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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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## Title:

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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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<sup>™</sup> 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 Dualenergy 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.

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<sup>™</sup> 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.

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#### 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.

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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<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> device for the purposes of examining safety and efficacy alongside the HiPRT/Impact protocol in a semi-randomised controlled trial design.

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#### **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.

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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<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> training. The third arm will be a non-randomised

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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<sup>TM</sup> 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 (<u>www.liftmor.org</u>), 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 selfselected 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<sup>™</sup> 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 17<sup>th</sup> 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

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

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# 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 semiguantitative 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<sup>™</sup>, 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). pQCTderived bone parameters will include: total content, density and cross-sectional area; trabecular content, density and cross-sectional area; cortical content, density, crosssectional 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

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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<sup>2</sup>; kg·m<sup>-2</sup>). 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 crosssectional 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 and the inferior endplate of 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

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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.

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#### 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 takeoff 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 ° (knee angle of 115 °), 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,

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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  $\alpha$  levels; physical health ( $\alpha$  = 0.82), psychological health ( $\alpha$  = 0.81), social relationships ( $\alpha$  = 0.68), and environment ( $\alpha$  = 0.80).[43]

#### Safety and compliance

Prior to each training session participants will rate their level of muscle soreness on a tenpoint 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.

Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Medi> DR, Medilink, France)
Secondary outcome measures	
Other hone 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 % sit pQCT scans (XCT-3000, Stratec Medizintechnik GmbH, Pforzheim Germany)
Anthropometry Height	Wall mounted stadiometer (Mode 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model 7 Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lufk Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix DF 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)

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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
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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

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.

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

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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<sup>™</sup> 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 eightmonth supervised HiPRT/Impact exercise program on determinants of fracture risk for older men with low bone mass, compared with supervised bioDensity<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> 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**

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

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# Project Title

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"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.

# <u>Method</u>

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
    - o 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 hedies (a.e. strapped) idelines.xhtml

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# **BMJ** Open

- 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. 22

# **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 31 meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. 32 33 The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will 34 not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with 35 restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further 36 information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375. 37

#### 38 Use of video recordings and photography

39 You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for 40 presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password 41 protected computer for a minimum of 5 years. 42

#### 43 **Contacting the Investigators**

44 We are happy to answer any questions you may have. For general inquiries please contact Miss Amy Harding (student 45 researcher), at amy.harding@griffithuni.edu.au or on 0410 616 596. If you have any concerns with the study, please do not 46 hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, or Prof Belinda Beck on (07) 5552 8793. 47

#### 48 Feedback

49 Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if 50 you're interested, the overall study findings. 51

#### 52 **Voluntary Participation**

53 Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to 54 participate, you are free to withdraw your consent and discontinue your involvement at any time. 55

#### 56 **Complaints Mechanism**

57 The University requires that all participants be informed that if they have any complaints concerning the manner in which a 58 research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, 59 Research Ethics, Office for Research, Room 4.25, Science, Engineering and Architecture (G11), Griffith University, Gold Coast 60 campus, Q 4222, Phone: 373 54375 or research-ethics@griffith.edu.au.

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# UNIVERSITY

# **CONSENT FORM**

<u>Project Title</u> *"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"* 

# **Investigators**

# Miss Amy Harding

BExSc(Hons), Cert III & IV in Fitness PhD Candidate School of Allied Health Sciences Griffith University, Gold Coast Mob: 0410 616 596 Email:<u>amy.harding@griffithuni.edu.au</u>

# Prof Belinda Beck

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# Dr Benjamin Weeks

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# Mr Steven Watson

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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 <u>research-ethics@griffith.edu.au</u>) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

(Participant)	(P
---------------	----

(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

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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 sexand 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

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	BMJ Open						
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).						
<u>Secon</u>	dary 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						
7)	questionnaires. All participants, pre (baseline) and post-intervention (8 months). Safety (adverse events and injuries) and compliance from training diaries across the whole						
<u>Contro</u> Usual a	activities						
<u>Recrui</u>	tment country						
Austra	lia						
<u>Recrui</u>	tment site location state						
Queen	sland						
<u>Recrui</u>	tment status						
Immin	ent						
<u>Anticip</u>	pated date of first participant enrolment						
<u>Ethics</u>	application status						
Approv	ved						

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

#### 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)

, in re⊾ 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

1	
2	Malignancy
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5	Hernia
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8	Medications know to adversely affect musculoskeletal health such as corticosteroids, anti-
9	convulsants
10	Medical conditions known to effect musculoskeletal health such as hyperparathyroidism. Paget's
11	disease, diabetes
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14	
15	Durpose of the study
16	Purpose of the study
17	Prevention of age-related musculoskeletal deterioration
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20	Allocation to treatment
21	
22	Semi-randomised controlled trial
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26	Enrolment procedure
27	
28	Block randomisation to exercise will occur after participants are stratified for the presence or
29	absence of medications for osteoporosis. The allocation sequence will be generated by a person
30	independent of the trial and filed in sealed opaque envelopes.
31	Random order generated by computer program
32	
33	Open trial (not masked)
35	Intervention assignment parallel
36	
37	Phase not applicable
38	Time of and a interofficeau
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42 43	Recruitment
44	Anticipated start date May 2016
45	
46	Anticipated date of last participant enrolled Nov 2017
47	Target cample size 150
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49	Not yet recruiting
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51	
53	Funding & sponsors
54	
55	Osteoporosis Australia Equipment award (bioDensity device supplied and installed by Performance
56	Health Systems)
57	
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59	For near review only http://hmiopon.hmi.com/site/shout/guidelines.yhtml
60	r or peer review only - http://binjopen.binj.com/site/about/guidelines.Xhtml

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> Osteoporosis Australia National Office Postal: PO Box 550, Broadway, NSW, Australia 2007 Street: Level 2, 255 Broadway, Glebe, NSW, Australia 2037 <u>research@osteoporosis.org.au</u> 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: 1<sup>st</sup> April 2014 Approval date of variations for the 3-arm trial LIFTMOR for Men: 18<sup>th</sup> January 2016 Approval expires: 17<sup>th</sup> Feb 2018

Contact details - Primary sponsor

University

**Griffith University** 

Parklands Drive, Southport, Gold Coast 4222, Queensland, Australia

Principle investigator and contact person for public enquiries

Prof Belinda Beck

School of Allied Health Sciences

Gold Coast campus



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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ltem No	Description	Addressed on page number
Administrative inf	formatior		
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)/Suppleme ntary file
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	26
Roles and	5a	Names, affiliations, and roles of protocol contributors	1, 26
responsibilities	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
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2 3 4 5		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
6 7 8 9 10				
11 12	Introduction			
13 14	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
15 16		6b	Explanation for choice of comparators	9-10
17 18	Objectives	7	Specific objectives or hypotheses	9
19 20 21 22	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
23	Methods: Particip	ants, int	erventions, and outcomes	
24 25 26	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
27 28 29	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
30 31 32	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
34 35 36		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
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2 3 4 5 6 7 8		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)
9 10		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8, 12
10 11 12 13 14 15	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
16 17 18 19	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
20 21 22	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
23 24 25	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
26 27	Methods: Assignme	ent of ir	nterventions (for controlled trials)	
28	Allocation:			
29 30 31 32 33 34	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
35 36 37 38	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
39 40 41	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
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44 45		-9	Protected by copyrighty.insulphonorpages.seifes.seifes.seifes.seifes.seifes.seifes.seides.einilar technologies	
46 47	e Bibliographique de l	onepA te	s 2025, 2025, 2025 on 12 June 2017. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 s Enseignement Superieur (ABBS) .	BMJ Open: first publi

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2 3 4	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	23			
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 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			
24 25 26 27	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			
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41		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			
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44 45		.8	Protected by copyrighty,មាន៤អ្រុមព្រុស្ត្រទេសទាស្ថារមេនស្ថានទៅទាំងសំខាញ់ខ្មែរស្ថារលាក្រហូលក្រុមព្រៃស្វាស្លាស់ស្លាន ទេកកាលlogies				
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3		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
5 6 7	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
8 9 10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
11				
13	Ethics and dissemined	nation		
14 15 16	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
17 18 19 20	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
21 22 23	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
24 25 26		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
27 28 29	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
30 31 32 33 34 35	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
36 37 38 39	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
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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
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# 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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<b>Primary Subject Heading</b> :	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Impact, Isometric exercise, Osteoporosis, Resistance training, Men



2 3		
4 5	1	Study Protocol (Rehabilitation Medicine)
6 7 8	2	
9 10	3	Title:
11 12	4	The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation
13 14	5	for Men) trial: A protocol to determine if a semi-randomised controlled trial of supervised
15 16 17	6	targeted exercise reduces risk of osteoporotic fracture in older men with low bone mass
18 19	7	
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18 19 20	27	
20 21	28	Word Count:
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25 26 27	30	
28 29	31	Keywords:
30 31 32	32	Impact; Isometric exercise; Men; Osteoporosis; Resistance training.
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ABSTRACT

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37	Introduction
38	The primary aim of the proposed study is to examine the efficacy of an eight-month
39	supervised, high-load progressive resistance training and impact loading program in
40	comparison to a supervised machine-based isometric exercise training program using the
41	bioDensity <sup>™</sup> system in older men with low bone mass. We will also determine the safety
42	and acceptability of each exercise training mode. Intervention group responses will be
43	compared with those of a self-selected, non-randomised control sample of sex- and age-
44	matched men who will follow their usual lifestyle activities for eight months.
45	

# 46 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.

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# 60 Discussion

61 Whether a high-load, low-repetition progressive resistance training plus impact loading

- 62 program or a machine-based isometric exercise program can improve determinants of
- 63 fracture risk, without causing injury, has not been examined in men. Determination of the
- 64 efficacy, safety and acceptability of such programs will facilitate formulation of future
- 65 exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who
- 66 have previously been underrepresented.

68	Ethics and dissemination
69	Participant confidentiality will be maintained with publication of results. The study has been
70	granted ethical approval from the Griffith University Human Research Ethics Committee
71	(Protocol number AHS/07/14/HREC).
72	
73	Trial registration number
74	Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)
75	ANZCTR12616000344493; Pre-results.
76	
77	Date and version identifier
78	Original protocol manuscript for submission (Version 1): November 2016.
79	Protocol manuscript for submission (Version 2) with revisions from peer review: December
80	2016
81	Authors: ATH, BKW, SLW, BRB.
82	

1		
2 3	83	STRENGTHS AND LIMITATIONS OF THIS STUDY
4 5	84	• To our knowledge, this will be the first trial to investigate the efficacy and safety of an
6 7	85	eight-month supervised high intensity, progressive resistance training and impact
8 9	86	loading program on several determinants of fracture risk for older men with low bone
10 11	87	mass, compared with a machine-based isometric exercise program using the
12 13	88	bioDensity™ system.
14 15 16	89	• There are few investigations into the effects of exercise on musculoskeletal health in
17 18	90	older men, thus the current unique focus on older men with poor bone health will
19 20 21	91	address a notable gap in the literature.
22 23	92	The engagement of a non-randomised control group of demographically-matched
24 25	93	men who have elected not to exercise for eight months is a design limitation that was
26 27 28	94	implemented for pragmatic reasons.
29	95	• Our study sample will include largely healthy older men, so our findings may not be
31 32	96	applicable to men with comorbidities or other exclusion characteristics.
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# 99 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]

107 It is widely accepted that bone adapts to the mechanical loads it habitually experiences. 108 Experimental data from animal models has revealed the most influential loading 109 characteristics for osteogenesis are magnitude, [7,8] rate [9] and frequency [10-12] of the 110 engendered strain. Evidence also indicates dynamic loading is more osteogenic than static 111 loading [13] The optimal exercise prescription for the prevention and management of 112 osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads, 113 applied at a rapid rate. High-load resistance training with high-impact jumping, the 114 combination of which will elicit high strains and strain rates in bone, is thus theoretically the 115 optimal exercise protocol for bone. Although such exercise is considered safe for healthy 116 individuals with normal bone mass, it is unclear whether it will be safe for individuals with 117 reduced bone mass who are at increased risk of fracture. Previous resistance exercise 118 recommendations for individuals with low bone mass, particularly those who have 119 experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate 120 level of intensity,[14,15] based on a lack of quality evidence that high intensity resistance 121 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

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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<sup>™</sup> 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<sup>™</sup> 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  $(14.9 \pm 11.5 \%)$  and spine  $(16.6 \pm 12.2 \%)$  – 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

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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<sup>™</sup> 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<sup>™</sup> 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<sup>™</sup> device for the purposes of examining safety and efficacy alongside the HiRIT protocol in a semi-randomised controlled trial design.

59

•		
2 3	170	METHODS AND ANALYSES
4 5	171	Ethics and dissemination
6 7	172	The study has been granted ethical approval from the Griffith University Human Research
8 9	173	Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities
10 11	174	will be conducted in accordance with the Declaration of Helsinki. The study is also
12 13	175	registered with the Australian New Zealand Clinical Trials Registry (Trial number
14 15	176	ANZCTR12616000344493). Written informed consent will be obtained from all participants
16 17 18	177	prior to testing by the investigator performing baseline assessments.
19 20	178	Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial [16]
21 22	179	(Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide
23 24	180	evidence of an extremely low risk of injuries from the current exercise protocols, with no
25 26	181	severe injuries reported from a total of 7300 training sessions. Similar to the current
27 28	182	protocol, ethical approval was granted by the GUHREC for both studies, and written
29 30	183	informed consent was obtained from all participants. Strategies were in place to reduce the
31 32	184	risk of injuries or adverse events occurring during the aforementioned trials, and included: 1)
33 34	185	full supervision of high-load resistance training sessions by a qualified exercise scientist; 2)
35 36	186	small group sizes in the supervised training sessions; 3) an initial familiarisation period
37 38	187	during which low-load exercise variants focused on proper lifting technique was
39 40	188	implemented, and 4) weight lifted was progressively increased with training exposure. In
41	189	order to monitor safety, participants were required to complete training diaries at every
43	190	training session to record illnesses, falls, fractures, injuries, and muscle soreness. Early
44 45 46	191	termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety
40	192	Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual
40 49	193	progress reports to the GUHREC. Any adverse events which occur between annual reports
50 51	194	will be reported independently to the GUHREC, in compliance with the Australian Code for
52 53	195	the Responsible Conduct of Research developed by the National Health and Medical
54 55	196	Research Council, and the University Code for the Responsible Conduct of Research. The
50 57 58		9

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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.

# 212 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<sup>™</sup> 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<sup>™</sup> 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. Page 11 of 56

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2 3 4	223		
5 6	224	Study design	
7 8	225	The current project is a three-arm, eight-month, semi-randomised, controlled exercise	
9 10	226	intervention trial. Proposed participant flow is outlined in Figure 1. The eight-month exercise	
11 12	227	intervention period has been chosen as the minimum time frame in which notable changes in	
13 14	228	bone mass are likely to be detected from densitometry.[31] Eligible volunteers to the	
15 16	229	intervention arm will be randomly assigned to one of two exercise programs; either	
17 18	230	supervised HiRIT or bioDensity™ training. The third arm will be a non-randomised control	
19 20	231	group of sex- and age-matched participants with lower than average bone mass recruited	
21 22	232	from the same community. The control group will follow their usual lifestyle for eight months,	
23 24	233	but undergo identical testing to the two exercise intervention groups at baseline and follow-	
25 26	234	up. We acknowledge the somewhat unorthodox semi-randomised design does not	
27 28	235	constitute the most rigorous clinical trial practice, but adopt it out of necessity. Pilot testing	
29 30	236	conducted in our laboratory revealed that male study volunteers who expect to participate in	
31 32	237	an exercise trial, but are randomised to a conventional inactive control group, refuse to	
33 34	238	adhere to the requirement to refrain from exercise for eight months. We also believe that it	
35 36	239	is unethical to withhold access to a potentially beneficial bone-targeted exercise program for	
37 38	240	older men at increased risk of fragility fracture who are specifically seeking exercise therapy.	
39 40	241	For pragmatic reasons then, we will independently recruit a demographically-matched	
41 42	242	sample of men who, for a variety of reasons (not including functional capacity), elect to	
43 44	243	remain sedentary for a minimum of eight months.	
45 46	244		
47	244		
49	245	Sample size	
50 51	246	There have been no published reports of men's studies comparing the effects of heavy	
52 53	247	progressive resistance training and machine-based isometric training using the bioDensity™	
54 55	248	system on FN BMD, thus estimates of sample size were based on the reported rate of	
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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.

# 258 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.

# 268 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 Page 13 of 56

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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.

# 294 Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity<sup>™</sup> 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 17<sup>th</sup> May
2016). To ensure concealment, the allocation sequence will be prepared in advance by an

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2 3	300	external source, and filed in sequentially-numbered, sealed, opaque envelopes. Upon
4 5	301	completion of baseline testing those identified as eligible will be randomly allocated to their
6 7	302	exercise group and their supervised exercise training sessions will be scheduled.
8 9 10	303	
12 13	304	Exercise interventions
14 15	305	Progressive resistance training and impact loading exercise program
16 17 18	306	The HiRIT group will perform approximately thirty minutes of supervised, high-load, free
19	307	weight training and impact loading, twice-weekly, on non-consecutive days. During the initial
20 21	308	two weeks, participants will perform low-load variants of each exercise focussing on
22	309	technique. Following this familiarisation period, sessions will comprise three fundamental
24 25 26	310	compound movement exercises (deadlift, squat and overhead press) at five sets of five
26 27 20	311	repetitions, corresponding to greater than 80 to 85 % of one repetition maximum. Load
28 29	312	magnitude will be progressively increased in increments of 2.5 kg over the course of the
30 31	313	intervention when they are able to easily complete seven repetitions at their current weight.
32 33	314	In addition, five sets of five repetitions of jumping chin-ups (interspersed with rest) with a
34 35	315	firm, flat-footed landing will be performed each session. Impact intensity will be gradually
36 37	316	increased by moving towards achieving a stiff-legged landing as tolerated. Participants will
38 39	317	provide a Rating of Perceived Exertion (RPE) with the aid of the 6-20 point Borg scale [35] at
40 41	318	completion of each training session. Maximal strength testing, to determine one repetition
42 43	319	maximum for the deadlift and squat, will be performed at weeks twelve and twenty-four.
44 45	320	Briefly, the maximal strength test protocol will begin with a warm-up set of five to ten
46 47	321	repetitions at a relatively light load (approximately 50 % of the heaviest weight they have
48 49	322	previously lifted for five repetitions). After a one-minute rest they will perform one set of
50 51	323	three to five repetitions at 60 to 80 % of their perceived maximum. Gradually the load will
52 53	324	increase in 2.5 to 5.0 kg increments until a failed attempt (within three to six attempts), with
54 55	325	each attempt interspersed with a two-minute rest. One repetition maximum is defined as the
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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.

331 Machine-based isometric exercise program

The supervised bioDensity<sup>™</sup> 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 gualified 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.

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# 349 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.

# 362 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.

366 Primary outcome

367 The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink,368 France).

369 Secondary outcomes

- 370 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.
- 372 Kyphosis will be examined in order to track angular changes of the spine with exercise
- 373 exposure. Vertebral fracture assessment using the Genant semiquantitative approach [38]

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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.

383 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<sup>™</sup>, 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

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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, crosssectional 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).

406 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<sup>2</sup>: kg·m<sup>-2</sup>). 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.

419 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

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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.

435 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.

442 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]

448 Functional reach

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A modified version of the original functional reach test (that incorporated a vardstick) 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.

459 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 takeoff phase according to the method described by Linthorne.[47]

466 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

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474	with the wall. This method has excellent validity against the 'gold standard' isokinetic
475	dynamometry (Pearson's correlation coefficient $r = 0.84$ , $p < 0.001$ ; test-retest reliability $r =$
476	0.97, $p < 0.001$ ). (Little A, Harding AT, Weeks BK, Horan SA, Watson SL, and Beck BR,
477	2016; unpublished data; conference abstract)
478	Maximal isometric back extensor muscle strength will be assessed in erect standing using a
470	handheld dynamometer (Lafavette Manual Muscle Testing Systems USA). The participant
479	will be positioned midway between two vertical wall mounted anchor rails, with their back
400	and heals against the wall. An inclusion balt between the two role will be festened
401	and neels against the wall. An melastic beit between the two rails will be fastened
482	horizontally around the hips in order to restrain the pelvis. The padded transducer pressure
483	plate will be positioned by the investigator between the wall and the seventh thoracic
484	vertebral spinous process, until held securely against the wall by the pressure of the
485	participant's back. Participants will be instructed to push back into the wall with their
486	shoulders, ensuring their feet remain flat with their heels in contact with the wall. This
487	method has excellent validity against the 'gold standard' isokinetic dynamometry (Pearson's
488	correlation coefficient $r = 0.85$ , $p < 0.001$ ; test-retest reliability $r = 0.93$ , $p < 0.001$ ). (Harding
489	AT, Weeks BK, Horan SA, Little A, Watson SL, and Beck BR, 2016; Unpublished data;
490	conference abstract)
401	Dietary calcium intake
401	
492	Calcium intake will be assessed using the AusCal, a calcium-focused food frequency
493	questionnaire designed and validated for the Australian diet.[48] Frequency of consumption
494	per day, week or month, and approximate serving size will be recorded for each of the listed
495	calcium-rich food and beverage items over the previous year. The AusCal will be
496	investigator-administered. Questionnaire responses will be entered into customised
497	FoodWorks analysis software to generate average daily calcium intake (Version 7, Xyris
498	Software, Brisbane, Australia).
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499 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]

512 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 gualitative software (Version 10, QRS International Pty Ltd) to determine barriers and facilitators to participation in higher-intensity, bone-targeted exercise.

Quality of life

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The World Health Organisation Quality of Life questionnaire was developed to assess four

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527	quality of life domains using a five-point Likert interval scale.[54] Higher scores are
528	indicative of higher quality of life. Participants will self-complete the questionnaire. Internal
529	consistency across a large heterogeneous population from a field trial during its
530	development showed each domain to have moderate to high Cronbach's $\alpha$ levels; physical
531	health ( $\alpha$ = 0.82), psychological health ( $\alpha$ = 0.81), social relationships ( $\alpha$ = 0.68), and
532	environment ( $\alpha = 0.80$ ).[55]
533	Safety and compliance
534	Prior to each training session participants will rate their level of muscle soreness on a ten-
535	point visual analogue scale, and note alterations to their diet, physical activity, health or
536	medications since their previous session. Illnesses, falls, fractures, and injuries other than
537	muscle soreness will be documented. Attendance will be entered to determine program
538	compliance, with 100 % being defined as completion of seventy sessions over the course of
539	eight months. Adverse events will be fully documented by investigators, and monitored
540	across the intervention period.

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Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Med 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 (Medi 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, an leg 4 %, 14 %, 38 % and 66 % s pQCT scans (XCT-3000, Strated Medizintechnik GmbH, Pforzhein Germany)
Anthropometry Height	Wall mounted stadiometer (Mod 216; Seca, Hamburg, Germany)
Weight	Mechanical beam scale (Model Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Luf Executive Thinline, Apex, USA)
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix D 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 Medic & Therapeutic Instruments, Australia)
		Lateral de cubitus thoracolumba spine DXA (Medix DR, Medilink, France)
	Vertebral fracture assessment	Lateral de cubitus thoracolumba spine DXA (Medix DR, Medilink, France)
	Functional performance	
	Timed up-and-go	Digital stopwatch (Fisher Scienti USA)
	Five-times sit-to-stand	Digital stopwatch (Fisher Scienti USA)
	Functional reach	Perspex board with measureme grid-lines
	Muscle power	
	Countermovement vertical jump	Load cell (Advanced Mechanica Technology Inc., Watertown, MA USA)
	Isometric muscle strength Lower extremity strength	Leg platform dynamometer (TTM Muscle Meter, Tokyo, Japan)
	Back extensor strength	Dynamometer (Lafayette Manua 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 Sca (PACES) questionnaire
	Quality of Life	World Health Organisation Quali of Life (WHOQOL) questionnaire
	Safety (adverse events and injuries) and compliance	Purpose designed lifestyle diarie and training diaries Trainer records
-	aBMD, areal bone mineral density; BMC, bon Physical Activity Questionnaire; DXA, Dual-er Activity Enjoyment Scale; pQCT, peripheral C volumetric bone mineral density; WHOQOL, M	Trainer records e mineral content; BPAQ, Bone-specific nergy X-Ray Absorptiometry; PACES, P quantitative Computed Tomography; vBN Vorld Health Organisation Quality of Life

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549	Data integrity
550	Participants will be allocated a unique study ID and data will be de-identified for analysis.
551	After final data collection and cleaning, the data will be locked before analysis. Paper
552	records will be stored securely at Griffith University in a laboratory with restricted swipe card
553	access, and retained for a minimum of fifteen years. Electronic data will be stored securely
554	on password-protected University computers. Management, storage and retention of
555	research data will be in line with Griffith University policy, the Griffith University Code for the
556	Responsible Conduct of Research. There will be no contractual agreements limiting data set
557	access. De-identified data will be shared for meta-analyses or other collaborations on a
558	case by case basis. De-identified data will be made available to the bioDensity™
559	manufacturer, Performance Health Systems, after the final study results have been
560	published.
561	

# 562 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.

571 Data analyses

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

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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<sup>™</sup> 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  $p \le 0.05$ .

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# 593 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<sup>™</sup> 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

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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<sup>™</sup>
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.

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# 639 Limitations

640 Several limitations warrant discussion. First, due to the somewhat unorthodox semi-641 randomised study design, there exists the possibility of self-selection bias. Pilot testing 642 demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of 643 older male study volunteers to adhere to a control requirement to refrain from exercise for 644 eight months. When volunteering under the premise of receiving an exercise program, we 645 argue that there are also ethical issues of withholding exercise from individuals who wish to 646 take it up. We have attempted to minimise the risk by applying uniform inclusion and 647 exclusion criteria for all study participants, with the exception of a willingness to participant in 648 an eight-month exercise intervention. The extent to which the self-selected control group 649 differs from the intervention groups will be determined and reported in the course of 650 descriptive analyses of baseline data. Any differences will be accounted for by adjusting for 651 baseline values in the final analyses. Second, the current trial is not powered to detect 652 significant differences in fractures as safety (adverse events and injuries) is a secondary 653 outcome. Nevertheless, reporting adverse events and injuries is informative when 654 determining if an exercise program can be translated to clinical practice. Third, the outcome 655 assessor will not be blind to group allocation, will deliver the intervention, and will be 656 responsible for documenting adverse events and reporting to the GUHREC. Participants will 657 be instructed to report even the slightest degree of discomfort/pain/muscle soreness or 658 injury, and a protocol is in place for independent review by a qualified Physiotherapist or 659 General Practitioner, as required. It is also an ethical requirement to report such events to 660 the GUHREC, and harms or unintended events must be included when reporting 661 randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse 662 event would contravene both Institutional and National research ethics guidelines. A blinded 663 outcome assessor is beyond the means of this unfunded project, and therefore our current 664 study design has been adopted out of necessity.

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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.	
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funding sources have no role in the design of this study and will not have any role during its	
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#### **Ethics Approval**

- The trial has received ethical approval from the Griffith University Human Research Ethics
- <text> 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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868	Figure legend
869	Figure 1. Proposed participant flow (CONSORT diagram)
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872	bioDensity™, machine-based isometric exercise using the bioDensity™ system; DXA, Dual-
873	energy X-Ray Absorptiometry; HiRIT, high-load progressive resistance training plus impact
874	loading; ITT, intention-to-treat; RM, repetition maximum; RT, resistance training.



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# 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

# <u>Study type</u>

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.

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# Comparator/control treatment

Arm 3 – the comparator will be a non-randomised sample of men, recruited independently but sexand 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

 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

- 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).

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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

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# 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, anticonvulsants

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)

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Osteoporosis Australia National Office Postal: PO Box 550, Broadway, NSW, Australia 2007 Street: Level 2, 255 Broadway, Glebe, NSW, Australia 2037 <u>research@osteoporosis.org.au</u> 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: 1<sup>st</sup> April 2014 Approval date of variations for the 3-arm trial LIFTMOR for Men: 18<sup>th</sup> January 2016 Approval expires: 17<sup>th</sup> Feb 2018

Contact details - Primary sponsor

University

**Griffith University** 

Parklands Drive, Southport, Gold Coast 4222, Queensland, Australia

Principle investigator and contact person for public enquiries

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School of Allied Health Sciences

Gold Coast campus

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# **Project Title**

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

School of Allied Health Sciences

Griffith University, Gold Coast

Email: <u>b.beck@griffith.edu.au</u>

**Dr Benjamin Weeks** 

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Supervisor

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Ph: (07) 5552 8793

# Investigators

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#### 16 **Mr Steven Watson**

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18 PhD Candidate 19

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20 Griffith University, Gold Coast 21

#### Mob: 0401 491 414 22

Ph: (07)5552 8281

23

# Email: steven.watson3@griffith.edu.au

## 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 0
    - 0 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 0 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 (egr staples, joint on lagence in foreign hodies (egr staple) idelines.xhtml

# **BMJ** Open

- 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

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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

30 Results will be kept as confidential as is possible by law and will not be disclosed to third parties without your consent, except to 31 meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. 32 33 The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will 34 not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with 35 restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further 36 information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375.

#### 38 Use of video recordings and photography

39 You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for 40 presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password 41 protected computer for a minimum of 5 years. 42

#### 43 **Contacting the Investigators**

44 We are happy to answer any questions you may have. For general inquiries please contact Miss Amy Harding (student 45 researcher), at amy.harding@griffithuni.edu.au or on 0410 616 596. If you have any concerns with the study, please do not 46 hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, or Prof Belinda Beck on (07) 5552 8793. 47

#### 48 Feedback

49 Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if 50 you're interested, the overall study findings. 51

#### 52 **Voluntary Participation**

53 Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to 54 participate, you are free to withdraw your consent and discontinue your involvement at any time. 55

#### 56 **Complaints Mechanism**

57 The University requires that all participants be informed that if they have any complaints concerning the manner in which a 58 research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, 59 Research Ethics, Office for Research, Room 4.25, Science, Engineering and Architecture (G11), Griffith University, Gold Coast 60 campus, Q 4222, Phone: 373 54375 or research-ethics@griffith.edu.au.

# Please retain this document for your information.

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# **CONSENT FORM**

Project Title

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

# **Investigators**

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# Mr Steven Watson

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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 <u>research-ethics@griffith.edu.au</u>) 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 For peer review only - http://bm/open.bm/.com/site/about/guidelines.xhtml coverage and publication of research findings.





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

11 12 13	Section/item	ltem No	Description	Addressed on page number
14 15	Administrative info	ormation		
16 17	Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
18 19	Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
20 21 22 23 24		2b	All items from the World Health Organization Trial Registration Data Set	ANZCTR trial registry (online)/Suppleme ntary file
25 26	Protocol version	3	Date and version identifier	4
27 28	Funding	4	Sources and types of financial, material, and other support	31
29 30 31 32	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Author affiliations – 1; Author contributions - 31
33 34		5b	Name and contact information for the trial sponsor	31
<ul> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> </ul>		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 1
44 45 46		9.	Enseignement Superieur (SBEA) Protected by copyrighty ທີ່ທີ່ທີ່ເຊຍີ່ມີອາດີເຊັ້ນ ອາດີເຊັ້ນ ອາດີເຊັ້ນ ເຫັນການເຮັດເຊັ່ນ ເພິ່ງເຫັນເຫັນເຮັດເຊັ່ນ ເ	

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2 3 4 5 6 7 8 9		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
9 10 11	Introduction			
12 13 14	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
15 16		6b	Explanation for choice of comparators	Study design - 11
17 18	Objectives	7	Specific objectives or hypotheses	Study aims - 10
19 20 21 22	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
23	Methods: Participa	ants, int	erventions, and outcomes	
24 25 26 27	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
27 28 29 30 31 32 33 34 35	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
36 37 38 39 40	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	14-15
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Page 52 of 56

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2 3 4		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
5 6 7 8 9 10 11 12		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)
13 14 15		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Eligibility and screening 12-13
<ol> <li>16</li> <li>17</li> <li>18</li> <li>19</li> <li>20</li> <li>21</li> <li>22</li> <li>23</li> <li>24</li> <li>25</li> </ol>	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
26 27 28 29	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
30 31 32	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
33 34 25	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Recruitment - 12
35 36 37	Methods: Assignme	ent of in	terventions (for controlled trials)	
38 39 40 41	Allocation:			
42 43				3
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Page	53	of	56
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1 2 3 4 5 6 7	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
7 8 9 10 11 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	Randomisation and allocation – 13-14; Blinding - 26
13 14 15 16 17	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
18 19 20 21 22 23	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
24 25 26 27 28 29 30		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
31 32	Methods: Data coll	ection, r	nanagement, and analysis	
33 34 35 36 37 38 39	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
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BMJ Open

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2 3 4 5 6 7 8		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
9 10 11 12	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
13 14 15	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
16 17 18		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Data analyses – 26-27
19 20 21 22		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
22	Methods: Monitorin	g		
24 25 26 27 28 29 30	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
31 32 33 34 35 36 37 38		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
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2 3 4 5 6 7	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
7 8 9 10 11 12	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
13 14	Ethics and dissemi	nation		
15 16 17 18	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination – 9- 10
19 20 21 22 23	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
24 25 26 27	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
28 29 30		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
31 32 33 34	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
35 36 37 38 39 40 41	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Competing interests and funding acknowledgement s - 31
42 43				6
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46 47	e Bibliographique de l	at Agenc	shed as 10.1136/bmjopen-2016-014951 on 12 June 2017. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 Enseignement Superieur (ABES)	BMJ Open: first publi

Page 56 of 56

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4 5 6 7 8	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	sponsor - 31 Ethics and dissemination – 9-
9 10				10
11 12 13 14 15 16	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
17 18		31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
19 20 21 22 23		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
24 25	Appendices			
26 27 28	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
29 30 31	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
<ul> <li>*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation &amp; Elaboration for important clarification</li> <li>Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commercial-NoDerivs 3.0 Unported" license.</li> <li>*Attribution-NonCommercial-NoDerivs 3.0 Unported</li> </ul>				ation on the items. ommons
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46 47	BMJ Open: first published as 10.1136/bmjopen-2016-014951 on 12 June 2017. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .			

**BMJ** Open

# **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

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-014951.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Feb-2017
Complete List of Authors:	Harding, Amy; Griffith University, School of Allied Health Sciences Weeks, Benjamin; Griffith University, School of Allied Health Sciences Watson, Steven; Griffith University, School of Allied Health Sciences Beck, Belinda; Griffith University, School of Allied Health Sciences
<b>Primary Subject Heading</b> :	Rehabilitation medicine
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Keywords:	Impact, Isometric exercise, Osteoporosis, Resistance training, Men


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ABSTRACT

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37	Introduction
38	The primary aim of the proposed study is to examine the efficacy of an eight-month
39	supervised, high-load progressive resistance training and impact loading program in
40	comparison to a supervised machine-based isometric exercise training program using the
41	bioDensity™ system in older men with low bone mass. We will also determine the safety
42	and acceptability of each exercise training mode. Intervention group responses will be
43	compared with those of a self-selected, non-randomised control sample of sex- and age-
44	matched men who will follow their usual lifestyle activities for eight months.
45	
46	Methods and analysis

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

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# **Discussion**

61 Whether a high-load, low-repetition progressive resistance training plus impact loading

- 62 program or a machine-based isometric exercise program can improve determinants of
- 63 fracture risk, without causing injury, has not been examined in men. Determination of the
- 64 efficacy, safety and acceptability of such programs will facilitate formulation of future
- 65 exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who
- 66 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 Protocol manuscript for submission (Version 3) with revisions from peer review: February

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# 86 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<sup>™</sup> 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.

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102	INTRODUCTION
103	Epidemiological data indicates the global prevalence of osteoporosis to be over 200
104	million,[1] with around 1.2 million Australians,[2] 10.2 million Americans [3] and 15 million
105	European men and women over fifty years of age being affected.[4] It has been suggested
106	that 285,000 Australian men aged over fifty will be diagnosed as osteoporotic, and a further
107	2.48 million older men diagnosed as osteopenic by 2022.[5] With the aging of the
108	population, there will undoubtedly be a corresponding increasing prevalence of low bone
109	mass and consequent increase in the incidence of low trauma fracture.[6]
110	It is widely accepted that bone adapts to the mechanical loads it habitually experiences.
111	Experimental data from animal models has revealed the most influential loading
112	characteristics for osteogenesis are magnitude, [7,8] rate [9] and frequency [10-12] of the
113	engendered strain. Evidence also indicates dynamic loading is more osteogenic than static
114	loading.[13] The optimal exercise prescription for the prevention and management of
115	osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads
116	applied at a rapid rate. High-load resistance training with high-impact jumping, the
117	combination of which will elicit high strains and strain rates in bone, is thus theoretically the
118	optimal exercise protocol for bone. Although such exercise is considered safe for healthy
119	individuals with normal bone mass, it is unclear whether it will be safe for individuals with
120	reduced bone mass who are at increased risk of fracture. Previous resistance exercise
121	recommendations for individuals with low bone mass, particularly those who have
122	experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate
123	level of intensity,[14,15] based on a lack of quality evidence that high intensity resistance
124	training is safe and effective.
125	Recently a hone-targeted, high intensity, progressive resistance training and impact loading
120	(HiDIT) everying program was undertaken with past management warman with law to very law
120	(TITT) exercise program was undertaken with post-menopausal women with low to very low

127 bone mass at the hip or spine - the LIFTMOR (Lifting Intervention For Training Muscle and

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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<sup>™</sup> 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<sup>™</sup> 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  $(14.9 \pm 11.5 \%)$  and spine  $(16.6 \pm 12.2 \%)$  – 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

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155	intake or physical activity, lack of control group, lack of disclosure of simultaneous bone
156	medications, and the fact that follow-up DXA scans were conducted sixty days after the
157	intervention was completed suggests that a more rigorous examination of efficacy of
158	bioDensity™ training is indicated.
450	
159	Short-duration (thirty minute), twice-weekly therapeutic exercise programs for older men with
160	low bone mass, such as the proposed HiRIT and bioDensity™ training protocols, provide an
161	attractive alternative to more burdensome and time consuming programs typically
162	recommended for osteoporosis. Indeed, trials examining the influence of progressive
163	resistance training, hopping/jumping or multicomponent programs on bone health in men
164	have adopted session frequencies of three, [23-28] four, [29] or even seven [30] per week.
165	Hinton and colleagues [28] compared thrice-weekly sessions of jump training with twice-
166	weekly sessions of periodised progressive resistance training; however, healthy physically
167	active men aged 25 to 60 years were recruited. Whether high-load, low-volume training
168	methods can safely improve bone strength in older men with low bone mass remains a
169	knowledge gap. Thus, the Griffith University Bone Densitometry Research Laboratory has
170	acquired a bioDensity™ device for the purposes of examining safety and efficacy alongside
171	the HiRIT protocol in a semi-randomised controlled trial design.
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# 173 METHODS AND ANALYSES

# 174 Ethics and dissemination

175 The study has been granted ethical approval from the Griffith University Human Research

- 176 Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities
- 177 will be conducted in accordance with the *Declaration of Helsinki*. The study is also
- 178 registered with the Australian New Zealand Clinical Trials Registry (Trial number
- 179 ANZCTR12616000344493). Written informed consent will be obtained from all participants
- 180 prior to testing by the investigator performing baseline assessments.

81 Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial [16] 82 (Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide 83 evidence of an extremely low risk of injuries from the current exercise protocols, with no 84 severe injuries reported from a total of 7300 training sessions. Similar to the current 85 protocol, ethical approval was granted by the GUHREC for both studies, and written 86 informed consent was obtained from all participants. Strategies were in place to reduce the 87 risk of injuries or adverse events occurring during the aforementioned trials, and included: 1) 88 full supervision of high-load resistance training sessions by a qualified exercise scientist; 2) 89 small group sizes in the supervised training sessions; 3) an initial familiarisation period 90 during which low-load exercise variants focused on proper lifting technique was 91 implemented, and 4) weight lifted was progressively increased with training exposure. In 92 order to monitor safety, participants were required to complete training diaries at every 93 training session to record illnesses, falls, fractures, injuries, and muscle soreness. Early 94 termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety 95 Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual 96 progress reports to the GUHREC. Any adverse events which occur between annual reports 97 will be reported independently to the GUHREC, in compliance with the Australian Code for 98 the Responsible Conduct of Research developed by the National Health and Medical 99 Research Council, and the University Code for the Responsible Conduct of Research. The

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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.

### 215 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<sup>™</sup> 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<sup>™</sup> 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. BMJ Open: first published as 10.1136/bmjopen-2016-014951 on 12 June 2017. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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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 exerci	ise
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 month	۱S,
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	1
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	t
242	is unethical to withhold access to a potentially beneficial bone-targeted exercise program for	or
243	older men at increased risk of fragility fracture who are specifically seeking exercise therap	уy.
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	тм
251	system on FN BMD, thus estimates of sample size were based on the reported rate of	
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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.

### 261 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.

# 271 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

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

#### 297 Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity<sup>™</sup> 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 17<sup>th</sup> May
2016). To ensure concealment, the allocation sequence will be prepared in advance by an

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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  $\geq$ 16 (6-20 point Borg scale [35]) to achieve a high intensity equivalent before one repetition Maximal strength testing, to determine one repetition maximum for the maximum testing. 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 

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(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.

339 Machine-based isometric exercise program

The supervised bioDensity<sup>™</sup> 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

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354	bioDensity <sup>™</sup> system, and ensure the exercises are performed correctly and safely. Peak	
355	force, average force and RPE will be recorded in participant training diaries.	
356		
357	Control group activities	
858	The sex- and age-matched control group will be encouraged to maintain their customary	
59	physical activity and dietary patterns over the eight month duration of the study. To monitor	
30	deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to	
51	list variations to their physical activity level and diet on a fortnightly basis. Space is also	
62	provided to record any illnesses, falls, fractures, changes to their medical conditions and	
33	medications (inclusive of over the counter medications), and injuries other than muscle	
64	soreness. Diaries are to be returned at follow-up. Fortnightly emails will act as reminders to	
65	complete diary entries, with a monthly email requiring a reply to the investigator to prompt	
66	recording of any relevant changes. To detect change in bone-relevant physical activity or	
67	dietary calcium intake over the course of the eight-month study, participants will complete	
68	questionnaires (described below) at baseline and follow-up.	
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70	Outcome measures	
71	All outcome measures will be performed at baseline and eight-month follow-up by a single	
'2	investigator who is not blind to group allocation, using identical facilities, procedures and	
73	equipment. A summary of outcome measures is presented in Table 1.	
574	Primary outcome	
75	The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink,	
76	France).	
377	Secondary outcomes	
	17	

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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 semiguantitative 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, guality of life and exercise appeal. Participant safety (adverse events and injuries) and compliance will be monitored across the intervention period using training diaries.

391 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

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404	malleolus, and radial length measured from the proximal tip of the olecranon process to the
405	distal tip of the ulnar styloid process. A planar scout view of the ankle joint line on the
406	skeletally non-dominant leg will be acquired so the anatomical reference line can be
407	adjusted to bisect the tibial endplate. A total of four image slices will be acquired at 4 $\%$ ,
408	14 %, 38 % and 66 % sites proximal to the distal edge of the tibial endplate. For the distal
409	tibia (4 $\%$ site) contour mode 3 at 169 mg/cm $^3$ and peel mode 4 at 650 mg/cm $^3$ , with a 10 $\%$
410	peel, will be used to determine total and trabecular content, total and trabecular volumetric
411	bone mineral density, and total and trabecular cross-sectional area. At the midshaft of the
412	tibia (38 % site) cort mode 2 at 710 mg/cm <sup>3</sup> will be used to define cortical content, volumetric
413	bone mineral density, area and thickness, and periosteal and endocortical circumference.
414	Cort mode 2 at 480 mg/cm <sup>3</sup> will be used to determine polar section modulus and the polar
415	strength strain index. A planar scout scan perpendicular to the long axis of the skeletally
416	non-dominant forearm will be performed at the level of the ulnar head, with the reference line
417	positioned at the distal edge of the most horizontal portion of the radial cortical endplate.
418	Two image slices will be acquired at the 4 % and 66 % sites proximal to the distal endplate
419	of the radius. For the distal radius (4 % site) contour mode 3 at 169 mg/cm <sup>3</sup> and peel mode
420	4 at 650 mg/cm <sup>3</sup> , with a 10 % peel, will be used to determine total and trabecular content,
421	total and trabecular volumetric bone mineral density, and total and trabecular cross-sectional
422	area. At the proximal radius (66 % site) cort mode 2 at 710 mg/cm <sup>3</sup> will be used to define
423	cortical content, volumetric bone mineral density, area and thickness, and periosteal and
424	endocortical circumference. Cort mode 2 at 480 mg/cm <sup>3</sup> will be used to determine polar
425	section modulus and the polar strength strain index. pQCT-derived bone parameters will
426	include: total content, density and cross-sectional area; trabecular content, density and
427	cross-sectional area; cortical content, density, cross-sectional area and thickness; periosteal
428	and endocortical circumference; and biomechanical strength indices calculated from density
429	and area (total and trabecular bone strength indices, polar section modulus, and polar

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430 strength strain index). All pQCT analyses will be conducted using host software Version

431 6.20 (Stratec Medizintechnik GmbH, Pforzheim, Germany).

432 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<sup>2</sup>; kg·m<sup>-2</sup>). 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.

445 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

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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.

461 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.

468 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

473 and colleagues for assessing older adults.[45]

474 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

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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.

485 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 takeoff phase according to the method described by Linthorne.[47]

492 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)

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

519 questionnaire designed and validated for the Australian diet.[48] Frequency of consumption

520 per day, week or month, and approximate serving size will be recorded for each of the listed

521 calcium-rich food and beverage items over the previous year. The AusCal will be

522 investigator-administered. Questionnaire responses will be entered into customised

523 FoodWorks analysis software to generate average daily calcium intake (Version 7, Xyris

524 Software, Brisbane, Australia).

525 Bone-specific physical activity

526 The Bone-specific Physical Activity Questionnaire (BPAQ) [49] will be used to quantify

527 current and historical physical activity of relevance to bone. Respondents will list all regular,

528 structured physical activity and years of participation, with a minimum of investigator

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529	assistance. BPAQ scores will be calculated using an on-line, custom-designed analysis
530	program (http://www.fithdysign.com/BPAQ/). Mathematical algorithms in the calculator were
531	developed using load ratings from vertical ground reaction forces of each activity,
532	participation frequency, years of involvement and an age-weighting factor. High loading
533	ratings represent high-impact activities, whilst the age-weighting factor reflects higher
534	mechanosensitivity to physical activity during youth. Previous research has found BPAQ
535	scores are predictive of variance in DXA-derived bone strength parameters at clinically
536	relevant sites in healthy middle-aged and older men.[50] This instrument has high reliability,
537	with intra-class correlation coefficients of 0.92 to 0.97.[51]
538	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.

551 Quality of life

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

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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 $\alpha$ levels; physical
health ( $\alpha$ = 0.82), psychological health ( $\alpha$ = 0.81), social relationships ( $\alpha$ = 0.68), and
environment ( $\alpha = 0.80$ ).[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
25

555	consistency across a large heterogeneous population from a field trial during its
556	development showed each domain to have moderate to high Cronbach's $\alpha$ levels; physical
557	health ( $\alpha$ = 0.82), psychological health ( $\alpha$ = 0.81), social relationships ( $\alpha$ = 0.68), and
558	environment ( $\alpha = 0.80$ ).[55]
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563	muscle soreness will be documented. Attendance will be entered to determine program
564	compliance, with 100 % being defined as completion of seventy sessions over the course of
565	eight months. Adverse events will be fully documented by investigators, and monitored
566	across the intervention period.

Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Me 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, Medilir 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 (Me DR, Medilink, France), 3D hip software (DMS Group, Maugui 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, a leg 4 %, 14 %, 38 % and 66 % pQCT scans (XCT-3000, Strat Medizintechnik GmbH, Pforzhe Germany)
Anthropometry Height	Wall mounted stadiometer (Mo 216; Seca, Hamburg, German
Weight	Mechanical beam scale (Mode Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; Lu Executive Thinline, Apex, USA
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix 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	Questionnaire (BPAQ)
	Barriers and facilitators	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
569 570 571 572	aBMD, areal bone mineral density; BMC, bone Physical Activity Questionnaire; DXA, Dual-ene Activity Enjoyment Scale; pQCT, peripheral Qu volumetric bone mineral density; WHOQOL, W	e mineral content; BPAQ, Bone-specific ergy X-Ray Absorptiometry; PACES, Phys uantitative Computed Tomography; vBMD /orld Health Organisation Quality of Life.
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data set

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575	Data integrity
576	Participants will be allocated a unique study ID and data will be de-identified for analysis.
577	After final data collection and cleaning, the data will be locked before analysis. Paper
578	records will be stored securely at Griffith University in a laboratory with restricted swipe card
579	access, and retained for a minimum of fifteen years. Electronic data will be stored securely
580	on password-protected University computers. Management, storage and retention of
581	research data will be in line with Griffith University policy, the Griffith University Code for the
582	Responsible Conduct of Research. There will be no contractual agreements limiting data se
583	access. De-identified data will be shared for meta-analyses or other collaborations on a
584	case by case basis. De-identified data will be made available to the bioDensity™
585	manufacturer, Performance Health Systems, after the final study results have been
586	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,

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

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# 622 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<sup>™</sup> 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. Kukulian and co-workers [26] examined the influence of twelve-months progressive

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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<sup>™</sup>
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.

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# 669 Limitations

670 Several limitations warrant discussion. First, due to the somewhat unorthodox semi-671 randomised study design, there exists the possibility of self-selection bias. Pilot testing 672 demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of 673 older male study volunteers to adhere to a control requirement to refrain from exercise for 674 eight months. When volunteering under the premise of receiving an exercise program, we 675 argue that there are also ethical issues of withholding exercise from individuals who wish to 676 take it up. We have attempted to minimise the risk by applying uniform inclusion and 677 exclusion criteria for all study participants, with the exception of a willingness to participate in 678 an eight-month exercise intervention. The extent to which the self-selected control group 679 differs from the intervention groups will be determined and reported in the course of 680 descriptive analyses of baseline data. Any differences will be accounted for by adjusting for 681 baseline values in the final analyses. Second, the current trial is not powered to detect 682 significant differences in fractures as safety (adverse events and injuries) is a secondary 683 outcome. Nevertheless, reporting adverse events and injuries is informative when 684 determining if an exercise program can be translated to clinical practice. Third, the outcome 685 assessor will not be blind to group allocation, will deliver the intervention, and will be 686 responsible for documenting adverse events and reporting to the GUHREC. Participants will 687 be instructed to report even the slightest degree of discomfort/pain/muscle soreness or 688 injury, and a protocol is in place for independent review by a gualified Physiotherapist or 689 General Practitioner, as required. It is also an ethical requirement to report such events to 690 the GUHREC, and harms or unintended events must be included when reporting 691 randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse 692 event would contravene both Institutional and National research ethics guidelines. A blinded 693 outcome assessor is beyond the means of this unfunded project, and therefore our current 694 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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#### 898 Figure legend

899 Figure 1. Proposed participant flow (CONSORT diagram)

902 bioDensity™, machine-based isometric exercise using the bioDensity™ system; DXA, Dual-

903 energy X-Ray Absorptiometry; HiRIT, high-load progressive resistance training plus impact

904 loading; ITT, intention-to-treat; RM, repetition maximum; RPE, Rating of Perceived Exertion;

905 RT, resistance training.; Wk, week





#### Project Title

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"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.

#### <u>Method</u>

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
    - o 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 hedies (g.e. shrappel) idelines.xhtml

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#### **BMJ** Open

- 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. 22

#### **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

30 Results will be kept as confidential as is possible by law and will not be disclosed to third parties without your consent, except to 31 meet government, legal or other regulatory authority requirements. All data will be kept in the possession of the investigators. 32 33 The information collected is confidential and a de-identified copy of this data may be used for other research purposes. You will 34 not be referred to by name during research reports or study discussions. All records will be stored in a locked filing cabinet with 35 restricted access for a minimum of five years in a private office. All computer records will be restricted by password. For further 36 information consult the University's Privacy Plan at http://www.griffith.edu.au/privacy-plan or telephone (07) 3735 4375.

#### 38 Use of video recordings and photography

39 You have an option to consent to being videoed or photographed during the study. Those images or recordings could be used for 40 presentations, media coverage and/or publication of research findings. All material will be stored in a locked file on a password 41 protected computer for a minimum of 5 years. 42

#### 43 **Contacting the Investigators**

44 We are happy to answer any questions you may have. For general inquiries please contact Miss Amy Harding (student 45 researcher), at amy.harding@griffithuni.edu.au or on 0410 616 596. If you have any concerns with the study, please do not 46 hesitate to contact Dr Benjamin Weeks, on (07) 5552 9336, or Prof Belinda Beck on (07) 5552 8793. 47

#### 48 Feedback

49 Following completion of data collection and analysis, you will be presented with a brief summary of your individual results and, if 50 you're interested, the overall study findings. 51

#### 52 **Voluntary Participation**

53 Whether you decide to participate in this study or not, your decision will not prejudice you in any way. If you do decide to 54 participate, you are free to withdraw your consent and discontinue your involvement at any time. 55

#### 56 **Complaints Mechanism**

57 The University requires that all participants be informed that if they have any complaints concerning the manner in which a 58 research project is conducted they may be given to the researcher, or, if an independent person is preferred: The Manager, 59 Research Ethics, Office for Research, Room 4.25, Science, Engineering and Architecture (G11), Griffith University, Gold Coast 60 campus, Q 4222, Phone: 373 54375 or research-ethics@griffith.edu.au.

#### Please retain this document for your information.

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# UNIVERSITY

#### **CONSENT FORM**

<u>Project Title</u> *"LIFTMOR for Men: Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation"* 

#### **Investigators**

#### Miss Amy Harding

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#### Prof Belinda Beck

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#### Dr Benjamin Weeks

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#### Mr Steven Watson

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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 <u>research-ethics@griffith.edu.au</u>) if I have any concerns about the ethical conduct of the project; and
- I agree to participate in the project.

(Participant)	
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(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 For peer review only http://bmjopen.bmj.com/site/about/guidelines.xhtml 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

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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 sexand 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

- 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

- 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

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#### **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

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# Malignancy

Hernia

Medications know to adversely affect musculoskeletal health such as corticosteroids, anticonvulsants

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: 1<sup>st</sup> April 2014 Approval date of variations for the 3-arm trial LIFTMOR for Men: 18<sup>th</sup> January 2016 Approval expires: 17<sup>th</sup> Feb 2018

Contact details – Primary sponsor

University

**Griffith University** 

Parklands Drive, Southport, Gold Coast 4222, Queensland, Australia

Principle investigator and contact person for public enquiries

Prof Belinda Beck

School of Allied Health Sciences

Gold Coast campus

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		STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS	
SPIRIT 2013 Check	klist: Reco	ommended items to address in a clinical trial protocol and related documents*	
Section/item	ltem No	Description	Addressed on page number
Administrative inf	ormation	t Super text ar	
Title	1	مَعْ مَعْ مَعْ مَعْ مَعْ مَعْ مَعْ مَعْ	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)/Suppleme ntary 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, and alysis, 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
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	1

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1 2 3 4 5 6 7 8 9 10 11 12 13	Introduction	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee endpoint adjudication committee, data management team, and other individuals or groups over the trial, if applicable (see Item 21a for data monitoring committee)	Ethics and dissemination – 10-11; Data integrity – 28; Author contributions - 33		
	Background and rationale	6a	Description of research question and justification for undertaking the trial, including gummary of relevant studies (published and unpublished) examining benefits and harms for each intervertion	Introduction - 7-9; Study aims - 11		
14 15		6b	Explanation for choice of comparators	Study design - 12		
16 17	Objectives	7	Specific objectives or hypotheses	Study aims - 11		
18         19         20         21         22         23         24         25         26         27         28         29         30         31         32         33         34         35         36	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, facted as single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploration)	Study design - 12		
	<sup>2</sup> <sub>3</sub> Methods: Participants, interventions, and outcomes					
	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of gountries 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		
37 38 39 40 41	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-17		
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	2		

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1 2		11b	Criteria for discontinuing or modifying allocated interventions for a given trial partie patt (eg, drug dose change in response to harms, participant request, or improving/worsening diseas	Eligibility and screening 13-14
3 4 5 6 7 8 9 10 11		11c	Strategies to improve adherence to intervention protocols, and any procedures for the modification of the second s	17 (Controls) 15-17 (Exercise interventions) 11 (Dissemination of results to participants)
12 13 14		11d	Relevant concomitant care and interventions that are permitted or prohibited durine trial	Eligibility and screening 13-14
15 16 17 18 19 20 21 22 23 24 25	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variation of aggregation (eg, pressure), analysis metric (eg, change from baseline, final value, time to event), near of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical restriction of	Primary outcome – 17; Secondary outcomes – 17-25; Data analyses – 28-29; Explanation for clinical relevance (Introduction) – 7-9
26 27 28 29	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), the set sments, and visits for participants. A schematic diagram is highly recommended (see Figure)	CONSORT (Figure 1); Study design - 12
30 31 32	Sample size	14	Estimated number of participants needed to achieve study objectives and how it vas certains certains clinical and statistical assumptions supporting any sample size calculations	Sample size calculation – 12-13
33 34 35	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Recruitment - 13
36 37	Methods: Assignme	ent of i	nterventions (for controlled trials)	
38 39 40 41	Allocation:		liographiqu	
42 43 44 45 46			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	3

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1 2 3 4 5	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random rainbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any (eg, blocking) should be provided in a separate document that is unavailable to the set who enrol participants or assign interventions	Randomisation and allocation – 14-15		
6 7 8 9 10 11	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentized) in the sequence until i	Randomisation and allocation – 14-15; Blinding - 28		
12 13 14 15 16	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will as sign participants to interventions	Randomisation and allocation – 14-15; Blinding - 28		
17 18 19 20 21 22	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		
23 24 25 26 27 28 29 30		17b	If blinded, circumstances under which unblinding is permissible, and procedure for recealing a participant's allocated intervention during the trial	Randomisation and allocation – 14-15; Blinding – 28; Study limitations - 32		
31 32	Methods: Data coll	ection,	management, and analysis			
<ol> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> </ol>	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		
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	4		

		BMJ Open Sy Sp B	Page
	18b	Plans to promote participant retention and complete follow-up, including list of an your come data to be collected for participants who discontinue or deviate from intervention protocols including of the second s	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 by promote data quality (eg, double data entry; range checks for data values). Reference to where details and the 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 ថ្នាំអ៊ីទី 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 rando	Data analyses – 28-29
Methods: Monitorin	ng	inin ç	
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
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	Ę

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1 2 3 4 5	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneous by ported adverse events and other unintended effects of trial interventions or trial conduct	Ethics and dissemination – 10-11; Study limitations - 32
6 7 8 9 10 11	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
12 13	Ethics and dissemi	nation	o text Sul	
14 15 16 17 18	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB)	Ethics and dissemination – 10-11
19 20 21 22	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility creteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
23 24 25 26	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
27 28 29 30		26b	Additional consent provisions for collection and use of participant data and biologinal specimens in ancillary studies, if applicable	N/A
31 32 33 34	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
35 36 37 38 39 40 41 42	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Competing interests and funding acknowledgement s - 33
43 44 45			For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6

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		BMJ Open by j. G ge	Page 58 c
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contract and 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 ឆ្នាំhoនៃuffer harm from trial participation	Ethics and dissemination – 10-11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, here is are professionals, the public, and other relevant groups (eg, via publication, reporting in results 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 datas	Dissemination of results – 11; Data set access - 28
Appendices		ning, a	
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 the current trial and for future use in ancillary studies, if applicable	N/A
*It is strongly recomm Amendments to the p " <u>Attribution-NonComr</u>	nended protocol <u>mercial</u>	that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarific I should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative C -NoDerivs 3.0 Unported" license.	ation on the items. ommons 7
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# **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

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-014951.R3
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<b>Primary Subject Heading</b> :	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Impact, Isometric exercise, Osteoporosis, Resistance training, Men



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11	4	The LIFTMOR–M (Lifting Intervention For Training Muscle and Osteoporosis Rehabilitation
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13	5	for Men) trial: Protocol for a semi-randomised controlled trial of supervised targeted exercise
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15	6	to reduce risk of osteoporotic fracture in older men with low bone mass
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23	29	6894 (1 Figure; 1 Table; 57 References)
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30	30	Impact: Isometric eversise: Mon: Osteonorosis: Resistance training
31	52	impact, isometric exercise, men, Osteoporosis, Resistance training.
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ABSTRACT

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

#### 46 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.

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# 60 Discussion

61 Whether a high-load, low-repetition progressive resistance training plus impact loading

- 62 program or a machine-based isometric exercise program can improve determinants of
- 63 fracture risk, without causing injury, has not been examined in men. Determination of the
- 64 efficacy, safety and acceptability of such programs will facilitate formulation of future
- 65 exercise guidelines for older men with low bone mass at risk of fragility fracture, a group who
- 66 have previously been underrepresented.

68	Ethics and dissemination
69	Participant confidentiality will be maintained with publication of results. The study has been
70	granted ethical approval from the Griffith University Human Research Ethics Committee
71	(Protocol number AHS/07/14/HREC).
72	
73	Trial registration number
74	Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)
75	ANZCTR12616000344493; Pre-results.
76	
77	Date and version identifier
78	Original protocol manuscript for submission (Version 1): November 2016.
79	Protocol manuscript for submission (Version 2) with revisions from peer review: December
80	2016
81	Protocol manuscript for submission (Version 3) with revisions from peer review: February
82	2017

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2 3	83	Protocol manuscript for submission (Version 4) with revisions from peer review: March 2017
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#### 87 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<sup>™</sup> 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.
- 96 The engagement of a non-randomised control group of demographically-matched
  97 men who have elected not to exercise for eight months is a design limitation that was
  98 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.

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103	INTRODUCTION
104	Epidemiological data indicates the global prevalence of osteoporosis to be over 200
105	million,[1] with around 1.2 million Australians,[2] 10.2 million Americans [3] and 15 million
106	European men and women over fifty years of age being affected.[4] It has been suggested
107	that 285,000 Australian men aged over fifty will be diagnosed as osteoporotic, and a further
108	2.48 million older men diagnosed as osteopenic by 2022.[5] With the aging of the
109	population, there will undoubtedly be a corresponding increasing prevalence of low bone
110	mass and consequent increase in the incidence of low trauma fracture.[6]
111	It is widely accepted that bone adapts to the mechanical loads it habitually experiences.
112	Experimental data from animal models has revealed the most influential loading
113	characteristics for osteogenesis are magnitude, [7,8] rate [9] and frequency [10-12] of the
114	engendered strain. Evidence also indicates dynamic loading is more osteogenic than static
115	loading.[13] The optimal exercise prescription for the prevention and management of
116	osteopenia and osteoporosis would therefore ideally impose dynamic, high magnitude loads
117	applied at a rapid rate. High-load resistance training with high-impact jumping, the
118	combination of which will elicit high strains and strain rates in bone, is thus theoretically the
119	optimal exercise protocol for bone. Although such exercise is considered safe for healthy
120	individuals with normal bone mass, it is unclear whether it will be safe for individuals with
121	reduced bone mass who are at increased risk of fracture. Previous resistance exercise
122	recommendations for individuals with low bone mass, particularly those who have
123	experienced a low trauma fracture, include 8 to 12 repetitions, which represents a moderate
124	level of intensity,[14,15] based on a lack of quality evidence that high intensity resistance
125	training is safe and effective.
126	Recently a bone-targeted, high intensity, progressive resistance training and impact loading
127	(HiRIT) exercise program was undertaken with post-menopausal women with low to very low
128	bone mass at the hip or spine - the LIFTMOR (Lifting Intervention For Training Muscle and

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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<sup>™</sup> 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<sup>™</sup> 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  $(14.9 \pm 11.5 \%)$  and spine  $(16.6 \pm 12.2 \%)$  – 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

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156	intake or physical activity, lack of control group, lack of disclosure of simultaneous bone
157	medications, and the fact that follow-up DXA scans were conducted sixty days after the
158	intervention was completed suggests that a more rigorous examination of efficacy of
159	bioDensity™ training is indicated.
400	
160	Short-duration (thirty minute), twice-weekly therapeutic exercise programs for older men with
161	low bone mass, such as the proposed HiRIT and bioDensity™ training protocols, provide an
162	attractive alternative to more burdensome and time consuming programs typically
163	recommended for osteoporosis. Indeed, trials examining the influence of progressive
164	resistance training, hopping/jumping or multicomponent programs on bone health in men
165	have adopted session frequencies of three, [23-28] four, [29] or even seven [30] per week.
166	Hinton and colleagues [28] compared thrice-weekly sessions of jump training with twice-
167	weekly sessions of periodised progressive resistance training; however, healthy physically
168	active men aged 25 to 60 years were recruited. Whether high-load, low-volume training
169	methods can safely improve bone strength in older men with low bone mass remains a
170	knowledge gap. Thus, the Griffith University Bone Densitometry Research Laboratory has
171	acquired a bioDensity™ device for the purposes of examining safety and efficacy alongside
172	the HiRIT protocol in a semi-randomised controlled trial design.
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#### 175 Ethics and dissemination

176 The study has been granted ethical approval from the Griffith University Human Research

177 Ethics Committee (GUHREC; Protocol number AHS/07/14/HREC), and all research activities

178 will be conducted in accordance with the *Declaration of Helsinki*. The study is also

179 registered with the Australian New Zealand Clinical Trials Registry (Trial number

180 ANZCTR12616000344493). Written informed consent will be obtained from all participants

181 prior to testing by the investigator performing baseline assessments.

182 Pilot men's data (Protocol number AHS/07/14/HREC) and the LIFTMOR for women trial [16] 183 (Protocol number AHS/07/14/HREC; Trial number ACTRN12616000475448) provide 184 evidence of an extremely low risk of injuries from the current exercise protocols, with no 185 severe injuries reported from a total of 7300 training sessions. Similar to the current 186 protocol, ethical approval was granted by the GUHREC for both studies, and written 187 informed consent was obtained from all participants. Strategies were in place to reduce the 188 risk of injuries or adverse events occurring during the aforementioned trials, and included: 1) 189 full supervision of high-load resistance training sessions by a qualified exercise scientist; 2) 190 small group sizes in the supervised training sessions; 3) an initial familiarisation period 191 during which low-load exercise variants focused on proper lifting technique was 192 implemented, and 4) weight lifted was progressively increased with training exposure. In 193 order to monitor safety, participants were required to complete training diaries at every 194 training session to record illnesses, falls, fractures, injuries, and muscle soreness. Early 195 termination of the trial is therefore exceedingly unlikely, and for this reason a Data Safety 196 Monitoring Board was not engaged. Instead, data will be monitored via compulsory annual 197 progress reports to the GUHREC. Any adverse events which occur between annual reports 198 will be reported independently to the GUHREC, in compliance with the Australian Code for 199 the Responsible Conduct of Research developed by the National Health and Medical 200 Research Council, and the University Code for the Responsible Conduct of Research. The

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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.

#### 216 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<sup>™</sup> 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<sup>™</sup> 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. BMJ Open: first published as 10.1136/bmjopen-2016-014951 on 12 June 2017. Downloaded from http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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:	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
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study) FN BMD mean of 0.790 g/cm<sup>2</sup> and standard deviation of 0.061 g/cm<sup>2</sup>, we determined a sample size of 54 is required to detect the minimum change difference of 0.033 g/cm<sup>2</sup> from a two-tailed test with a power of 80 % and  $\alpha$  = 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.

260

261 Setting and recruitment

262 Baseline and follow-up assessments will be conducted in the Bone Densitometry Research 263 Laboratory, School of Allied Health Sciences, Griffith University, Gold Coast campus, 264 Queensland, Australia. All supervised training sessions will be conducted in the Strength 265 Training Research Facility, co-located in the School of Allied Health Sciences. Both 266 measurements and interventions will be conducted at this single location. Methods of 267 recruitment include local media outlets (print media and radio), social media, official website 268 (www.liftmor.org), word of mouth, and notice board flyer advertisement at local lawn bowls 269 clubs, golf clubs and senior citizens clubs.

270

#### 271 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);

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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.

## 297 Randomisation and allocation

Allocation of eligible participants to the supervised HiRIT and bioDensity<sup>™</sup> 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 17<sup>th</sup> 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

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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

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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.

339 Machine-based isometric exercise program

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

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2 3	356		
4 5 6	357	Control group activities	
7	358	The sex- and age-matched control group will be encouraged to maintain their customary	
9 10	359	physical activity and dietary patterns over the eight month duration of the study. To monite	or
11 12	360	deviations from their usual lifestyle, diaries will be issued, in which they will be instructed to	0
13 14	361	list variations to their physical activity level and diet on a fortnightly basis. Space is also	
15 16	362	provided to record any illnesses, falls, fractures, changes to their medical conditions and	
17 18	363	medications (inclusive of over the counter medications), and injuries other than muscle	
19 20	364	soreness. Diaries are to be returned at follow-up. Fortnightly emails will act as reminders	to
20 21 22	365	complete diary entries, with a monthly email requiring a reply to the investigator to prompt	
23 24	366	recording of any relevant changes. To detect change in bone-relevant physical activity or	
25 26	367	dietary calcium intake over the course of the eight-month study, participants will complete	
20 27 28	368	questionnaires (described below) at baseline and follow-up.	
20 29 20			
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32 33	370	Outcome measures	
34 35 26	371	All outcome measures will be performed at baseline and eight-month follow-up by a single	•
36 37	372	investigator who is not blind to group allocation, using identical facilities, procedures and	
38 39	373	equipment. A summary of outcome measures is presented in Table 1.	
40 41	074	Drimen contenne	
42 43	374	Primary outcome	
44 45	375	The primary outcome will be change in DXA-derived FN areal BMD (Medix DR, Medilink,	
46 47	376	France).	
48 49	277	Secondary outcomes	
50 51	511	Secondary outcomes	
52 53	378	Secondary outcomes (described in more detail below) will include: changes in	
54 55	379	anthropometrics, as well as in whole body and regional measures of bone, muscle and fat	
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Kyphosis will be examined in order to track angular changes of the spine with exercise exposure. Vertebral fracture assessment using the Genant semiguantitative 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.

391 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

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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<sup>3</sup> and peel mode 4 at 650 mg/cm<sup>3</sup>, 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<sup>3</sup> 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<sup>3</sup> 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<sup>3</sup> and peel mode 4 at 650 mg/cm<sup>3</sup>, 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<sup>3</sup> 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<sup>3</sup> 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).

432 Anthropometrics and body composition

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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<sup>2</sup>; kg/m<sup>2</sup>). 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.

445 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

deformity.

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vertebral body are used to grade (mild, moderate or severe)

wedge, biconcave or crush	Open: first published
and dynamic balance.[41] <i>v</i> ithout using their hands for	as 10.1136/ Protectec
ance of three meters away,	omjop I by c
ill be timed from the point at	oen-20 opyrig
hen they return to the start and	16-014951 on 12 June Ens ht, including for uses
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ncorporated a yardstick) will be as an important component of cular to a Perspex board rm located nearest the board d forming a fist. The participant hip, maintaining a fixed base of t makes contact with the e repeated. The start and finish	m http://bmjopen.bmj.com/ on June 13, 2025 at Agence Bibli ABES) . a mining, Al training, and similar technologies.
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Timed up-and-go The timed up-and-go test is a measure of functional mobility, Participants will be instructed to rise from a seated position w assistance, walk at a brisk pace to a mark on the floor a dista pivot, and return to assume the start position. Participants wi which their back no longer makes contact with the chair, to w adopt the correct seated position. Five-times sit-to-stand The five-times sit-to-stand is a reliable assessment of the abi seated position, with relevance to functional mobility, dynamic muscle strength.[42] Participants will be asked to move from without the use of their arms, for five repetitions following the and colleagues for assessing older adults.[43] Functional reach A modified version of the original functional reach test (that in used to assess dynamic balance, which has been identified a falls risk.[44] Participants will stand with shoulders perpendic marked with vertical measurement lines, with the dominant an and extended forwards to 90 ° shoulder flexion, with the hand will be instructed to reach forward by flexing the trunk at the h support, without stepping or losing balance. If the participant Perspex board, takes a step or loses balance, the trial will be

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483 positions of the third metacarpal in respect to the measurement lines will be recorded to484 determine displacement.

485 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 takeoff phase according to the method described by Linthorne.[45]

492 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

506 will be positioned midway between two vertical wall-mounted anchor rails, with their back

507 and heels against the wall. An inelastic belt between the two rails will be fastened

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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]

515 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).

523 Bone-specific physical activity

524 The Bone-specific Physical Activity Questionnaire (BPAQ) [48] will be used to quantify 525 current and historical physical activity of relevance to bone. Respondents will list all regular. 526 structured physical activity and years of participation, with a minimum of investigator 527 assistance. BPAQ scores will be calculated using an on-line, custom-designed analysis 528 program (http://www.fithdysign.com/BPAQ/). Mathematical algorithms in the calculator were 529 developed using load ratings from vertical ground reaction forces of each activity, 530 participation frequency, years of involvement and an age-weighting factor. High loading 531 ratings represent high-impact activities, whilst the age-weighting factor reflects higher 532 mechanosensitivity to physical activity during youth. Previous research has found BPAQ

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533 scores are predictive of variance in DXA-derived bone strength parameters at clinically

534 relevant sites in healthy middle-aged and older men.[49] This instrument has high reliability,

535 with intra-class correlation coefficients of 0.92 to 0.97.[50]

536 Barriers and facilitators

537 The Physical Activity Enjoyment Scale (PACES), designed by Mullen and colleagues.[51] is 538 a self-reported eight-item questionnaire which uses a seven-point Likert scale for each item. 539 The respondent is required to circle the number corresponding to their current thoughts 540 about physical activity. Higher PACES scores indicate a greater level of exercise appeal. 541 Inclusion of this instrument was based on physical activity enjoyment being identified as a 542 potential determinant of exercise adherence.[52] Semi-structured interviews to determine 543 exercise appeal, barriers and facilitators to participation in HiRIT or bioDensity<sup>™</sup> training 544 programs will be conducted within one month of completing the eight-month intervention by 545 an independent investigator. Interviews will be tape-recorded with participant consent, and 546 transcribed verbatim. Interview transcripts will be thematically coded using NVivo qualitative 547 software (Version 10, QRS International Pty Ltd) to determine barriers and facilitators to 548 participation in higher-intensity, bone-targeted exercise.

549 Quality of life

550 The World Health Organisation Quality of Life questionnaire was developed to assess four 551 quality of life domains using a five-point Likert interval scale.[53] Higher scores are 552 indicative of higher quality of life. Participants will self-complete the questionnaire. Internal 553 consistency across a large heterogeneous population from a field trial during its 554 development showed each domain to have moderate to high Cronbach's  $\alpha$  levels; physical 555 health ( $\alpha = 0.82$ ), psychological health ( $\alpha = 0.81$ ), social relationships ( $\alpha = 0.68$ ), and 556 environment ( $\alpha = 0.80$ ).[54]

557 Safety and compliance

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Prior to each training session participants will rate their level of muscle soreness on a tenpoint 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.

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Variables	Data collection method
Primary outcome measure	
Femoral neck aBMD	Proximal femur DXA scan (Me 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, Medili 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 (Me DR, Medilink, France), 3D hip software (DMS Group, Maugu France)
Calcaneal broadband ultrasound attenuation, speed of sound and stiffness index	Calcaneal QUS (Lunar Achille 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, leg 4 %, 14 %, 38 % and 66 % pQCT scans (XCT-3000, Stra Medizintechnik GmbH, Pforzh Germany)
Anthropometry Height	Wall mounted stadiometer (M 216; Seca, Hamburg, Germar
Weight	Mechanical beam scale (Mode Seca, Hamburg, Germany)
Waist circumference	Steel tape (Model W606PM; L Executive Thinline, Apex, USA
Body composition	
Lean mass, fat mass, appendicular lean mass and percent body fat	Whole body DXA scan (Medix 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,
	Vertebral fracture assessment	France) Lateral de cubitus thoracolumbar spine DXA (Medix DR, Medilink, France)
	Eunctional performance	Trance,
	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
	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
67 68 69 70	aBMD, areal bone mineral density; BMC, bone mineral content; BPAQ, Bone-specific Physical Activity Questionnaire; DXA, Dual-energy X-Ray Absorptiometry; PACES, Phys Activity Enjoyment Scale; pQCT, peripheral Quantitative Computed Tomography; vBMD volumetric bone mineral density; WHOQOL, World Health Organisation Quality of Life.	
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# 573 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.

## 586 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.

595 Data analyses

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

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599	biometric and dependent variables will be presented as means $\pm$ standard deviations and
600	frequencies where appropriate. Between-group comparisons of descriptive statistics at
601	baseline will be evaluated using Analysis of Variance (ANOVA) for normally distributed
602	continuous data, non-parametric equivalents for non-normally distributed data (Kruskal-
603	Wallis one-way ANOVA), and Chi-Square for categorical data. Between-group comparis
604	for outcome measures will be examined using repeated measures Analysis of Covarianc
605	(RMANCOVA) for group, time and group-by-time interaction effects using raw baseline a
606	follow-up data, adjusting for age, initial weight, calcium intake and baseline values.
607	Secondary exploratory RMANCOVA analyses adjusting for age, initial weight, calcium
608	intake, baseline values, and training program compliance will be performed. In accordan
609	with the principles of a classic intention-to-treat approach, all randomised participants wil
610	included in the final analyses, regardless of withdrawal or compliance. In the case of
611	missing follow-up data due to study withdrawal, imputation of the mean percentage chan
612	value for the specific group will be employed. Per-protocol exploratory analyses will be
613	performed comparing outcome measures between the HiRIT, bioDensity™ and control
614	groups for those with training program compliance of greater than 70 % to examine
615	maximum treatment efficacy. Multiple linear regression analyses of absolute change from
616	baseline will be employed to examine the relative influence of certain variables, found to
617	significantly correlate with outcomes measures, on the bone response. Statistical
618	significance will be set at $p \le 0.05$ .
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p data, adjusting for age, initial weight, calcium intake and baseline values.
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620 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<sup>™</sup> 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. Kukulian and co-workers [26] examined the influence of twelve-months progressive

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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<sup>™</sup>
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.

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#### 667 Limitations

668 Several limitations warrant discussion. First, due to the somewhat unorthodox semi-669 randomised study design, there exists the possibility of self-selection bias. Pilot testing 670 demonstrated a lack of feasibility for a fully randomised design based on an unwillingness of 671 older male study volunteers to adhere to a control requirement to refrain from exercise for 672 eight months. When volunteering under the premise of receiving an exercise program, we 673 argue that there are also ethical issues of withholding exercise from individuals who wish to 674 take it up. We have attempted to minimise the risk by applying uniform inclusion and 675 exclusion criteria for all study participants, with the exception of a willingness to participate in 676 an eight-month exercise intervention. The extent to which the self-selected control group 677 differs from the intervention groups will be determined and reported in the course of 678 descriptive analyses of baseline data. Any differences will be accounted for by adjusting for 679 baseline values in the final analyses. Second, the current trial is not powered to detect 680 significant differences in fractures as safety (adverse events and injuries) is a secondary 681 outcome. Nevertheless, reporting adverse events and injuries is informative when 682 determining if an exercise program can be translated to clinical practice. Third, the outcome 683 assessor will not be blind to group allocation, will deliver the intervention, and will be 684 responsible for documenting adverse events and reporting to the GUHREC. Participants will 685 be instructed to report even the slightest degree of discomfort/pain/muscle soreness or 686 injury, and a protocol is in place for independent review by a gualified Physiotherapist or 687 General Practitioner, as required. It is also an ethical requirement to report such events to 688 the GUHREC, and harms or unintended events must be included when reporting 689 randomised controlled trials (CONSORT guidelines). Failure to promptly report any adverse 690 event would contravene both Institutional and National research ethics guidelines. A blinded 691 outcome assessor is beyond the means of this unfunded project, and therefore our current 692 study design has been adopted out of necessity.

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696	heavy resistance training program implemented in the LIFTMOR trial.
697	Author Contributions
698	Conception and design of the study: ATH, BKW, SLW, BRB; Obtained the equipment a
699	brokered by Osteoporosis Australia: BRB; Manuscript preparation and editing the final
700	for submission: ATH, BKW, SLW, BRB; Preparation of Information Sheets, Consent Fo
701	and Case Report Forms: ATH, BKW, SLW, BRB; Participant recruitment and data colle
702	ATH; Principle investigator: BRB.
703	Competing Interests
704	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
- uval fi. LHSU7/14/HL L Clinical Trials Regis. 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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# 893 Figure legend

894 Figure 1. Proposed participant flow (CONSORT diagram)

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

