Build better bones with exercise (B3E Pilot Trial): results of a feasibility study of a multicenter randomized controlled trial of 12 months of home exercise in older women with vertebral fracture

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Abstract

Purpose: Osteoporotic fragility fractures create a substantial human and economic burden. There have been calls for a large randomized controlled trial examining the effect of exercise on fracture incidence. The B3E pilot trial was designed to evaluate the feasibility of a large trial examining the effects of home exercise on individuals at high risk of fracture.

Methods: Community-dwelling women ≥65 years with radiographically-confirmed vertebral compression fractures were recruited at seven sites in Canada and Australia. We randomized participants in a 1:1 ratio to a 12-month home exercise program or equal attention control group, both delivered by a physiotherapist (PT). Participants received six PT home visits in addition to monthly phone calls from the PT and a blinded research assistant. The primary feasibility outcomes of the study were recruitment rate (20 per site in 1 year), retention rate (75% completion), and intervention adherence rate (60% of weeks meeting exercise goals). Secondary outcomes included falls, fractures and adverse events.

Results: 141 participants were recruited; an average of 20 per site, though most sites took longer than anticipated. Retention and adherence met the criteria for success: 92% of participants completed the study; average adherence was 66%. The intervention group did not differ significantly in the number of falls or fractures compared to the control group. There were 18 serious adverse events in the intervention group and 12 in the control group.

Conclusion: Recruitment was a challenge and future trials should consider expanding the inclusion criteria, alternative study designs or other recruitment strategies.

Mini-Abstract

We pilot-tested a trial of home exercise on individuals with osteoporosis and spine fracture.

Our target enrollment was met, though it took longer than expected. Participants stayed in the study and completed the exercise program with no safety concerns.

Future trials should expand the inclusion criteria and consider other changes.

Vertebral fractures are a common, and often painful, consequence of osteoporosis. [1] One woman in five who have a vertebral fracture will have another fracture within a year while the risk of death in the year after a fracture has a nearly four-fold increase.[2, 3] Osteoporosis management guidelines recommend exercise for individuals with osteoporosis, including those at high risk, such as those with vertebral fractures.[4–6] However, the evidence regarding both the risks and benefits of exercise in individuals at high risk is limited, and no randomized controlled trials (RCTs) of exercise have had fractures as a primary endpoint.[7]

Much of the evidence to date regarding the effects of exercise on fracture risk has been indirect in that it examined surrogate outcomes (e.g., falls, bone mineral density [BMD]) or was conducted in lower risk populations (e.g., postmenopausal women with no history of fracture).[8] Meta-analyses have demonstrated a small benefit of exercise for BMD, but trial heterogeneity may influence the conclusions.[9–13] In particular, estimates of effect change when analyses are performed by exercise type[12]: Exercises that challenge balance can prevent falls by 20-40%[14], but generalizability to people with vertebral fractures is unclear. Excessive kyphosis, pain, and altered trunk muscle control can affect adherence to and efficacy of exercise and contribute to falls or fracture risk.[15, 16] Alterations in posture and spine loading can increase the risk of vertebral fracture without a fall.[16, 17]

There are limited data from which to develop direct inferences about the efficacy and safety of exercise for high-risk individuals, in whom unsupervised exercise may possibly increase fracture risk. Fractures and injuries attributable to exercise in patients with hip and vertebral fractures have been reported.[18–21] Adverse events are more frequently reported in exercise trials of individuals with health conditions and functional limitations.[22] In a recently-updated Cochrane

review,[7] only 8 trials evaluated the efficacy of exercise after vertebral fracture; many trials were subject to bias and were underpowered, and few trials had long-term follow-up. There are limited data from which to develop exercise recommendations for people with vertebral fractures, and an RCT is needed to determine whether exercise does more good than harm.

There have been calls for a large RCT examining the effect of exercise on fracture incidence.[11, 23] Although several meta-analyses have attempted to estimate the effects of exercise on fracture risk, the estimates often have wide confidence intervals or are driven by underpowered studies.[12, 24–26] However, such a trial would require a large sample size, and a commensurate number of enrolling sites, to reliably detect benefit or harm of exercise for fracture prevention.[11] To reduce the required sample size, individuals at high risk for fracture should be studied. Indeed, trials of osteoporosis medication often study women with vertebral fractures.[4] Furthermore, it is in individuals at high risk for fracture that the question of whether exercise does more good than harm is most relevant. Given the magnitude of resources required to conduct a definitive RCT in to address this question, we designed a pilot RCT to determine the feasibility of a RCT examining the efficacy and safety of exercise for reducing fractures in individuals with existing vertebral fractures.

Methods

Study Design

The full protocol for this two-arm, 1:1 pilot multi-centre, international, single-blinded parallel RCT has been previously described [27] (ClinicalTrials.gov registration NCT01761084). Briefly, the Build Better Bones with Exercise (B3E) trial recruited community-dwelling women over the age of 65 years with at least one radiographically-confirmed vertebral compression fracture of Genant [28] Grade II or higher who were randomized via computer algorithm, using permuted

block sizes of two or four, into either the exercise intervention or an attention control group. Individuals presenting with clinical fractures were sent for confirmation of the presence of a radiographic fracture. Eight enrolling centres were originally planned to include heterogeneity in city population, structure, services, presence of a medical school, and other variables. However, one site closed prior to enrollment as the local site lead investigator left the centre and there was no available replacement, leaving five Canadian and two Australian sites. The University of Waterloo site served as the coordinating centre. Participants were enrolled through primary care or specialist osteoporosis clinics, to best identify individuals with vertebral fractures, and avoid a high screen failure rate. We advertised the study via the Canadian Osteoporosis Patient Network or other mailing lists.

Participants completed outcome assessment at baseline and 12 months, administered by a blinded research assistant (RA) at a research facility, though home visits occasionally were necessary. The blinded RA called participants monthly to query about falls, fractures or adverse events. To limit unblinding of site RAs, physical activity-related questionnaires, and mid-point and endpoint interviews were conducted by an unblinded RA who was otherwise not involved in participant recruitment or assessments. Participants were instructed to complete daily diaries (mailed monthly) to record physical activity, falls and health-related events.[29] Study sites received a written study protocol and videos of the assessments being performed by an experienced researcher. In-person training was provided for Canadian sites. All participants gave their informed, written consent and the study was approved by the research ethics board of each enrolling centre.

Participants

Individuals were eligible if they were: female; ≥65 years of age; and had radiographic evidence of non-traumatic fracture of ≥1 vertebrae between T4 and L4 (defined as radiographic presence of ≥25% reduction in anterior, middle, or posterior height of a vertebra, centrally-adjudicated by the study radiologist from lateral thoracic and lumbar spine X-rays using the Genant method).[30] The exclusion criteria included: index vertebral fracture due to trauma; medical disorder likely to prevent study completion or preventing exercise participation; exercise participation ≥3 times per week that addresses ≥2 of 5 domains in the B3E exercise prescription [27] ; impaired capacity to give informed consent (e.g., known or suspected cognitive impairment); inability to communicate in English; unable to stand or walk 10m with or without a walking/mobility aid; or contraindication to exercise as determined by a physician.[27] Males were not included in the pilot because we were concerned about the need to stratify by sex, and the potential for strata with low numbers. Two sites recorded if the males they screened would have been eligible for the trial otherwise, to determine the potential sample for a future trial.

Over the course of the trial, the exclusion criteria of no history of cancer and the limit of impaired ability to give informed consent were adjusted. The cancer criterion was revised to no history of cancer in the past five years (excluding basal cell carcinoma) and required physician approval. We used the Mini-Cog to screen for cognitive impairment [31] but then revised the criterion such that those who failed Mini-Cog screening were asked to reiterate the purpose of the study and what they were being asked to do in the study and, if able to do so accurately, were considered able to give informed consent.

Intervention/Control Activities

The home exercise intervention has been described in detail, and included resistance, balance and posture exercises, and encouragement to perform daily moderate to vigorous aerobic physical activity for a minimum of 30 minutes.[27] Both groups received six home visits from a physiotherapist (PT) over the course of the 12-month study; the exercise group received instruction on exercise and the attention control group discussed health-related topics (excluding exercise). The PT also called participants monthly for social discussion with control participants, and to address safety, adherence, and exercise progression in the intervention group.[27] The PTs were instructed to prescribe a minimum of 5-8 exercises to start, and a minimum of 2 sets of 8-10 repetitions maximum (or isometric holds for 3-5 seconds if applicable), and progressively increase the volume or intensity over time. Exercise domains included: lower extremity strengthening (e.g., sit/stand or squat, lunges, step-ups), upper extremity strengthening (e.g., wall/floor pushups, tubing pulldowns, upright rows), balance exercises (e.g., single leg balance, tandem stance or tandem walk, walking on toes), and posture/core exercises (e.g., planks, thoracic/lumbar extension using bird-dog, or in supine).

Outcome Measures

The primary outcomes of the study reflected feasibility of a larger trial. Feasibility outcomes were: the number of participants recruited, the number of participants retained until study completion, and the proportion of participants who adhered to strength and balance exercises [27].

A Priori Criteria for success

Recruitment was considered feasible if at least twenty participants per site were recruited.[27] Retention was considered feasible if at least 75% of the sample completed the final study visit at

12 months (partial visit completion was acceptable). Adherence was defined as completing strength or balance exercises at least three days per each complete seven-day epoch in their daily diaries. The *a priori* criterion for success was defined as at least 60% adherence to strength and balance exercises three times weekly.[27] The daily diaries were one-page recording sheets designed like a weekly calendar, with a column for each date with a box for participants to record each of the following:

1) Did you fall today? (yes/no checkboxes);

2) Did you do any exercise today? If no, move to #3. If yes - How many minutes of aerobic exercise? On a 0-10 scale, how hard was it? Did you do strengthening or balance exercises today? How many strength or balance exercises did you do?

3) Did you take: osteoporosis medication? vitamin D? (yes/no checkboxes)

4) Did you receive health care e.g., see a doctor or health care worker, or have any tests done? (yes/no checkbox). If yes, what type of doctor, therapist or test? e.g., family doctor, specialist, physical therapist, nurse, home care worker, MRI, blood test, X-ray. If yes, what was the reason for your test or visit? E.g. check-up, for arthritis, need help with meals, test for iron levels.

Incident fracture was a composite outcome of any fragility fracture (i.e., nontraumatic vertebral, hip, or other nonvertebral fracture, excluding skull, ankle, feet, or fingers). Questionnaires were used to ascertain fracture cause and timing. Each reported non-vertebral fracture was assessed independently by two blinded investigators to confirm whether they were fragility fractures. Lateral thoracic and lumbar spine X-rays were performed at baseline and follow-up and were read centrally by the blinded study radiologist.

A fall was defined as "an unexpected event in which the participant comes to rest on the ground, floor, or other lower level."[32] Falls were assessed retrospectively at baseline by self-report of falls in the previous twelve months and prospectively through a daily diary and probing during the monthly calls. Prospective falls were counted if they were reported on the diary, or reported during the monthly calls if it was not within one week of a fall reported in the diary.

Participants were instructed to report adverse events or injuries, and were asked about them during monthly calls. Three types of adverse events represent secondary outcomes: 1) serious adverse events (SAE, Health Canada definition: death or event that is life-threatening, requires hospitalization, or results in disability); 2) events linked to intervention; and 3) events leading to study withdrawal or intervention cessation. The RA confirmed the event date, circumstances, and associated health service use and reported them to the ethics boards as necessary. Secondary outcomes will be reported elsewhere, and included measures of physical function , occiput to wall distance, quality of life, fear of falling, pain, behaviour change questionnaires, the intervention cost, and health resource utilization.[27]

Statistical Analysis

Descriptive data are presented as mean and standard deviation for continuous data, and count and percent for categorical data. Recruitment rates were defined as the total number of participants randomized at a site over the number of months a site was actively recruiting. Retention was the count of participants that did not withdraw from the study. No imputation of missing feasibility data was performed. For the primary outcomes, only data on adherence was missing. A sensitivity analysis was performed on adherence data, where weekly adherence was calculated per participant for months 1-11 due to reduced response rate during month 12, including weeks with sufficient data to infer adherence or lack of adherence. A negative binomial regression

accounting for number of observations per participant was used to model the total number of falls per group, to explore whether there were fewer falls in the intervention group than the control group. The relative risk of being a participant who fell in the intervention group was also computed. All statistical analyses were conducted using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

Results

Participant Characteristics

There were 2822 older adults screened for eligibility, mostly at specialist clinics or primary care offices (Figure 1). Of these, 180 passed initial screening and 176 consented to participate. Twenty participants failed the Mini-Cog but could recall relevant details about the study and so were included, though one withdrew prior to randomization for other reasons. Sixteen consenting participants did not go on to complete a baseline assessment or randomization: 11 did not have a qualifying fracture on X-ray, including one with ankylosing spondylitis; and five withdrew consent due to a change in their health status or that of their spouse. After baseline assessment, 16 were deemed to be ineligible: 13 did not have a qualifying fracture on X-ray; two failed the Mini-Cog and were unable to correctly answer questions about the study; one fractured her ankle prior to randomization, which resulted in her no longer meeting the mobility criterion; and three participants withdrew consent prior to randomization (two due to a health decline in the participant or their spouse, and one who did not wish to complete the study X-ray). 141 participants were randomized between September 2013 and December 2015, with 71 being allocated to intervention and 70 to control (Table 1). Three participants (one intervention and two control) revealed their group allocation to the RA despite instruction not to do so. Eleven participants (8%, five intervention, six control) withdrew from the study. Nine withdrew consent

(five intervention, four control) and two (controls) had a change in health that resulted in their choosing to withdraw: one experienced cognitive decline and the other developed a cardiac condition and was prescribed an alternate exercise program by her physician. 130 completed the study. No participants who withdrew from the study opted to withdraw their data.

Recruitment

We randomized 141 participants at 7 sites, or just over 20 participants per site, on average (Table 2), with an average of 1.37 participants randomized per month per site. Initially, we had planned to recruit 160 participants at eight sites but a site investigator changed affiliations prior to starting recruitment, leaving only seven enrolling sites. Some sites did not meet the target 20 participants or took much longer than anticipated, while others successfully over-enrolled in the target timeframe. The main drivers of ineligibility, accounting for nearly three-quarters of ineligible screens, were no suspected vertebral fracture, being too young, and being male (Fig. 1). Reasons for declining study participation were variable, with the most common being a lack of interest in either the B3E study specifically or research generally, or difficulty contacting the person after they were referred by the physician. There were 345 men screened at these sites, of which 70 (20%) were excluded only on the basis of sex as opposed to meeting other exclusion criteria, though they did not have a study X-ray to confirm reported fractures.

We identified efficient recruitment strategies at two sites. At one site, the osteoporosis clinic nurse at a large regional medical centre was also the site RA. She pre-screened medical records of all patients attending the clinic prior to their visits so they could be recruited while in clinic, rather than referred to the study staff for future contact. Another site with efficient enrollment had an established database of over 11,000 individuals who had indicated an interest in being informed of future studies. The database could be filtered based on the study eligibility criteria.

Other recruitment mechanisms were less successful. An advertisement with the Canadian Osteoporosis Patient Network resulted in few inquiries, and most were already too active to be eligible (eight inquiries resulting in one participant). Letters and flyers to local endocrinologists, bone specialists, diagnostic imaging facilities, and physiotherapists, did not result in any referrals. Some of the Ontario sites appear to have seasonal variation in recruitment, with spring being the most productive season.

Retention

Only eleven participants (8%) withdrew from the study. The most common reasons given for withdrawal were that the participant no longer had the time or desire to participate (7, 5%) or there was a decline in the health of the participant or a close relative (3, 2%). Health changes were unrelated to osteoporosis or the study (e.g. cancer, cognitive decline). An additional nine participants (five intervention, four control) opted out of a portion of the study. Eight (four from each group) chose not to complete the daily diary, four (two from each group) declined monthly calls from the RA, and six (three from each group) discontinued visits and calls from the PT. Only one participant who did not withdraw from the study opted out of the 12-month study visit. An additional four did not have physical performance measured at 12 months (reported elsewhere), and it was not possible to acquire follow-up X-rays for 17 participants. Therefore, our completion rate of 91% was well above the *a priori* criterion for success (75%). Sensitivity analysis examining potential modifiers of retention did not reveal any significant factors. Additionally, 85% of the RA calls and visits were done within the allotted time window, although only 61% of PT calls and visits were conducted within the appropriate timeframe (*a priori* determined as ±2 weeks of the scheduled date). Feedback in semi-structured midpoint and exit interviews revealed that the participants enjoyed the contact with study staff, and sometimes

wished for more frequent in-person PT visits. Control participants reported enjoying the home visits from the PT and having flexibility in choosing health topics of personal interest as opposed to a set curriculum. Some participants reported that they did not enjoy completing the daily diaries, or questionnaires and telephone calls. Intervention participants reported wanting more variability in the exercise program. Many in the control group expressed a desire to have been in the exercise group.

Adherence

The overall adherence was 66%, meeting our *a priori* criterion of 60% adherence to thrice weekly strength and balance exercises. However, adherence to the exercise program and to diary completion decreased over time. The final weeks in the study (close to the final study visit) saw a marked increase in the amount of missing entries (Fig. 2). The control group demonstrated low levels of contamination, with an average of 20% of participants reporting doing any strength or balance exercises at least three times per week over the duration of the study. There was a decrease in diary completion in month 12, which appeared to be due to confusion regarding when to stop and start recording. As a sensitivity analysis, we examined adherence rates over the period from month 1 to month 11, finding 68% adherent using our feasibility criterion definition. Expanding to include inferred adherence levels for incomplete weeks over the same time period, 73% were adherent. Ignoring missing diary entries results in an 88% adherence rate. The sensitivity analysis comparing those with ≥80% adherence in months 1-11 to those with <80% adherence found no significant associations. Furthermore, we examined PT call notes to supplement missing diary weeks (126 weeks from 41 participants). Of these, 71 (57%) seemed likely to be adherent, 49 (39%) seemed unlikely to be adherent, and 5 (4%) did not have enough information to make an assessment.

Falls, Fractures, and Adverse Events

At baseline, there were 168 fractures that met the inclusion criteria in the intervention group, compared to 163 fractures in the control group. On the 12-month X-ray, 12 new qualifying vertebral fractures were identified in the intervention group compared to 13 in the control group. When incident vertebral and non-vertebral fragility fractures were combined, each group had incident 16 fragility fractures. An additional three non-vertebral fractures were reported that were deemed not to be fragility fractures (2 intervention, 1 control; Table 3). There were no significant between group difference in new vertebral fractures (OR=1.01, 95%CI=0.51-2.03), all fragility fractures (OR=1.11, 95%CI=0.60-2.05), or total fractures (OR=1.17, 95%CI=0.64-2.13).

There were 48 people who fell in the intervention group (68%) and 36 fallers in the control group (51%), resulting in a relative risk of a faller being in the intervention group of 1.32 (95%CI=.99-1.74). The negative binomial regression revealed no significant group differences in number of falls (IRR=0.97, 95%CI 0.58-1.63).

In the intervention group, 18 participants reported a SAE compared with 12 controls (χ^2 (1)=0.025, p=0.874). SAEs included stroke, heart problems, fall-related injuries, fractures, severe vertigo and breathing difficulties (Table 4). One participant experienced worsening of her pre-existing COPD, causing a significant decline in lung function, and resulting in an SAE and withdrawal from the study. One participant who had a stroke was not able to have her physical performance assessed at the end of the study. Only three adverse events related to the intervention were reported, none of which were considered SAEs (Table 4). One participant developed bilateral knee pain a few days after the initial PT visit. Lower body strengthening and balance exercises were discontinued. At the time of the second PT visit, the pain had resolved to

"tightness", and lower body strengthening and balance exercises were resumed and progressed over the remainder of the study. Another participant reported an increase in pain after adding additional activities to her exercise plan. The participant was unable to indicate which activities worsened her symptoms but decided to reduce her activity. The third event involved a participant who fell in her hallway while doing fast walking as part of her exercise program. Initially, a hairline fracture of the elbow was suspected but was ruled out with subsequent imaging. The participant later resumed her exercise program.

Discussion

Our feasibility trial provides important lessons that can inform future large exercise trials in individuals at high risk of fracture (Box 1). Once recruited, women over age 65 years with a history of a vertebral fracture exhibited satisfactory adherence and study completion, such that over 90% were retained at 12-month follow-up and average adherence to the intervention was 66%. For a large multicentre trial with a fracture outcome to be feasible, there is a need to expand the inclusion criteria and address challenges to recruitment or include more sites. We were able to systematically document falls, fractures and adverse events, and did not observe significant between group differences in these outcomes. However, the relatively high incidence of fragility fractures, falls and adverse events over the course of the study suggests that we captured a sample of individuals for whom the question of risk versus benefit of unsupervised exercise is very relevant. Indeed, we observed one fall directly attributable to exercise, during indoor walking. Future trials of exercise in individuals at moderate-high risk of fractures should include a systematic process for capturing and verifying adverse events and fragility fractures.

There are distinct challenges to recruiting for exercise trials in older adults with chronic conditions, and some strategies that work well (see Box 1). Individuals who are interested in

exercise are often already exercising or not interested in a trial where they might be randomized to control. Some recruiting sites offered or advertised other exercise programs, resulting in competition. Some potential participants reported age (or perception that they are "too old"), health conditions, the need to travel, or caregiving as barriers to participation in exercise or in a research trial, consistent with barriers to exercise participation among older adults that have been previously reported.[34–36] Therefore, those that agree to participate represent a potentially limited middle ground: individuals who are not already exercising but are interested enough to participate, are willing to be randomized to control, and do not have any real or perceived barriers. We targeted osteoporosis clinics to ensure that referred participants had at least one fracture, to limit screen failures and associated costs and X-ray exposure. As a result, our population was often medically complex or did not meet our language (i.e., English speaking), mobility or health-related criteria, or the recruiting physician felt the patient was too frail or was otherwise not appropriate. A unique feature of our protocol compared to many prior exercise studies was that we required at least one radiographically confirmed Grade 2 or 3 fracture, rather than self-reported diagnosed fractures, or clinical fractures. Therefore, we chose recruitment in clinics where data to confirm potential fracture history was available, which may have limited our sampling frame. Two sites in particular that were in large cities (i.e., Toronto and Melbourne) had the most difficulty with recruitment, and attributed it to barriers which may not be uncommon in larger cities or academic medical centres: other available exercise services, multiple studies recruiting participants, diverse populations who speak limited English, and high proportion of medically complex patients who don't meet inclusion criteria. Multilingual support for recruitment and intervention delivery would enhance recruitment and leads to a more representative sample. That said, our screen failure rate was only 6%, and our study population

was likely more representative of the high-risk patient for whom the question of risk versus benefit of unsupervised exercise is most relevant, as compared to previous studies. Indeed, we observed a relatively high incidence of fragility fractures and adverse events. To increase the potential sampling frame in future exercise trials with a fracture outcome, one could expand the definition of high risk (e.g., high risk according to Canadian Association of Radiologists and Osteoporosis Canada tool[37] (CAROC) or WHO Fracture Risk Assessment tool[38] (FRAX), history of fragility fracture, osteoporosis plus history of falls), include males with stratification by sex, and reduce the minimum age. Future trials might consider an active comparator with or without deception to enhance recruitment. Retention rates were much higher than our predefined criterion for success and are higher than similar 12 month studies.[39–41] Strategies that we used to enhance retention include bi-monthly or more frequent contact from study personnel, birthday cards, and personalized feedback letters with performance data at the conclusion of the study.

Adherence to prescribed exercise was similar to that previously reported, though rates for 12 month studies are heterogeneous.[18, 39–41] Adherence to home exercise programs can be challenging to measure; indeed a variety of methods are found in the literature.[18, 42, 43] It may be over-reported when only those who completed the study are included in the estimates, or if based on retrospective self-report from participants. We modeled our adherence data collection after the gold standard for monitoring falls.[44] We used an additive approach (e.g., daily diaries and monthly calls) to ensure a more robust estimate of total falls, adherence and adverse events. We aimed to provide a transparent assessment of adherence and factors influencing adherence to inform future trials. Accordingly, we monitored physical activity participation in controls, and discovered contamination. A key challenge in exercise trials is that people often sign up because

they want the intervention, and it is hard to blind participants to group allocation. Therefore, those who are keen may pursue it despite allocation to control. Some participants found the diaries onerous to complete, or stated that they wanted to be in the study but they refused to complete the diaries at all, or when they were travelling; many Canadian retirees spend the winters in Florida, including several of our participants. Not unexpectedly, adherence decreased over the course of the study, an observation partially confounded by a corresponding increase in missing diary entries. However, even when ignoring missing data, adherence rates decreased over time. PT monthly call data indicate that missing diaries are not exclusively from participants not completing their exercises.

Our intervention was designed to be pragmatic, and comparable to home care physiotherapy received after hip fracture. There is a trade-off between an intervention that is cost-efficient and feasible to deliver in individuals who may not be willing or able to travel to a centre weekly, and the potential for greater fidelity, safety and efficacy of a supervised intervention. In-person visits from the PT appeared to increase adherence, suggesting that a trial with a focus on efficacy may wish to include frequent contact or supervision, and more opportunities for progression. Home exercise programs with intermittent supervision by a physical therapist may be seen as a preferred option because it reduces time and resource burden and is more convenient. That is explicitly why we chose to test it in a pilot before moving towards a full trial. We also chose this model of delivery because of its potential scalability in existing home care models. We now have good evidence that it may not be a feasible option for a long-term efficacy trial in individuals with vertebral fractures, and that future trials (and perhaps, real-world implementation) should use a direct supervised intervention. Further, a home exercise intervention with only intermittent PT visits may not allow for sufficient engagement or progression. Indeed, we have established

that people with osteoporosis report the following barriers to implementing exercise recommendations: disease-related symptoms, lack of exercise-related knowledge, low exercise self-efficacy, access to exercise programs that meet needs and preferences, limited resources and time, physical activity norms and preferences, incentives to exercise, fear of fracturing, and trust in exercise providers[45].

We did not design the trial to have sufficient statistical power to examine the safety or efficacy of the intervention with respect to falls and fractures. Accordingly, there were no between group differences in falls, fractures, or AEs. In our study, there were no serious adverse events directly attributable to the intervention. There is already strong evidence that exercise, particularly challenging balance exercises, can reduce falls by 20-40%.[26] Emerging meta-analyses that are pooling smaller trials are generally in support of the anti-fracture effects of exercise.[25, 46] Some of the estimates reported in smaller trials may be spurious, or subject to bias. For example, few trials list fracture as a primary outcome, include a systematic and unbiased method for adjudication of fractures, or distinguish fragility fractures from non-fragility fractures. That said, the strong evidence that exercise prevents falls, combined with emerging evidence from meta-analyses related to anti-fracture efficacy is promising. There is a strong need for trials examining the effects of exercise on falls, fractures and BMD in individuals at moderate-high risk of fracture, as well as pragmatic trials that examine strategies for effective implementation.[47]

Strengths and Limitations

Strengths of this study include attention to sources of bias, an intervention informed by existing evidence and theory-driven behaviour-change techniques, and the inclusion of diverse enrolling sites in two countries. Further, we carefully monitored AEs and captured physical activity behaviour in both the exercise and control group to examine potential contamination.

We acknowledge several limitations. We could not verify adherence. We used participant self-report to evaluate adherence, which means we could have over-estimated adherence. With an inactive control group, participants are not blind to group allocation. There did not appear to be differences in retention between the control and intervention group. It may influence patient-reported outcome measures like adherence, pain or quality of life, and we will report on the latter two elsewhere. Future trials might consider an active control group, with or without deception, and measuring adherence or physical activity levels in both intervention and control groups. In addition, because participants are not blind to group allocation, ensuring that outcome assessors are blind to group allocation can be difficult and requires extra, unblinded staff to assist with data collection. Despite reminding participants at the start of every assessment not to reveal group allocation, a few participants forgot or did not understand. Fall calendars used in previous studies measured falls only, and our diaries required documentation of several outcomes, which may have made them onerous.

Conclusions

Our pilot trial demonstrates the feasibility of retention and satisfactory adherence for a large, multicentre randomized controlled trial of home exercise in women with vertebral fracture. Recruiting individuals with Grade 2 vertebral fractures to a 1-year RCT of exercise was a challenge. Suggestions for future trials include: an active control group; large number of recruiting sites; multi-lingual support, sites with a history of successful recruitment or a participant recruitment pool; recruitment integrated with clinical visits instead of via referral; and a broader definition of high risk (e.g., history of any osteoporotic fracture, history of fall(s)/high fall risk plus osteoporosis). There were no between group differences in the rate of falls or fractures in our sample. There is a need to develop a network of collaborators dedicated to

research examining the anti-fracture efficacy of exercise and pragmatic trials of implementation

to ensure the successful conduct of multicentre trials with fracture outcomes.

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Measure	Intervention (n=71)	Control (n=70)
Age (y): Mean (SD)	76 (6.4)	77 (7.3)
Height (cm) : Mean (SD)	156.5 (6.2)	156.3 (7.1)
Weight (kg) : Mean (SD)	65.1 (12.8)	66.5 (15.4)
Body mass index: Mean (SD)	26.6 (5.0)	27.2 (5.9)
Occiput to wall distance (cm) : Mean (SD)	5.3 (4.0)	6.2 (4.4)
Balance outcome measure for elder rehabilitation:	13.3 (2.2)	13.2 (2.0)
Short physical performance battery[33]: Mean (SD)	9.4 (2.4)	8.7 (2.3)
Mean number of qualifying fractures: Mean (SD)	2.4 (1.8)	2.3 (1.8)
Distance lived from enrolling centre (km): Mean (SD)	16.3 (29.2)	14.32 (14.7)
Bisphosphonate use: n (%)	50 (70%)	49 (70%)
People using assistive aids: n (%)	22 (31%)	25 (36%)
Falls within the past year: Median (Min-Max)	0 (0-7)	0 (0-3)
People who fell in the past year: n (%)	26 (37%)	21 (30%)
People living in the community: n (%)	70 (99%)	69 (99%)
People receiving homecare: n (%)	3 (4%)	7 (10%)
People reporting an annual income ≤$60,000: n (%)	39 (55%)	43 (61%)
People reporting working: n (%)	5 (7%)	6 (9%)
People reporting volunteering: n (%)	18 (25%)	15 (21%)

Table 1. Baseline participant characteristics

Site	Number Randomized	Months of Recruitment	Randomized per Month
BNH[a]	13	24	0.54
MAC[b]	25	27	0.93
RMH[a]	6	24	0.25
UBC[b]	32	8	4.00
UHN[b]	8	21	0.38
UW[b]	26	28	0.93
UWO[b]	31	12	2.58
Mean(SD)	**20.14(10.92)**	**21(7.66)**	**1.37(1.40)**

Table 2. Count of randomized participants per site. BNH=Broadmeadows Northern Health, MAC=McMaster University, RMH=Royal Melbourne Hospital, UBC=University of British Columbia, UHN=University Health Network, UW=University of Waterloo, UWO=University of Western Ontario
a: Australian site; b: Canadian site

Group	Fracture Type	bone	how
Intervention	Fragility	hip	Slipped or tripped inside the home
		ribs	Slipped or tripped outside the home
		wrist/forearm	Slipped or tripped inside the home
		wrist/forearm	Slipped or tripped outside the home
	Non-Fragility	wrist/forearm	knocked over by big dog
		foot	Fell on ice
Control	Fragility	pelvis	Slipped or tripped inside the home
		ribs	Slipped or tripped outside the home
		ribs	Unclear; found on x-ray.
	Non-Fragility	2 toes	Stepped into garden and hit foot against brick pavement.

Table 3. Non-vertebral fractures reported by participants

Adverse event type	Intervention	Control
Anemia	1 (1 SAE)	0
Diarrhea	1	0
Dizziness	1 (1 SAE)	0
Injurious fall/trip	17 (1 SAE)	18
Flu syndrome	3 (1 SAE)	1
Clinical Fracture	6 (4 SAE)	4 (1 SAE)
Headache	2	0
Increased pain	30 (3 SAE)	16 (1 SAE)
Other	38 (6 SAE)	30 (8 SAE)
Rash	1	0
Respiratory infection	5	0
Stroke	0	2 (2 SAE)
Urinary tract infection	0	4
Vision problems	2	1
Wound infection	1 (1 SAE)	0
Total	*108 (18 SAE)*	*76 (12 SAE)*
Treatment type	**Intervention**	**Control**
ER visit	18	4
Hospitalization	10	13
Medication/Treatment	30	22
No Treatment	27	28
Other	23	9

Table 4. Adverse event types and treatments reported

Lessons learned

Recruitment
 	
• The observed rate of recruitment would mean that it would take 3 years and 8 months for 40 sites to enroll 2400 participants with the current inclusion/exclusion criteria and recruitment strategies.
• Barriers to recruitment:
    o Willingness to be randomized to control
    o Language or personal barriers (e.g., time, travel, health conditions)
    o Competing programs, services or studies (e.g., exercise programs available at centre)
• Key facilitators of recruitment were:
    o Enthusiastic recruiting physicians
    o Recruiting from osteoporosis-specific clinics
    o Having access to a research pool of potential participants
• Potential ways to expand recruitment:
    o Expand the definition of high risk
    o Include males
    o Reduce minimum age
    o Use an active comparator
Retention
 	
• Successful strategies:
    o Frequent contact from study personnel
    o Birthday cards
    o Personalized feedback letters with performance data at the conclusion of the study
Adherence
 	
• A key challenge in exercise trials is that people often sign up because they want the intervention, and it is hard to blind participants to group allocation
• Some participants found the diaries onerous to complete
• There is a trade-off between home-based and supervised interventions in being cost-efficient and feasible to deliver without travel to a centre weekly, and the potential for greater fidelity, safety and efficacy.

Box 1. Lessons learned regarding main trial feasibility

Fig. 1. Participant flow. BNH=Broadmeadows Northern Health, RMH=Royal Melbourne Hospital, UBC=University of British Columbia, UHN=University Health Network, UW=University of Waterloo, UWO=University of Western Ontario

Fig. 2. Per-protocol rate of adherence over the course of the study. The dashed line represents the criterion for success, arrows represent the scheduled time of PT home-visits

Enrolment

Assessed for eligibility
n = 2822

Excluded (n = 2254)
- Age <65 years (n=651)
- Unable to understand instructions in English (n=88)
- No known or suspected vertebral fracture (n=677)
- Cognitive impairment (n=58)
- Current or prior cancer (n=37)
- On dialysis/liver, kidney or malabsorption disease (n=48)
- Progressive neurological disorder (n=6)
- Progressive disorder likely to prevent study completion (n=49)
- Unable to stand/walk for 10 m with/without gait aid (n=6)
- Current strength or similar exercise program (>= 3x/wk) (n=67)
- Uncontrolled hypertension or other contraindications (n=5)
- Men (n=308)
- Doctor deemed ineligible/data not recorded (n=134)
- Unknown/Other (n=120)

UW Assessed for Eligibility n = 154	**McMaster** Assessed for Eligibility n = 288	**UHN** Assessed for Eligibility n = 131	**UWO** Assessed for Eligibility n = 1572	**UBC** Assessed for Eligibility n = 110	**BNH** Assessed for Eligibility n = 248	**RMH** Assessed for Eligibility n = 319
·Ineligible (n=89) ·Declined to participate (n=25)	·Ineligible (n=116) ·Declined to participate (n=144)	·Ineligible (n=106) ·Declined to participate (n=15)	·Ineligible (n=1529) ·Declined to participate (n=9)	·Ineligible (n=39) ·Declined to participate (n=35)	·Ineligible (n=168) ·Declined to participate (n=63)	·Ineligible (n=207) ·Declined to participate (n=97)
Consented n = 40	Consented n = 28	Consented n = 10	Consented n = 34	Consented n = 36	Consented n = 17	Consented n = 11
Study Visit #1 Completed n = 35	Study Visit #1 Completed n = 28	Study Visit #1 Completed n = 10	Study Visit #1 Completed n = 31	Study Visit #1 Completed n = 33	Study Visit #1 Completed n = 14	Study Visit #1 Completed n = 9
Ineligible (n = 9) Withdrew Consent (n=5)	Ineligible (n = 3) Withdrew Consent (n=0)	Ineligible (n = 2) Withdrew Consent (n=0)	Ineligible (n = 1) Withdrew Consent (n=2)	Ineligible (n = 3) Withdrew Consent (n=1)	Ineligible (n = 4) Withdrew Consent (n=0)	Ineligible (n = 5) Withdrew Consent (n=0)
Randomized n = 26	Randomized n = 25	Randomized n = 8	Randomized n = 31	Randomized n =32	Randomized n = 13	Randomized n = 6

Allocation

Allocated to Exercise Group (n = 71)	Allocated to Control Group (n = 70)
- UW (n = 14)	- UW (n = 12)
- McMaster (n = 12)	- McMaster (n = 13)
- UHN (n = 4)	- UHN (n = 4)
- UWO (n = 16)	- UWO (n = 15)
- UBC (n = 16)	- UBC (n = 16)
- BNH (n = 6)	- BNH (n = 7)
- RMH (n = 3)	- RMH (n = 3)

Follow-up

Lost to follow-up (n = 0)	Lost to follow-up (n = 0)
Discontinued intervention (n = 4)	Discontinued control activities (n = 4)
Withdrew from study (n = 5)	Withdrew from study (n = 6)
Study Completed (n = 66)	Study Completed (n = 64)

Analysis

Analyzed (n = 71)	Analyzed (n = 70)
- Excluded from analysis (n = 0)	- Excluded from analysis (n = 0)