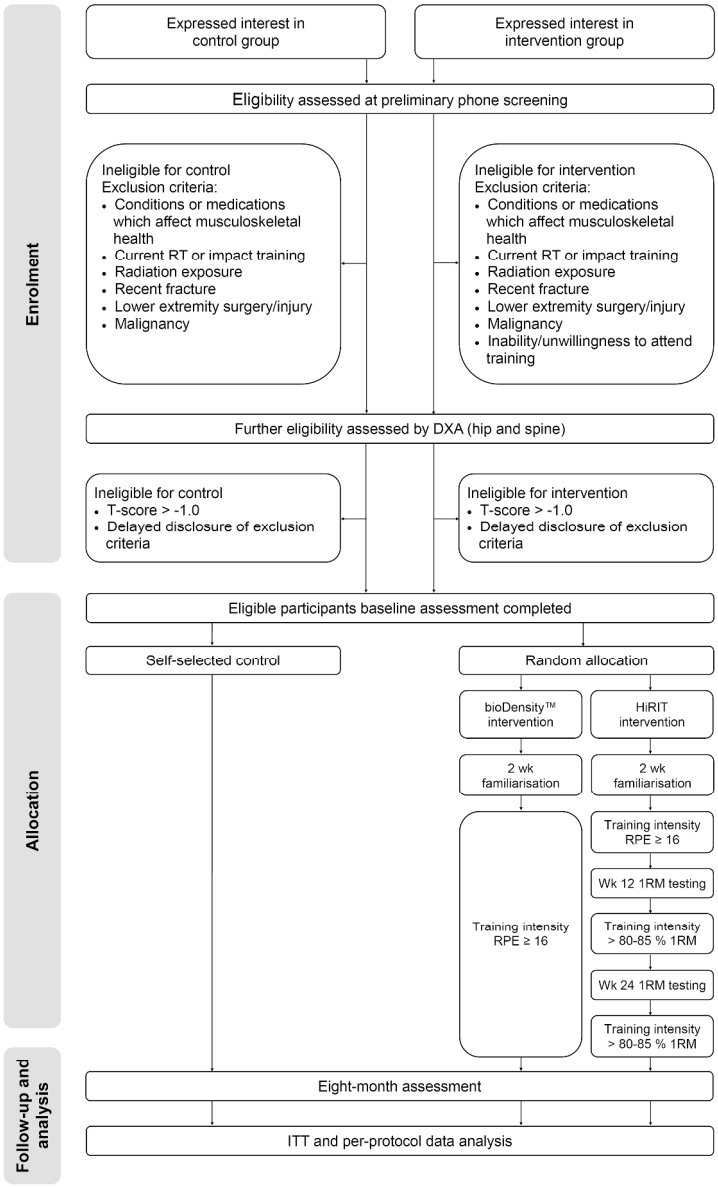
Figure legend

Figure 1. Proposed participant flow (CONSORT diagram)

bioDensity™, machine-based isometric exercise using the bioDensity™ system; DXA, Dual-energy X-Ray Absorptiometry; HiRIT, high-load progressive resistance training plus impact loading; ITT, intention-to-treat; RM, repetition maximum; RPE, Rating of Perceived Exertion; RT, resistance training.; Wk, week



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242x399mm (300 x 300 DPI)

INFORMATION SHEET

Project Title

"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"

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Background

As a person ages there is a gradual reduction in bone health and an increased risk of falling which, when combined, increases the risk of fractures. This study will help to determine if one or both of two different types of heavy resistance training safely and effectively improve bone strength, muscle and fat, and physical function in older men with low bone mass.

Method

Who:

- Healthy men over 50 years of age with low bone mass

What:

- You will be *randomly* assigned to either a high-load resistance training program, or a machine-based isometric exercise program, or you will choose to be in a no-exercise control group.
- Training for the resistance and machine-based exercise programs will occur twice a week for 8 months.
- If you are a control, all we require is your attendance at two testing sessions, 8 months apart.
- Before and after the 8-month exercise period you will be asked to complete:
  - Questionnaires regarding your health, diet and the amount of exercise you undertake
  - Some simple physical tasks including: standing jump, reaching, back and leg strength tests, and walking
  - Body composition scans using a dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and a peripheral quantitative computed tomographer (pQCT). Those tests are painless and non-invasive but involve either sitting beside or lying still on special scanners for between 3-10 minutes per scan.
- The total time for each testing session will be approximately 2 hours.
- In the final month of your training program you may be asked to attend a 30 minute interview to discuss your experiences throughout the training period
- We may video or photograph some activities, but you may opt out of those if you would prefer.

Where:

- Testing will take place at Griffith University Gold Coast campus (Southport) in the School of Allied Health Sciences.
- Both heavy resistance training and machine-based training will take place at Griffith University Gold Coast campus (Southport).

Inclusion Criteria

You may be eligible to participate in this study if you are over the age of 50 and have low bone mass (we can tell you if you do) and are willing to undertake an 8-month exercise program comprised of two exercise sessions per week, or merely attend Griffith University for two testing sessions 8 months apart (no new exercise for 8 months).

Exclusion Criteria

You may be excluded if any of the following apply to you:

- Any reason why you cannot safely participate in vigorous physical activity (i.e. uncontrolled cardiovascular disease, certain musculoskeletal conditions, etc.)
- Metal implants (e.g. staples, joint replacement) or foreign bodies (e.g. shrapnel)

- More than two x-ray examinations in the past year or radiation treatment
- Malignancy
- Cognitive impairment
- Certain kinds of current physical activity
- Medications and/or conditions know to influence bone health (e.g. Paget's Disease)

Risks

The risks associated with the project are relatively minor. For those unaccustomed to physical activity, it is likely that you will experience muscle soreness following any change in exercise exposure. There is also a risk of injury during exercise. Such injuries are uncommon but may include low back pain, joint sprains, or muscle strains. All physical testing and both exercise training programs will be closely supervised by the investigators to help reduce those risks. If you have low bone mass, you are at greater risk of fracture during heavy lifting exercises than people with higher bone mass. It will be important to perform the exercises as instructed by your trainer to make sure you are doing them safely. Should an injury occur during a study training session, an initial consult and one follow-up consultation will be available free of charge at the Griffith University *Physiotherapy and Active Health Centre*. If further treatment is required, investigators can refer you to an appropriate healthcare professional. The *Physiotherapy and Active Health Centre* has undertaken to provide discounted rates to physiotherapy patients referred by study investigators.

There are also slight risks associated with some of our tests. DXA and pQCT scans are non-invasive and painless, but they do involve exposure to small quantities of ionising radiation. The amount of radiation exposure during a chest x-ray is 8 times greater than that for either pQCT or DXA tests. The radiation exposure for DXA and pQCT scans is less than 0.01 mSv. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year. The exposure to radiation during plane travel is approximately 0.005 mSv per hour, thus a 14 hour international flight from Australia to Los Angeles would expose an individual to approximately 0.07 mSv, or 28 times the radiation from a single DXA scan.

Benefits

- Each participant will receive free bone, muscle and fat scans and an estimate of calcium consumption.
- Participants assigned to the exercise groups will receive a free 8-month exercise training program.
- Your involvement in this study will help contribute to the understanding of exercise as a treatment strategy for bone health, which will help countless individuals suffering from osteoporosis.

Confidentiality

Results will be kept as confidential as is possible by law and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375.

Use of video recordings and photography

You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password protected computer for a minimum of 5 years.

Contacting the Investigators

We are happy to answer any questions you may have. For general inquiries please contact Miss Amy Harding (student researcher), at amy.harding@griffithuni.edu.au or on 0410 616 596. If you have any concerns with the study, please do not hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, or Prof Belinda Beck on (07) 5552 8793.

Feedback

Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if you're interested, the overall study findings.

Voluntary Participation

Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to participate, you are free to withdraw your consent and discontinue your involvement at any time.

Complaints Mechanism

The University requires that all participants be informed that if they have any complaints concerning the manner in which a research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, Research Ethics, Office for Research, Room 4.25, Science, Engineering and Architecture (G11), Griffith University, Gold Coast campus, Q 4222, Phone: 373 54375 or research-ethics@griffith.edu.au.

Please retain this document for your information.

CONSENT FORM

Project Title

"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"

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Consent Statement

By signing below, I confirm that I have read and understood the information package and in particular have noted that:

- I understand that will I be *randomly* assigned to a high-load resistance training program, or a machine-based isometric exercise program, or I can choose to be in the no exercise group
- If I am assigned to an exercise group I understand that I will be asked to undertake an 8-month training program, consisting of 2 roughly 30 min sessions per week.
- I understand that there will be a testing session approximately 2 hours in duration both before and after the 8-month exercise period;
- I understand that I will undergo dual-energy x-ray absorptiometer (DXA), quantitative ultrasound (QUS) and peripheral quantitative computed tomographer (pQCT) scans and measurement of height, weight and waist circumference, to determine body composition;
- I understand that I will be asked to complete several questionnaires relating to physical activity, quality of life, evaluation of the exercise program and diet;
- I understand that I will be asked to perform a series of physical tasks including: standing jump, walking, back and leg strength tests, and reaching tasks;
- I have had any questions answered to my satisfaction;
- I understand the risks involved;
- I understand the benefits of my participation in this research;
- I understand that my participation in this research is voluntary;
- I understand that if I have any additional questions I can contact the research team;
- I understand that I am free to withdraw at any time, without comment or penalty;
- I understand that I can contact the Manager, Research Ethics, on 373 54375 (or research-ethics@griffith.edu.au) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

_____	_____	_____
(Participant)	(Participant signature)	(Date)

Optional video and photography consent:

☐ I agree to be video recorded while performing the physical activities to be used during presentations, media coverage and publication of research findings.

☐ I agree to be photographed while performing the physical activities to be used during presentations, media coverage and publication of research findings.

Public title

The LIFTMOR for Men trial: Is heavy resistance training or a machine-based isometric exercise program more effective at reducing risk of fracture in older men with reduced bone mass?

Scientific title

A randomised controlled trial to determine the effectiveness of heavy progressive resistance training versus high load machine-based isometric resistance training to reduce the risk of osteoporotic fracture in older men with low bone mass

Secondary ID

Nil known

Universal Trial Number

N/A

Trial acronym

LIFTMOR (for Men): Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation

Private notes (not publicly viewable)

Nil

Health condition

Osteopenia, osteoporosis, vertebral fracture, kyphosis, hip fracture

Condition category & condition code

Musculoskeletal health- osteoporosis

Injuries and accidents: Fracture

Study type

Interventional

Intervention code

Rehabilitation: 'Treatment: other' and/or 'Prevention'

Description of intervention(s)/exposure

The study is a three-arm, semi-randomised controlled exercise intervention trial. Eligible volunteers will be randomly allocated to one of two eight month, twice-weekly, 30-minute exercise programs; either supervised heavy progressive resistance training and impact loading, or machined-based isometric resistance training using the bioDensity system.

Arm 1 – supervised heavy progressive resistance training and weight-bearing impact loading.

Three compound movement exercises (deadlift, overhead press, and back squat) using olympic weights will be completed. For each exercise, 5 sets of 5 repetitions, corresponding to an intensity of 80-85 % of 1 repetition maximum will be performed. 5 sets of 5 repetitions of weight-bearing impact loading exercises (i.e. drop jumps) will also be performed, with height of the jump progressively increasing across the intervention period.

Arm 2 – supervised high-load isometric exercise using the bioDensity system.

A single set of four isometric exercises (chest press, leg press, core and arm pull, and vertical lift) will be performed according to bioDensity device specifications. For each exercise, one repetition of a self-initiated 75%-maximum contraction will be held for 5 seconds.

Sessions are supervised by a single qualified trainer (Bachelor of Exercise Science graduate, Certificate III in Fitness, Level 1 Sports Trainer Sports Medicine Australia). The training is also certified in First Aid and Cardiopulmonary Resuscitation.

Training diaries will be used to record participant attendance at training sessions, and completion of each element of the training session. Compliance will be determined as the number of sessions attended as a percentage of total possible sessions.

Comparator/control treatment

Arm 3 – the comparator will be a non-randomised sample of men, recruited independently but sex- and age-matched to the exercise arms. They will simply continue with their usual activities for 8 months, but will undergo the identical testing protocol at baseline and follow-up as the two randomised arms. Weekly email contact will be maintained to approximate investigator exposure and track alterations to habitual diet or physical activity levels over the 8 month period.

Diaries will be provided and all participants will be encouraged to record any changes to medication, medical conditions and general health.

Primary outcomes

1) Whole body, bilateral proximal femur (femoral neck, trochanter and total hip regions of interest) and lumbar spine bone mineral density determined by Dual-energy X-ray Absorptiometry. All participants, pre (baseline) and post-intervention (8 months).

Secondary outcomes

1) Indices of bone and muscle strength of the forearm and leg determined from peripheral Quantitative Computed Tomography. All participants, pre (baseline) and post-intervention (8 months).
2) Heel bone quality determined by Quantitative Ultrasonometry. All participants, pre (baseline) and post-intervention (8 months).
3) Body composition (lean mass, fat mass, appendicular lean mass and percentage body fat) from whole body Dual-energy X-ray Absorptiometry. All participants, pre (baseline) and post-intervention (8 months).
4) Muscle strength, physical function and balance will be measured using previously validated techniques. All participants, pre (baseline) and post-intervention (8 months).
5) Kyphosis will be measured using inclinometer
6) Daily average calcium intake, quality of life and bone-specific physical activity using validated questionnaires. All participants, pre (baseline) and post-intervention (8 months).
7) Safety (adverse events and injuries) and compliance from training diaries across the whole exercise intervention period.

Control group

Usual activities

Recruitment country

Australia

Recruitment site location state

Queensland

Recruitment status

Imminent

Anticipated date of first participant enrolment

Ethics application status

Approved

Brief summary

Recent work undertaken at Griffith University (the LIFTMOR trial) has revealed that brief exposure to a bone-targeted heavy progressive resistance training program is both safe, and effective for enhancing musculoskeletal health and function, in postmenopausal women with low to very low bone mass. Similar claims have been made by the developers of the bioDensity system, designed around the premise that low volume machine-based isometric resistance training produces beneficial effects on balance, physical function, muscle strength and bone mass. Whether dynamic or isometric resistance training will be more effective in men over the age of 50 with reduced bone mass at the hip and spine remains to be seen.

Key inclusion criteria

Men

Apparently healthy

With low bone mineral density (hip or spine BMD T-score less than or equal to -1.0)

Not currently or recently participating in regular resistance training or impact-type exercise

Minimum age

50 years

Maximum age

No limit

Gender

Males

Can healthy volunteers participate?

No; as participants have low bone mineral density. They are in fact 'apparently-healthy'.

Key exclusion criteria

Current participation in resistance training or exercise with an impact-loading component

Uncontrolled cardiovascular disease/respiratory conditions

Neurological conditions which might limit an individual's ability to perform resistance training

Malignancy

Hernia

Medications know to adversely affect musculoskeletal health such as corticosteroids, anti-convulsants

Medical conditions known to effect musculoskeletal health such as hyperparathyroidism, Paget's disease, diabetes

Purpose of the study

Prevention of age-related musculoskeletal deterioration

Allocation to treatment

Semi-randomised controlled trial

Enrolment procedure

Block randomisation to exercise will occur after participants are stratified for the presence or absence of medications for osteoporosis. The allocation sequence will be generated by a person independent of the trial and filed in sealed opaque envelopes.

Random order generated by computer program

Open trial (not masked)

Intervention assignment parallel

Phase not applicable

Time of endpoints efficacy

Recruitment

Anticipated start date May 2016

Anticipated date of last participant enrolled Nov 2017

Target sample size 150

Not yet recruiting

Funding & sponsors

Osteoporosis Australia Equipment award (bioDensity device supplied and installed by Performance Health Systems)

Osteoporosis Australia National Office

Postal: PO Box 550, Broadway, NSW, Australia 2007

Street: Level 2, 255 Broadway, Glebe, NSW, Australia 2037

research@osteoporosis.org.au

Phone: 02 9518 8140

Fax: 02 9518 6306

Secondary Funding & sponsors

Performance Health Systems

International head office:

401 Huehl Road, Suite 2A,

Northbrook, Illinois, 60062

United States of America

Ethical approval

Approved Griffith University Human Research Ethics Committee

170 Kessels Road Nathan, QLD 4111 Australia AHS/07/14/HREC

Submitted for approval for the initial LIFTMOR (for women) trial: 1st April 2014

Approval date of variations for the 3-arm trial LIFTMOR for Men: 18th January 2016

Approval expires: 17th Feb 2018

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	ANZCTR trial registry (online)/Supplementary file
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	33
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Author affiliations – 1; Author contributions - 33
	5b	Name and contact information for the trial sponsor	33
	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	Data access – 28; Statement - 33

	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)	Ethics and dissemination – 10-11; Data integrity – 28; Author contributions - 33
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	Introduction - 7-9; Study aims - 11
	6b	Explanation for choice of comparators	Study design - 12
Objectives	7	Specific objectives or hypotheses	Study aims - 11
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)	Study design - 12
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	Setting - 13
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)	Inclusion/Exclusion criteria – 13-14; Trainer delivering the intervention - 15-17; Investigator performing assessments - 33
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-17

	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)	Eligibility and screening 13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17 (Controls) 15-17 (Exercise interventions) 11 (Dissemination of results to participants)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Eligibility and screening 13-14
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	Primary outcome – 17; Secondary outcomes – 17-25; Data analyses – 28-29; Explanation for clinical relevance (Introduction) – 7-9
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)	CONSORT (Figure 1); Study design - 12
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	Sample size calculation – 12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Recruitment - 13

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	Randomisation and allocation – 14-15
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 assigned	Randomisation and allocation – 14-15; Blinding - 28
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Randomisation and allocation – 14-15; Blinding - 28
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Randomisation and allocation – 14-15; Blinding - 28
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Randomisation and allocation – 14-15; Blinding – 28; Study limitations - 32
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 protocol	Primary outcome – 17; Secondary outcomes – 17-25

	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	Provision of participant results summary - 11; Data analyses ITT approach 29
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	Data integrity - 28
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	Data analyses – 28-29
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Data analyses – 28-29
	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)	Data analyses – 28-29
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	Ethics and dissemination – 10-11; Data integrity – 28; Author contributions - 33
	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	Ethics and dissemination – 10-11; Data integrity – 28; Author contributions - 33

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	Ethics and dissemination – 10-11; Study limitations - 32
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Data integrity – 28; Statement regarding study sponsor - 33
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination – 10-11
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)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Ethical clearance – 10; Informed consent - 10
	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	Ethical clearance – 10; Data integrity - 28
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Competing interests and funding acknowledgements - 33

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	Statement regarding study sponsor - 33
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	Ethics and dissemination – 10-11
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	Dissemination of results – 11; Data provisions for study sponsors - 28
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset and statistical code	Dissemination of results – 11; Data set access - 28
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
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	N/A

*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

The LIFTMOR-M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: Protocol for a semi-randomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Impact, Isometric exercise, Osteoporosis, Resistance training, Men

Study Protocol (Rehabilitation Medicine)

Title:

The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation for Men) trial: Protocol for a semi-randomised controlled trial of supervised targeted exercise to reduce risk of osteoporotic fracture in older men with low bone mass

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Word Count:

6894 (1 Figure; 1 Table; 57 References)

Keywords:

Impact; Isometric exercise; Men; Osteoporosis; Resistance training.

ABSTRACT

Introduction

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training and impact loading program in comparison to a supervised machine-based isometric exercise training program using the bioDensity™ system in older men with low bone mass. We will also determine the safety and acceptability of each exercise training mode. Intervention group responses will be compared with those of a self-selected, non-randomised control sample of sex- and age-matched men who will follow their usual lifestyle activities for eight months.

Methods and analysis

Apparently-healthy men over fifty years with low bone mass, screened for medical conditions and medications known to adversely affect bone health, will be recruited. Eligible participants will be randomly allocated to eight months of either exercise program with block randomisation based on presence or absence of osteoporosis medications. A twice-weekly, thirty-minute, supervised exercise program will be conducted for both groups. The primary outcome will be change in femoral neck areal bone mineral density determined by Dual-energy X-ray Absorptiometry (DXA). Secondary outcomes, assessed at baseline and eight months, will include: DXA-derived whole body, bilateral proximal femur and lumbar spine areal bone mineral density; proximal femur bone geometry and volumetric density extracted using 3D hip analysis software; anthropometry; body composition; kyphosis; vertebral fracture assessment; physical function; safety (adverse events and injuries); and compliance. Intention-to-treat and per-protocol analyses will be conducted.

Discussion

Whether a high-load, low-repetition progressive resistance training plus impact loading program or a machine-based isometric exercise program can improve determinants of fracture risk, without causing injury, has not been examined in men. Determination of the efficacy, safety and acceptability of such programs will facilitate formulation of future exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who have previously been underrepresented.

Ethics and dissemination

Participant confidentiality will be maintained with publication of results. The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC).

Trial registration number

Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)

ANZCTR12616000344493; Pre-results.

Date and version identifier

Original protocol manuscript for submission (Version 1): November 2016.

Protocol manuscript for submission (Version 2) with revisions from peer review: December 2016

Protocol manuscript for submission (Version 3) with revisions from peer review: February 2017

Protocol manuscript for submission (Version 4) with revisions from peer review: March 2017

Authors: ATH, BKW, SLW, BRB.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised high intensity, progressive resistance training and impact loading program on several determinants of fracture risk for older men with low bone mass, compared with a machine-based isometric exercise program using the bioDensity™ system.
- There are few investigations into the effects of exercise on musculoskeletal health in older men, thus the current unique focus on older men with poor bone health will address a notable gap in the literature.
- The engagement of a non-randomised control group of demographically-matched men who have elected not to exercise for eight months is a design limitation that was implemented for pragmatic reasons.
- Our study sample will include largely healthy older men, so our findings may not be applicable to men with comorbidities or other exclusion characteristics.

INTRODUCTION

Epidemiological data indicates the global prevalence of osteoporosis to be over 200 million,[1] with around 1.2 million Australians,[2] 10.2 million Americans [3] and 15 million European men and women over fifty years of age being affected.[4] It has been suggested that 285,000 Australian men aged over fifty will be diagnosed as osteoporotic, and a further 2.48 million older men diagnosed as osteopenic by 2022.[5] With the aging of the population, there will undoubtedly be a corresponding increasing prevalence of low bone mass and consequent increase in the incidence of low trauma fracture.[6]

It is widely accepted that bone adapts to the mechanical loads it habitually experiences. Experimental data from animal models has revealed the most influential loading characteristics for osteogenesis are magnitude,[7,8] rate [9] and frequency [10-12] of the engendered strain. Evidence also indicates dynamic loading is more osteogenic than static loading.[13] The optimal exercise prescription for the prevention and management of osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads, applied at a rapid rate. High-load resistance training with high-impact jumping, the combination of which will elicit high strains and strain rates in bone, is thus theoretically the optimal exercise protocol for bone. Although such exercise is considered safe for healthy individuals with normal bone mass, it is unclear whether it will be safe for individuals with reduced bone mass who are at increased risk of fracture. Previous resistance exercise recommendations for individuals with low bone mass, particularly those who have experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate level of intensity,[14,15] based on a lack of quality evidence that high intensity resistance training is safe and effective.

Recently a bone-targeted, high intensity, progressive resistance training and impact loading (HiRIT) exercise program was undertaken with post-menopausal women with low to very low bone mass at the hip or spine - the LIFTMOR (Lifting Intervention For Training Muscle and

Osteoporosis Rehabilitation) trial. Interim results indicated the HiRIT protocol was well tolerated (no injuries sustained during supervised training sessions) and effective, exhibiting positive changes to musculoskeletal health in post-menopausal women at increased risk of fragility fracture.[16] Although the lifetime risk of fracture is greater in women over the age of fifty (one in three), than men of the same age (one in five), older men are more likely to suffer serious post-fracture consequences.[4,17] The most devastating low-trauma fracture site for older men is the hip, with mortality exceeding that of similarly aged women within the first year post-fracture.[18] In light of the fact that osteoporosis, and low-trauma fractures, affect men as well as women, it was necessary to replicate the protocol in older men to determine if it will be similarly effective.

Separately, but simultaneously with the LIFTMOR trial, an isometric device (the bioDensity™ system, Performance Health Systems, Northbrook, IL, USA) was developed in the USA to facilitate near-maximal isometric contractions against instrumented external resistance, with a goal to increase bone mass. The developers are currently marketing the device on the grounds that short-duration, low-volume, high-load bioDensity™ training can enhance bone mass in individuals with osteoporosis: however, concrete evidence is lacking. To date, four studies examining the bioDensity™ training protocol have been published,[19-22] only one of which included bone outcome measures.[22] In the latter observational study seventy post-menopausal women with low bone mass were invited by their general practitioner to take part in a six-month bioDensity™ intervention (one training session per week) for which the primary outcome was maximal isometric muscle force production. A sub-group of nine participants underwent Dual-energy X-ray Absorptiometry (DXA) examinations for bone density. Those individuals reportedly sustained increases in bone mineral density (BMD) at the hip (14.9 ± 11.5 %) and spine (16.6 ± 12.2 %) – responses that far exceed the BMD responses to previously reported exercise interventions. The lumbar spine T-score of one participant improved from -3.1 to -0.10. As considerable methodological shortcomings were evident in the latter study design, including low sample size, no monitoring of dietary calcium

intake or physical activity, lack of control group, lack of disclosure of simultaneous bone medications, and the fact that follow-up DXA scans were conducted sixty days after the intervention was completed suggests that a more rigorous examination of efficacy of bioDensity™ training is indicated.

Short-duration (thirty minute), twice-weekly therapeutic exercise programs for older men with low bone mass, such as the proposed HiRIT and bioDensity™ training protocols, provide an attractive alternative to more burdensome and time consuming programs typically recommended for osteoporosis. Indeed, trials examining the influence of progressive resistance training, hopping/jumping or multicomponent programs on bone health in men have adopted session frequencies of three,[23-28] four,[29] or even seven [30] per week. Hinton and colleagues [28] compared thrice-weekly sessions of jump training with twice-weekly sessions of periodised progressive resistance training; however, healthy physically active men aged 25 to 60 years were recruited. Whether high-load, low-volume training methods can safely improve bone strength in older men with low bone mass remains a knowledge gap. Thus, the Griffith University Bone Densitometry Research Laboratory has acquired a bioDensity™ device for the purposes of examining safety and efficacy alongside the HiRIT protocol in a semi-randomised controlled trial design.

METHODS AND ANALYSES

Ethics and dissemination

The study has been granted ethical approval from the Griffith University Human Research Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities will be conducted in accordance with the *Declaration of Helsinki*. The study is also registered with the Australian New Zealand Clinical Trials Registry (Trial number ANZCTR12616000344493). Written informed consent will be obtained from all participants prior to testing by the investigator performing baseline assessments.

Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial [16] (Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide evidence of an extremely low risk of injuries from the current exercise protocols, with no severe injuries reported from a total of 7300 training sessions. Similar to the current protocol, ethical approval was granted by the GUHREC for both studies, and written informed consent was obtained from all participants. Strategies were in place to reduce the risk of injuries or adverse events occurring during the aforementioned trials, and included: 1) full supervision of high-load resistance training sessions by a qualified exercise scientist; 2) small group sizes in the supervised training sessions; 3) an initial familiarisation period during which low-load exercise variants focused on proper lifting technique was implemented, and 4) weight lifted was progressively increased with training exposure. In order to monitor safety, participants were required to complete training diaries at every training session to record illnesses, falls, fractures, injuries, and muscle soreness. Early termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual progress reports to the GUHREC. Any adverse events which occur between annual reports will be reported independently to the GUHREC, in compliance with the *Australian Code for the Responsible Conduct of Research* developed by the National Health and Medical Research Council, and the University *Code for the Responsible Conduct of Research*. The

GUHREC is a registered institution with the National Health and Medical Research Council (Registration number EC00162). For participants who are unaccustomed to physical activity it is likely they will experience some degree of muscle soreness following any change in exercise exposure. In the unlikely event that a participant experiences significant intervention-related muscle soreness, or an injury occurs during the study period, consultations with a qualified Physiotherapist (external to the trial) at the Griffith University Allied Health Clinic will be available. If further treatment is required they will be referred to an appropriate healthcare professional.

All participants will be supplied with a full summary of individual and overall study results to encourage retention for the duration of the study, and to comply with ethical requirements. The usual scientific reporting practices will take place, including presentations at discipline meetings and publication in peer reviewed journals. There will be no interim analyses published prior to completion of the trial. Community and clinical talks will also be given as appropriate. Participant confidentiality will be maintained with publication of results.

Study aims

The primary aim of the proposed study is to examine the efficacy of an eight-month supervised, high-load progressive resistance training plus impact loading (HiRIT) program in comparison to supervised bioDensity™ machine-based isometric exercise training, or no intervention (control), for improving femoral neck (FN) areal bone mineral density (BMD) in older men with low bone mass. The primary outcome measure was selected according to clinical relevance, in light of the large personal and economic impact of hip fracture. It is hypothesised that eight months of twice-weekly HiRIT training will improve FN BMD more than bioDensity™ training or control, and similar benefit will be observed in secondary outcome measures. Furthermore, we hypothesise that there will not be a higher rate of adverse events during eight months of HiRIT compared with bioDensity™ training or control.

227

228 **Study design**

229 The current project is a three-arm, eight-month, semi-randomised, controlled exercise
230 intervention trial. Proposed participant flow is outlined in Figure 1. The eight-month exercise
231 intervention period has been chosen as the minimum time frame in which notable changes in
232 bone mass are likely to be detected from densitometry.[31] Eligible volunteers to the
233 intervention arm will be randomly assigned to one of two exercise programs; either
234 supervised HiRIT or bioDensity™ training. The third arm will be a non-randomised control
235 group of sex- and age-matched participants with lower than average bone mass recruited
236 from the same community. The control group will follow their usual lifestyle for eight months,
237 but undergo identical testing to the two exercise intervention groups at baseline and follow-
238 up. We acknowledge the somewhat unorthodox semi-randomised design does not
239 constitute the most rigorous clinical trial practice, but adopt it out of necessity. Pilot testing
240 conducted in our laboratory revealed that male study volunteers who expect to participate in
241 an exercise trial, but are randomised to a conventional inactive control group, refuse to
242 adhere to the requirement to refrain from exercise for eight months. We also believe that it
243 is unethical to withhold access to a potentially beneficial bone-targeted exercise program for
244 older men at increased risk of fragility fracture who are specifically seeking exercise therapy.
245 For pragmatic reasons then, we will independently recruit a demographically-matched
246 sample of men who, for a variety of reasons (not including functional capacity), elect to
247 remain sedentary for a minimum of eight months.

248

249 **Sample size**

250 Using the coefficient of variation for our device for FN BMD (1.5 %) to calculate least
251 significant change (1.5 % x 2.77 = 4.2 %) and pilot (apparently-healthy men over 50 years
252 with low bone mass screened for identical inclusion and exclusion criteria to the current

study) FN BMD mean of 0.790 g/cm^2 and standard deviation of 0.061 g/cm^2, we determined a sample size of 54 is required to detect the minimum change difference of 0.033 g/cm^2 from a two-tailed test with a power of 80 % and α = 0.05. Allowing for a 20 % dropout, a total of 64 participants per group is required. The 20 % dropout rate reflects that reported in previous bone-targeted exercise interventions in men,[28-30] and the dropout rate of randomised controlled intervention trials in adults (20.9 %).[32] Recruitment for this study started in May 2016, and will continue until the planned sample size is achieved.

Setting and recruitment

Baseline and follow-up assessments will be conducted in the Bone Densitometry Research Laboratory, School of Allied Health Sciences, Griffith University, Gold Coast campus, Queensland, Australia. All supervised training sessions will be conducted in the Strength Training Research Facility, co-located in the School of Allied Health Sciences. Both measurements and interventions will be conducted at this single location. Methods of recruitment include local media outlets (print media and radio), social media, official website (www.liftmor.org), word of mouth, and notice board flyer advertisement at local lawn bowls clubs, golf clubs and senior citizens clubs.

Eligibility and screening

Apparently healthy, able-bodied men over fifty years of age will be recruited. Volunteers are to be excluded if they have any of the following: uncontrolled cardiovascular or respiratory disease; disclosure of musculoskeletal or neurological conditions likely to affect their ability to perform exercise; medications known to affect bone metabolism (e.g. corticosteroids, thyroxine, antiepileptic, and antiretroviral agents); medical conditions known to affect musculoskeletal health (e.g. Paget's disease, hyperparathyroidism, and thyrotoxicosis);

current participation in high-load resistance or impact-type exercise; metal implants (e.g. joint prostheses); recent radiation therapy or radiographic investigations; recent fracture or lower extremity surgery; or malignancy. Further exclusion for the exercise arm will be based on an inability or unwillingness to take part in eight months of twice-weekly exercise training due to motivation, travel or work commitments. No upper age limit is stipulated. Potential participants who contact the investigator will initially undergo a preliminary phone screening for inclusion and exclusion criteria. If eligibility is established, prospective participants will be invited to attend the University research facility for BMD screening and, when relevant, to undergo baseline assessments. Potential exercise intervention participants and self-selected age-matched men will then undergo preliminary Dual-energy X-ray Absorptiometry (DXA) scans. If osteopenia (T-score between -1.0 and -2.5) or osteoporosis (T-score < -2.5) is detected at the lumbar spine and/or proximal femur, the individual will be eligible for inclusion and the full suite of scans. Participants will be discontinued if they: 1) withdraw consent, 2) cease to attend training sessions for longer than three weeks, 3) initiate or discontinue osteoporosis medications, or initiate medications known to affect bone metabolism, 4) become injured and unable to participate, 5) perform additional forms of exercise such as resistance training or impact-type exercise external to the trial, and 6) are advised by their general practitioner to cease training.

Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity™ training groups will be achieved via block randomisation, stratified by the presence (more than twelve months exposure) or absence (lack of exposure) of osteoporosis medications, using a computer-generated randomisation sequence (www.randomization.com, accessed 17th May 2016). To ensure concealment, the allocation sequence will be prepared in advance by an external source, and filed in sequentially-numbered, sealed, opaque envelopes. Upon

completion of baseline testing those identified as eligible will be randomly allocated to their exercise group and their supervised exercise training sessions will be scheduled.

Exercise interventions

Progressive resistance training and impact loading exercise program

The HiRIT group will perform approximately thirty minutes of supervised, high-load, free weight training and impact loading, twice-weekly, on non-consecutive days. Sessions will comprise three fundamental compound movement exercises (deadlift, squat and overhead press). During the initial two weeks, participants will perform low-load variants of each exercise focussing on technique for the purposes of familiarisation. During training weeks three to twelve participants will perform five sets of each exercise, lifting the maximum weight possible for five repetitions while maintaining correct form. The Rating of Perceived Exertion (RPE) scale will be used to subjectively select exercise intensity and guide weight progression prior to determining one repetition maximum. Participants will aim for a RPE ≥ 16 (6-20 point Borg scale [33]) to achieve a high intensity equivalent before one repetition maximum testing. Maximal strength testing, to determine one repetition maximum for the deadlift and squat, will be performed at weeks twelve and twenty-four. Briefly, the maximal strength test protocol will begin with a warm-up set of five to ten repetitions at a relatively light load (approximately 50 % of the heaviest weight they have previously lifted for five repetitions). After a one-minute rest they will perform one set of three to five repetitions at 60 to 80 % of their perceived maximum. Gradually the load will increase in 2.5 to 5.0 kg increments until a failed attempt (within three to six attempts), with each attempt interspersed with a two-minute rest. One repetition maximum is defined as the heaviest weight a participant can lift once with correct lifting technique. A similar one repetition maximum testing protocol was found to be reliable for untrained middle-aged adults (intraclass correlation coefficients > 0.97).[34] From training week twelve onwards

participants will perform five sets of five repetitions for each exercise, corresponding to an intensity of greater than 80 to 85 % of one repetition maximum. Load magnitude will be progressively increased in increments of 2.5 kg over the course of the intervention when they are able to easily complete seven repetitions at their current weight. In addition, five sets of five repetitions of jumping chin-ups (interspersed with rest) with a firm, flat-footed landing will be performed each session. Impact intensity will be gradually increased by moving towards achieving a stiff-legged landing as tolerated. Training will be fully supervised by a qualified exercise scientist. Weight progressions and RPE will be recorded in training diaries.

Machine-based isometric exercise program

The supervised bioDensity™ group will exercise twice-weekly, on non-consecutive days to match the HiRIT group protocol. Four exercises will be performed; chest press, leg press, core pull, and vertical lift. The chest press and leg press closely mirror conventional strength training equipment, the core pull movement combines an abdominal crunch with an underhand chin-up, and the vertical lift simulates a high-hang deadlift position. During the initial two weeks, participants will perform a lower intensity repetition of each exercise focussing on technique. Following this familiarisation period, one self-initiated near-maximal five-second isometric contraction will be performed for each of the four exercises (per manufacturer's recommendations). Integrated monitors provide real-time peak muscle force production feedback. Participants will provide an RPE with the aid of the 6-20 point Borg scale [33] for each exercise. They will be instructed to achieve a near-maximal five second isometric contraction at an intensity corresponding to greater than 80 to 85 % of one repetition maximum, translating to an RPE of greater than or equal to sixteen on the 6-20 point Borg scale.[35] A single qualified trainer will supervise all sessions to operate the bioDensity™ system, and ensure the exercises are performed correctly and safely. Peak force, average force and RPE will be recorded in participant training diaries.

Control group activities

The sex- and age-matched control group will be encouraged to maintain their customary physical activity and dietary patterns over the eight month duration of the study. To monitor deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to list variations to their physical activity level and diet on a fortnightly basis. Space is also provided to record any illnesses, falls, fractures, changes to their medical conditions and medications (inclusive of over the counter medications), and injuries other than muscle soreness. Diaries are to be returned at follow-up. Fortnightly emails will act as reminders to complete diary entries, with a monthly email requiring a reply to the investigator to prompt recording of any relevant changes. To detect change in bone-relevant physical activity or dietary calcium intake over the course of the eight-month study, participants will complete questionnaires (described below) at baseline and follow-up.

Outcome measures

All outcome measures will be performed at baseline and eight-month follow-up by a single investigator who is not blind to group allocation, using identical facilities, procedures and equipment. A summary of outcome measures is presented in Table 1.

Primary outcome

The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink, France).

Secondary outcomes

Secondary outcomes (described in more detail below) will include: changes in anthropometrics, as well as in whole body and regional measures of bone, muscle and fat.

Kyphosis will be examined in order to track angular changes of the spine with exercise exposure. Vertebral fracture assessment using the Genant semiquantitative approach [36] from lateral thoracolumbar spine imaging will be conducted pre- and post-intervention by DXA. A series of commonly utilised performance tasks will be employed to examine changes in lower extremity muscle force and power, dynamic balance, and maximal trunk extensor strength in keeping with standard protocols. Standardised instructions will be provided for all performance tasks, with the best performance of three trials to be included in the analyses. Previously validated questionnaires will be used to estimate dietary calcium consumption, current and past bone-relevant physical activity, quality of life and exercise appeal. Participant safety (adverse events and injuries) and compliance will be monitored across the intervention period using training diaries.

Bone strength indices

Whole body, bilateral proximal femur (trochanter and total hip regions), and lumbar spine areal BMD, bone mineral content and bone area will also be determined by DXA. Parameters of proximal femur (femoral neck and total hip regions) trabecular and cortical bone geometry and volumetric density will be extracted from standard DXA scans using 3D hip analysis software (DMS Group, Mauguio, France). Quantitative Ultrasonography will be used to evaluate changes in calcaneal bone quality (QUS; Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA). Volumetric BMD and geometric parameters contributing to bone strength at the tibia and radius will be determined from peripheral Quantitative Computed Tomography scans of the forearm and leg (pQCT; XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany; voxel size 0.5 mm, slice thickness 2.3 mm and scan speed 25 mm/sec). Tibial length will be measured by means of palpation as the distance from the proximal border of the medial tibial plateau to the distal tip of the medial malleolus, and radial length measured from the proximal tip of the olecranon process to the distal tip of the ulnar styloid process. A planar scout view of the ankle joint line on the

skeletally non-dominant leg will be acquired so the anatomical reference line can be adjusted to bisect the tibial endplate. A total of four image slices will be acquired at 4 %, 14 %, 38 % and 66 % sites proximal to the distal edge of the tibial endplate. For the distal tibia (4 % site) contour mode 3 at 169 mg/cm^3 and peel mode 4 at 650 mg/cm^3, with a 10 % peel, will be used to determine total and trabecular content, total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional area. At the midshaft of the tibia (38 % site) cort mode 2 at 710 mg/cm^3 will be used to define cortical content, volumetric bone mineral density, area and thickness, and periosteal and endocortical circumference. Cort mode 2 at 480 mg/cm^3 will be used to determine polar section modulus and the polar strength strain index. A planar scout scan perpendicular to the long axis of the skeletally non-dominant forearm will be performed at the level of the ulnar head, with the reference line positioned at the distal edge of the most horizontal portion of the radial cortical endplate. Two image slices will be acquired at the 4 % and 66 % sites proximal to the distal endplate of the radius. For the distal radius (4 % site) contour mode 3 at 169 mg/cm^3 and peel mode 4 at 650 mg/cm^3, with a 10 % peel, will be used to determine total and trabecular content, total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional area. At the proximal radius (66 % site) cort mode 2 at 710 mg/cm^3 will be used to define cortical content, volumetric bone mineral density, area and thickness, and periosteal and endocortical circumference. Cort mode 2 at 480 mg/cm^3 will be used to determine polar section modulus and the polar strength strain index. pQCT-derived bone parameters will include: total content, density and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, density, cross-sectional area and thickness; periosteal and endocortical circumference; and biomechanical strength indices calculated from density and area (total and trabecular bone strength indices, polar section modulus, and polar strength strain index). All pQCT analyses will be conducted using host software Version 6.20 (Stratec Medizintechnik GmbH, Pforzheim, Germany).

Anthropometrics and body composition

Height will be measured via the stretch stature method with a wall-mounted stadiometer (Model 216; Seca, Hamburg, Germany). Weight will be measured using a mechanical beam scale without shoes and in light clothing (Model 700; Seca, Hamburg, Germany). Body mass index will be determined per the accepted method (Body Mass Index = weight/height^2; kg/m^2). Waist circumference, a predictor of visceral abdominal adiposity, will be measured using a steel tape following National Institute of Health guidelines (Model W606PM; Lufkin Executive Thinline, Apex, USA).[37] Briefly, the tape will be positioned on the horizontal plane at the level of the iliac crests on bare skin, and recorded at the end of gentle expiration. Body composition parameters inclusive of lean mass, fat mass, appendicular lean mass and percentage body fat will be derived from whole body DXA. Muscle cross-sectional area, an index of muscle size, and muscle density, an index of intramuscular fat, will be determined from pQCT scans of the forearm and leg at the 66 % site.

Thoracic kyphosis and vertebral fracture assessment

Thoracic kyphosis will be assessed in relaxed standing (neutral posture) and standing 'at attention' using a gravity-referenced inclinometer, following a procedure similar to MacIntyre and colleagues (Plurimeter, Australasian Medical & Therapeutic Instruments, Australia).[38] The inclinometer will be zeroed at the twelfth thoracic to first lumbar intervertebral space, and the angle at the seventh cervical to first thoracic intervertebral space recorded. Lateral thoracolumbar spine DXA will be performed in the lateral de cubitus position to calculate Cobb angle via two methods: 1) vertebral body endplates, and 2) anterior vertebral body margins. The superior endplate of the fourth thoracic vertebra and the inferior endplate of the twelfth thoracic vertebra will be manually digitized, perpendicular lines extended and the angle at their intersection measured.[39] To account for endplate angulation and tilt due to vertebral irregularity, the anterior margins will be digitized and the angle at their intersection measured.[40] In addition, lateral thoracolumbar spine DXA allows vertebral fracture identification using the Genant method.[36] The anterior, medial and posterior heights of the

vertebral body are used to grade (mild, moderate or severe) wedge, biconcave or crush deformity.

Timed up-and-go

The timed up-and-go test is a measure of functional mobility, and dynamic balance.[41] Participants will be instructed to rise from a seated position without using their hands for assistance, walk at a brisk pace to a mark on the floor a distance of three meters away, pivot, and return to assume the start position. Participants will be timed from the point at which their back no longer makes contact with the chair, to when they return to the start and adopt the correct seated position.

Five-times sit-to-stand

The five-times sit-to-stand is a reliable assessment of the ability to rise unassisted from a seated position, with relevance to functional mobility, dynamic balance and lower extremity muscle strength.[42] Participants will be asked to move from a sitting to standing position, without the use of their arms, for five repetitions following the recommendations of Bohannon and colleagues for assessing older adults.[43]

Functional reach

A modified version of the original functional reach test (that incorporated a yardstick) will be used to assess dynamic balance, which has been identified as an important component of falls risk.[44] Participants will stand with shoulders perpendicular to a Perspex board marked with vertical measurement lines, with the dominant arm located nearest the board and extended forwards to 90 ° shoulder flexion, with the hand forming a fist. The participant will be instructed to reach forward by flexing the trunk at the hip, maintaining a fixed base of support, without stepping or losing balance. If the participant makes contact with the Perspex board, takes a step or loses balance, the trial will be repeated. The start and finish

positions of the third metacarpal in respect to the measurement lines will be recorded to determine displacement.

Muscle power

Lower extremity muscle power will be assessed by a countermovement vertical jump test. Participants will be instructed to perform a jump for maximum height, without arm swing, whilst positioned on a floor-mounted 900 mm x 600 mm load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA). Impulse and impulse relative to body weight will be calculated from the vertical component of the ground reaction force of the loading and take-off phase according to the method described by Linthorne.[45]

Isometric muscle strength

Maximal isometric force of the lower extremity will be estimated using a leg strength platform dynamometer (TTM Muscle Meter, Tokyo, Japan). The participant will stand on the dynamometer platform assuming a semi-squat position with knees flexed (knee angle of 115 °, hip flexion angle of 65 °), trunk extended and back flat against the wall. A straight bar handle is affixed to the dynamometer by a chain at a length so the arms are fully extended to grip it. After ensuring the chain is taut, the dynamometer is manually zeroed. Participants will be instructed to attempt to straighten their legs, whilst keeping their back fully in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.84$, $p < 0.001$; test-retest reliability $r = 0.97$, $p < 0.001$). (Little A, Harding AT, Weeks BK, Horan SA, Watson SL, and Beck BR, 2016; unpublished data; conference abstract)

Maximal isometric back extensor muscle strength will be assessed in erect standing using a handheld dynamometer (Lafayette Manual Muscle Testing Systems, USA). The participant will be positioned midway between two vertical wall-mounted anchor rails, with their back and heels against the wall. An inelastic belt between the two rails will be fastened

horizontally around the hips in order to restrain the pelvis. The padded transducer pressure plate will be positioned by the investigator between the wall and the seventh thoracic vertebral spinous process, until held securely against the wall by the pressure of the participant's back. Participants will be instructed to push back into the wall with their shoulders, ensuring their feet remain flat with their heels in contact with the wall. This method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's correlation coefficient $r = 0.85$, $p < 0.001$; test-retest reliability $r = 0.93$, $p < 0.001$).[46]

Dietary calcium intake

Calcium intake will be assessed using the AusCal, a calcium-focused food frequency questionnaire designed and validated for the Australian diet.[47] Frequency of consumption per day, week or month, and approximate serving size will be recorded for each of the listed calcium-rich food and beverage items over the previous year. The AusCal will be investigator-administered. Questionnaire responses will be entered into customised FoodWorks analysis software to generate average daily calcium intake (Version 7, Xyris Software, Brisbane, Australia).

Bone-specific physical activity

The Bone-specific Physical Activity Questionnaire (BPAQ) [48] will be used to quantify current and historical physical activity of relevance to bone. Respondents will list all regular, structured physical activity and years of participation, with a minimum of investigator assistance. BPAQ scores will be calculated using an on-line, custom-designed analysis program (http://www.fithdysign.com/BPAQ/). Mathematical algorithms in the calculator were developed using load ratings from vertical ground reaction forces of each activity, participation frequency, years of involvement and an age-weighting factor. High loading ratings represent high-impact activities, whilst the age-weighting factor reflects higher mechanosensitivity to physical activity during youth. Previous research has found BPAQ

scores are predictive of variance in DXA-derived bone strength parameters at clinically relevant sites in healthy middle-aged and older men.[49] This instrument has high reliability, with intra-class correlation coefficients of 0.92 to 0.97.[50]

Barriers and facilitators

The Physical Activity Enjoyment Scale (PACES), designed by Mullen and colleagues,[51] is a self-reported eight-item questionnaire which uses a seven-point Likert scale for each item. The respondent is required to circle the number corresponding to their current thoughts about physical activity. Higher PACES scores indicate a greater level of exercise appeal. Inclusion of this instrument was based on physical activity enjoyment being identified as a potential determinant of exercise adherence.[52] Semi-structured interviews to determine exercise appeal, barriers and facilitators to participation in HiRIT or bioDensity™ training programs will be conducted within one month of completing the eight-month intervention by an independent investigator. Interviews will be tape-recorded with participant consent, and transcribed verbatim. Interview transcripts will be thematically coded using NVivo qualitative software (Version 10, QRS International Pty Ltd) to determine barriers and facilitators to participation in higher-intensity, bone-targeted exercise.

Quality of life

The World Health Organisation Quality of Life questionnaire was developed to assess four quality of life domains using a five-point Likert interval scale.[53] Higher scores are indicative of higher quality of life. Participants will self-complete the questionnaire. Internal consistency across a large heterogeneous population from a field trial during its development showed each domain to have moderate to high Cronbach's α levels; physical health (α = 0.82), psychological health (α = 0.81), social relationships (α = 0.68), and environment (α = 0.80).[54]

Safety and compliance

Prior to each training session participants will rate their level of muscle soreness on a ten-point visual analogue scale, and note alterations to their diet, physical activity, health or medications since their previous session. Illnesses, falls, fractures, and injuries other than muscle soreness will be documented. Attendance will be entered to determine program compliance, with 100 % being defined as completion of seventy sessions over the course of eight months. Adverse events will be fully documented by investigators, and monitored across the intervention period.

Table 1. Summary of outcome measures

Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Medix DR, Medilink, France)
Secondary outcome measures	
Other bone outcomes	
Whole body aBMD, BMC and bone area; lumbar spine aBMD, BMC and bone area; and proximal femur (trochanter and total hip regions) aBMD, BMC and bone area	DXA scans (Medix DR, Medilink, France)
Femoral neck (trabecular, cortical and total) BMC, vBMD and volume; total hip (trabecular, cortical and total) BMC, vBMD and volume	Proximal femur DXA scan (Medix DR, Medilink, France), 3D hip software (DMS Group, Mauguio, France)
Calcaneal broadband ultrasound attenuation, speed of sound and stiffness index	Calcaneal QUS (Lunar Achilles InSight™, GE Healthcare, Wisconsin, USA)
Total content, vBMD and cross-sectional area; trabecular content, density, and cross-sectional area; cortical content, vBMD, cross-sectional area and thickness; periosteal and endocortical circumference; total and trabecular bone strength indices; polar section modulus; polar strength strain index	Forearm 4 % and 66 % sites, and leg 4 %, 14 %, 38 % and 66 % sites pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)
Anthropometry	
Height	Wall mounted stadiometer (Model 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model 700; Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lufkin Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix DR, Medilink, France)
Muscle cross-sectional area and muscle density	Forearm 66 % site and leg 66 % site pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim, Germany)

Thoracic kyphosis	Plurimeter gravity referenced inclinometer (Australasian Medical & Therapeutic Instruments, Australia) Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Vertebral fracture assessment	Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
Functional performance	
Timed up-and-go	Digital stopwatch (Fisher Scientific, USA)
Five-times sit-to-stand	Digital stopwatch (Fisher Scientific, USA)
Functional reach	Perspex board with measurement grid-lines
Muscle power	
Countermovement vertical jump	Load cell (Advanced Mechanical Technology Inc., Watertown, MA, USA)
Isometric muscle strength	
Lower extremity strength	Leg platform dynamometer (TTM Muscle Meter, Tokyo, Japan)
Back extensor strength	Dynamometer (Lafayette Manual Muscle Testing Systems, USA)
Dietary calcium intake	AusCal questionnaire
Bone-specific physical activity	Bone-specific Physical Activity Questionnaire (BPAQ)
Barriers and facilitators	Physical Activity Enjoyment Scale (PACES) questionnaire Semi-structured interviews
Quality of Life	World Health Organisation Quality of Life (WHOQOL) questionnaire
Safety (adverse events and injuries) and compliance	Purpose designed lifestyle diaries and training diaries Trainer records

aBMD, areal bone mineral density; BMC, bone mineral content; BPAQ, Bone-specific Physical Activity Questionnaire; DXA, Dual-energy X-Ray Absorptiometry; PACES, Physical Activity Enjoyment Scale; pQCT, peripheral Quantitative Computed Tomography; vBMD, volumetric bone mineral density; WHOQOL, World Health Organisation Quality of Life.

Data integrity

Participants will be allocated a unique study ID and data will be de-identified for analysis. After final data collection and cleaning, the data will be locked before analysis. Paper records will be stored securely at Griffith University in a laboratory with restricted swipe card access, and retained for a minimum of fifteen years. Electronic data will be stored securely on password-protected University computers. Management, storage and retention of research data will be in line with Griffith University policy, the *Griffith University Code for the Responsible Conduct of Research*. There will be no contractual agreements limiting data set access. De-identified data will be shared for meta-analyses or other collaborations on a case by case basis. De-identified data will be made available to the bioDensity™ manufacturer, Performance Health Systems, after the final study results have been published.

Blinding

The study will be single-blind; participants in the two exercise groups will only be aware of the details of their allocated exercise protocol. They will train separately, and will not be apprised of study hypotheses. The investigator performing baseline assessments will be blinded to the allocation sequence, which will be revealed to both investigator and participant only after baseline testing. As the assessor will also be training the participants, in order to maintain the highest level of test-retest reliability, follow-up testing will not be assessor blinded.

Data analyses

Statistical analyses will be undertaken using SPSS Version 24.0 (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous outcome variables will be examined using the Kolomogorov-Smirnov test. Descriptive statistics of participant characteristics,

biometric and dependent variables will be presented as means ± standard deviations and frequencies where appropriate. Between-group comparisons of descriptive statistics at baseline will be evaluated using Analysis of Variance (ANOVA) for normally distributed continuous data, non-parametric equivalents for non-normally distributed data (Kruskal-Wallis one-way ANOVA), and Chi-Square for categorical data. Between-group comparisons for outcome measures will be examined using repeated measures Analysis of Covariance (RMANCOVA) for group, time and group-by-time interaction effects using raw baseline and follow-up data, adjusting for age, initial weight, calcium intake and baseline values. Secondary exploratory RMANCOVA analyses adjusting for age, initial weight, calcium intake, baseline values, and training program compliance will be performed. In accordance with the principles of a classic intention-to-treat approach, all randomised participants will be included in the final analyses, regardless of withdrawal or compliance. In the case of missing follow-up data due to study withdrawal, imputation of the mean percentage change value for the specific group will be employed. Per-protocol exploratory analyses will be performed comparing outcome measures between the HiRIT, bioDensity™ and control groups for those with training program compliance of greater than 70 % to examine maximum treatment efficacy. Multiple linear regression analyses of absolute change from baseline will be employed to examine the relative influence of certain variables, found to significantly correlate with outcomes measures, on the bone response. Statistical significance will be set at $p \leq 0.05$.

DISCUSSION

To our knowledge, this will be the first trial to investigate the efficacy and safety of an eight-month supervised HiRIT exercise program on determinants of fracture risk for older men with low bone mass, compared with supervised bioDensity™ training or control. In the past, exercise prescription recommendations for individuals with osteoporosis have stipulated an emphasis on low to moderate intensity exercise,[14,15] with a goal to prevent falls; however, such exercises are unlikely to provide an adequate stimulus to elicit notable osteogenic adaptation. Both of the current HiRIT and bioDensity™ exercise programs have been designed around key loading characteristics shown to be osteogenic in animal models, and adhere to the principle of progressive overload. The execution of the current trial is warranted in order to progress exercise recommendations for older men with low to very low bone mass, who are at increased risk of fracture.

Although some knowledge exists, exercise intervention studies targeting older men with low bone mass are yet to be conducted over an adequate time period to detect changes in bone with confidence. There is, however, evidence that high intensity (> 80 to 85 % of one repetition maximum) compound movement resistance training exercises can be safely tolerated (with no significant adverse events), and elicit positive effects on bone mass and muscle strength in older adults.[16,24,26,55] While the aforementioned studies suggest such high intensity exercise prescription elicits bone and muscle strength changes, little is known about the response in men with low to very low bone mass, or men with low bone mass who have previously sustained a low-trauma fracture. The original high-load LIFTMOR trial [16] implemented in post-menopausal women with low to very low bone mass, enhanced bone mass with a high level of safety. Maddalozzo and Snow [24] also examined the ability of high-intensity resistance training (functional standing free-weights program) to enhance bone in older men and post-menopausal women, but as no baseline T-scores were reported it is not clear if their participants were at increased risk of fracture. Kukuljan and co-workers [26] examined the influence of twelve-months progressive

resistance training and weight-bearing impact on musculoskeletal health in men over the age of fifty with normal to low bone mass. While positive changes were observed at the hip and spine, individuals with osteoporosis and/or a history of osteoporotic fracture were excluded from the intervention. A short (twelve week) trial conducted by Mosti and colleagues [55] randomly allocated post-menopausal women with osteopenia and osteoporosis to a supervised high-intensity hack squat program or control. Four sets of three to five repetitions at 85 to 90 % of one repetition maximum were performed thrice weekly. The significant increases in bone mineral content and area at the lumbar spine and femoral neck observed in the exercise group must be interpreted with caution in light of the small sample (eight women in the strength training group completed the study), and the short study duration which is not normally considered long enough to detect BMD change from densitometry.

Evidence confirming the ability of high-load, low-volume, machine-based bioDensity™ training to improve bone health in older men with osteopenia or osteoporosis is essentially absent. The study will establish preliminary efficacy of two potentially beneficial exercise interventions and provides the opportunity to examine comparative efficacy. By examining the effects of two non-traditional exercise programs on musculoskeletal health and risk factors for falls in a poorly researched population our findings will contribute evidence towards developing efficacious non-pharmacological osteoporosis therapy.

Limitations

Several limitations warrant discussion. First, due to the somewhat unorthodox semi-randomised study design, there exists the possibility of self-selection bias. Pilot testing demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of older male study volunteers to adhere to a control requirement to refrain from exercise for eight months. When volunteering under the premise of receiving an exercise program, we argue that there are also ethical issues of withholding exercise from individuals who wish to take it up. We have attempted to minimise the risk by applying uniform inclusion and exclusion criteria for all study participants, with the exception of a willingness to participate in an eight-month exercise intervention. The extent to which the self-selected control group differs from the intervention groups will be determined and reported in the course of descriptive analyses of baseline data. Any differences will be accounted for by adjusting for baseline values in the final analyses. Second, the current trial is not powered to detect significant differences in fractures as safety (adverse events and injuries) is a secondary outcome. Nevertheless, reporting adverse events and injuries is informative when determining if an exercise program can be translated to clinical practice. Third, the outcome assessor will not be blind to group allocation, will deliver the intervention, and will be responsible for documenting adverse events and reporting to the GUHREC. Participants will be instructed to report even the slightest degree of discomfort/pain/muscle soreness or injury, and a protocol is in place for independent review by a qualified Physiotherapist or General Practitioner, as required. It is also an ethical requirement to report such events to the GUHREC, and harms or unintended events must be included when reporting randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse event would contravene both Institutional and National research ethics guidelines. A blinded outcome assessor is beyond the means of this unfunded project, and therefore our current study design has been adopted out of necessity.

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Author Contributions

Conception and design of the study: ATH, BKW, SLW, BRB; Obtained the equipment award brokered by Osteoporosis Australia: BRB; Manuscript preparation and editing the final paper for submission: ATH, BKW, SLW, BRB; Preparation of Information Sheets, Consent Forms, and Case Report Forms: ATH, BKW, SLW, BRB; Participant recruitment and data collection: ATH; Principle investigator: BRB.

Competing Interests

The Authors declare that there is no conflict of interest in preparing this article.

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Ethics Approval

The trial has received ethical approval from the Griffith University Human Research Ethics Committee (Protocol number AHS/07/14/HREC), and has been prospectively registered with the Australian New Zealand Clinical Trials Registry (#ANZCTR12616000344493).

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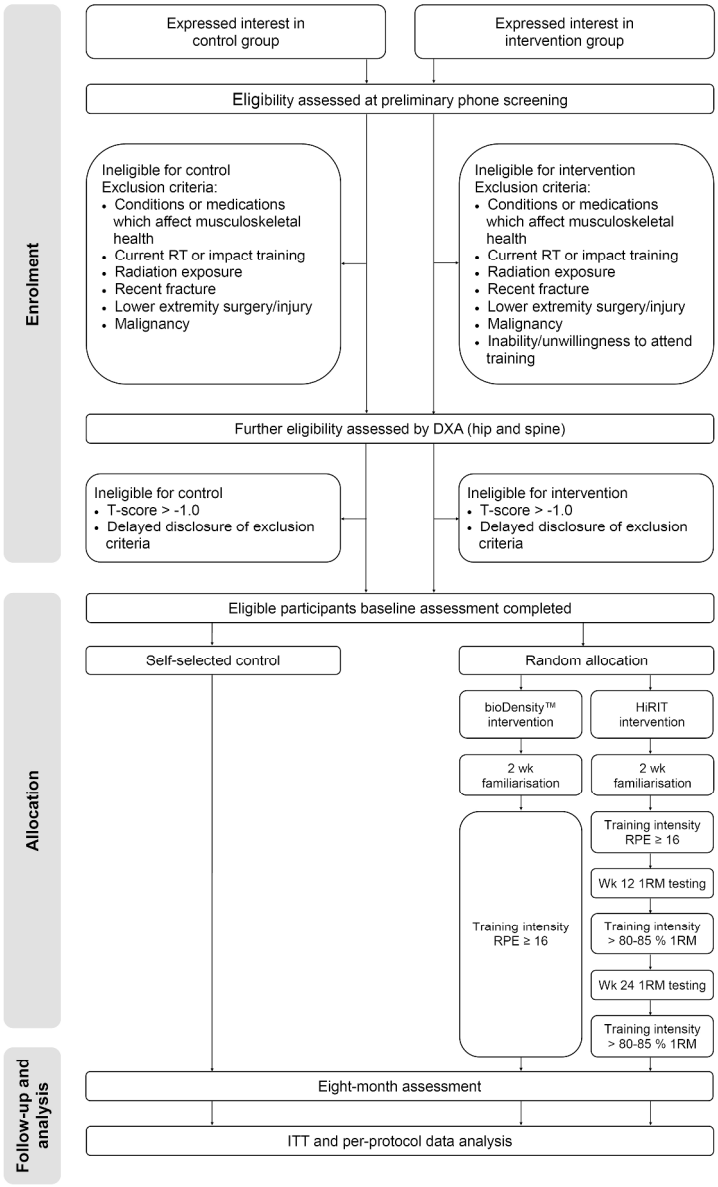
Figure legend

Figure 1. Proposed participant flow (CONSORT diagram)

bioDensity™, machine-based isometric exercise using the bioDensity™ system; DXA, Dual-energy X-Ray Absorptiometry; HiRIT, high-load progressive resistance training plus impact loading; ITT, intention-to-treat; RM, repetition maximum; RPE, Rating of Perceived Exertion; RT, resistance training.; Wk, week



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242x399mm (300 x 300 DPI)