Deprescribing To Reduce Polypharmacy: Study Protocol For A Randomised Controlled Trial Assessing Deprescribing of Anticholinergic and Sedative Drugs In A Cohort of Frail Older People Living In The Community

Ulrich Bergler
University of Otago Christchurch
Nagham Ailabouni
University of South Australia - City East Campus
John W. Pickering
University of Otago Christchurch
Sarah Hilmer
University of Sydney
Dee Mangin
McMaster University Faculty of Health Sciences
Prasad Nishtala
University of Bath
Hamish Jamieson (hamish.jamieson@otago.ac.nz)
University of Otago Christchurch https://orcid.org/0000-0002-2462-1595

Study protocol

Keywords: Deprescribing, elderly, polypharmacy, anticholinergic, sedatives, drug burden index

Posted Date: May 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-533256/v1

Abstract

Background: Targeted deprescribing of anticholinergic and sedative medications in older people can improve their health outcomes. This trial will determine if pharmacist-led reviews lead to general practitioners deprescribing anticholinergic and sedative medications in older people living in the community.

Methods and analysis: The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist was used to develop and report the protocol. The trial will involve three groups of older adults stratified by frailty (low, medium, and high). This will be a pragmatic two-arm randomised controlled trial to test general practitioner uptake of pharmacist recommendations to deprescribe anticholinergic and sedative medications that are causing adverse side effects in patients.

Study population: Community dwelling frail adults, 65 years or older, living in the Canterbury region of New Zealand, seeking publicly funded home support services or admission to aged residential care and taking at least one anticholinergic or sedative medication regularly.

Intervention: New Zealand registered pharmacists using peer-reviewed deprescribing guidelines will visit participants at home in the community, review their medications, and recommend to general practitioners' anticholinergic and sedative medications that could be deprescribed. Total use of anticholinergic and sedative medications will be quantified using the Drug Burden index (DBI).

Outcomes: The primary outcome will be the change in total DBI between baseline and six-months follow-up. Secondary outcomes will include entry into aged residential care, prolonged hospitalisation, and death.

Data collection points: Data will be collected at the time of interRAI assessments (T0), at the time of the baseline review (T1), at 6 months following the baseline review (T2), and at the end of the study period, or end of study participation for participants admitted into aged residential care, or who died (T3).

Ethics and dissemination: Ethics approval has been obtained from the Human, Disability and Ethics Committee. Ethical number (17CEN265).

Trial registration: The trial was registered on 2 May 2018 with the Australian New Zealand Clinical Trials Registry: ACTRN12618000729224 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374924)

Background

Polypharmacy is prevalent amongst older adults positioning them at a higher risk of drug-drug interactions and one or more inappropriate medications. Inappropriate medications are defined as those whose potential harm outweighs their possible benefits (1). Deprescribing, the process of safely reducing

or discontinuing unnecessary or harmful medicines with clinical supervision, has the potential to decrease polypharmacy, reduce inappropriate medicine use and improve health outcomes (2).

Disease-specific guidelines offer little advice regarding deprescribing of potentially harmful medications (3, 4) for people with multimorbidity. Of note, anticholinergic and sedative medications are medications that can be inappropriately prescribed for older adults (5). The cumulative, long-term use of these medications is associated with several negative health consequences including impaired muscle strength, worsening cognition, increased frailty, poorer physical functioning (e.g. balance), heightened risk of falls, increased rate of hospitalisations, entry into residential care, and even death (6, 7). Polypharmacy is associated with frailty (8), a geriatric syndrome, present in many older adults. Frailty increases with age due to age-related physiological deterioration. Up to half of people aged over 85 years' experience frailty (2). Small trigger events, like a seasonal illness or fall, can cause a sudden decline in health and negative outcomes in already frail individuals (2, 9, 10). Little is known on how a quantified measure of frailty could inform and help in targeting frail individuals for deprescribing.

Deprescribing of unnecessary anticholinergic and sedative medications has been shown to potentially improve health outcomes of older people (2, 9) including cognition (10), and reducing risk of falls (11) and hip fractures. Although inconclusive to date, evidence suggests that deprescribing could result in improved reported quality of life (12, 13).

Although, previous studies have demonstrated the feasibility and overall safety of deprescribing, questions remain regarding how to best do it in practice (14, 15). Pharmacist-led interventions, in a multi-disciplinary residential aged care setting, have successfully reduced unnecessary prescribing of sedative and anticholinergic medications (16, 17). A cluster randomised controlled trial of clinical decision support software targeting deprescribing of anticholinergic and sedative medications for pharmacists conducting Home Medicines Review in Australia, increased pharmacists' recommendations to reduce anticholinergic and sedative medications but not their uptake (18).

The drug burden index (DBI) is a linear, additive pharmacological model that uses both pharmacokinetic and pharmacodynamic principles to calculate an individual's total exposure to anticholinergic and sedative medications (14). Exposure to each additional unit of DBI has been shown to have a negative effect on the physical function of older people equivalent to three additional physical comorbidities (14). An association between increasing DBI and impaired function has been demonstrated in a cross-sectional analysis of two populations of older people in the United States (19), in older Australian men (20) and in a longitudinal study of community dwelling older people in the United States (21). Furthermore, increasing DBI is associated with prevalent and incident frailty (22) and with frailty transitions (23).

In this randomised controlled trial in a community setting, we will test a targeted approach to pharmacist led deprescribing of medications contributing to DBI in frail older adults. Specifically, this study will test the utility of a frailty measure for targeting deprescribing on individuals with the greatest potential for improvement. We will identify older adults seeking funded care support who therefore undergo a

structured comprehensive needs assessment, develop a frailty measure using data obtained through these assessments, and stratify our participants into three groups based on their frailty index. Pharmacists will visit participants in their home, record current medication use, and develop recommendations for deprescribing which are passed to the patient's primary physician for consideration. We will measure change in DBI medication use and differences in hospitalisation and entry into aged residential care.

Methods

Hypotheses and aims

We hypothesise that deprescribing anticholinergic and sedative medications that are having deleterious side effects on frail older people will improve their health. We further hypothesise that a frailty measure will help identify people who will benefit the most from the intervention.

The primary objective is to determine if pharmacist-led medication reviews focused on reducing anticholinergic and sedative medications can influence primary care doctors to deprescribe these medications for older people living in the community. The secondary objective is to determine if a frailty measure based on data collected in the interRAI Home Care(24) and Contact assessment (25) can identify a group of older people who could benefit the most from deprescribing.

The interRAI is a comprehensive assessment database system, utilised internationally and in New Zealand to standardise the evaluation of complex care needs of older people. It is routinely used to collect data regarding patients' medical and functional status (26). In New Zealand, the comprehensive Home Care assessment (24) is used for persons seeking admission into publicly funded aged residential care, while the shorter Contact assessment (25) is for home-based support services. The reliability of the interRAI™ has been tested and shown to meet or exceed the standard cut-offs for acceptable reliability (27).

Study design

This will be a pragmatic two-arm randomised controlled trial to test general practitioner uptake of pharmacist recommendations to deprescribe anticholinergic and sedative medications that are causing adverse side effects in patients. The cumulative use of anticholinergic and sedative medications listed in Table 1 for each participant will be quantified, using the drug burden index (DBI) (14). New Zealand registered pharmacists will use peer-reviewed and previously tested deprescribing guidelines to recommend to primary care doctors' sedative and anticholinergic medications with a potential to be deprescribed (28, 29).

After enrolment, participants will be stratified using a frailty index (FI), which will be based on a cumulative deficit model using 15 relevant items common to the interRAI Homecare and Contact assessments. Cut-off values for each stratum will create three equal sized frailty strata on the basis of New Zealand interRAI HC and CA data used for developing the frailty index. Participants will be stratified

into one of three frailty strata and allocated in equal numbers to the intervention and control arms of the trial.

Study setting

This trial will be conducted at the University of Otago, Christchurch, in the Canterbury provincial region of New Zealand. Study pharmacists will visit participants in their homes, where they will review medication use at the time of their visit.

Participants

Participants will be eligible for inclusion if they:

1) Are aged ≥ 65 years

2) Have undergone an interRAI Home Care (24) or Contact (25) assessment,

3) Are regularly taking at least one anticholinergic or sedative medication as shown in the interRAI or dispensing records.

Participants will be excluded from the study for any of the following reasons:

1) Not consenting for their interRAI data to be used for research

2) Having a psychiatric disorder, or dementia disease (e.g. Alzheimer's disease, dementia, schizophrenia, abnormal thought processes, delusions, hallucinations)

3) Scoring 3 or higher on the interRAI Cognitive Performance Scale

4) Having a terminal illness with life expectancy ≤ 6 months

5) Determined as non-frail by having no deficits in the frailty index

6) Identifying as not taking any anticholinergic or sedative drugs

7) Having an initial DBI score of < 0.5 (DBI score of 0.5 is the equivalent of one DBI medication being taken at the minimum efficacious dose) (14).

8) Having a potentially life-threatening drug interaction requiring urgent medical intervention (during the study period)

Procedure

Recruitment

There will be three layers of consent involved in this study: 1) when people undergo an interRAI assessment they are asked to consent for their data to be used for planning and research, 2) when the

assessing health care provider asks the person to give consent to be contacted by the research team, and 3) the person consents to take part in the trial.

Potential participants will be contacted via two pathways: 1) interRAI assessors will invite eligible older adults to participate in the study during their interRAI assessment home visit, and 2) the local district health board will post letters to older adults who have recently had an interRAI assessment. The letters will outline a brief overview of the study with 'Consent to Contact' (CtC) forms and free post return envelopes.

Once the research team has received the signed CtC forms, the study administrator will contact potential participants and explain the study in detail. The CtC form has two tick boxes whereby a potential participant can 1) permit the study team to contact his/her community pharmacist to confirm regular prescriptions of sedative or anticholinergic medications, and 2) permit access to the electronic interRAI assessment record. This information will confirm the medication participants are taking at the start of the study.

During enrolment, the study administrator will confirm prescribed medications with participants and their eligibility to participate in the study. If potential participants indicate verbally their willingness to take part in the study a home visit by a study pharmacist will be scheduled. During visits study pharmacists will explain the study to the potential participants, answer any questions, and obtain informed written consent to take part in the study.

Once consent to participate in the study has been received, each participant's primary care physician / general practitioner (GP) will be advised in writing that their patient has consented to take part in this study.

Stratification

Using each consenting participant's interRAI data, the Study Administrator will calculate their frailty index (FI) and classify each participant into one of the three frailty strata: low, medium, or high prior to the pharmacist's visit.

Randomization and allocation

Predefined randomisation lists will be calculated by the study's data manager using a Mersenne Twister algorithm and ensuring that the total of intervention and control arm participants will not be greater than three participants at any given point in the process. Each frailty strata will have its own separate randomisation sequence. Allocations will be made by the study administrator, who will select the next allocation from a sequence of sealed envelopes matching a participant's frailty strata at the time the participant home visit is booked. The envelopes are opened after completion of the pre-intervention medication review.

Baseline medication review

Participants' medication use will be reviewed before the intervention and six months following the intervention. To avoid unnecessary complexity in obtaining prescribing records for people living in community settings, focus will be given to the in-person review process in the participants' home. Here the pharmacist will inquire about, view and record the daily dose of all medications the participant is taking.

Intervention arm

In the intervention arm of the trial, pharmacists will discuss with participants the medical conditions with which the DBI medications have been prescribed, and their experiences with these medications. The consultation will determine if the potential harm of DBI medications prescribed outweigh their possible benefits. The participant and their family's beliefs about the continued need for these medications and their preferences regarding willingness to discontinue these medications will also be determined via the consultation. After the consultation, target anticholinergic/sedative medications will be documented along with the participant's concerns regarding these medications. Study pharmacists will consider the participants' medical history as conveyed by the participants, their interRAI assessments, and their electronic medication records, if available.

The deprescribing implementation strategy that will be employed will focus on reducing or stopping anticholinergic and sedative medications to reduce participants' DBI scores, using a process that was adapted from (2) and previously trialled in a New Zealand residential aged care setting (28, 29). The process used in this study will differ from that used in the above residential care study because our study pharmacists will not have access to prescribing lists and clinical records before meeting the participants. Nevertheless, face to face consultations with the study pharmacists will capture rich data on participants' medical history, medication lists, and their beliefs about their medications.

The deprescribing medication review will involve:

- Pharmacist review of medication use
- Participant consultation
- Pharmacists suggesting changes in DBI medications to GPs
- GP consultation with the participants,
- GP decision to revise or not to revise DBI medication prescriptions

All medication reviews and DBI calculations will be reviewed and verified independently by a senior pharmacist (author PSN). Suggestions developed for potential deprescribing will be peer reviewed by the study pharmacists, with additional expertise being available from the senior pharmacist.

Table 1 lists all the target medications that are being considered for deprescribing in this trial, along with their corresponding anatomical therapeutic classification (ATC) code [30]. These medications are classified as anticholinergic based on The New Zealand Formulary [31], and sedative if they cause

drowsiness and sedation. This group of medications will encompass antipsychotics, anti-depressants, and benzodiazepines, and non-benzodiazepine hypnotics.

Control arm

If allocated to the control arm, the pharmacist will conduct the medication review without discussing deprescribing options with participants. The control group participants will continue to receive routine care from their GP.

Clinical responsibility

Clinical responsibility for all participants remains with their primary care doctor. Participants will be asked to contact their doctor if they feel unwell during drug withdrawal. If disease relapse occurs or unwanted adverse drug effects occur, the medicine will re-prescribed as seen appropriate by a participant's doctor.

Reasons for withdrawal or dropout, other than death, will not be recorded in the study. The research team will access and analyse hospital admissions. Any notification of incidents received from participants or their GPs will be passed onto an internal data monitoring committee for review (data monitoring and safety is explained in the latter part of the document).

Six months follow-up

For all participants', medication use will be recorded prior to randomisation and repeated at six months follow up. At six months follow up, research pharmacists will revisit participants and ascertain medication usage in both study arms using the same processes as in the baseline review. To avoid bias, each participant will be visited by a different pharmacist at follow-up than the one who saw them at baseline. The post intervention medication review will be provided to the participants' primary care doctors for information purposes only.

Data Collection Methods

All observations and results will be recorded in a custom-designed Research Electronic Data Capture (REDCap https://www.project-redcap.org/) database hosted at the University of Otago, Christchurch, New Zealand, which will allow for secure online data entry from multiple sites into a central data depository (30, 31).

Data will be collected at the time of the interRAI assessment (T0), during preparation of the intervention (T1), at least 6 months following the baseline pharmacist's review (T2), and at the end of the study period or end of study participation for admission into aged residential care or death (T3) as detailed in Table 2.

Medication use will be recorded prior to randomisation and repeated at six months follow up. Secondary health information such as mortality, hospital admissions, and fractures will be obtained from the health provider and New Zealand Ministry of Health. These data will be linked with the study data using each participant's unique national health index (NHI) number (32).

Outcome data

The dataset for analysis will include all interRAI assessments, admissions into residential care, hospital admissions, mortality, and the New Zealand Pharmaceutical Management Agency (PHARMAC) dispensing records. These will be classified into several groups as follows:

- Demographic data
- interRAI™ assessment data
- interRAI™ scales and Clinical Assessment Protocols (CAPs)
- New interRAI™ based Frailty Indices
- Drug Burden Indices (DBI)
- Medical and pharmaceutical notes that support the pharmacist deprescribing reviews
- Admissions into aged residential care
- New Zealand mortality data
- Dispensing records from PHARMAC
- Emergency department presentations and hospital admissions

Data from consented participants will be linked using each participant's unique study ID. The final de-identified dataset will be provided to the study statistician for analysis. The dataset will be archived upon completion of the study.

Data monitoring and safety

The study is considered low risk. An internal data monitoring committee (DMC) independent from the funder and the investigators with no conflict of interest will be established to regularly monitor the study data integrity and quality as described above.

Any notification of unexpected events received by the study administrator will be recorded and passed to the data monitoring and safety committee for review. Unexpected events, trends in data that require corrective action will be passed from the committee to the principal investigator (HJ) for follow up.

Outcomes

In this study, five outcome scenarios are possible: 1) completion of the trial; 2) entry into aged residential care (ARC) prior to completion (this would be linked to a change in GP and medication control); 3) prolonged hospitalisation; 4) death; and 5) withdrawal or other loss to follow up. The first two outcome scenarios would involve the post medication review being undertaken either with the participant or via the medical records of a care facility. The third outcome scenario could lead to delays in recording the post intervention review or may lead to any of the four other scenarios.

Primary Outcome

The primary outcome will be the change in a participant's DBI (ΔDBI) between the time of the baseline interRAI assessment (T1) and time of 6 months follow-up (T2; $\Delta DBI = DBI_{T1} - DBI_{T2}$). Data for the calculation will be collected by comparing medication use pre- and post- intervention. We will determine if there is a greater reduction in the DBI of participants in the experimental arm of the trial compared with participants with the same level of frailty in the control arm. Subgroup analysis will determine if deprescribing is more pronounced for those with more severe frailty.

Secondary Outcomes

Secondary outcomes measures will be compared between the two arms of the trial after 6 months and are outlined in Table 3. These include number of hospitalisations, entry into aged residential care, all-cause mortality, and cost utility from the funder's perspective. We will measure the number of emergency department visits and unplanned hospital admissions. Data on entry into or change in level of care in aged residential care will be extracted from relevant national databases by the analytical services of the Ministry of Health. Patient mortality data will be matched using Participants' national health index (NHI) number and added to the dataset and analysed using competing risk regression. In a separate analysis we will conduct a health cost utility assessment.

Statistics Methods

Power and Sample size

For this RCT we define the clinically significant change in DBI as 0.5, the equivalent of one medication contributing to DBI given at the minimal efficacious dose (14). Approximately 4% of recent interRAI assessments show a $\Delta DBI \geq 0.5$ over a six-month period. A meaningful outcome from deprescribing in this study would be to increase the percentage, in the intervention cohort, with a DBI change ≥ 0.5 by 10% points. This would bring the percentage $\Delta DBI \geq 0.5$ over a six-month period to 14%.

The null hypothesis is that there is no difference in proportions with a ΔDBI of ≥ 0.5 over a six-month period between the control and intervention groups given that 4% of participants in the control group have a ΔDBI of ≥ 0.5. To disprove the null hypothesis, we need to detect a change in number of participants of 10% or more with a ΔDBI of ≥ 0.5 with a power of 90% at an $\alpha = 0.05$. This requires 167 participants in each arm of the study, 334 in total.

For each frailty stratum under the null hypothesis there will be no difference in change in DBI between the control and intervention groups, and assume 4% of participants in the control group have a reduction in DBI of ≥ 0.5, then to detect a change in number of participants of 20% or more with a reduction in DBI of ≥ 0.5 with a power of 80%, and at $\alpha = 0.017$ (0.05/3), requires 56 participants in each arm of the study (112 in each strata, 336 in all).

It is estimated that over 12 months within the target areas of the district health boards' approximately 650 participants will meet the basic inclusion criteria including the minimum DBI. Previous data suggests that approximately 50% of the study's cohort will take the target medicines and therefore 325 people would be eligible to take part in the study per annum.

Statistical analysis

The data analysis will use the intention-to-treat principle (where all available data from participants will be included in the analysis).

We will compare the proportions of the outcome measures using a chi-squared test and present results with a 95% confidence interval.

We will present Kaplan-Meier survival curves for subgroup analysis. Subgroups will include control low frailty, control medium frailty, control high frailty, intervention low frailty, intervention medium frailty, intervention high frailty. This analysis will be controlled for age and sex, with death as a censored event. We will then conduct a competing risk analysis using cumulative incidence functions (CIF). For example, for entry into residential care, entry is the primary event of interest and death is the competing event and the CIFs are the probability of observing these events before the end of the 6-month follow-up period.
Cost benefit analysis

As a separate analysis, a health economist will oversee an analysis of financial costs of routine screening for frailty compared to the expected benefits from more appropriate prescribing, reduced pharmaceutical costs, and avoided hospital admissions and entry into residential care. Given that we will stratify our cohort by frailty, we anticipate identifying a group of participants, with a degree of frailty, who will benefit most from targeted medication reviews.

The cost-effectiveness analysis will include costs and benefits both for the participants and for the health care system. Standard robustness checks will be performed.

A desirable feature is that the benefits of implementing the intervention are likely to be realized soon after implementing, and this will contribute to a favourable cost-effectiveness ratio. (33)
Reporting

We will report according to the CONSORT reporting guidelines (34).

Blinding

Participants will be blinded to their study arm. The pharmacists conducting the first medication reviews will be made aware of which arm of the trial participants are allocated to when they open the envelopes at the first home visit. In the follow-up home visits, pharmacists conducting the post intervention medication reviews will be blinded to the participants' allocation. Patient unblinding is permitted in case of health concerns requiring immediate attention.

The study administrator and the data manager will have access to all participant data. The primary investigator and the study statistician will be blinded to participant data and allocation during the trial.

Ethics and Protocol changes

Ethics approval has been obtained from the Health and Disability Ethics Committee (HDEC) based on this study protocol in revision 8 under amendment AM06. Minor changes to consent forms and participant information sheet were made under amendments AM07 – AM10. Changes to allow conducting the second medication review over the phone during covid-19 lockdown were approved under amendment AM12. Any further changes made to protocol revision 8 will be communicated to the Health and Disability Ethics Committee and approval will be sought to implement the amended protocol. Incremental changes to the Participant Information Sheet (PIS) and Consent to Contact form will be made under subsequent amendments.

Any protocol modifications will be internally reviewed by the DMC, by the funder HRC and if required approved by HDEC.

Discussion

This protocol is for a large multi-centred single blinded randomized control trial that will test deprescribing of anticholinergic and sedative medications in frail older patients living in a community setting. The study will determine if pharmacist-led medication reviews of DBI medications will lead to community GPs deprescribing DBI medications that are having adverse side effects on their patients.

The trial design is unique in aiming to determine if a frailty measure will help to identify older adults who would most benefit from deprescribing.

If the trial is successful, deprescribing could be directly translated into clinical practice, providing a collaborative approach to reducing the burden of anticholinergic and sedative medications in older adults.

Trial Status

The trial is underway using protocol version 8, dated 20 December 2018. Participant recruitment commenced on 2 June 2018 for the pilot phase, and 12 February 2019 for the formal trial. Recruitment is expected to be completed by 31 October 2020, with data capture completed by 31 May 2021.

Abbreviations

ANZCTR: Australian and New Zealand Clinical Trials Registry

ATC: anatomical therapeutic chemical

CAP: Clinical Assessment Protocol

CDHB: Canterbury District Health Board

CIF: Cumulative Interference Function

CRRA: Competing Risk Regression Analyses

DBI: Drug Burden Index

DHB: District Health Board

GP: general practitioner

HDEC: Health and Disability Ethics Committees

HRC: Health Research Council of New Zealand

InterRAI-CA: InterRAI Contact Assessment

InterRAI-HC: InterRAI Home Care Assessment

NHI: National Health Index number

SPIRIT: The Standard Protocol Items: Recommendations for Interventional trials

WSR: Wilcoxon signed rank test

Declarations

Ethics and dissemination: Ethics approval (17CEN265) has been granted by the Human Disability and Ethics Committee (HDEC).

Informed consent will be obtained from all study participants.

Consent for publication

Availability of data and materials: Study materials are provided as supplementary materials. New Zealand ethics laws do not permit free sharing of data. Although aggregate and de-identified data may be provided to collaborating research groups under an appropriate data sharing agreement.

Competing interests

The authors declare that they have no competing interests.

Funding

This work is funded via grant 17/363 of the New Zealand Health Research Council, Level 3, 110 Stanley St, Grafton, Auckland 1010, (HRC) grant. HRC will have no role in the design of the study, and its execution, analyses, interpretation of data, or decision to submit results.

Canterbury District Health Board, 32 Oxford Terrace, Christchurch 8011, New Zealand (CDHB) and South Canterbury District Health Board, High Street, Parkside, Timaru 7910, New Zealand (SCDHB) are sponsors and co-funders of the study, with involvement in participant recruitment and dissemination of study results.

Authors' contributions

The study was conceived by HJ with input from SH, PSN, and DM; the protocol was developed by UB, NA, with input from all authors. HJ leads the research team; JP will conduct statistical analysis; UB will manage the project, data storage, ethics approval, and reporting; SH, PSN, NA will provide pharmaceutical expertise and review; DM will provide guidance and support throughout all aspects of the study. All authors reviewed the study protocol and approved the final manuscript.

Acknowledgements

We acknowledge the contributions of the Canterbury District Health Board, South Canterbury District Health Board, and Pegasus Health of New Zealand for supporting the development of the study. We also acknowledge the Canterbury District Health Board, South Canterbury District Health Board, Nurse Maude, Healthcare New Zealand, and Access Community Health for supporting participant recruitment and execution of the study. We are grateful to Dr Joanne Deely for writing and editing the HRC grant and the study protocol.

References

1. Gnjidic D, Hilmer S, Le Couteur D. High-risk prescribing in older people: more harm than good? Aging Health. 2012;8(4):325–7.
2. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of ‘deprescribing’ with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80(6):1254–68.
3. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. BMJ Open. 2015;5(12):e009235.
4. Declercq T, Petrovic M, Azermai M, Vander Stichele R, De Sutter AIM, van Driel ML, et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. Cochrane database of systematic reviews. 2013(3):CD007726.
5. Wouters H, Hilmer SN, Gnjidic D, Van Campen JP, Teichert M, Van Der Meer HG, et al. Long-Term Exposure to Anticholinergic and Sedative Medications and Cognitive and Physical Function in Later Life. J Gerontol A Biol Sci Med Sci. 2020;75(2):357–65.
6. Johansson G, Eklund K, Gosman-Hedström G. Multidisciplinary team, working with elderly persons living in the community: a systematic literature review. Scandinavian Journal of Occupational Therapy. 2010;17(2):101–16.

7. Crotty M, Rowett D, Spurling L, Giles LC, Phillips PA. Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. Am J Geriatr Pharmacother. 2004;2(4):257–64.
8. Gutiérrez-Valencia M, Izquierdo M, Cesari M, Casas-Herrero Á, Inzitari M, Martínez-Velilla N. The relationship between frailty and polypharmacy in older people: A systematic review: Frailty and polypharmacy: A systematic review. Br J Clin Pharmacol. 2018;84(7):1432–44.
9. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. The benefits and harms of deprescribing. Medical journal of Australia. 2014;201(7):386–9.
10. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. Arch Intern Med. 2010;170(18):1648–54.
11. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic Medication Withdrawal and a Home-Based Exercise Program to Prevent Falls: A Randomized, Controlled Trial. J Am Geriatr Soc. 1999;47(7):850–3.
12. Kua CH, Mak VSL, Huey Lee SW. Health Outcomes of Deprescribing Interventions Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis. J Am Med Dir Assoc. 2019;20(3):362 – 72.e11.
13. Cumming RG, Couteur DGL. Benzodiazepines and Risk of Hip Fractures in Older People: A Review of the Evidence. CNS Drugs. 2003;17(11):825–37.
14. Hilmer SN, Mager DE, Simonsick EM, Cao Y, Ling SM, Windham BG, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med. 2007;167(8):781–7.
15. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. Br J Clin Pharmacol. 2016;82(3):583–623.
16. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease. N Engl J Med. 2006;355(15):1525–38.
17. Croucher M, Crawford D, Fisher M, Fox C, Hosford I, Malone D, et al. The Use of Antipsychotics in Residential Aged Care Clinical Recommendations developed by the RANZCP Faculty of Psychiatry of Old Age. New Zealand): The Royal Australian and New Zealand College of Psychiatrists (RANZCP); 2011.
18. Kouladjian O'Donnell L, Sawan M, Reeve E, Gnjidic D, Chen TF, Kelly PJ, et al. Implementation of the Goal-directed Medication review Electronic Decision Support System (G-MEDSS)© into home medicines review: a protocol for a cluster-randomised clinical trial in older adults. BMC Geriatr. 2020;20(1):51–12.
19. Cao YJ, Mager DE, Simonsick EM, Hilmer SN, Ling SM, Windham BG, et al. Physical and Cognitive Performance and Burden of Anticholinergics, Sedatives, and ACE Inhibitors in Older Women. Clin Pharmacol Ther. 2008;83(3):422–9.

20. Gnjidic D, Cumming RG, Le Couteur DG, Handelsman DJ, Naganathan V, Abernethy DR, et al. Drug Burden Index and physical function in older Australian men. Br J Clin Pharmacol. 2009;68(1):97–105.
21. Hilmer SN, Mager DE, Simonsick EM, Ling SM, Windham BG, Harris TB, et al. Drug Burden Index Score and Functional Decline in Older People. Am J Med. 2009;122(12):1142-9.e2.
22. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, et al. High-Risk Prescribing and Incidence of Frailty Among Older Community-Dwelling Men. Clin Pharmacol Ther. 2012;91(3):521–8.
23. Jamsen KM, Bell JS, Hilmer SN, Kirkpatrick CMJ, Ilomäki J, Le Couteur D, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions Between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. J Am Geriatr Soc. 2016;64(1):89–95.
24. Morris JM, Fries BE, Bernabei R, Steel K, Ikegami N, Carpenter GI, et al. interRAI Home Care (HC) Assessment Form and User's Manual. version 9.1.3 Canadian English Edition ed. Washington, DC: interRAI; 2019.
25. Hirdes JP, Curtin-Telegdi N, Poss JW, Gray L, Berg K, Stolee P, et al. interRAI Contact Assessment (CA) Form and User's Manual: A screening Level Assessment for Emergency Department and Intake from Community/Hospital. Version 9.2 ed. Washington DC: interRAi; 2010.
26. interRAI. The interRAI Organization: Who We Are: interRAI; 2020 [Available from: https://www.interrai.org/organization/.
27. Hirdes JP, Ljunggren G, Morris JN, Frijters DHM, Finne Soveri H, Gray L, et al. Reliability of the interRAI suite of assessment instruments: a 12-country study of an integrated health information system. BMC Health Serv Res. 2008;8(1):277-.
28. Ailabouni N, Mangin D, Nishtala P. DEFEAT-polypharmacy: deprescribing anticholinergic and sedative medicines feasibility trial in residential aged care facilities. International Journal of Clinical Pharmacy. 2019;41(1):167–78.
29. Ailabouni N, Mangin D, Nishtala PS. Deprescribing anticholinergic and sedative medicines: protocol for a Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities. BMJ Open. 2017;7(4):e013800.
30. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
31. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81.
32. Hauora MoH-M. 2020 [Available from: https://www.health.govt.nz/our-work/health-identity/national-health-index/nhi-information-health-consumers/national-health-index-questions-and-answers#bwhatis.

33. Spackman M. Time Discounting and of the Cost of Capital in Government. Fiscal Studies. 2004;25(4):467–518.
34. Schulz KF, Altman DG, Moher D. for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Trials. 2010;11:32. PMID: 20334632 [Available from: https://www.equator-network.org/reporting-guidelines/consort/.

Tables

Table 1: Anticholinergic and sedative medications

Generic medicine name	ATC code	Generic medicine name	ATC code
Alprazolam	N05BA12	Methyldopa	C02AB01
Amitriptyline	N06AA09	Metoclopramide	A03FA01
Aripiprazole	N05AX12	Mianserin	N06AX03
Amantadine	N04BB01	Mirtazapine	N06AX11
Benztropine	NO4AC01	Moclobemide	N06AG02
Benzhexol	N04AA01	Morphine	NO2AA01
Biperidin	N04AA02	Nitrazepam	N05CD02
Buprenorphine	N02AE01	Nortryptyline	N06AA10
Buspirone	N05BE01	Olanzapine	N05AH03
Carbamazepine	N03AF01	Orphenadrine	N04AB02
Cetirizine	R06AE07	Oxazepam	N05BA04
Chlorpheniramine	R06AB05	Oxybutynin	G04BD04
Chlorpromazine	N05AA01	Oxycodone	N02AA05
Citalopram	N06AB04	Paroxetine	N06AB05
Clemastine	D04AA14	Pericyazine	NO5AC01
Clomipramine	N06AA04	Phenobarbital	N03AA02
Clonazepam	N03AE01	Phenytoin	N03AB02
Clonidine	S01EA04	Pizotifen	N02CX01
Codeine	R05DA04	Pramipexole	N04BC05
Cyproheptadine	R06AX02	Prazosin	C02CA01
Darifenacin	G04BD10	Pregabalin	N03AX16
Dexchlorpheniramine	R06AB02	Primidone	N03AA03
Dextromethorphan	N02AC04	Prochlorperazine	N05AB04
Diazepam	N05BA01	Promethazine	R06AD02
Dihydrocodeine	N02AA08	Quetiapine	NO5AH04
Diphenhydramine	D04AA32	Risperidone	N05AX08
Disopyramide	C01BA03	Ropinirole	N04BC04
Doxazosin	C02CA04	Selegiline	N04BD01

Dothiepin	N06AA16	Sertraline	N06AB06
Doxepin	N06AA12	Solifenacin	G04BD08
Escitalopram	N06AB10	Tamsulosin	G04CA02
Fentanyl	N02AB03	Temazepam	N05CD07
Fexofenadine	R06AX26	Terazosin	G04CA03
Flunitrazepam	N05CD03	Tolterodine	G04BD07
Fluoxetine	N06AB03	Tramadol	NO2AX02
Fluphenazine	NO5AB02	Tranylcypromine	N06AF04
Fluvoxamine	N06AB08	Triazolam	N05CD05
Gabapentin	N03AX12	Trifluoperazine	N05AB06
Haloperidol	N05AD01	Trihexyphenidyl	N04AA01
Imipramine	N06AA02	Trimipramine	N06AA06
Lamotrigine	N03AX09	Valproic Acid	N03AG01
Levetiracetam	N03AX14	Venlafaxine	N06AX16
Loperamide	A07DA03	Ziprasidone	N05AE04
Loratadine	R06AX13	Zopiclone	N05CF01
Lorazepam	N05BA06	Zolpidem	N05CF02
Lormetazepam	N05CD06	Zuclopenthixol	N05AF05
Methadone	N07BC02		

Table 2: Participant data to be collected during the study

	STUDY PERIOD					
	Pre-enrolment	Enrolment	Baseline	Allocation	Intervention	Close out
TIMEPOINT	T0	T1			T2	T3
Eligibility screen	X	(X)				
Consent to Contact	X					
Informed Consent		X				
Stratified randomisation				X		
Notify GP		X				X
INTERVENTION						
Intervention arm			●	———	———	●
Control arm			●	———	·····	●
DATA						
InterRAI data	X					
Frailty Score	X	(X)				
Medication use report			X			X
De-prescribing options to GP					X	
Mortality						X
ARC						X
Hospital admissions						X
ED visits						X

T0=Time of participant's interRAI assessment; T1= intervention preparation; T2= 6 months following baseline pharmacist's review; T3= end of study period / end of study participation; (X) denotes optional completion if activity was not performed at T0

Table 3: Outcome measures and analysis

Outcome	Measure	Alternative Hypothesis	Analysis
Drug burden change	Proportion ΔDBI ≥ 0.5	Intervention greater	x^2 comparison of proportions
Emergency department visits	Proportion	Remain the same or decrease	X^2 comparison of proportions
Unplanned hospital admissions	Proportion	Remain the same or decrease	X^2 comparison of proportions
Admissions into aged residential care	HR	Remain the same or decrease	CRRA
Mortality	HR	Remain the same or decrease	CRRA

ΔDBI = Change in Drug Burden Index; **WSR** = Wilcoxon signed rank test; **CRRA** = Competing Risk Regression Analyses ; χ^2 = Chi-square

Figures

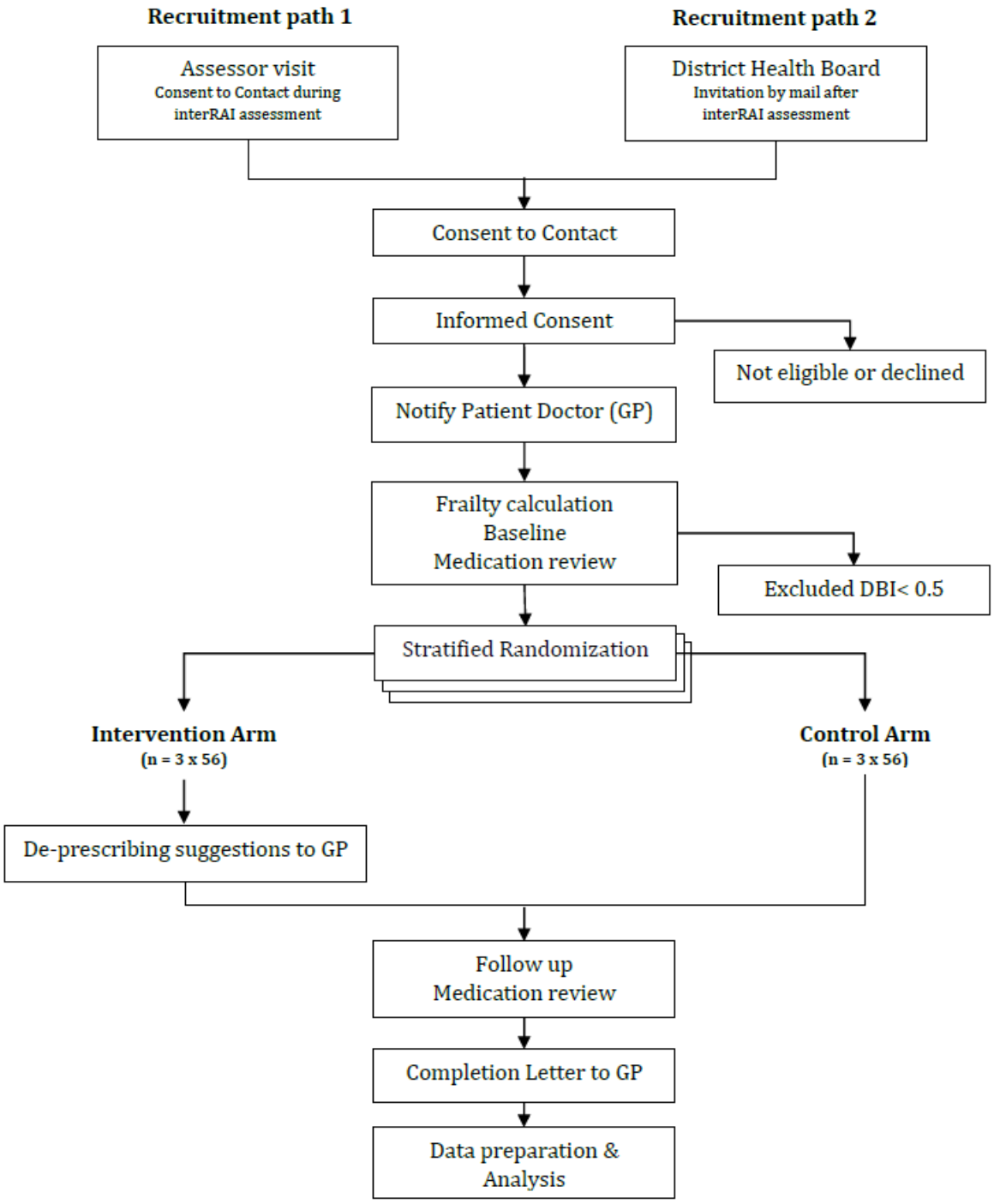

Figure 1

Study Process Flowchart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist20210318.doc