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Safer medicines To reduce falls and refractures for OsteoPorosis (#STOP): a study protocol for a randomised controlled trial of medical specialist-initiated pharmacist-led medication management reviews in primary care

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ABSTRACT

Introduction Minimal trauma fractures (MTFs) often occur in older patients with osteoporosis and may be precipitated by falls risk-increasing drugs. One category of falls risk-increasing drugs of concern are those with sedative/anticholinergic properties. Collaborative medication management services such as Australia's Home Medicine Review (HMR) can reduce patients' intake of sedative/anticholinergics and improve continuity of care. This paper describes a protocol for an randomised controlled trial to determine the efficacy of an HMR service for patients who have sustained MTF.

Method and analysis Eligible participants are as follows: ≥65 years of age, using ≥5 medicines including at least one falls risk-increasing drug, who have sustained an MTF and under treatment in one of eight Osteoporosis Refracture Prevention clinics in Australia. Consenting participants will be randomised to control (standard care) or intervention groups. For the intervention group, medical specialists will refer to a pharmacist for HMR focused on reducing falls risk predominately through making recommendations to reduce falls risk medicines, and adherence to antiosteoporosis medicines. Twelve months from treatment allocation, comparisons between groups will be made. The main outcome measure is participants' cumulative exposure to sedative and anticholinergics, using the Drug Burden Index. Secondary outcomes include medication adherence, emergency department visits, hospitalisations, falls and mortality. Economic evaluation will compare the intervention strategy with standard care.

Ethics and dissemination Approval was obtained via the New South Wales Research Ethics and Governance Information System (approval number: 2021/ETH12003) with site-specific approvals granted through Human Research Ethics Committees for each research site. Study outcomes will be published in peer-reviewed journals. It will provide robust insight into effectiveness of a pharmacist-based intervention on medicine-related falls risk for patients with osteoporosis. We anticipate that this study will take 2 years to fully accrue including follow-up.

Trial registration number ACTRN12622000261718.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This large-scale randomised controlled trial is designed to determine the efficacy of a pharmacist-led Home Medicine Review service for patients who have sustained a minimal trauma fracture and determine its effect on reducing risk of falls via the Drug Burden Index (DBI).
⇒ The success of deprescribing sedative and anticholinergic medicines, measured via the DBI, may depend on additional factors beyond the scope of this intervention and trial design.
⇒ The ultimate purpose of the intervention is to decrease refracture rates and falls, but these outcomes may not be achievable within the time frame of the trial and require follow-up study.
⇒ It is possible that medical specialists' exposure to the medication reviews may influence their prescribing practices of falls risk-increasing drugs for both control and intervention patients. This will be explored in a separate qualitative substudy.

INTRODUCTION

The ageing process is accompanied by an increased risk of falling and subsequent injury. The potential for harm associated with falling

is compounded by the high prevalence of osteoporosis among older people, with minimal trauma fracture, an all-too common consequence of poor bone health.[1] Associated with significant morbidity, mortality and burden on the health system and society as a whole, minimal trauma fractures are not uncommon. These fractures, (otherwise known as fragility fractures), were for example, the fourth leading cause of chronic disease morbidity in Europe in 2010.[2] In Europe, 3.5 million new fragility fractures were sustained in 2010[2] and in Australia, more than 140 000 minimal trauma fractures are estimated to occur annually.[3] Minimal trauma fractures are painful and expensive to treat and linked with increased dependency, disability and need for carer support in-home or in residential care. For health services, the financial burden arises through the provision of emergency assistance, surgery, hospital stays, rehabilitation and community services. In Europe, the total direct cost of osteoporotic fractures was €56.9 billion in 2019.[4] The cost to Australians in 2017 was $3.44 billion dollars, with the treatment of fractures accounting for 68% of total direct costs.[5] Any osteoporotic fracture increases the risk of further fractures, with around 50% of those experiencing minimal trauma fracture will have another fracture within their lifetime.[6] Australian data show that after minimal trauma fracture, 13.7% of female patients and 11.3% of male patients refracture within 5 years, more than half of which occur within the first 12 months of the sentinel fracture.[7] These refractures predispose people to premature mortality.[8 9] An Australian study of persons aged 60 and older after minimal trauma fracture reporting that 51% of men and 39% of women died within 5 years, often associated with refracture.[10] Effective refracture prevention requires assessment and timely initiation of long-term antiosteoporosis medicines.[11] Good adherence to osteoporosis treatment is associated with decreased risk of mortality,[12] however sustaining adherence for the long-term can be problematic for a variety of reasons.[13]

Multidisciplinary approaches that integrate services from acute diagnosis and initiation of care to long-term sustainable support are required to reduce the burden of refracture. These include hospital-based Osteoporosis Refracture Prevention (ORP) services to deliver comprehensive assessment and management for people who sustain a minimal trauma fracture, including prescription of antiosteoporosis medicines where appropriate.[14] Operating to best practice standards, ORP services have demonstrated to improve treatment uptake and adherence,[15 16] reduce refracture[16–19] and be cost-effective.[20]

One area of focus for ORP clinics is minimising the risk of refracture through falls prevention.[21 22] The risk of falling among older patients (>65 years) is intensified by the use of multiple medicines (polypharmacy), with a dose–response relationship between the number of drugs an older person takes and their risk of injurious falls.[23] However, the effect of polypharmacy is most likely mediated by the presence of fall-risk-increasing drugs, since when the number of falls risk increasing drugs consumed is taken into account, the independent contribution of polypharmacy is relatively low.[23]

The range of drugs classed as falls risk increasing drugs both includes medicines which are sedative and also diuretics, beta-blockers and non-steroidal anti-inflammatory drugs.[23] Of particular interest, however, are medicines with specific sedative and/or anticholinergic properties, which have adverse effects associated with falls, including day-time sedation and impaired balance, gait, grip strength and coordination, as well as other impairments.[24] The sedative/anticholinergic classes include antidepressants, anxiolytics, hypnotics and sedatives and antipsychotics, many of which, are commonly prescribed for older persons with multiple morbidities. The negative effect of sedative/anticholinergic properties on health outcomes has been quantified using the Drug Burden Index (DBI).[25] The DBI is a measure of cumulative exposure to any and all sedative/anticholinergic medicines, utilising both the relative strength of sedative/anticholinergic effect and daily dose consumed.[25] Research has established links between higher DBI and cognitive and functional decline.[25 26] Reports from two very large observational studies in New Zealand, demonstrated positive association of high DBI with falls,[27] fall-related hospitalisation, frequency of GP visits and risk of mortality, even taking polypharmacy into account.[28]

Comprehensive medication review services can reduce the rates at which older persons fall.[29] Medication review enables health providers to promote adherence to antiosteoporosis medicines and affords an opportunity to deprescribe unnecessary sedative/anticholinergics, which may have been started for short-term problems not currently present.[30] Pharmacist-led medication review has resulted in successful deprescribing of sedative/anticholinergic medicines measured with the DBI,[30–32] and a lower DBI is associated with reduced falls for persons living in community[28 33]-aged care.[34] Geriatrician-led medication review is a component of some ORP services.[14] However, challenges remain with how ORP clinics can sustainably translate the impact of medication review, as evidenced in a Dutch study where medication review failed to reduce the risk of falls.[35] Further, little research has specifically examined the impact of pharmacist-led medication review on falls risk and injury for patients with osteoporosis and minimal trauma fracture.

This randomised controlled trial was designed to test the effectiveness of an intervention comprising a medical specialist-initiated pharmacy-led medication review service for persons who have experienced minimal trauma fracture. The medication review pharmacist will be asked to focus on reducing risk of subsequent falls and fractures, through deprescribing sedative/anticholinergics, many of which are indicated for short-term problems and improving adherence to antiosteoporotic drugs. Therefore, the aim of this study is to determine whether, compared with those who receive usual care, participants who have been provided with the intervention will, at 12 months post-ORP clinic visit have an overall lower DBI,

and demonstrate improved adherence to prescribed antiosteoporosis medicines.

METHODS AND ANALYSIS

Study design and description

This protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement (see online supplemental file 1). A randomised controlled trial design was used to determine the effect of an intervention which occurs in primary care but is initiated within medical specialist-led ORP clinics. As randomisation and initiation of the intervention occurs after the ORP clinic treatment plan has been determined for that visit, the intervention should have no effect on the care provided *within* the clinic and vice-versa.

Study setting

Eligible participants (target, n=1092) will be recruited via ORP clinics (n=8) across a range of Local Health Districts in New South Wales (n=5) and Victoria (n=3), Australia. Patients entering ORP clinics have been referred to the clinics for the management of osteoporosis after having sustained a minimal trauma fracture or identified as part of a screening process. A majority will not have previously attended the clinic, but some may have been seen previously and present for ongoing care. Therefore, in this study, the index visit refers to the first visit to the ORP clinic during the study period.

Inclusion/exclusion criteria for ORP clinics vary between clinics but usually specify that patients have a documented minimal trauma fracture but have no record of other follow-up related to osteoporosis care, for example by another relevant medical specialty. Some clinics exclude patients older than a particular age cut-off (eg, 75 years old), since it is deemed that the care of such a patient is better served by other teams, for example in orthogeriatric medicine. Other clinics, however, deliberately target patients of older age. Another factor affecting patient characteristics is that one clinic specifically caters for women while another, men. Some clinics focus on a limited range of fracture sites.

Study sample

To be eligible for recruitment, patients referred to an ORP clinic study site (n=8) will meet the following criteria: ≥65 years of age; taking five or more medicines, one of which is a falls risk increasing drug;[26] have a diagnosis or presumptive diagnosis of osteoporosis because they have sustained a minimal trauma fracture[36 37] and not living in a residential-aged care facility. Patients who are non-English speaking will be offered the opportunity to participate using qualified interpreters, wherever available. Patients who are unable to supply informed consent or are receiving palliative care will be excluded.

Sample size was estimated pragmatically in reference to two studies estimating the impact of pharmacist-led medication review on DBI. In one study, median DBI was reduced from 0.82 to 0.67 at 3 months after a single medication review.[30] Another pre–post study (n=46) showed that 6 months after the review, median, DBI was reduced by 0.34 and which was associated with a significant reduction in falls ($p<0.04$) and a range of clinically relevant parameters such as indices of physical and mental well-being.[32] Given the 12 month observation period, we expect that an overall decrease in DBI of 20% could be achievable and sample size was estimated based on this. We expect that this would be associated with clinically relevant reduction in falls risk. Therefore, a total of 1092 participants (546 participants/group) are to be recruited to have 90% power to detect a significant difference between intervention and control at 12 months, at an alpha level of 0.05 (two-sided). This sample size also allows for up to a 20% loss to follow-up. Over a 12 month timeframe, most sites (n=6) will recruit approximately 156 patients and the two smaller sites running sex-specific clinics will recruit 78 patients each. The trial will use competitive recruitment so that all sites will recruit until 1092 participants are recruited or time available for recruitment is exceeded.

Randomisation and blinding

Participants will be randomised to either the intervention arm or the control arm (standard care) *after* participants have been seen by the medical specialists. In this way, the ORP clinicians and the participants will be blind to trial arm allocation *during* their index clinic visit.

After consent and baseline details have been collected, participants will be randomly assigned (1:1) to either the intervention or the control arm. Computer-generated random numbers with balance variable blocks[38] will be used to produce a randomisation scheme which is stratified by participating centres (n=8), sex (male vs female, where possible) and exposure to sedative/anticholinergic medicine (taking a medicine listed as having DBI>0, yes/no). Once allocated to intervention or control group, the specialists, care team, clinic research assistant and participants will become aware of group allocation and will consequently be unblinded from that point onwards. Centrally located research assistants capturing outcome data at 12 months (see below) will remain blind to group allocation.

Standard care

Standard care involves the provision of an ORP service by teams led by medical specialists in endocrinology, rheumatology or gerontology. The eight sites provide diagnostic and care planning with subtle variations in the way each clinic identifies and recruit patients; conducts investigations, including radiological, pathological and physical assessment and the time spent in the clinic. Each team includes a range of personnel including medical specialists at various stages of training, nurses and therapists, at least one of which per site specialises in fracture liaison services, while sometimes physiotherapists, exercise physiologists and other health professionals are utilised.

Pharmacists are not currently utilised in the clinics and medication review by pharmacists is not part of usual care. Medical specialists review patients' medicines and may prescribe new medicines and/or deprescribe or adjust current medicines as deemed appropriate. Any changes to prescribed medicines are communicated to the patient's general practitioner (GP) by local reporting mechanisms. Following this, their medical care is coordinated by the participant's GP and prescriptions are dispensed by the patient's preferred pharmacy or pharmacies. Some ORP clinics follow-up their patients after 3–12 months. As part of standard care, it is possible that participants could experience GP-initiated government-funded Home Medicine Reviews (HMRs) provided by accredited pharmacists who are not part of the trial. Based on a report by the Australian Commission on Safety and Quality in Healthcare, approximately 2% of people aged over 75 years of age received an HMR in 2018/2019.[39] Extrapolating these figures to the population recruited into this study, the number of GP initiated HMRs predicted to occur in this study cohort would be approximately 22, with half in the control arm. As this trial applies an intention-to-treat approach, these participants will not be excluded.

Intervention

The intervention provided in this study is a collaborative comprehensive medication review, known as HMR. The process for HMR is broadly consistent with Australian Government funding mechanism for HMR[40] and Guidelines for Comprehensive Medication Management Reviews.[41] Table 1 outlines the HMR intervention pathway to be utilised in this study.

Briefly, the HMR is initiated by a medical specialist using a standardised template for referral. It provides patient specific information and requests that the pharmacist review the medicines, focussing on preventing refracture. The clinic research assistant provides the names, sex and cultural background of locally available accredited pharmacists and asks the patient (or their carer) to select a preferred pharmacist. Many of the HMR pharmacists are bilingual. If language problems cannot be managed, interpreter services will be offered. The Research Assistant then sends the referral to the accredited pharmacist. The HMR pharmacist arranges a convenient time to conduct their review within 2 weeks of the ORP clinic attendance (wherever possible). The pharmacist visits the patient in their home, reviews the medicines via observation (looking at patients' medications) and discussion and completes a report with findings and recommendations. The HMR report is first sent to the medical specialist to provide them an opportunity to discuss the report with the reviewing pharmacist. The medical specialist can choose to engage with the reviewing pharmacist within a prearranged period (up to 2 weeks from the HMR) before the report is sent to the patient's preferred GP and

Table 1 HMR intervention pathway

Stage 1. Referral	After participant seen by ORP clinicians (ORP Clinic Index visit): ► HMR referral provided by ORP clinician with reasons for referral including: 'review falls risk-increasing medicines and identify adherence to antiosteoporosis medicine barriers and provide solutions'. ► The referring ORP clinician may include the participant's clinical details in the referral for example, any available laboratory results, height, weight, age and sex, blood pressure and the results of any other relevant tests or investigations available (such as bone mineral density).
Stage 2. Home Service	Accredited HMR pharmacist: ► Contacts participant to arrange time and location (preferably the participant's home) for the review. ► Conducts the review, at which all medicines are collected and recorded, and the participant interviewed. The interview consists of the participant's experiences using their medicines, such as administration and perceived effectiveness with a special focus on potentially reducing falls risk increasing drugs and antiosteoporosis medicine adherence. ► Addresses any urgent medication-related problems.
Stage 3. Report	After the review, the Accredited HMR pharmacist: ► Reconciles medical conditions with medicines, identifies any medicine-related problems and writes a report with recommendations for consideration by the participant's General Practitioner and a lay copy for the participant and/or their caregiver. ► Shares the report with the ORP clinician with an invitation to discuss prior to a copy being shared with the participant's GP and community pharmacist and the lay version provided to the participant and/or their caregiver.
Stage 4. MMP	Participant: ► Visits GP and discusses the HMR report, with a view to forming an agreed MMP.
Stage 5. Follow-up	Accredited HMR pharmacist: ► Arranges for a follow-up service at three and if appropriate, 6 months to review medication changes, any medication-related problems and discuss antiosteoporosis adherence.

GP, general practitioner; HMR, Home Medicines Review; MMP, Medication Management Plan; ORP, Osteoporosis Refracture Prevention.

community pharmacist. GPs and community pharmacists are also provided with links to a bespoke continuing professional development (CPD) opportunity. This CPD content was designed by the research team and provides updates on osteoporosis, medication management to minimise falls risk and improve bone health. It consists of three × 20 min modules with embedded videos and review questions.

When the HMR report is sent to the GP, the pharmacist provides the patient with a current medicines list along with suggestions for self-care and a lay summary of recommendations to the GP. The pharmacist then makes an appointment to follow-up with the patient at 3 months. A third follow-up at 6 months may be recommended by the pharmacist, if, for example deprescribing is underway or adherence requires attention. The pharmacist completing the review must be accredited to perform medication management reviews by an approved accrediting body.[40] For this study, the accredited pharmacists are required to have completed a 3 hour face-to-face or videoconference workshop. This orientates the pharmacists to the study, highlights issues of deprescribing falls risk increasing drugs and enhancing medication adherence to antiosteoporotic medicines. To ensure consistency, an HMR report template is utilised by the accredited pharmacists and the training also focusses on HMR report and lay summary writing.

In this study, fees for the provision of the HMR service are paid directly to the pharmacist by the grant funds, not by the Australian Government. No payments will be made by the grant to medical specialists or GPs, such that any fees for the medical consultations are claimed through Australia's Medical Benefit Fund and/or paid privately.

Trial outcomes

Use of sedative and anticholinergic medicines

The study primary outcome is an overall decrease in participants' DBI score. The DBI was selected because it is a valid and reliable measure of the extent to which a medication-related intervention may reduce falls risk.[28 42 43] The development of the DBI tool has accelerated understanding of the extent to which this subset of falls risk increasing drugs contributes to functional decline among older persons and the consequential increase in falls risk.[25 44] The DBI score is calculated for medicines with established anticholinergic and sedative properties, the list of which is defined, curated and maintained by the DBI tool developers.[25] For the length of this study, the DBI calculations will rely on the DBI list provided as at 1 November 2022. The DBI score is calculated as the sum of drug burden attributable to each anticholinergic and sedative medicine, which is a function of the dose taken and the minimum efficacious dose, calculated using the equation:

$$Drug\ Burden\ Index_i(DBI_i) = D_i/(D_i + {}_i)$$

Where D_i is the daily dose of that drug taken by the individual, and δ_i is the minimum efficacious daily dose for the drug. For example, among community-dwelling older persons aged 65+ (mean: 82.7 years), the mean (SD) DBI was 0.93 (0.95).[45] There is a dose–response curve for the effect of DBI on falls. For example, compared with those having no exposure (DBI score=0), the adjusted OR for injurious falls was 2.24 for low DBI score (0–< 0.2), 2.46 for medium DBI score (0.2–<0.5), 3.16 for high DBI score (0.5–1) and 5.32 for very high DBI score (>1).[33] A secondary outcome for this study is reduction in the proportion of patients taking drugs with DBI>0 (yes or no).

The source of data for recording exposure to DBI-listed medicines and the DBI calculation will be the patient's medicines list recorded in the purpose-built secure database. The process of medication reconciliation, using the best possible medication history, will be used to generate the medicine list.[46] This rigorous and standardised history will be performed by research assistants (pharmacists or nurses) working in the clinic at baseline (prior to randomisation) and repeated at 12 months by centrally located research assistants by telephone call, validated against dispensing records. To conduct best possible medication history, research assistants will have access to hospital clinic records (only at baseline), verbal history from the patient/carer, along with prescription dispensing records obtained from the participant's two preferred community pharmacies. Any discrepancies[46] will be reconciled by the research assistant and the resulting medicines list used for all calculations.

Medication adherence

A secondary outcome relates to the impact of the intervention on adherence to prescribed antiosteoporosis medicines. The source of data for adherence calculations will be prescriptions collected under the Pharmaceutical Benefits Scheme (PBS), Australia's national medicines subsidy scheme which subsidises the cost of many approved medicines in Australia. PBS records do not contain prescribed directions or instructions for use. Therefore, prescription records from the participants' two most preferred community pharmacies will also be accessed to validate that the pack size obtained aligns with prescribed instructions, which are routinely captured in dispensing data. The PBS data set and dispensing records will be obtained at 18 months postindex clinic visit to allow for the capture of 12+1 months' records, reducing the potential for errors in calculation of adherence data occurring through delayed recording which is inherent to the PBS data set. Rates of initiation, estimates of maintenance (using mean possession ratio and/or proportion of days covered) and rates of persistence at 12 months with osteoporosis medicines will be reported,[13] along with self-reported adherence scales, Medication Adherence Reporting Scale (MARS 5)[47] for medication taking behaviour and Beliefs about Medication Questionnaire (BMQ)[48] for beliefs associated with adherence.

Table 2 Outcomes and timepoints for measurement

Measure	Baseline*	3 months†	12 Months‡	12+1 Months§
Primary outcome				
Drug Burden Index[25] based on medicines list generated through medication reconciliation using hospital records, dispensed medication history and self-report	X		X	
Secondary outcomes				
Exposure to DBI drugs (yes/no)	X		X	
Initiation, maintenance and persistence with osteoporosis medicines[13] via PBS records and validated against dispensed medication history of preferred community pharmacies				X
Self-reported adherence using MARS 5[47] and BMQ[48]	X		X	
Self-reported quality of life using EQ-5D-5L[67]	X		X	
No. of falls, fractures and hospitalisations postrecruitment recorded in a calendar and collected by phone call; data validated against linked data			X	
Mortality			X	
Medication appropriateness indicators[49–51]	X	X	X	
Drug-related problem causes[51]		X	X	
Recommendations made by HMR pharmacists vs number taken up/implemented		X	X	

*Data collected in the clinic (before randomisation and treatment allocation).
†Data collected for the intervention group only.
‡Data collected by telephone interview.
§Data captured at 18 months postindex ORP clinic attendance for completeness. For the estimation of adherence using dispensed data, it is traditional to capture 12+1 months to allow for (appropriate) delayed dispensing.
BMQ, Brief Medication Questionnaire; DBI, Drug Burden Index; HMR, Home Medicines Review; MARS 5, Medication Adherence Report Scale 5; ORP, Osteoporosis Refracture Prevention.

Other secondary outcomes

Additional secondary outcome measures include number of falls, refractures and osteoporosis-related emergency department visits, hospitalisations, GP visits. Two methods will be used to estimate these. The first method involves the use of self-report, with falls, refractures and hospitalisations documented in a Calendar provided to all participants at baseline. The data captured in this Calendar will be relayed to a Research Assistant during the telephone interview at 12 months postrecruitment. The incidence of falls, refractures and osteoporosis-related hospitalisations and GP visits will be triangulated against data obtained through linked data sets, which will also provide mortality data (see table 2). This study will also obtain self-reported Quality of Life (EQ-5D-5L scores) and a range of process measures for medication review including medication appropriateness indicators,[49–51] causes of drug-related problems and recommendations made by HMR pharmacists versus number taken up/implemented.[51] Three specific medication appropriateness criteria developed by Basger *et al*[50 51] will be compared between groups. These will include comparing proportions of patients that are not taking psychotropic medicines (criteria 27), proportions of patients not taking medicines with anticholinergic activity (criteria 29) and proportions of patients on antiosteoporosis medicines (criteria 38)[50] using χ^2 analyses.

Twelve months was chosen as a pragmatic trial endpoint for outcome analysis as the primary outcome could be demonstrated and the direction of secondary outcomes indicated within this period.

The trial start date is March 2023 and final recruitment of patients should be completed by end June 2024. This means final patient follow-up is due to be completed in June 2025.

Data analysis plan

The statistical analyses of data will be conducted according to a prespecified statistical analysis plan with an intention-to-treat approach. Baseline characteristics will be descriptively analysed. Both unadjusted and adjusted analyses will be carried out to assess the effectiveness of the intervention; conclusions about the effects of intervention will be drawn from the adjusted results. The primary analyses will make adjustment for stratification factors, such as centre, sex and exposure to DBI medicine (yes/no) and the baseline value (for continuous outcomes). Exploratory analysis will make additional adjustments for any important baseline predictors identified during the analysis which show evidence of substantial imbalance

between the study groups. Continuous outcomes will be analysed using linear regression, and mean difference and corresponding 95% CI will be reported. Analyses of binary and count outcomes will use log binomial and Poisson regression, respectively. Proportional hazards will be used for fall and fracture data. Relative risk (95% CI) will be reported for binary outcomes and ratio of means (95% CI) for count outcomes. A sensitivity per-protocol analysis will be conducted based on the intervention the participants receive. Missing data will be examined in the blinded review. A complete-case analysis will be considered for the primary analysis, whereas a predefined sensitivity analysis using multiple imputation will be considered for a predefined sensitivity analysis.

A within trial cost-effectiveness analysis and a cost-utility analysis based on economic modelling will also be conducted to evaluate the economic merits of the intervention strategy compared with the conventional treatment. Costs will be collected and analysed using the healthcare perspective. We will include costs related to the implementation of intervention, healthcare services utilisation and medicines. The primary outcome of the study, that is, reduction in DBI scores will be used as the effectiveness measure and the incremental cost per one DBI score reduction will be calculated in the within trial cost-effectiveness analysis. A Markov model will be used to simulate a series of long-term possible consequences that would flow from the intervention and the conventional treatment being evaluated in the trial.[52] The possible consequences arising from the intervention will include fracture risk, quality of life and mortality. The demographic and clinical characteristics of simulated patients in the health economics model will be modelled on trial participants. The Incremental Cost-Effectiveness Ratio (ICER) using a lifetime simulation horizon will be completed, and a series of one-way, multiway and probabilistic sensitivity analyses undertaken to address the uncertainty of the cost-effectiveness results. A detailed statistical and economic analysis plan will be generated prior to analysis and will be available from the authors on request.

Ethics and dissemination

Approval to conduct this trial has been obtained via the New South Wales Research Ethics and Governance Information System (approval number: 2021/ETH122003) with site-specific approvals granted through the Human Research Ethics Committees responsible for each ORP clinic site.

Potential participants will be provided a participant information statement outlining the project, randomisation and group allocation processes. At recruitment, participants will provide consent for the researchers to extract data from their medical record and receive a copy of their HMR reports, Medication Management Plan (if applicable) and dispensing history records via their preferred community pharmacy. Participants will also be asked to provide consent at baseline for access to relevant linked data sets using Centre for Health Record Linkage in New South Wales and The Centre for Data Linkage (in Victoria for emergency department visits and hospitalisations and Services Australia data for Medical Benefits Schedule and Pharmaceutical Benefits data). Participants will be able to withdraw from the study and/or the collection of linked data at any time. Participants in the control group will receive standard care and, as the trial is intended to test intervention effects, there is currently no evidence that this will be inferior to the service provided to the intervention group.

Project outcomes will be disseminated via publications in peer-reviewed journals and results may be presented at national and international conferences. No identifiable participant data will be made publicly available. All participant data will be stored in a password-protected database to which only project team members will have access. A unique participant identification number will be used to maintain participants' confidentiality. The identity of participants will be safeguarded through their unique study participant number with a hierarchy of researchers given access to only the data pertaining to their role.

Public and patient involvement

We included a consumer representative with lived experience of chronic disease, as a chief investigator. She is an active consumer representative on a range of health and medical research projects (see Acknowledgements). The consumer representative: contributed to the grant application including the recruitment and study processes; advised on intervention and time burden; did not have a major role in selecting primary or secondary outcomes and is a member of the Intervention and Implementation Committee. We have ethical approval to undertake an implementation science evaluation of the trial, led by a coauthor (LP). That study includes patient experience and will be reported separately. This implementation science substudy allows the research team to capture intervention fidelity through studying first-hand patient and provider experience in both study arms, along with interrogation and analysis of intervention-specific data including copies of HMR reports. Qualitative data captured pretrial, along with previous studies conducted by RM and SC (on patient and carer experiences of medication review), informed intervention design and training.

DISCUSSION

International[53] and Australian[54] best practice guidelines recommend medication review for patients at risk of falls, to facilitate deprescribing of unnecessary falls risk increasing drugs. In the present context, international[55] and Australian[37] osteoporosis management guidelines recommend a range of falls risk reduction strategies, including medication review specifically with a view to deprescribe falls risk increasing drugs, if possible. However, these International[55] and local[37] guidelines

have no explicit mention of pharmacist-led medication review. This is likely due to lack of awareness and robust evidence to support the role of collaborative medication reviews for patients with minimal trauma fracture. Indeed, recent systematic reviews reporting pharmacist interventions for patients with osteoporosis highlighted a range of interventions but no studies included pharmacist-led medication reviews.[56 57] This trial is intended to determine whether incorporating collaborative medication reviews in the transition between tertiary care and primary care can optimise medication management for patients with minimal trauma fracture.

Pharmacist-led medication reviews centres the patient within a collaborative team including the patient's GP and a review pharmacist.[58] Patients[59 60] and their caregivers[61] have high regard for Australia's HMR service and are generally willing to participate, especially if they believe their GP wants them to.[60] However, the success of the intervention will likely depend on capacity of medication review pharmacists to foster relationships with patients and their GPs[62] in order to deprescribe falls risk increasing drugs. Recent changes to business rules have facilitated this trial, in that funding is now provided for pharmacists to conduct HMRs initiated by medical specialists, rather than GPs. However, at the time of writing, there have been no published comparative trials of the effectiveness of the medical specialist-referral pathway on patient or process outcomes.

International[63] and local guidance[41] for pharmacist-led medication reviews recommend that, where possible reviews are followed-up by the pharmacist to ensure continuity of care. However, an overview of systematic reviews of pharmacist-led medication reviews in primary care highlighted an absence of evaluation of medication reviews that included more than a single service event.[64] In this study, up to two follow-up reviews within 6 months are designed to assist with the implementation of the agreed medication management plan. This should facilitate deprescribing (see below) and may improve adherence to antiosteoporotic medicines by reinforcing tailored messages.

Another design feature of the intervention is the provision of a lay summary of the HMR report to consumers. This is a novel addition to regular practice and arises from pilot work conducted by team members which showed that such a step resulted in improved uptake of pharmacists' recommendations. The effect of this strategy may, however, be limited by the amount and level of information that patients can assimilate in shared decision-making to set and achieve goals of therapy.[65]

Training is an important component of this intervention. A module has been provided for the accredited pharmacists to assist them to focus on osteoporosis and facilitate relationships with GPs around deprescribing. In regard to deprescribing, the training module highlights and incorporates the five-step process for deprescribing, (1) capturing a comprehensive medication history, (2) identifying potentially inappropriate medicines, (3) determining whether the potentially inappropriate medicines can be ceased, (4) planning the withdrawal regimen (eg, tapering where necessary) and (5) provision of monitoring, support and documentation.[66] To further optimise the uptake of deprescribing recommendations, the trial includes bespoke CPD opportunities for intervention patients' GPs and community pharmacists.

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

Section/item	Item No	Description #STOP study	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	3
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 ACTRN12622000261718	4 (ANZCTR
Protocol version	3	Date and version identifier	each page 23
Funding	4	Sources and types of financial, material, and other support	
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	23
	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	23
	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)	23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	7
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)	7-8
Methods: Participants, interventions, and outcomes			**8**
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	
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	nil
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	nil
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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	13,16 Table 2

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			9
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	
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
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	18

	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	n/a
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	n/a
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	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	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)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 19

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19-20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
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	n/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
	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	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.