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PROTOCOL: Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities

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Abstract

Introduction: Deprescribing is the process of reducing and/or discontinuing medicines that are deemed to be harmful or inappropriate. Anticholinergic and sedative medicines commonly prescribed in older people have been shown to impair cognition and physical functioning. Targeted deprescribing of these medicines can lead to positive health outcomes in older people. This study will examine whether the proposed intervention is feasible at reducing the prescription of anticholinergic and sedative medicines in older people.

Methods and analysis: This study will examine the feasibility of reducing the prescription of anticholinergic and sedative medicines in older people. The Standard Protocol Items: Recommendations for Interventional trials (SPIRIT checklist) was used to develop and report the protocol. Single group (pre and post comparison) feasibility study design. Study Population: Three residential care homes have been recruited. Intervention: The cumulative use of anticholinergic and sedative medicines for each participant will be quantified, using the drug burden index (DBI). The intervention will involve a New Zealand registered pharmacist using peer-reviewed deprescribing guidelines, to make recommendations to GPs on targeted sedative and anticholinergic medicines that can be deprescribed. Outcomes: The primary outcome will be the change in the participants' drug burden index scores six months after the implementation of the deprescribing intervention. Secondary outcomes will include the number of recommendations taken up by the GP, participants' cognitive functioning, quality of life and activities of daily living. Data collection points: Participants' demographic and clinical data will be collected at the time of enrolment, along with the DBI. Outcome measures will be collected at the time of enrolment, three and six months post enrolment.

Ethics and dissemination: Ethical approval has been granted by the Human Disability and Ethics Committee of New Zealand. Ethical approval number (16/NTA/61)

Trial registration: Australian New Zealand Clinical Trial registry (ANZCTR; trial registration number (ACTRN12616000721404)

Keywords

Deprescribing, elderly, feasibility study, anticholinergic, sedatives, drug burden index

Strengths and Limitations

Strengths:

- Utilising a quantitative measure (i.e. the Drug burden Index) will help to determine the effects that could result from deprescribing anticholinergic and sedative medicines.
- A pharmacist conducting in-depth medicine reviews could help to alleviate the time constraints often faced by GPs when reviewing medicine charts in the residential care setting.

Limitations:

- Six months may not be adequate to fully investigate the effects of deprescribing long-term.

Introduction

Deprescribing, the process of safely reducing or discontinuing unnecessary or harmful medicines, has the potential to decrease polypharmacy, reduce inappropriate medicine use and improve health outcomes [1, 2]. Two recent studies have shown that frail older people can have their medicines safely discontinued without any detrimental effects to their health [3, 4]. A non-randomised controlled study (n=119) carried out in six rest homes, showed a decreased prescription of 2.8 medicines per patient that led to lower annual acute hospital admissions (12% in the study group *vs.* 30% in the control group, p<0.002); and decreased one year mortality rates (21% in the study group *vs.* 45% in the control group, p<0.001) [4]. Improvement of cognition [3], reduction of falls by up to 66% [5] and a decrease of hip fractures by up to 10%, were some of the benefits noted when benzodiazepines and other psychotropic medicines were tapered down or discontinued [6].

Deprescribing also results in improved medication adherence [7] and reduced costs. An Australian study projected that if the average number of medications taken per person could be reduced by one this would result in an annual cost saving of $463 million [8]. Deprescribing has been shown to produce positive health outcomes for older people [3-6]. However, the best approach to implement this intervention is not yet clear. Therefore, this study aims to test the feasibility of an intervention to carry out deprescribing of a targeted medicine group in older people living in a residential care setting in New Zealand. A targeted intervention of deprescribing medicines with anticholinergic and sedative effects will be conducted. The key aspects of this are: a pharmacist led intervention using a collaborative approach with the residents and general practitioner (GP), supported by evidence based tools.

Anticholinergic and sedative medicines commonly prescribed in older people [9-11] are associated with impairments in both cognitive and physical functioning [12, 13]. The Drug Burden Index (DBI) tool will be used to quantify each participant's prescription of anticholinergic and sedative medicines. The DBI is a linear, additive pharmacological model that utilises both pharmacokinetic and pharmacodynamic principles to calculate an individual's total exposure to anticholinergic and sedative medicines [14]. The 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 [15], in older Australian men [16] and longitudinally in community dwelling older people in the United States [17]. Hilmer *et al*., showed that each additional unit of DBI had a negative effect on the physical function of older people similar to that of three additional physical comorbidities [14]. It is important to test whether these observed associations are reversible, as this would affect the timing of any interventions. In planning a full randomised trial, it is appropriate to examine the feasibility of implementing an intervention to assess whether it can reduce this focussed drug burden among older people living in residential aged care.

The Standard Protocol Items: Recommendations for Interventional trials (SPIRIT checklist) was followed in designing the study protocol **(Appendix 1)**.

Methods and analysis

Aims

We hypothesise that the burden of anticholinergic and sedative medicines can be reduced in a residential aged care setting using a collaborative, pharmacist-led, evidence supported intervention.

Study setting and design

A single group (pre and post comparison) feasibility study will be carried out in people aged 65 years and above living in a residential care setting. Participants will be recruited from three residential aged Care Facilities (RACFs) from the South Island of New Zealand.

Participant characteristics

Inclusion criteria:

1. Age ≥ 65 years
2. DBI > 0.5
3. Prescribed at least one anticholinergic medication or sedative medicine. **Table 1** lists all the target medicines that will be considered for deprescribing, along with their corresponding Anatomical Therapeutic Classification (ATC) code. This list was adapted to suit New Zealand medicines, from the sedative and anticholinergic drug burden index (DBI) medicines listed by Hilmer *et al.,* [17]. In addition to this, a medicine will be considered as an anticholinergic medicine if it is clearly described as an anticholinergic medicine in the medicine information. Similarly, a medicine will be considered as a 'sedative' if it causes considerable drowsiness and sedation. This group of medicines will encompass antipsychotics, antidepressants and benzodiazepines or non-benzodiazepine hypnotics.

Exclusion criteria:

1. Limited life expectancy: resident is receiving palliative care or their life expectancy ≤ 3 months based on the Holmes life expectancy calculator [19].
2. Residents admitted for hospice care (short-duration of stay of less than 4 weeks).
3. Residents who suffer from severe dementia, as indicated by the InteRAI-Long Term Care Facilities (LTCF) cognitive performance scale.
4. Residents are not prescribed any anticholinergic or sedative medicines.

Recruitment and consent

The RACF's Medi-Map electronic prescribing computer system will be used to screen for all residents who fulfil the study's inclusion and exclusion criteria as outlined above. Of these potential participants, the RACFs' caregiver(s) or nurse(s) will determine which eligible potential participants are cognitively able to give their own consent, and those potential participants who would not be able to provide their own consent. To determine this, the nurses will use the interRAI-LTCF cognitive performance scale routinely applied to all residents (the pharmacist would not be able to gain access to the residents' medical electronic records before consent). The pharmacist will provide potential participants who are able to provide their own consent, the participant information sheet and consent form detailed in **Appendix 2**. Residents will be encouraged to consult and discuss participating in the study with their family, before consenting to take part.

For potential participants unable to provide their own consent the pharmacist and principal investigator (PI) will send a participation information sheet and declaration form to the person who is their nominated enduring power of attorney (EPOA), as detailed in **Appendix 3**. If the EPOA agrees that this study might be beneficial for their relative/donor and the potential participant's GP believes that a deprescribing intervention could result in an improvement of the resident's quality of life, the resident will be enrolled in the study. If the EPOA does not agree for their relative take part in the study, the GP will not enrol the resident into the study. In the case of the EPOA not responding to the initial letter posted to them, the pharmacist and principal investigator (PI) will attempt to contact the EPOA via telephone or e-mail, and if there is no response, the resident might be enrolled into the study if the resident's GP believes it is in the best interest of the resident.

The pharmacist will provide the GPs a list of the potential participants with cognitive impairment whose EPOAs have agreed for them to take part in the study as well as a list of the potential participants whose EPOAs have not responded **(Appendix 4).** The decision to enrol those potential participants with cognitive impairment, will ultimately be the decision of their GP.

There is a small probability that the participant's level of cognition may improve considerably during the study as a result of decreasing or stopping some of their medicines. On the other hand, participants' level of cognition could naturally deteriorate during the study, as participants become increasingly unwell. Participants' level of cognition will be assessed formally at 3 months after the date of enrolment. If their cognition has deteriorated slightly and they are still deemed by residential care staff to be able to provide their own consent, their willingness to remain enrolled in the study will be reconfirmed by nurses or caregivers (i.e. personnel independent from the research team). If their cognition has deteriorated

considerably that they can no longer provide their own consent to take part in the study, then their EPOAs will have to be contacted via e-mail, letter or telephone. If they do not respond to the pharmacist's initial contact, the pharmacist will attempt to follow up. If the pharmacist doesn't receive a response from the EPOA, their relative/representative will remain enrolled in the study if the GP agrees that the deprescribing intervention is still beneficial to them.

Intervention

A collaborative pharmacist-led medication review with the GP will be employed, as this model has shown to improve success of implementing deprescribing in this setting [20-23]. General practitioners (GPs) who prescribe for the residents across the three RACFs will receive a personalised invitation letter prior to the study initiation date. A copy of the GP invitation letter is included in **Appendix 5.** Participating GPs will be provided with a list of residents who are under their medical care and who have consented to participate in the study. Reasons for GP non-participation will be formally documented and the residents under their care will be excluded from the study sample (see **Figure 1**). Figure 1 was adapted from the CONsolidated Standards of Reporting Trials (CONSORT) flow diagram [24].

Study participants will receive a pharmacist-led medication review intervention. The medication review will be based on the Medication Therapy Assessment (MTA) Framework endorsed by the Pharmaceutical Society of New Zealand (PSNZ) [25].

Step 1: Medical history

The InteRAI-Long term Care Facilities (InteRAI-LTCF) is a comprehensive assessment database system, utilised in residential aged care facilities internationally and in New Zealand to improve the quality of life of vulnerable people. It comprises of a wide array of cognitive performance, activities of daily living and health quality assessments. The reliability of the inteRAI suite of assessment instruments has been tested and has been shown that all items tested met or exceeded standard cut-offs for acceptable reliability, and a substantial proportion of items showed excellent reliability [26]. It is a versatile, viable way of recording health information from routine practice in a way that permits aggregation of accurate, reliable, valid data, safe for use in health services research and pragmatic studies where randomised controlled trials are impossible [27]. We will use this routinely collected data to record the patients' medical and functional status.

Step 2: Intitial consultation

Participants will have an initial consultation with the study pharmacist about their medicines and their medical conditions. The participant may invite their representative/relative to attend this consultation. In this study, anticholinergic and sedative medicines will be specifically targeted for review with the aim of deprescribing where ever possible. Any potential anticholinergic and/or sedative medicine(s) that can be targeted for deprescribing will be flagged and any patient concerns around these medications (either current side effects or concerns around stopping) will be noted.

Step 3: Deprescribing Medication Review

A detailed medication review will be carried out, focussed on reducing the burden of these medications. The review will utilise peer-reviewed deprescribing guidelines for anticholinergic and sedative medicines developed for the intervention and attached in **Appendix 6.** The drug classes include benzodiazepines, antidepressants, and antipsychotics. These protocols were developed as part of NA's doctoral studies and were peer reviewed by an international advisory group including geriatricians, pharmacists, general practitioners and critical appraisal experts. They are designed to serve as guidance for prescribers and clinical pharmacists involved in the process of deprescribing. The process for the development of these protocols is summarised in **Figure 2.**

The protocols appraise the evidence-based literature regarding the appropriateness of anticholinergic and sedative medicines in older people. They also provide guidance on when it may be appropriate for the prescriber to consider reviewing, reducing or stopping a targeted medicine. If a prescribed anticholinergic or

sedative medicine is not included in these drug-specific deprescribing protocols, deprescribing recommendations will be based on the most recent clinical evidence available alongside appropriate clinical judgement.

When anticholinergic and/or sedative medicines are reduced or discontinued, adverse drug withdrawal effects (ADWEs) may develop. Therefore, it is important to slowly taper the dose of the medicine(s) and monitor the participants regularly. It is also important to determine the order in which the medicines will be deprescribed before deprescribing is initiated.

The deprescribing medication review plan will list:

1) The medicine(s) that can be targeted for deprescribing.
2) The reasons as to why these medicines would be appropriate for deprescribing
3) Suggestions for tapering and monitoring if indicated

A copy of the form that will be used for the deprescribing medication review report is included in the **Appendix 7.** The report will be provided to the GP who will endorse or reject the recommendations. Reasons for rejection will be recorded.

Step 4: Medication management plan

A medication management plan (MMP) will be developed by the pharmacist from this medication review plan list of recommendations,and will include the detailed individualised tapering and monitoring recommendations for clear communication to the participant and/or their relative/representative, the participant's GP and nurse.

The MMP report will ensure that all recommendations and concerns are communicated clearly to all parties **(Appendix 8)** and will help ensure that deprescribing occurs in a safe manner. The MMP will specifically include the following:

- Medicines to be deprescribed (i.e. reduced or discontinued)
- The recommended order in which medicines are to be deprescribed, accompanied by appropriate reasoning if necessary
- Specific tapering or stopping guidance for each targeted medicine
- Anticipated adverse drug withdrawal effects (ADWEs)
- Monitoring and appropriate management options if withdrawal effects are to occur

The participant and/or the participant's relative/representative will be provided with a copy of the MMP along with the participant's GP and will explain to them the recommendations contained in the report. The recommendations will be discussed with the GP face-to-face, via telephone or at the 3 monthly resident clinical review meeting. If the participant, the GP and the participants' nurse agree to the recommendations listed in the MMP, the GP will initiate deprescribing for the resident at the next GP visit.

Step 5: Monitoring and follow-up

Participants will be reviewed twice weekly by the study pharmacist for adverse drug withdrawal effects (ADWEs) after the cessation or the dose reduction of the first target medicine. If symptoms are stable according to pre-defined criteria and no ADWEs are reported after two weeks, the dose will be further reduced or the next target medicine will be withdrawn. The participant will continue to be reviewed twice weekly for a further two weeks and, if symptoms are stable, the dose of the next target medication will be reduced or ceased. This will continue until all target medicines are withdrawn and the participants are stable. The participant will be monitored on a weekly basis for two more visits and, if stable, no additional visits will be conducted.

Monitoring for ADWEs will also occur independently by nursing staff and participating GPs who will observe withdrawal symptoms or recurrence of symptoms or signs that were the original indication for the drug. Details of this will be documented on the MMP form, and the staff will be encouraged to contact the pharmacist at any time the resident develops ADWEs. The GP will then be notified in a timely fashion, and

an appropriate course of action, such as a GP visit and/or conducting necessary tests, will be undertaken in order to ensure the safety of the participant.

Multi-disciplinary clinical review meetings are usually held for each resident every three months in the recruited RACFs. The residents' GP, nurses, caregivers, the resident, and/or the residents' representative/relative usually attend these meetings. The study pharmacist will attend each multi-disciplinary clinical review meeting when feasibly possible. Any concerns regarding deprescribing and the health of the resident will be discussed and the study pharmacist will address these concerns. At these meetings, the resident's willingness to remain enrolled in the study will be discussed. If the resident or the resident's representative/relative expresses their wishes to withdraw from the study, the resident will be excluded.

All reasons for withdrawal or dropout will be recorded in the study. Deprescribed medication status and intentions will be recorded at the time the patient exists. All dropouts with no information will be assumed to not have a change in their DBI.

Participant timeline

The participants' GP(s) will be advised that their patients have consented to take part in this study close to the date after enrolment. A New Zealand registered pharmacist will conduct a deprescribing medication review and compile a list of appropriate deprescribing recommendations, summarised in the medication review form **(Appendix 7)**. A medication management plan will be formulated for each participant **(Appendix 8)**. Details of the MMP will be finalised within two weeks after the participant enrolment is completed.

Data Collection

All data and/or covariates will be collected at baseline (T0), after 3 months (T1) and after 6 months (T3) as detailed in **Table 1**. These are classified in three groups as per below:

Demographic data:

- Age
- Sex
- Ethnicity

Medical problem and medicine(s) history:

- Regular and PRN medicines prescribed as per ATC
- List of current medical conditions
- History of medical conditions
- List of medicines with no valid indication

Frailty and comorbidity:

- Edmonton frailty scale [28]
- Charlson comorbidity index (CCI) [29]
- Geriatric depression scale (GDS) [30]

Data monitoring and safety

A committee independent from the funder and the investigators/supervisors and who have no conflicts of interest will be set up. The committee will have access to the de-identified study data , and will regularly monitor the study data integrity, mortality, hospitalisations, original indication re-emergence and ADWEs with a particular focus on events deemed to be attributable to medication discontinuation. If the rate of deaths or serious ADEs or ADWEs in the intervention group is exceptionally high or increases rapidly after the intervention has been implemented, the committee can recommend the trial be terminated. As this is a feasibility study no formal statistical stopping rules have been set, and the decision will rest on the

judgement of the DSMB informed by the data. The decision to terminate the trial will rest with the data monitoring committee. Participating GPs, RACFs managers, residential care staff members and residents will be involved in this decision, and will be informed expediently.

Outcomes

Primary Outcome: The DBI will be quantified using the DBI tool at baseline 6 months post-intervention. Secondary Outcomes: Quality of life will also be assessed at baseline and 6 months post-intervention. All other outcome measures will be collected at baseline (T0), after 3 months (T1) and after 6 months (T3) as outlined in **Table 3**.

The rationale behind the use of these tools and assessments is summarised in **Table 4.** Nurses will also be asked to monitor the appearance of specific ADWEs for each medicine to be deprescribed. Monitoring will be conducted for each individual and all ADWEs will be noted on the participant's MMP form.

Primary outcome:

The change in the participants' drug burden index (DBI) 6 months after the deprescribing intervention has been implemented.

Secondary outcomes:

1) Change in the mean number of medicines prescribed. This will be described by the Anatomical Therapeutic Chemical (ATC) classification system.
2) Proportion of recommendations taken up by the GP(s).
3) Proportion of recommendations agreed to by patients
4) Difference in counts of anticholinergic-induced adverse effects assessed using the UKU side effect rating scale (UKU-SERS) adverse effect rating scale.
5) Cognitive function measured using the InteRAI-LTCF cognitive performance scale.
6) Activities of Daily living measured using sub-domains in the InteRAI-ADL hierarchy scale.
7) Quality of life measured using the EQ-5D-5L tool. The resident and/or proxy version will be used.
8) Number of falls

The UKU-SERS adverse effect rating scale consists of 48 questions assessing side effects caused by antipsychotics. These are grouped under four components psychic, neurological, autonomic and other side effects. Some of the questions included in the 'other side effects' section, assess the presence or absence of inappropriateness in sexual activity. As this may not apply to all residents and/or some residents may feel uncomfortable answering these questions, a sub-analysis will be performed excluding the scores attained for these questions.

Power and sample size

Sample size:

In the majority of participants, cessation of one DBI drug will decrease the DBI score by 0.5. To detect a difference in the primary outcome (reduction in DBI score 0.5 or more) with 80% power and alpha of 0.05, the total sample size required is150 participants. This effect size is derived from a pilot randomized study conducted in RACFs in Australia that aimed at decreasing the DBI load in a nursing home population [31]. Power calculations were generated using Stata 13.1 (Copyright 1985-2013 StataCorp LP). A sample size of 150 participants will detect if the measured outcome measures are sensitive to change. However as this is a feasibility study, aimed at informing power calculations for further studies, so smaller numbers may suffice orthe study sample size may not be adequate to detect a significant change. In the latter case, it will provide useful estimates of effect size and measurement tool properties for use in designing a larger randomised controlled trial

Statistical methods and analysis:

We will use intention-to-treat and per-protocol analyses. All data will be analysed using the IBM SPSS version 23 statistical software. Means and standard deviations will be calculated for continuous data that follow a normal distribution. Mann Whitney U test will be used for continuous data that does not follow a normal distribution. Proportions and frequencies will be calculated for categorical data. Chi-square statistics or apposite statistical tests will be employed to analyse categorical data. Sensitivity analyses will be undertaken to examine the influence of missing data on the study findings. All statistical tests will be two-tailed, and p-values of <0.05 will be deemed significant.

Ethics and dissemination

Ethics approval has been obtained from the Health and Disability Ethics Committee (Reference number: 16/NTA/61). The research team members (NA, PN and DM) will have access to the final study dataset. The results will be published in a peer-reviewed international journal and the dataset will be made available on Research Gate. Participants and/or enduring power of attorneys will be given the option to receive a summary of the published work. GPs, nurse managers and residential care staff involved will have access to the publication. No publication restrictions exist.

Study limitations

No blinding will occur as it is not practical to blind staff and participants. The pharmacist making the deprescribing recommendations will be extracting data for assessment and outcome measures and so is not blinded. These measures, however, are hard rather than subjective measures, mitigating the risk of bias to some extent.. The possibility that a placebo effect may underpin some changes seen is another limitation as it is a before and after study. This however will not affect the study's primary outcome.

Discussion

Anticholinergic and sedative medicines are commonly prescribed in older people and several studies have shown that these medicines are associated with impairments in cognition and physical functioning. This study aims to implement a targeted systematic intervention of deprescribing anticholinergic and sedative medicines in older people living in residential care. The intervention will involve a five-step approach, where a registered pharmacist will conduct a medical history and have a discussion with the participant about their medicines, to highlight potential medicines suitable for deprescribing. Deprescribing recommendations will be summarised on a deprescribing medication use review form. This will be forwarded to the participant's GP for their approval. Once the decision to deprescribe medicines is finalised, the pharmacist will formulate a medication management plan (MMP) for each participant to guide deprescribing in a gradual and safe manner. Participants will be thoroughly followed up by the pharmacist, and monitored closely by the pharmacist, GP and residential care staff for adverse drug withdrawal effects (ADWEs). Data resulting from this study will shed light on the effect of this intervention on the participants' DBI scores as well as their level of cognition and quality of life.

Trial status

Recruitment is set to start on 01/06/2016. Follow up is set to continue till 01/01/2017. The planned end date for data collection is 01/02/2017.

Abbreviations

SPIRIT: The Standard Protocol Items: Recommendations for Interventional trials, DBI: drug burden index, GP: general practitioner, ANZCTR: Australian and New Zealand Clinical Trials Registry, RACF: residential aged care facility, ADWE: adverse drug withdrawal effect, MMP: medicine management plan, MTA: medicine therapy assessment, InterRAI-LTCF: InterRAI long-term care facilities, InterRAI-ADL: InterRAI Activities of Daily living, ATC: anatomical therapeutic chemical

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Competing interests

The author(s) declare that they have no competing interests and are responsible for the content of this report.

Authors' contributions

NA, PN & DM made substantial contribution to the conception and design of the study. NA wrote the manuscript drafts. PN & DM revised the manuscript critically. All authors read and approved the final manuscript.

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Table 1: Target medicines

Generic medicine name	ATC code
1. Alprazolam	N05BA12
2. Amitriptyline	N06AA09
3. Aripiprazole	N05AX12
4. Benztropine	NO4AC01
5. Buprenorphine	N02AE01
6. Buspirone	N05BE01
7. Carbamazepine	N03AF01
8. Cetirizine	R06AE07
9. Chlorpheniramine	R06AB05
10. Chorpromazine	N05AA01
11. Citalopram	N06AB04
12. Clomipramine	N06AA04
13. Clonazepam	N03AE01
14. Clonidine	S01EA04
15. Codeine	R05DA04
16. Dexchlorphaniramine	R06AB02
17. Dextromethorphan	N02AC04
18. Diazepam	N05BA01
19. Dihydrocodeine	N02AA08
20. Disopyramide	C01BA03
21. Doxazosin	C02CA04
22. Doxepin	N06AA12
23. Escitalopram	N06AB10
24. Fentanyl	N02AB03
25. Fexofenadine	R06AX26
26. Flunitrazepam	N05CD03
27. Fluoxetine	N06AB03
28. Fluphenazine	NO5AB02
29. Fluphenazine	N05AB02
30. Gabapentin	N03AX12
31. Haloperidol	N05AD01
32. Imipramine	N06AA02
33. Lamotrigine	N03AX09
34. Levetiracetam	N03AX14
35. Loperamide	A07DA03

36. Loratadine	R06AX13
37. Lorazepam	N05BA06
38. Methadone	N07BC02
39. Methyldopa	C02AB
40. Metoclopramide	A03FA01
41. Mianserin	N06AX03
42. Mirtazepine	No code found
43. Moclobemide	N06AG02
44. Morphine	NO2AA01
45. Nitrazepam	N05CD02
46. Nortryptyline	N06AA10
47. Olanzapine	N05AH03
48. Orphenadrine	N04AB02
49. Oxazepam	N05BA04
50. Oxybutynin	G04BD04
51. Oxycodone	N02AA05
52. Paroxetine	N06AB05
53. Pericyazine	NO5AC01
54. Phenobarbital	N03AA02
55. Phenytoin	N03AB02
56. Pizotifen	N02CX01
57. Pramipexole	N04BC05
58. Prazosin	C02CA01
59. Primidone	N03AA03
60. Prochlorperazine	N05AB04
61. Promethazine	R06AD02
62. Quetiapine	NO5AH04
63. Risperidone	N05AX08
64. Ropinirole	N04BC04
65. Selegiline	N04BD01
66. Sertraline	N06AB06
67. Solifenacin	G04BD08
68. Tamsulosin	G04CA02
69. Temazepam	N05CD07
70. Terazosin	G04CA03
71. Tolterodine	G04BD07
72. Tramadol	NO2AX02
73. Tranylcypromine	N06AF04
74. Triazolam	N05CD05
75. Trifluoperazine	N05AB06
76. Trihexyphenidyl	N04AA01
77. Trimipramine	N06AA06
78. Valproic Acid	N03AG01
79. Venlafaxine	N06AX16
80. Ziprasidone	N05AE04
81. Zopiclone	N05CF01
82. Zuclopenthixol	N05AF05

ATC = Anatomical Therapeutic Classification

Table 2: Participant data to be collected during the study

	T0*	T1*	T2*
Demographic data			
Sex	x		
Age	x		
Ethnicity	x		
Medical problem and medicine(s) history			
Regular and PRN medicines prescribed as per ATC*	x		x
List of current medical conditions	x		x
History of medical conditions	x		
List of medicines with no valid indication	x		x
Frailty & comorbidity			
Edmonton frailty scale	x		x
Charlson comorbidity index (CCI)	x		x
Geriatric Depression Scale (GDS)	x	x	x

T0= Time of participant enrolment; **T1**= 3 months after participant enrolment; **T2**= 6 months after participant enrolment; **PRN**= as required medicines; **ATC**= anatomical therapeutic classification

Table 3: Outcome measures to be collected at various time points in the study

Outcome	Measure	Hypothesis	Analysis	T0	T1	T2
Drug burden	DBI*	Decrease	t-test	x		x
Quality of life	EQ-5D-5L*	Remain the same/improve	t-test	x		x
Cognition	InteRAI-Long Term Care Facilities (LTCF)*	Remain the same or deteriorate	t-test	x	x	x
Adverse effects caused by psychotropics	UKU-SERS*	Decrease	t-test	x	x	x

T0= Time of participant enrolment; **T1**= 3 months after participant enrolment; **T2**= 6 months after participant enrolment**; DBI**= Drug Burden Index; **EQ-5D-5L**= Descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses, which record the level of severity; **InteRAI-LTCF=** An assessment system that informs and guides comprehensive care and service planning and can be used to assess persons with chronic needs for care; **UKU-SERS**= UKU-Side effect rating scale is a clinician-rated scale and documents the unwanted effects of psychotropics using a semi-structured interview

Table 4: Outcome measures

Full name of assessment tool	Reasoning
Drug Burden Index (DBI) [1]	• Assesses the cumulative effect of both anticholinergic and sedative medicines in a quantitateive score • Increasing DBI has been associated with poorer physical function, falls, frailty, hospitalisation and mortality in studies of polypharmacy • A change of 0.5 in score is clinically significant
InteRAI-Long Term Care Facilities (InteRAI-LTCF) [2]	• Includes a wide array of cognitive performance, activities of daily living (ADL) using the InteRAI Hierarchy ADL scale [3] and health quality assessments. • The reliability of the inteRAI suite of assessment instruments has been tested and has been shown that all items tested met or exceeded standard cut-offs for acceptable reliability and a substantial proportion of items showed excellent reliability [4]. • It is a versatile, viable way of recording health information from routine practice in a way that permits aggregation of accurate, reliable, valid data, safe for use in health services research and pragmatic studies where randomised controlled trials are impossible [5].
EuroQoL-5 dimension-5 level (EQ-5D-5L) Quality of Life measure [6]	This measure will be used to monitor the participants' quality of life during the study and has been used in a number of interventional studies in this population. It allows for economic evaluation.
UKU Side effect rating scale (UKU-SERS) [7]	As we aim to deprescribe anticholinergic and sedative medicines (i.e. which include psychotropic medicines) and we expect our participants to be prescribed a large amount of these medicines inappropriately, it is pertinent to choose an adverse effect rating scale such as the UKU-SERS, which specifically reports on the unwanted adverse effects associated with the use of psychotropic medicines.

References:

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4. Hirdes JP, Ljunggren G, Morris JN, Frijters DH, 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;8:277.

5. Carpenter GI. Accuracy, validity and reliability in assessment and in evaluation of services for older people: the role of the interRAI MDS assessment system. Age and ageing. 2006 Jul;35(4):327-9.

6. The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990 16(3):199-208.

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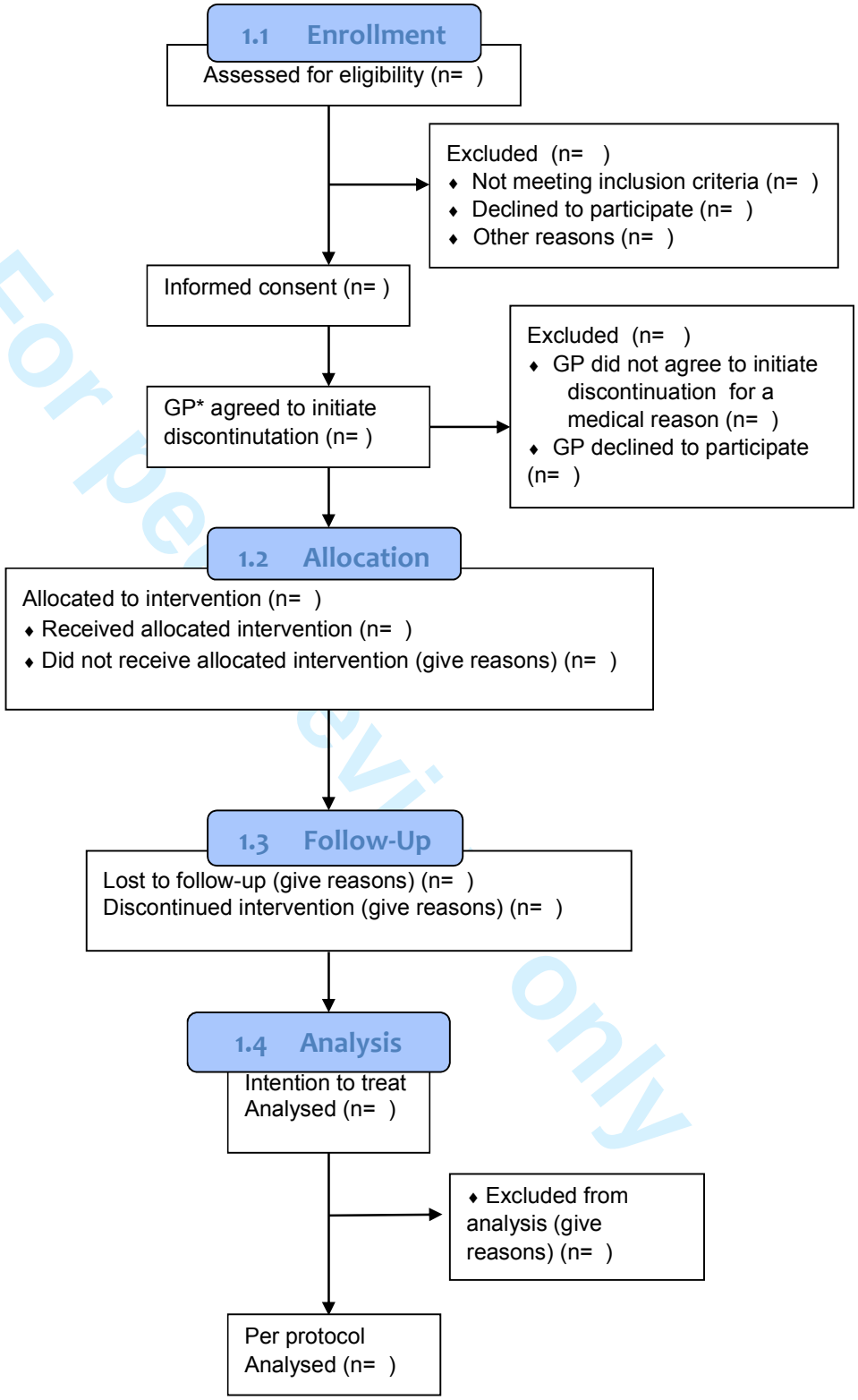
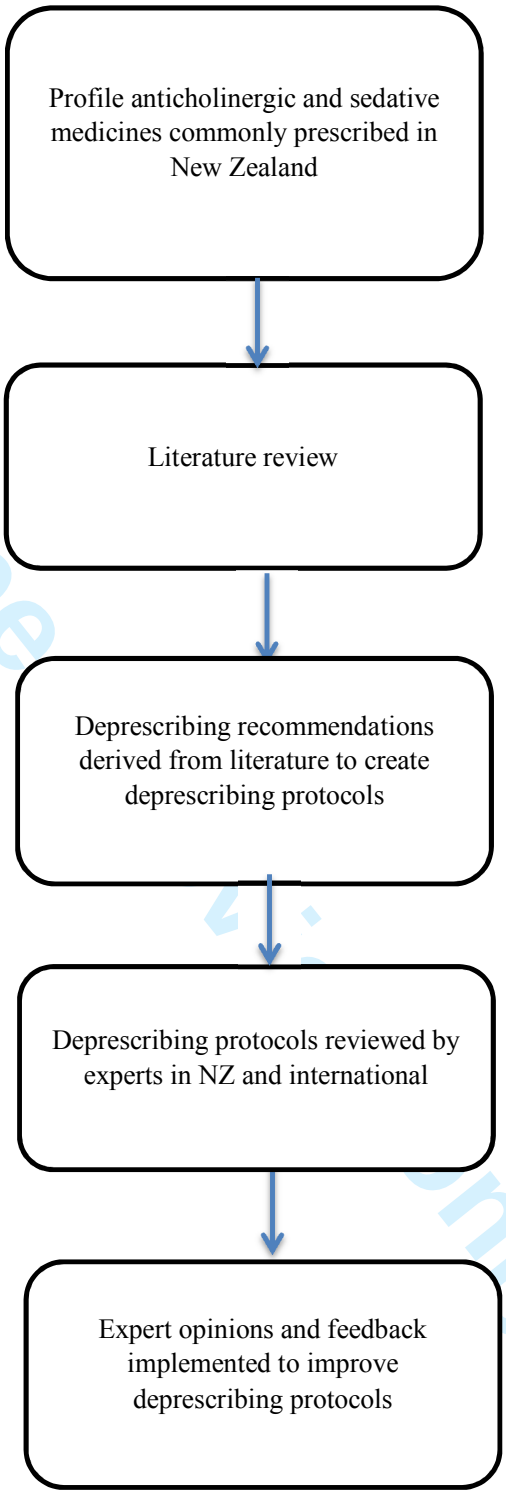
Figure 1: Flow diagram for the DEFEAT study using CONSORT*



CONSORT: CONsolidated Standards of Reporting Trials; **GP:** general practitioner

Figure 2: Flow diagram for the development of the deprescribing drug protocols



Appendix 1: The Standard Protocol Items: Recommendations for Interventional trials (SPIRIT checklist)

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

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

	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
		The study design will be revised and set upon recommendations of
	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)

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
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
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)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
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)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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
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)

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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
	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
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

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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
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
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
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)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site

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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Appendix 2: Patient information and consent forms for participants

Participant Information Sheet

Study title: Deprescribing anticholinergic and sedative medicines: A Feasibility study (DEFEAT-study) in residential aged care facilities

Locality: Timaru, NZ

Ethics committee ref.:

Lead investigator: Nagham Ailabouni

Contact phone number: 021-1226416

You are invited to take part in a study about Deprescribing. Deprescribing is the process of reducing and/or discontinuing medicines that may be inappropriate, harmful or no longer necessary. Whether or not you take part is your choice. If you do not wish to take part, you don't have to give a reason, and it won't affect the care you receive. If you wish to take part now, but change your mind later, you can withdraw from the study at any time.

This participant information sheet will help you decide if you wish to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. We expect this will take approximately 20 minutes. You may also want discuss the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 6 pages long, including the Consent Form. Please make sure that you have read all the pages.

Why are we doing the study?

Residents living in residential care aged care facilities are sometimes prescribed medicines they no longer need. The more medicines you take, the more susceptible you are to experiencing one or more negative health effects. These can include, for example, falling or experiencing

uncomfortable drug side effects. Side effects can include having blurred vision, dry mouth, constipation or experiencing constant muscle pain or nightmares.

In particular, sedative and anticholinergic medicines, such as sleeping tablets or antidepressants tend to be overprescribed to older people. Side effects such as confusion, dizziness, poor quality of sleep and an increased number of falls have been reported with use of these medicines. This study aims to investigate whether it is feasible to reduce or discontinue these medicines and whether this will improve your quality of life and wellbeing.

In this study, a New Zealand registered pharmacist and PhD candidate from the University of Otago, Mrs. Nagham Ailabouni, will work alongside you and your general practitioner (GP) to review all medicines you are currently taking, in an attempt to discontinue or reduce anticholinergic and sedative medicines.

The study is being carried out by the following researchers:

- Dr Prasad Nishtala, Senior Lecturer, School of Pharmacy, University of Otago
- Professor Dee Mangin, Professor, University of Otago, Christchurch and David Braley Nancy Gordon, Chair in Family Medicine, McMaster University, Canada
- Nagham Ailabouni, PhD Candidate, School of Pharmacy, University of Otago

Nagham Ailabouni is conducting this study as the basis for the degree of Doctor of Philosophy at The University of Otago. This will take place under the supervision of Dr. Prasad Nishtala and Professor Dee Mangin.

This study is funded by an independent organization, the New Zealand Lotteries Health Research. Ethics approval to carry out this study has been granted, by the Human and Disability Human Ethics committee on this date xx/xx/xx (TBC).

If you have any questions regarding this project, you may contact the Principal investigator, Nagham Ailabouni, or any of the other principal researchers involved. Their details are listed on the page 7 of this document.

What would your participation involve?

If you choose to participate in this study, you will be asked to read this information sheet carefully and sign the consent form on page 8 of this document. In total, you will be asked to attend four main appointments with the pharmacist over a period of six months. You may wish to invite any of your relatives, family or whānau to this appointment and all future appointments. These appointments will include:

1) Initial appointment

Prior to this appointment, the pharmacist will thoroughly read your clinical notes and assess your medicine chart. With the help of the nurse, the pharmacist will schedule an appointment at a time that is convenient to you. At this appointment, the pharmacist will have an in-depth discussion with you about your current beliefs and ideas regarding your medicines, and any concerns you may have about any of your prescribed medicines. The purpose of this discussion is to ascertain any medicine(s) that you may be having trouble taking or would not like to continue taking.

In addition to this, the pharmacist will ask you, with the help of your chosen relative or friend to complete a survey. The survey will include a number of questions, for example, it will help to assess your current quality of life, and the appropriateness of all your medicines. The pharmacist

will record this information alongside information from your medical notes in a secure and password protected computer database. This information will be de-identified and will be securely stored in such a way that only the principal researchers whose details are available on page 7, can access it. The data monitoring committee of the study, consisting of another pharmacist and a biostatistician will also have access to this de-identified data in order for them to monitor the validity of the study data and the overall safety of the study.

The pharmacist will document the discussion that took place at this initial appointment in a purposive developed study document. You and your relative or family member will be provided with a hard copy of this document. If you are unhappy with any of the document's content, you have the right to request the pharmacist to change this.

2) Multi-disciplinary clinical review meeting

The pharmacist will submit recommendations to your GP based on the scientific evidence to reduce or discontinue the anticholinergic or sedative medicines that you may be prescribed. The pharmacist and your GP will discuss these recommendations. A meeting may be thought to be helpful to plan for you, and if so, you will be invited to attend this meeting with your chosen friend or relative. The registered nurse and general practitioner who are involved with your care, along with the pharmacist, will also be present at this meeting.

The recommendations that the pharmacist has made to your GP will be discussed. At any point, you have the freedom to refuse any of the recommendations that have been put forward.

An appropriate medication management plan (MMP) to reduce these medicines in a way that is safe and appropriate will be formulated. Certain monitoring might need to take place to ensure that you are healthy and fit. Standard blood tests will be ordered by your GP for monitoring.

After a medicine is reduced or discontinued, the pharmacist will follow up with you and review your wellbeing, twice a week. After two weeks, if you are stable and doing well, the dose will be further reduced or the next target medicine will be reduced. This process will continue until all target medicines are withdrawn and you are deemed to be stable. The pharmacist will then follow up with you, weekly for a further two visits and, if stable, no additional visits, besides those outlined above, will be conducted.

3) Three month appointment

At three months, the pharmacist will review all of your current medical information. The pharmacist will ask you about any medication side effects, in the presence of your relative or family member. This will be carried out in order to ascertain any changes to your health that could have resulted after reducing or discontinuing one or more of the medicines that you had been taking.

4) Six month appointment

At six months, the pharmacist will recollect all of your current medical information. She will carry out the same tests outlined above in the presence of your relative or family member. This will be carried out in order to ascertain any changes to your health that could have resulted after reducing or discontinuing one or more of the medicines you had been taking.

What are the possible benefits and risks to you of participating?

If you decide to participate in this study, you may experience one or more possible health benefits. You may feel better overall as you will have a reduced risk of suffering from the harmful effects your medicines. These include symptoms such as a dry mouth, blurred vision, confusion, agitation and even nightmares. You also may feel more mobile and active.

On the other hand, you may not experience any benefits from stopping any of your medicines. When reducing or stopping anticholinergic and sedative medicines (defined above), some patients may be susceptible to developing adverse drug withdrawal effects (ADWEs). ADWEs occur because your body may have become used to the medicines after being prescribed them for a long period of time. To prevent ADWEs and reduce your risk of developing them, all target medicines will be slowly reduced or discontinued. In addition, you will be thoroughly monitored by the pharmacist and nursing staff. If any unexpected adverse effect is noted, or if you report to us that you are not feeling well, your GP will be immediately contacted for prompt medical attention.

The reason to why you have been feeling unwell will be ascertained, and explained to you. We will inform you that if the reason is likely to be as a result of reducing or discontinuing your medicines. If this is the case, you will be reminded of your option to withdraw from the study with no disadvantage being made to yourself. No payment or reimbursement will be provided for participants in this study.

What would happen if you were injured in the study?

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover. If you were injured in this study, which is unlikely, you would be eligible for compensation from Accident Compensation Corporation (ACC) just as you would be if you were injured in an accident at work or at home.

What are the rights of participants in the study?

If you decide to participate in the study, you will be assigned a specific study ID number. This will prevent your personal name being linked to any information that will be collected. All of the collected health information will be securely stored in a password-protected file, on a password-protected computer. This information will be backed up on a secure University of Otago network. Members of the research team (listed on page 6) are the only individuals who may access this information, during the course of the study.

Participation in this study is not obligatory. We expect that you might benefit from participating, however it is completely up to you whether you accept to participate or decline. You are also free to seek advice from your family member(s), relatives or friends about participating in this study. If you decide to participate in this study, you have the right to withdraw from the study and decline continuing to participate at any stage. You do not have to provide a full reason for why you do not wish to continue. However, this information would be very helpful and useful to the study.

During the outlined appointments or follow-ups the pharmacist will conduct during the study, you will be informed of any marked improvements to your health that could be attributed to your medicines being reduced or discontinued. You and your family member(s) or relative will also receive a copy of all formal documentation that may arise from meetings during the study. The pharmacist will explain these documents to you as necessary and you may ask her any questions you may have regarding these documents or the study. You have the right to request your health information to be deleted or altered. The pharmacist will amend your health information records according to your feedback, as appropriate.

As explained above, if you were to suffer from a harmful effect that is thought to be linked to stopping or reducing your medicines, the pharmacist or the GP will inform you of this. At this point,

you will be reminded of your right to withdraw participation from the study. If you wish to withdraw, no disadvantage will be made to you as a result. You will continue to receive your usual medical care by your GP and nursing staff.

What will happen after the study ends, or if you pull out?

No study intervention will occur after the conclusion of the study. Health information (i.e. study data) collected will be securely stored in such a way that only those researchers mentioned below will be able to gain access to it. At the end of the project, any personal information will be destroyed immediately except that any raw data on which the results depend will be retained in secure storage for ten years after which it will be destroyed.

Any reports about this project will contain information that is amalgamated for all the participants as a group, so it will not be possible to identify any individual in any of these reports. You are welcome to request a copy of the results of the project from the investigators.

The results of the project may be published in a peer-reviewed scientific journal. This may occur one to two years after the completion of the study. The publication will be emailed to the managers of the residential care aged facility. You may request for it to be emailed to yourself or designated family member(s) or relative.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any question or concerns about the study at any stage, you can contact:

Mrs Nagham Ailabouni
PhD candidate
School of Pharmacy
University of Otago
PO Box 56, Dunedin 9054
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This information sheet is for you to keep. If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@hdc.org.nz

If you are concerned about the way this study is being conducted or you wish to make a formal compliant. Please contact the health and disability ethics committee (HDEC) that approved this study. Please quote the study title and protocol number.

Phone: xx xxx xxxx Email: xxx@moh.govt.nz

Consent Form

Declaration by participant:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

Appendix 3: Patient information and declaration form for participants' enduring power of attorney (EPOA)

Participant Information Sheet

Study title: Deprescribing anticholinergic and sedative medicines: A Feasibility study (DEFEAT-study) in residential aged care facilities

Locality:
Timaru, NZ

Ethics committee ref.:

Lead investigator:
Nagham Ailabouni

Contact phone number: 021-1226416

Your relative/donor is invited to take part in a study about Deprescribing. Deprescribing is the process of reducing and/or discontinuing medicines that may be inappropriate, harmful or no longer necessary. Whether or not your relative/donor takes part is your choice. If you do not wish for them to take part, you don't have to provide a reason, and it won't affect the care that they receive. If you decide they may take part in the study, but change your mind later, you can withdraw your relative/donor from the study at any time.

This participant information sheet will help you decide if you wish for the relative/donor to take part. It sets out why we are doing the study, what their participation would involve, what the benefits and risks to them might be, and what would happen after the study ends. You may also want discuss the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree for your relative/donor to take part in this study, you will be asked to sign the declaration Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the declaration Form to keep.

This document is 6 pages long, including the declaration Form. Please make sure that you have read all the pages.

Why are we doing the study?

Residents living in residential care aged care facilities are sometimes prescribed medicines they no longer need. The more medicines they take, the more susceptible they are to one or more negative health effects. These can include, for example, falling or experiencing uncomfortable drug side effects. Side effects can include having blurred vision, dry mouth, constipation or experiencing constant muscle pain or nightmares.

In particular, sedative and anticholinergic medicines, such as sleeping tablets or antidepressants tend to be overprescribed to older people. Side effects such as confusion, dizziness, poor quality of sleep and an increased number of falls have been reported with use of these medicines. This study aims to investigate whether it is feasible to reduce or discontinue these medicines and whether this will improve your relative/donor's quality of life and wellbeing.

In this study, a New Zealand registered pharmacist and PhD candidate from the University of Otago, Mrs. Nagham Ailabouni, will work alongside you and your general practitioner (GP) to review all medicines you are currently taking, in an attempt to discontinue or reduce anticholinergic and sedative medicines.

The study is being carried out by the following researchers:

- Dr Prasad Nishtala, Senior Lecturer, School of Pharmacy, University of Otago
- Professor Dee Mangin, Professor, University of Otago, Christchurch and David Braley Nancy Gordon, Chair in Family Medicine, McMaster University, Canada
- Nagham Ailabouni, PhD Candidate, School of Pharmacy, University of Otago

Nagham Ailabouni is conducting this study as the basis for the degree of Doctor of Philosophy (PhD) at The University of Otago. This will take place under the supervision of Dr. Prasad Nishtala and Professor Dee Mangin.

This study is funded by an independent organization, the New Zealand Lotteries Health Research. Ethics approval to carry out this study has been granted, by the Human and Disability Human Ethics committee on this date xx/xx/xx (TBC).

If you have any questions regarding this project, you may contact the Principal investigator, Nagham Ailabouni, or any of the other principal researchers involved. Their details are listed on the page 7 of this document.

What would your relative/donor's participation involve?

If you agree for your relative/donor to take part in the study, they will be asked to attend in total four main appointments with the pharmacist over a period of six months. You may wish to invite any of your relatives, family or whānau to this appointment and all future appointments. These appointments will include:

1) Initial appointment

Prior to this appointment, the pharmacist will thoroughly read your relative/donor's clinical notes and assess their medicine chart. With the help of the nurse, the pharmacist will schedule an appointment at a time that is convenient to your relative. You are also welcome to attend this meeting. At this appointment, the pharmacist will have an in-depth discussion with you about your relative/donor's medicines, and discuss any concerns you may have about any of their prescribed medicines. The purpose of this discussion is to ascertain any medicine(s) that you might think your relative/donor doesn't need to continue taking.

In addition to this, the pharmacist will ask your relative/representative, with your help to complete a survey. The survey will include a number of questions to help to assess your relative/donor's current quality of life, and the appropriateness of all their medicines. The pharmacist will record this information alongside information from their medical notes in a secure and password protected computer database. This information will be de-identified and will be securely stored in such a way that only the principal researchers whose details are available on page 7, can access it. The data

monitoring committee of the study, consisting of another pharmacist and a biostatistician will also have access to this de-identified data in order for them to monitor the validity of the study data and the overall safety of the study.

The pharmacist will document the discussion that took place at this initial appointment in a purposive developed study document. You and your relative or family member will be provided with a hard copy of this document. If you are unhappy with any of the document's content, you have the right to request the pharmacist to change this.

2) Multi-disciplinary clinical review meeting

The pharmacist will submit recommendations to your relative/donor's GP based on the scientific evidence to reduce or discontinue the anticholinergic or sedative medicines that your relative/donor may be prescribed. The pharmacist and your GP will discuss these recommendations. A meeting may be thought to be helpful to plan the process for your relative/donor. If so, you will be invited to attend this meeting along with the registered nurse, the pharmacist and the general practitioner who are involved with your relative/donor's care.

The recommendations that the pharmacist has made to your GP will be discussed openly at this meeting. At any point, you have the freedom to refuse any of the recommendations that have been put forward.

An appropriate medication management plan (MMP) to reduce these medicines in a way that is safe and appropriate will be formulated. Certain monitoring might need to take place to ensure that your relative/donor are healthy and fit. Standard blood tests will be ordered by the GP for monitoring.

After a medicine is reduced or discontinued, the pharmacist will follow up with your relative/donor to review their wellbeing, twice a week. After two weeks, if your relative/friend are stable and are doing well, the dose of the medicine will be further reduced or the next target medicine will be reduced. This process will continue until all target medicines are withdrawn and your relative/donor are deemed to be stable.

3) Three month appointment

At three months, the pharmacist will review all of your relative/donor's current medical information. The pharmacist will carry out the same tests outlined above, in your presence if feasible. This will be carried out in order to ascertain any changes to your relative/donor's health that could have resulted after reducing or discontinuing one or more of the medicines that they had been taking.

4) Six month appointment

At six months, the pharmacist will recollect all of your relative/donor's current medical information. She will carry out the same tests outlined above. This will be carried out in order to ascertain any changes to your health that could have resulted after reducing or discontinuing one or more of the medicines they had been taking.

What are the possible benefits and risks to your relative/donor of participating?

If you agree for your relative/donor to participate in this study, they may experience one or more possible health benefits. They may feel better overall as they will have a reduced risk of suffering from the harmful effects caused by some of their medicines. They may also feel more mobile and active.

On the other hand, your relative/donor may not experience any benefits from stopping any of their medicines. When reducing or stopping anticholinergic and sedative medicines (defined above), some patients may be susceptible to developing adverse drug withdrawal effects (ADWEs). ADWEs occur because your body may have become used to the medicines after being prescribed them for a long period of time.

To prevent ADWEs and reduce your risk of developing them, all target medicines will be slowly reduced or discontinued. In addition, your relative/donor will be thoroughly monitored by the pharmacist and nursing staff. If any unexpected adverse effect is noted, their GP will be immediately contacted for prompt medical attention.

The reason to why your relative/donor may have been feeling unwell will be ascertained, and explained to them and yourself. We will inform you if the reason is likely to be as a result of reducing or discontinuing their medicines. If this is the case, you will be reminded of your option to withdraw your relative/friend from the study with no disadvantage being made to them or yourself. No payment or reimbursement will be provided for participants in this study.

What would happen if your relative/donor were injured in the study?

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover. If you were injured in this study, which is unlikely, you would be eligible for compensation from Accident Compensation Corporation (ACC) just as you would be if you were injured in an accident at work or at home.

What are the rights of participants in the study?

Your relative/donor will be assigned a specific study ID number. This will prevent their personal name being linked to any information that will be collected. All of the collected health information will be securely stored in a password-protected file, on a password-protected computer. This information will be backed up on a secure University of Otago network. Members of the research team (listed on page 6) are the only individuals who may access this information, during the course of the study.

Participation in this study is not obligatory. We expect that your relative/donor might benefit from participating, however it is completely up to you whether you accept for them to participate or decline this request.

You are also free to seek advice from your family member(s), relatives or friends about your relative/donor participating in this study. If you decide for your relative/donor to participate in this study, you have the right to withdraw from the study and decline continuing to participate at any stage. You do not have to provide a full reason for why you do not wish for your relative/donor to continue to participate in the study. However, this information would be very helpful and useful to the study.

During the outlined appointments or follow-ups the pharmacist will conduct during the study, you will be informed of any marked improvements to your health that could be attributed to your medicines being reduced or discontinued. You and your relative/donor will also receive a copy of all formal documentation that may arise from meetings during the study. The pharmacist will explain these documents to you as necessary and you may ask her any questions you may have regarding these documents or the study. You have the right to request your relative/donor's health information to be deleted or altered. The pharmacist will amend your health information records according to your feedback, as appropriate.

As explained above, if your relative/donor were to suffer from a harmful effect that is thought to be linked to stopping or reducing your medicines, the pharmacist or the GP will inform you of this. At this point, you will be reminded of your right to withdraw your relative/donor from participating in the study. No disadvantage will be made to your relative/donor as a result. They will continue to receive their usual medical care by their GP and nursing staff.

What will happen after the study ends, or if you pull out?

No study intervention will occur after the conclusion of the study. Health information (i.e. study data) collected will be securely stored in such a way that only those researchers mentioned below will be able to gain access to it. At the end of the project, any personal information will be destroyed immediately except that any raw data on which the results depend will be retained in secure storage for ten years after which it will be destroyed.

Any reports about this project will contain information that is amalgamated for all the participants as a group, so it will not be possible to identify any individual in any of these reports. You are welcome to request a copy of the results of the project from the investigators.

The results of the project may be published in a peer-reviewed scientific journal. This may occur one to two years after the completion of the study. The publication will be emailed to the managers of the residential care aged facility. You may request for it to be emailed to yourself or designated family member(s) or relative.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any question or concerns about the study at any stage, you can contact:

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Professor Derelie Mangin*
Co-supervisor
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*School of Medicine, University of Otago, Christchurch

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Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

If you are concerned about the way this study is being conducted or you wish to make a formal compliant. Please contact the health and disability ethics committee (HDEC) that approved this study. Please quote the study title and protocol number.

Phone: xx xxx xxxx Email: xxx@moh.govt.nz

Declaration Form

Declaration by enduring power of attorney (EPOA), on behalf of the participant:

I have read, or have had read to me in my first language, the participant information sheet, and I understand it. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

I believe that this study might benefit my relative/donor, and would be in line with his/her interests:

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant's EPOA, and have answered their questions about it.

I believe that the participant's EPOA understands the study and believes that the participation of his/her relative would be in line with their relative's interests.

Researcher's name:

Signature: Date:

Appendix 4: GP participant enrolment form

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Insert Date

Dear Dr X,

Please find below a list of the names of potential participants who are unable to provide their own consent and their EPOA have either agreed for them to take part in the study, or their EPOA have not yet responded.

Please indicate, by ticking the box next to the potential participant's name, if you agree that the deprescribing intervention, proposed in the study, might be beneficial to them. If you disagree for any potential participant to take part in the study, please indicate this in the designated box provided, along with a brief reason as to why the intervention would be unsuitable for them (e.g:. previous unsuccessful attempt at discontinuing medicines, resident receiving palliative care etc.)

Potential participants whose EPOAs have agreed for their resident to take part			**Potential participants whose EPOAs have not responded**		
Name	✓ / X	Reason for disagreeing to enrol participant	Name	✓ / X	Reason for disagreeing to enrol participant

GP signature: _____

Appendix 5: General practitioner invitation letter

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Insert Date

Dear Dr X,

I am writing to inform you of a study that is set to take place this year in three residential care homes in Timaru and Temuka. I would be most grateful if I can organise a fifteen-minute appointment over the next month, in order to discuss and explain the study's protocol in-depth, and address any of your question(s).

This study aims to test a method for reducing polypharmacy. I am a New Zealand (NZ) registered pharmacist and this study is a component of my doctoral studies at the School of Pharmacy, University of Otago. My PhD supervisors are Dr. Prasad Nishtala at the University of Otago, and Professor Dee Mangin from General Practice in Christchurch. The residential age care facilities (RACFs) that will be part of the study are The Croft and Margaret Wilson in Timaru, as well as the Wallingford Complex in Temuka. It is my understanding that you currently provide medical care for one or more of the residents residing in these RACFs. This letter will explain the purpose of the study, the intervention we intend to implement and the health outcomes we hope to achieve.

Deprescribing is the process of safely reducing or discontinuing medicines that are deemed to be inappropriate or no longer necessary. This study will involve deprescribing anticholinergic and sedative medicines, as these medicines are commonly prescribed in older people and are associated with many adverse effects including poor cognitive and physical functioning. Deprescribing has been associated with a lower annual acute hospital admission rate, an improvement in quality of life. No deprescribing studies have been conducted in NZ to indicate whether or not it is feasible.

If one or more of your residents would like to participate in the study, you will be notified of their names and dates of enrolment using your preferred method of contact as soon as possible. After reviewing the participant's medication regimen, drug-specific deprescribing protocols will be utilised to put forward suggestions to you as the participants' general practitioner of drugs that may be suitable to deprescribe (i.e. reduce or discontinue). The details of these recommendations will be summarised in a deprescribing medication review report and this will be emailed to you. Details of the intervention are outlined in-depth in the study protocol, attached to this letter.

We have registered this feasibility study in xxxxx. Testing this method and its effects may benefit you and your patients. It may also provide benefit to others if it proves feasible and successful. Ethical approval for this study has been obtained from the Human & Disability Ethics Committee (HDEC) board.

Yours sincerely,

Nagham Ailabouni, *PhD Candidate, RegPharm NZ, PGCertResPharm (Dist)*
Contact phone number: 021-1226416
Contact email address: Nagham.ailabouni@otago.ac.nz

Appendix 6: Deprescribing drug protocols

Consider reducing if	Consider reviewing & reducing if	Consider resuming if	Consider reviewing & stopping if	Withdrawal effects/ Monitoring
Central Nervous System Antipsychotics (APS)				
Patient has dementia and experiences severe neuropsychiatric symptoms (NPS). Studies suggest that worsening of symptoms occurs upon discontinuation of antipsychotics in this group of patients [1].	Patient has been prescribed APS for > 3 months and has mild/moderate behavioural and psychological symptoms of dementia (BPSD); APS should be reviewed and tapering of dose should be trialled. Clinical trial evidence has shown no difference to patient's quality adjusted life years (QALY) when APS's such as quetiapine, olanzapine & risperidone were discontinued compared to placebo [2]. The risk versus benefit of continuing APS's in older people is unfavourable [3] N.B.: Specific symptom/target behaviours need to be set for all patients initiating or continuing therapy. If the patient has been symptom/target behavior free for at least 3-6 months, then APS withdrawal should be considered [4].	Withdrawal of APS have caused recurrence/worsening of severe symptoms (e.g.: hallucinations, fixed delusions) in the patient, non-pharmacological options have failed and the patient is a threat to self or others [5].	- Prescribed for non-psychotic indications, unless patient is a threat to self or others [5, 6]. - There is no demonstrated benefit or there are undue side effects [4]. N.B.: Reduce dose gradually (e.g. by 50% every two weeks or longer according to patient's response. Stop after the patient is stable on the minimum dose)	- Evidence suggests that the majority of older people with dementia can be withdrawn from long-term APS with no detrimental effects on their behavior [1]. - Monitor recurrence or emergence of new target symptoms for several months after reducing/discontinuing APS as symptoms might relapse even after a longer period of time [1].
Antidepressants				
Discontinuation of antidepressants:				

1. If a patient has been taking an antidepressant for any period greater than six weeks, this should be reduced gradually over at least four weeks or longer if withdrawal symptoms emerge [7]. There is less evidence for continuing antidepressant treatment in older people for a period > 12 months [8, 9]
2. Rapid discontinuation may result in antidepressant discontinuation syndrome. This syndrome is associated with symptoms such as **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances and **H**yperarousal (anxiety/agitation) (i.e: FINISH). These usually appear about a week after abrupt discontinuation of the antidepressant [10].
3. For patients with more severe symptoms, the pre-reduction dose may need to be restarted which results in resolution of symptoms within 24 hours. Tapering can then be reinstated at a slower rate[11].
4. Patients should be monitored carefully as a high risk of suicide attempts exists during dosage changes and discontinuation[12].
5. **Antidepressants and dementia:**

- Evidence suggests that antidepressants may not be effective for treating depression in dementia [13].
- The use of antidepressants with anticholinergic properties may exacerbate cognitive decline [14].
- When discontinuing antidepressants in those who have dementia, the cornell scale of depression in dementia can help to determine the severity of depressive symptoms in these patients. Attaining a similar score to that attained while the patients were on the antidepressants indicates good tolerability to discontinuing therapy[15].

Consider continuing if	Consider reviewing & reducing if	Consider resuming if	Consider reviewing & stopping if	Withdrawal effects Monitoring
Tricyclic Antidepressants (TCAs)				
Patient has been suffering from moderate/severe depressive symptoms and antidepressants have been prescribed for less than six months [16, 17]	Deemed necessary to be prescribed, reduce dose to <100mg per day[18].	Patient is suffering from worsening depressive syndromes or showing signs of suicidality[12]	Patient has: ➢ Dementia; as there is a risk of worsening cognitive impairment [14]. ➢ Cardiac conduction abnormalities (e.g: pro-arrhythmic effects)[19] ➢ ALT levels three times greater than the upper limit of normal, or has high bilirubin levels or experiences other signs/symptoms of heptatotoxicity [20] ➢ Prostatism or history of urinary retention [21].	➢ Should be withdrawn slowly (e.g: by 25% every four weeks) [10] ➢ Antidepressant discontinuation syndrome (explained above) [7] ➢ Depressive symptoms may re-occur
Selective Serotonin Reuptake Inhibitors (SSRIs)				

Consider continuing if	Consider reviewing & reducing if	Consider resuming if	Consider reviewing & stopping if	Withdrawal effects
Patient has been suffering from moderate/severe depressive symptoms for a period lasting at least three months		Patient is suffering from worsening depressive syndromes or showing signs of suicidality [12]	➢ Co-prescribed with a non-steroidal anti-inflammatory drug (NSAID) or an antiplatelet drug due to an increased risk of upper gastrointestinal (GI) bleeding [22] ➢ Patient has any of the following factors, as they are at a high risk of developing hyponatremia [23]: - > 65 years, female - Low body weight - Concurrent use of medicines that contribute to hyponatremia (e.g.: thiazides, carbamazepine) - Prescribed fluoxetine as an SSRI [24] - Previous history of antidepressant-induced hyponatremia.	- Taper slowly (by 25%) every four to six weeks for medicines with a shorter half-life. Fluoxetine at low doses can be stopped abruptly and does not have to be tapered down, as it has a long half-life [10] - Mild self-limiting symptoms (listed above) could occur within a few days[11]. - These are more common with short-acting antidepressants such as paroxetine and immediate release venlafaxine[11]. - Could be a delay in the presentation of symptoms when fluoxetine is discontinued due to its longer half-life[11]. - Switching patients prescribed paroxetine or venlafaxine to fluoxetine, can decrease the severity of withdrawal symptoms. [25]

Benzodiazepines (BZDs)/Non-benzodiazepines (Non-BZDs)				
	- Any high dose of BZD or non-BZDs (such as zopiclone) are prescribed. [5] as the risk of harm is dose-related. Although non-BZDs have been thought to be safer than BZDs, they work on the same receptors as BZDs and have a similar adverse effect profile to BZDs in older people[26]. A recent study showed that older men prescribed non-BZDs are more likely to have a fall than those prescribed a BZD[27]. - The patient has been prescribed the BZD or BZD-agonist for a period longer than 1-4 weeks, as the cumulative use of benzodiazepines for a few weeks has been shown to result in a greater risk of falls and developing withdrawal upon stopping [5, 28-30].		- Any BZD is prescribed as the risk of harm with BZD's has been found to be independent of the medicine's half-life [5]. - Patient experiences recurrent falls or has a history of previous fracture. The highest risk for falls and fractures exists for older people who have recently been prescribed a high dose of BZD or non-BZD [31, 32].	Need to be withdrawn over a minimum period of 6 months in patients who have been treated long-term. - This reduces the chances of the patient experiencing "BZD withdrawal syndrome", characterised by insomnia, weight loss, sweating, tinnitus (ringing in the ears) and disturbances of perception [33]. - Appearance of this condition can vary from one day after stopping a short-acting BZD, up to three weeks after stopping a long-acting BZD. - Alternative methods to treating insomnia might need to be implemented such as sleep compression (reducing sleep hours to a fixed inadequate period each night, then gradually increasing the number of hours)[10]. - A suggested withdrawal protocol, which could take from 4 weeks up to one year, is as follows [33]: 1) Transfer the patient to the equivalent daily dose of diazepam (preferably taken at night). Equivalent doses for diazepam are listed in the New Zealand Formulary (NZF). 2) Reduce the diazepam dose every 2-3 weeks. If

				withdrawal symptoms start to appear, maintain the dose until symptoms start to improve. 3) Reduce the dose further, in smaller stops if necessary and stop completely.

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Appendix 7: Deprescribing medication use review form

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Deprescribing Medication Use Review Form

Date: xx/xx/xx

Study ID number: xxxxx
Full name: Mrs./Mr. X
NHI No: XXX123
GP: Dr. X

Your resident has consented to take part in a deprescribing feasibility study. I, Nagham Ailabouni, a New Zealand registered pharmacist and PhD candidate have conducted a deprescribing medication review, after completing an extensive clinical and medical history and having a discussion with the resident regarding their medicines.

The table below provides a summary of the potential medicines that would be appropriate for deprescribing. Please tick the relevant box to indicate whether or not you agree to the discontinuation (i.e. reducing or stopping) of these medicines. If you disagree to initiate discontinuation for any of these medicines in this patient, please state the reason in the far right column.

Medicines appropriate for deprescribing	Reasons for deprescribing	I, as the participant's GP		
		Agree	Disagree	Reasons for disagreeing to initiate discontinuation
1.				
2.				

GP signature: _____

Thank you for completing the table above. I will formulate a medicine management plan (MMP) for this resident within two weeks of receiving this form. This will guide deprescribing for this resident and will ensure deprescribing occurs in a safe manner. The MMP will only include those medicines you have agreed to deprescribe. A copy of this MMP will be emailed to you for approval, prior to providing a copy to the residential care staff or the resident.

Best wishes,

Nagham Ailabouni

PhD Candidate, RegPharm NZ, PGCertResPharm (Dist)

Appendix 8: Medication management plan (MMP) form

Depresscribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Medication Management Plan

Date: xx/xx/xx

Study ID number: xxxxx
Full name: Mrs./Mr. X
NHI No: XXX123
GP: Dr. X

Mrs./Mr. X's GP has agreed to deprescribe some of Mrs./Mr. X's medicines. The recommended order in which the medicines are to be deprescribed accompanied by appropriate reasoning for deprescribing, is included in the table below.

Medicines	Reasoning for deprescribing	Deprescribing (reducing/stopping) instructions
1.		
2.		
3.		

When anticholinergic and/or sedative medicines are reduced or discontinued, adverse drug withdrawal effects (ADWEs) may develop in some participants. Therefore, it is important to slowly taper the dose of the medicine(s), and monitor the participants closely. We appreciate your help in monitoring the participants.

The following chart is a guide to what you can do, if you note that the resident is experiencing ADWEs.

These ADWEs require **immediate medical attention.**

If the resident develops any of these symptoms, please contact NA immediately (Ph: 021-1226416) and the resident's GP as soon as possible.

- Significantly increased aggressive behaviour
- Significantly increased anxiety
- Harm to one self or another resident/staff member
- Delirium
- Flushing
- Hand tremor
- Seizures
- Increased heart rate or blood pressure

(Next page)

Notes:

These ADWEs **do not require immediate medical attention.**

If the resident develops any of these symptoms, please note them in the designated section below and notify NA (Ph: 021-1226416) and the resident's GP at the next GP visit.

- Change in bowel motions
- Increased headaches
- Blurry vision
- Dry mouth

_____

_____

_____

_____

Thank you for your valued cooperation and for monitoring the participants. If you would like to discuss any aspects of this study, please do not hesitate to contact any of the principal investigators whose details are listed below.

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Deprescribing anticholinergic and sedative medicines: protocol for a Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities

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Keywords:	Deprescribing, Elderly, Feasibility study, anticholinergics, sedatives, drug burden index

Deprescribing anticholinergic and sedative medicines: protocol for a Feasibility Trial (DEFEAT-polypharmacy) in residential aged care facilities

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Word count: Text= 4629**; abstract=** 299

Key words: Deprescribing, elderly, feasibility study, anticholinergic, sedatives, drug burden index

Abstract

Introduction: Targeted deprescribing of anticholinergic and sedative medicines can lead to positive health outcomes in older people; as they have been associated with cognitive and physical functioning decline. This study will examine whether the proposed intervention is feasible at reducing the prescription of anticholinergic and sedative medicines in older people.

Methods and analysis: The Standard Protocol Items: Recommendations for Interventional trials (SPIRIT checklist) was used to develop and report the protocol. Single group (pre and post comparison) feasibility study design. Study Population: Three residential care homes have been recruited. Intervention: This will involve a New Zealand registered pharmacist using peer-reviewed deprescribing guidelines, to recommend to general practitioners (GPs), sedative and anticholinergic medicines that can be deprescribed. The cumulative use of anticholinergic and sedative medicines for each participant will be quantified, using the drug burden index (DBI). Outcomes: The primary outcome will be the change in the participants' DBI total and DBI PRN three and six months after implementing the deprescribing intervention. Secondary outcomes will include the number of recommendations taken up by the GP, participants' cognitive functioning, depression, quality of life, activities of daily living and number of falls. Data collection points: Participants' demographic and clinical data will be collected at the time of enrolment, along with the DBI. Outcome measures will be collected at the time of enrolment, three and six months post enrolment.

Ethics and dissemination: Ethics approval has been granted by the Human Disability and Ethics Committee. Ethical approval number (16/NTA/61)

Trial registration: Australian New Zealand Clinical Trial registry (ANZCTR; trial registration number (ACTRN12616000721404). Protocol version 2 (10/01/2017)

Funding: This work is funded by Lotteries Health Research and is being carried out as part of NA's doctoral studies at the University of Otago, School of Pharmacy. No other funding was requested or received for this study.

Keywords

Deprescribing, elderly, feasibility study, anticholinergic, sedatives, drug burden index

Strengths and Limitations

Strengths:

- Utilising a quantitative measure (i.e. the Drug Burden Index) will help to determine the effect of deprescribing anticholinergic and sedative medicines.
- A pharmacist conducting in-depth medicine reviews could help to alleviate time constraints often faced by GPs in the residential care setting.

Limitations:

- Six months may not be adequate to fully investigate the effects of deprescribing long-term.

Introduction

Deprescribing, the process of safely reducing or discontinuing unnecessary or harmful medicines, has the potential to decrease polypharmacy, reduce inappropriate medicine use and improve health outcomes [1, 2]. Two recent studies have shown that frail older people can have their medicines safely discontinued without any detrimental effects to their health [3, 4]. A non-randomised controlled study (n=119) carried out in six rest homes, showed a decreased prescription of 2.8 medicines per patient that led to lower annual acute hospital admissions (12% in the study group *vs.* 30% in the control group, p<0.002); and decreased one year mortality rates (21% in the study group *vs.* 45% in the control group, p<0.001) [4]. Improvement of cognition [3], reduction of falls by up to 66% [5] and a decrease of hip fractures by up to 10%, were some of the benefits noted when benzodiazepines and other psychotropic medicines were reduced or discontinued [6].

Deprescribing also results in improved medication adherence [7] and reduced costs. An Australian study projected that if the average number of medications taken per person could be reduced by one; this would result in an annual cost saving of $463 million dollars [8]. Deprescribing has been shown to produce positive health outcomes for older people [3-6]. However, the best approach to implement this intervention is not yet clear. This study therefore aims to test the feasibility of an intervention to carry out deprescribing of a targeted medicine group in older people living in the residential care setting in New Zealand. A targeted intervention of deprescribing medicines with anticholinergic and sedative effects will be conducted. The fundamental aspect of this study is a pharmacist-led intervention that utilises a collaborative patient-centred approach involving the residents and general practitioners (GPs), and aims to implement deprescribing recommendations supported by evidence-based tools.

Anticholinergic and sedative medicines commonly prescribed in older people [9-11] are associated with impairments in both cognitive and physical functioning [12, 13]. The Drug Burden Index (DBI) tool will be used to quantify each participant's prescription of anticholinergic and sedative medicines. The DBI is a linear, additive pharmacological model that utilises both pharmacokinetic and pharmacodynamic principles to calculate an individual's total exposure to anticholinergic and sedative medicines [14]. The 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 [15], in older Australian men [16] and longitudinally in community dwelling older people in the United States [17]. Hilmer *et al*., showed that each additional unit of DBI had a negative effect on the physical function of older people similar to that of three additional physical comorbidities [14]. In planning a full randomised controlled trial, it is appropriate to examine the feasibility of implementing an intervention to assess whether it can reduce this focussed drug burden among older people living in residential aged care.

The Standard Protocol Items: Recommendations for Interventional trials (SPIRIT checklist) was followed in designing the study protocol **(Appendix 1)**.

Methods and analysis

Aims

We hypothesise that the burden of anticholinergic and sedative medicines can be reduced in a residential aged care setting using a collaborative, pharmacist-led, evidence supported intervention.

Study setting and design

A single group (pre and post comparison) feasibility study will be carried out in people aged 65 years and above living in a residential care setting. Participants will be recruited from three residential aged Care Facilities (RACFs) from the South Island of New Zealand.

Participant characteristics

Inclusion criteria:

1. Age ≥ 65 years

2. DBI > 0.5
3. Prescribed at least one anticholinergic medication or sedative medicine. **Table 1** lists all the target medicines that will be considered for deprescribing, along with their corresponding Anatomical Therapeutic Classification (ATC) code. This list was adapted to suit New Zealand medicines, from the sedative and anticholinergic drug burden index (DBI) medicines listed by Hilmer *et al.,* [17]. In addition to this, a medicine will be considered as an anticholinergic medicine if it is clearly described as an anticholinergic medicine in the medicine information. Similarly, a medicine will be considered as a 'sedative' if it causes considerable drowsiness and sedation. This group of medicines will encompass antipsychotics, antidepressants and benzodiazepines or non-benzodiazepine hypnotics.

Exclusion criteria:

1. Limited life expectancy: resident is receiving palliative care or their life expectancy ≤ 3 months based on the Holmes life expectancy calculator [18].
2. Residents admitted for hospice care (short-duration of stay of less than 4 weeks).

Recruitment and consent

The RACF's Medi-Map electronic prescribing computer system will be used to screen for all residents who fulfil the study's inclusion and exclusion criteria as outlined above. Of these potential participants, the RACFs' caregiver(s) or nurse(s) will determine which eligible potential participants are cognitively able to give their own consent, and those potential participants who would not be able to provide their own consent. To determine this, the nurses will use the interRAI-LTCF cognitive performance scale routinely applied to all residents (the pharmacist would not be able to gain access to the residents' medical electronic records before consent). The pharmacist will provide potential participants who are able to provide their own consent, the participant information sheet and consent form detailed in **Appendix 2**. Residents will be encouraged to consult and discuss participating in the study with their family, before consenting to take part.

For potential participants with cognitive impairment who are deemed by residential care staff to be unable to provide their own permission to take part in the study; the pharmacist and principal investigator (PI) will send a participation information sheet and declaration form to the person who is their nominated enduring power of attorney (EPOA), as detailed in **Appendix 3**. If the EPOA agrees that this study might be beneficial for their relative/donor, the resident will be enrolled in the study. If the EPOA does not agree for their relative to take part in the study, the GP will not enrol the resident into the study. In the case of the EPOA not responding to the initial letter posted to them, the pharmacist and principal investigator (PI) will attempt to contact the EPOA via telephone or e-mail, and if there is no response, the resident might be enrolled into the study if the resident's GP believes it is in the best interest of the resident. The pharmacist will provide the GPs a list of the potential participants with cognitive impairment whose EPOAs have agreed for them to take part in the study as well as a list of the potential participants whose EPOAs have not responded **(Appendix 4).**

There is a small probability that the participant's level of cognition may improve considerably during the study as a result of decreasing or stopping some of their medicines. On the other hand, participants' level of cognition could naturally deteriorate during the study, as participants become increasingly unwell. Participants' level of cognition will be assessed formally at 3 months after the date of enrolment. If their cognition has deteriorated slightly and they are still deemed by residential care staff to be able to provide their own consent, their willingness to remain enrolled in the study will be reconfirmed by nurses or caregivers (i.e. personnel independent from the research team). If their cognition has deteriorated considerably that they can no longer provide their own consent to take part in the study, then their EPOAs will have to be contacted via e-mail, letter or telephone. If they do not respond to the pharmacist's initial contact, the pharmacist will attempt to follow up. If the pharmacist doesn't receive a response from the EPOA, their relative/representative will remain enrolled in the study if the GP agrees that the deprescribing intervention is still beneficial to them.

Intervention

A collaborative pharmacist-led medication review with the GP will be employed, as this model has shown to improve success of implementing deprescribing in this setting [19-22]. General practitioners (GPs) who prescribe for the residents across the three RACFs will receive a personalised invitation letter prior to the study initiation date. A copy of the GP invitation letter is included in **Appendix 5.** Participating GPs will be provided with a list of residents who are under their medical care and who have consented to participate in the study. Reasons for GP non-participation will be formally documented and the residents under their care will be excluded from the study sample (see **Figure 1**). Figure 1 was adapted from the Consolidated Standards of Reporting Trials (CONSORT) flow diagram [23].

Study participants will receive a pharmacist-led medication review intervention conducted by the primary investigator who is a New Zealand registered pharmacist. The medication review will be based on the Medication Use Review (MUR) and Medication Therapy Assessment (MTA) Framework endorsed by the Pharmaceutical Society of New Zealand (PSNZ) [24]. The primary investigator and New Zealand pharmacist has completed the required formal training to be able to conduct such reviews in this study, and has previous work experience where she had conducted these reviews in hospital settings. We anticipate that the deprescribing intervention might provide greater benefits in participants who suffer from a smaller number of co-morbidities and are less frail, in comparison to participants who are frailer or suffer from severe cognitive impairment.

Step 1: Medical history

The InteRAI-Long term Care Facilities (InteRAI-LTCF) is a comprehensive assessment database system, utilised in residential aged care facilities internationally and in New Zealand to improve the quality of life of vulnerable people. It comprises of a wide array of cognitive performance, activities of daily living and health quality assessments. The reliability of the inteRAI suite of assessment instruments has been tested and has been shown that all items tested met or exceeded standard cut-offs for acceptable reliability, and a substantial proportion of items showed excellent reliability [25]. It is a versatile, viable way of recording health information from routine practice in a way that permits aggregation of accurate, reliable, valid data, safe for use in health services research and pragmatic studies where randomised controlled trials are impossible [26]. We will use this routinely collected data to record the patients' medical and functional status.

Step 2: Intitial consultation

Participants will have an initial consultation with the study pharmacist about their medicines and their medical conditions. The pharmacist will ask the participant questions relating to their health and medicines in order to determine if any medicines may be causing unwanted adverse effects. The participant may invite their representative/relative to attend this consultation. In this study, anticholinergic and sedative medicines will be specifically targeted for review with the aim of deprescribing when possible. Any potential anticholinergic and/or sedative medicine(s) that can be targeted for deprescribing will be flagged and any patient concerns around these medications (either current side effects or concerns around stopping) will be noted. For participants with diminished cognition, the pharmacist will invite the registered nurse to attend this consultation. This will help the participant feel at ease, and facilitate communication between them and the pharmacist. When a response from the participant is not possible, the test/scale is recorded as 'not assessed', and the information is gathered from the participant's clinical notes and interRAI data, when possible.

Step 3: Deprescribing Medication Review

A detailed medication review will be carried out, focussed on reducing the burden of these medications. The review will utilise peer-reviewed deprescribing guidelines for anticholinergic and sedative medicines developed for the intervention and attached in **Appendix 6.** The drug classes include benzodiazepines, antidepressants, and antipsychotics. These protocols were developed as part of NA's doctoral studies and were peer reviewed by an international advisory group including geriatricians, pharmacists, general practitioners and critical appraisal experts. They are designed to serve as guidance for prescribers and

clinical pharmacists involved in the process of deprescribing. The process for the development of these protocols is summarised in **Figure 2.**

The protocols appraise the evidence-based literature regarding the appropriateness of anticholinergic and sedative medicines in older people. They also provide guidance on when it may be appropriate for the prescriber to consider reviewing, reducing or stopping a targeted medicine. If a prescribed anticholinergic or sedative medicine is not included in these drug-specific deprescribing protocols, deprescribing recommendations will be based on the most recent clinical evidence available alongside appropriate clinical judgement.

When anticholinergic and/or sedative medicines are reduced or discontinued, adverse drug withdrawal effects (ADWEs) may develop. Therefore, it is important to slowly taper the dose of the medicine(s) and monitor the participants regularly. It is also important to determine the order in which the medicines will be deprescribed before deprescribing is initiated.

The deprescribing medication review plan will list:

1) The medicine(s) that can be targeted for deprescribing.
2) The reasons as to why these medicines would be appropriate for deprescribing
3) Suggestions for tapering and monitoring if indicated

A copy of the form that will be used for the deprescribing medication review report is included in the **Appendix 7.** The report will be provided to the GP who will endorse or reject the recommendations. Reasons for rejection will be recorded.

Step 4: Medication management plan

A medication management plan (MMP) will be developed by the pharmacist from this medication review plan list of recommendations and will include the detailed individualised tapering and monitoring recommendations for clear communication to the participant and/or their relative/representative, the participant's GP and nurse.

The MMP report will ensure that all recommendations and concerns are communicated clearly to all parties **(Appendix 8)** and will help ensure that deprescribing occurs in a safe manner. The MMP will specifically include the following:

- Medicines to be deprescribed (i.e. reduced or discontinued)
- The recommended order in which medicines are to be deprescribed, accompanied by appropriate reasoning if necessary
- Specific tapering or stopping guidance for each targeted medicine
- Anticipated adverse drug withdrawal effects (ADWEs)
- Monitoring and appropriate management options if withdrawal effects are to occur

The participant and/or the participant's relative/representative will be provided with a copy of the MMP along with the participant's GP and will explain to them the recommendations contained in the report. The recommendations will be discussed with the GP face-to-face, via telephone or at the 3 monthly resident clinical review meeting. If the participant, the GP and the participants' nurse agree to the recommendations listed in the MMP, the GP will initiate deprescribing for the resident at the next GP visit. All other aspects of care will continue as per normal.

Step 5: Monitoring and follow-up

Participants will be reviewed twice weekly by the study pharmacist for adverse drug withdrawal effects (ADWEs) after the cessation or the dose reduction of the first target medicine. If symptoms are stable according to pre-defined criteria and no ADWEs are reported after two weeks, the dose will be further reduced or the next target medicine will be withdrawn. The participant will continue to be reviewed twice weekly for a further two weeks and, if symptoms are stable, the dose of the next target medication will be reduced or ceased. This will continue until all target medicines are withdrawn and the participants are stable.

The participant will be monitored on a weekly basis for two more visits and, if stable, no additional visits will be conducted.

Monitoring for ADWEs will also occur independently by nursing staff and participating GPs who will observe withdrawal symptoms or recurrence of symptoms or signs that were the original indication for the drug. Details of this will be documented on the MMP form, and the staff will be encouraged to contact the pharmacist at any time the resident develops ADWEs. The GP will then be notified in a timely fashion, and an appropriate course of action, such as a GP visit and/or conducting necessary tests, will be undertaken in order to ensure the safety of the participant.

Multi-disciplinary clinical review meetings are usually held for each resident every three months in the recruited RACFs. The residents' GP, nurses, caregivers, the resident, and/or the residents' representative/relative usually attend these meetings. The study pharmacist will attend each multi-disciplinary clinical review meeting when feasibly possible. Any concerns regarding deprescribing and the health of the resident will be discussed and the study pharmacist will address these concerns. At these meetings, the resident's willingness to remain enrolled in the study will be discussed. If the resident or the resident's representative/relative expresses their wishes to withdraw from the study, the resident will be excluded.

All reasons for withdrawal or dropout will be recorded in the study. Deprescribed medication status and intentions will be recorded at the time the patient exists. All dropouts with no information will be assumed to not have a change in their DBI.

Participant timeline

The participants' GP(s) will be advised that their patients have consented to take part in this study close to the date after enrolment. A New Zealand registered pharmacist will conduct a deprescribing medication review and compile a list of appropriate deprescribing recommendations, summarised in the medication review form **(Appendix 7)**. A medication management plan will be formulated for each participant **(Appendix 8)**. Details of the MMP will be finalised within two weeks after the participant enrolment is completed.

Data Collection

All data and/or covariates will be collected at baseline (T0), after 3 months (T1) and after 6 months (T3) as detailed in **Table 2**. Data will be stored in a password protected Excel spreadsheet. These are classified in three groups as per below:

Demographic data:

- Age
- Sex
- Ethnicity

Medical problem and medicine(s) history:

- Regular and PRN medicines prescribed as per ATC
- List of current medical conditions
- List of medicines with no valid indication

Frailty and comorbidity:

- Edmonton frailty scale [27]
- Charlson comorbidity index (CCI) [28]
- InterRAI Changes in Health, End-Stage disease, Signs and Symtpoms (CHESS) score (Appendix 9) [29]

Data monitoring and safety

A committee independent from the funder and the investigators/supervisors and who have no conflicts of interest will be set up. The committee will have access to the de-identified study data, and will regularly monitor the study data integrity, mortality, hospitalisations, original indication re-emergence and ADWEs with a particular focus on events deemed to be attributable to medication discontinuation. If the rate of deaths or serious ADEs or ADWEs is noted to be exceptionally high or increases rapidly after the intervention has been implemented, the committee can recommend the trial be terminated. As this is a feasibility study, no formal stopping rules have been set. The decision will rest on the judgement of the Data Safety Monitoring Board (DSMB) informed by the data. The decision to terminate the trial will rest with the data monitoring committee. Participating GPs, RACFs managers, residential care staff members and residents will be involved in this decision, and will be informed expediently.

Outcomes

Primary Outcome: The DBI will be quantified using the DBI tool at the time of recruitment and 3 and 6 months post-intervention. Participants' DBI will reflect both dose reductions and medicines stopped post-intervention. Secondary Outcomes: Quality of life will also be assessed at baseline and 6 months post-intervention. Other outcome measures as outlined in **Table 3**.

The rationale behind the use of these tools and assessments is summarised in **Table 4.** Nurses will also be asked to monitor the appearance of specific ADWEs for each medicine to be deprescribed. Monitoring will be conducted for each individual and all ADWEs will be noted on the participant's MMP form.

Primary outcome:

The change in the participants' drug burden index (DBI total and DBI PRN) 3 and 6 months after the deprescribing intervention has been implemented. As required DBI medicines that have been administered more than once in the past three months, will be included in the total DBI score. A separate DBI PRN will also be calculated for each participant.

Secondary outcomes:

1) Change in the mean number of medicines prescribed. This will be described by the Anatomical Therapeutic Chemical (ATC) classification system.
2) Proportion of recommendations taken up by the GP(s).
3) Proportion of recommendations agreed to by patients
4) Cognitive function measured using the interRAI cognitive performance scale (CPS1 & CPS2) **(Appendix 9)**
5) Quality of life (QoL) measured using the EQ-5D-3L tool. The resident and/or proxy version will be used.
6) Activities of Daily living using sub-domains in the InterRAI-ADL scales **(Appendix 9)**
7) InterRAI aggressive behaviour scale **(Appendix 9)**
8) Geriatric depression scale (GDS) [30]
9) InterRAI depression rating scale **(Appendix 9)**
10) InterRAI pain scale **(Appendix 9)**
11) Difference in counts of adverse effects assessed using the UKU side effect rating scale (UKU-SERS-PAT) adverse effect rating scale, using 36/48 questions [30]
12) Falls risk and number of falls in the past 6 months.

The UKU-SERS adverse effect rating scale consists of 48 questions assessing side effects caused by antipsychotics. These are grouped under four components psychic, neurological, autonomic and other side effects. Some of the questions included in the 'other side effects' section, assess the presence or absence of inappropriateness in sexual activity. As this may not apply to all residents and/or some residents may feel uncomfortable answering these questions and clinical notes do not consistently record this information, these questions will be excluded and a sub-analysis will be performed using 36 of the 48 questions.

Measures that are to be completed by interviewing participants include QoL using the EQ-5D-3L, frailty using the Edmonton Frailty Scale, depression using GDS and adverse effects using the UKU-SERS-PAT score. Cumulatively these assessments are estimated to take about an hour to complete for each participant.

Power and sample size

Sample size:

In the majority of participants, the cessation of one DBI drug will decrease the DBI score by 0.5. To detect a difference in the primary outcome (reduction in DBI total score of 0.5 or more) with 80% power and alpha of 0.05, the total sample size required is 72 participants. This effect size is derived from a pilot randomized study conducted in RACFs in Australia that aimed at decreasing the DBI load in a nursing home population [31]. Power calculations were generated using Stata 13.1 (Copyright 1985-2013 StataCorp LP). As this is a feasibility study, aimed at informing power calculations for further studies, it will provide useful estimates of effect size and measurement tool properties that can be used to design larger randomised controlled trials.

Statistical methods and analysis:

We will use intention-to-treat and per-protocol analyses. All data will be analysed using the IBM SPSS version 23 statistical software. Means and standard deviations will be calculated for continuous data that follow a normal distribution. Wilcoxon signed-rank test will be used for continuous data that does not follow a normal distribution. Proportions and frequencies will be calculated for categorical data. Chi-square statistics or apposite statistical tests will be employed to analyse categorical data. Sensitivity analyses will be undertaken to examine the influence of missing data on the study findings. All statistical tests will be two-tailed, and p-values of <0.05 will be deemed significant. If data points are missing, multiple imputation techniques will be appropriately implemented during the analysis. For participants who pass away before the completion of the study, transfer to another facility or withdraw consent, the reason(s) for loss of the participant will be noted. Their data will be included in the final data analysis as per an intention-to-treat analysis.

Ethics and dissemination

Ethics approval has been obtained from the Health and Disability Ethics Committee (Reference number: 16/NTA/61). Any changes made to the original protocol, will be communicated to the Health and Disability Ethics Committee and approval will be sought to implement the amended protocol. The research team members (NA, PN and DM) will have access to the final study dataset. The results will be published in a peer-reviewed international journal and the dataset may be made available on Research Gate. Participants and/or enduring power of attorneys will be given the option to receive a summary of the published work. GPs, nurse managers and residential care staff involved will have access to the publication. No publication restrictions exist.

Study limitations

No blinding will occur as it is not practical to blind staff and participants. The pharmacist making the the deprescribing recommendations will be extracting data for assessment and outcome measures and so is not blinded. These measures however are hard rather than subjective measures, mitigating the risk of bias to some extent. In addition, adverse drug withdrawal effects (ADWEs), will be monitored subjectively by the pharmacist and the residential care staff, introducing a risk of bias. The possibility that a placebo effect may underpin some changes seen is another limitation as it is a before and after study. This however will not affect the study's primary outcome (DBI). There is no prevention in place in this study to prevent medicines being re-prescribed by physicians. This could result in medicines deprescribed being re-prescribed or additional new anticholinergic or sedative medicines being prescribed. If this occurs, the reasons for each participant will be noted. According to other deprescribing studies, recruitment of residents can be difficult. Therefore, we anticipate that recruitment of 72 participants might be challenging; particularly because we do not presently know how many potential participants are present across the three residential aged care

facilities. In addition, it is likely that EpoAs might not respond to the request of their relative/friend to be included in the study. This could ultimately affect our resulting sample size.

Discussion

Anticholinergic and sedative medicines are commonly prescribed in older people and several studies have shown that these medicines are associated with cognition and physical functioning impairment. This study aims to implement a targeted systematic intervention of deprescribing anticholinergic and sedative medicines in older people living in residential care. The intervention will involve a five-step approach, where a registered pharmacist will conduct a medical history and have a discussion with the participant about their medicines, to highlight potential medicines suitable for deprescribing. Deprescribing recommendations will be summarised on a deprescribing medication use review form. This will be forwarded to the participant's GP for their approval. Once the decision to deprescribe medicines is finalised, the pharmacist will formulate a medication management plan (MMP) for each participant to guide deprescribing in a gradual and safe manner. Participants will be thoroughly followed up by the pharmacist, and monitored closely by the pharmacist, GP and residential care staff for adverse drug withdrawal effects (ADWEs). Data resulting from this study will shed light on the effect of this intervention on the participants' DBI scores as well as their level of cognition and quality of life.

Trial status

Recruitment is set to start on 01/06/2016. Follow up is set to continue till 01/07/2017. The planned end date for data collection is 01/07/2017.

Abbreviations

SPIRIT: The Standard Protocol Items: Recommendations for Interventional trials, DBI: drug burden index, GP: general practitioner, ANZCTR: Australian and New Zealand Clinical Trials Registry, RACF: residential aged care facility, ADWE: adverse drug withdrawal effect, MMP: medicine management plan, MTA: medicine therapy assessment, InterRAI-LTCF: InterRAI long-term care facilities, InterRAI-ADL: InterRAI Activities of Daily living, ATC: anatomical therapeutic chemical

Funding statement

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Competing interests

The author(s) declare that they have no competing interests and are responsible for the content of this report.

Authors' contributions

NA, PN & DM made substantial contribution to the conception and design of the study. NA wrote the manuscript drafts. PN & DM revised the manuscript critically. All authors read and approved the final manuscript.

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Table 1: Target medicines

Generic medicine name	ATC code
1. Alprazolam	N05BA12
2. Amitriptyline	N06AA09
3. Aripiprazole	N05AX12
4. Benztropine	NO4AC01
5. Buprenorphine	N02AE01
6. Buspirone	N05BE01
7. Carbamazepine	N03AF01
8. Cetirizine	R06AE07
9. Chlorpheniramine	R06AB05
10. Chorpromazine	N05AA01
11. Citalopram	N06AB04
12. Clomipramine	N06AA04
13. Clonazepam	N03AE01
14. Clonidine	S01EA04
15. Codeine	R05DA04
16. Dexchlorphaniramine	R06AB02
17. Dextromethorphan	N02AC04
18. Diazepam	N05BA01
19. Dihydrocodeine	N02AA08
20. Disopyramide	C01BA03
21. Doxazosin	C02CA04
22. Doxepin	N06AA12
23. Escitalopram	N06AB10
24. Fentanyl	N02AB03
25. Fexofenadine	R06AX26
26. Flunitrazepam	N05CD03
27. Fluoxetine	N06AB03
28. Fluphenazine	NO5AB02
29. Fluphenazine	N05AB02
30. Gabapentin	N03AX12
31. Haloperidol	N05AD01
32. Imipramine	N06AA02
33. Lamotrigine	N03AX09
34. Levetiracetam	N03AX14
35. Loperamide	A07DA03
36. Loratadine	R06AX13
37. Lorazepam	N05BA06
38. Methadone	N07BC02
39. Methyldopa	C02AB
40. Metoclopramide	A03FA01
41. Mianserin	N06AX03
42. Mirtazepine	No code found
43. Moclobemide	N06AG02

44. Morphine	NO2AA01
45. Nitrazepam	N05CD02
46. Nortryptyline	N06AA10
47. Olanzapine	N05AH03
48. Orphenadrine	N04AB02
49. Oxazepam	N05BA04
50. Oxybutynin	G04BD04
51. Oxycodone	N02AA05
52. Paroxetine	N06AB05
53. Pericyazine	NO5AC01
54. Phenobarbital	N03AA02
55. Phenytoin	N03AB02
56. Pizotifen	N02CX01
57. Pramipexole	N04BC05
58. Prazosin	C02CA01
59. Primidone	N03AA03
60. Prochlorperazine	N05AB04
61. Promethazine	R06AD02
62. Quetiapine	NO5AH04
63. Risperidone	N05AX08
64. Ropinirole	N04BC04
65. Selegiline	N04BD01
66. Sertraline	N06AB06
67. Solifenacin	G04BD08
68. Tamsulosin	G04CA02
69. Temazepam	N05CD07
70. Terazosin	G04CA03
71. Tolterodine	G04BD07
72. Tramadol	NO2AX02
73. Tranylcypromine	N06AF04
74. Triazolam	N05CD05
75. Trifluoperazine	N05AB06
76. Trihexyphenidyl	N04AA01
77. Trimipramine	N06AA06
78. Valproic Acid	N03AG01
79. Venlafaxine	N06AX16
80. Ziprasidone	N05AE04
81. Zopiclone	N05CF01
82. Zuclopenthixol	N05AF05

ATC = Anatomical Therapeutic Classification

Table 2: Participant data to be collected during the study

	T0*	T1*	T2*
Demographic data			
Sex	x		
Age	x		x
Ethnicity	x		
Medical problem and medicine(s) history			
Regular and PRN* medicines prescribed as per ATC*	x		x
List of current medical conditions	x		x
History of medical conditions	x		
List of medicines with no valid indication	x		x
Frailty & comorbidity			
Edmonton frailty scale	x		x
Charlson comorbidity index (CCI)	x		x
Changes in Health, **E**nd-Stage disease, **S**igns and **S**ymptoms (CHESS)	x		x
Other			
Activities of Daily living (ADL)	x		x
BMI (Bone Mass Index)	x		x

T0= Time of participant enrolment; **T1**= 3 months after participant enrolment; **T2**= 6 months after participant enrolment; **PRN**= as required medicines; **ATC**= anatomical therapeutic classification

Table 3: Outcome measures to be collected at various time points in the study

Outcome	Measure	Hypothesis	Analysis	T0	T1	T2
Primary outcome						
Drug burden	DBI*	Decrease	Paired t-test/WSR* test	x	x	x
Secondary outcomes						
Quality of health measures, cognition & adverse effects						
Quality of life	EQ-5D-5L*	Remain the same/improve	Paired t-test/ WSR* test	x		x
Cognition	InteRAI-Long Term Care Facilities (LTCF)*	Remain the same or deteriorate	Paired t-test/ WSR* test	x	x	x
Adverse effects caused by psychotropics	UKU-SERS*	Decrease	Paired t-test/ WSR* test	x	x	x
Number of falls in the past 6 months	Resident records	Remain the same or decrease	Paired t-test/ WSR* test	x		x
Specific morbidities						
Depression	Geriatric Depression Scale (GDS) InterRAI Depression Rating Scale (DRS)	Remain the same	Paired t-test/ WSR* test	x	x	x
Pain	InterRAI Pain Scale	Remain the same or be improve	Paired t-test/ WSR* test	x		x
Aggressive behaviour	InterRAI Aggressive Behaviour Scale	Remain the same or improve	Paired t-test/ WSR* test	x		x
Deprescribing recommendations						
Proportion of recommendations taken up by GPs			Chi-squared			
Proportion of recommendatons taken up by patients			Chi-squared			
Medicines						
Change in the mean number of medicines prescribed		Remain the same or decrease	Paired t-test/ WSR* test	x		x

T0= Participant enrolment time; **T1**= 3 months after participant enrolment; **T2**= 6 months after participant enrolment**; DBI**= Drug Burden Index; **EQ-5D-5L**= Descriptive system of health-related quality of life; **InteRAI-LTCF=** An assessment system that informs and guides comprehensive care and service planning and can be used to assess persons with chronic needs for care; **UKU-SERS**= UKU-Side effect rating scale is a scale that documents unwanted effects of psychotropics using a semi-structured interview; **WSR=** Wilcoxon signed rank test

Table 4: Outcome measures

Full name of assessment tool	Reasoning
Drug Burden Index (DBI) [1]	• Assesses the cumulative effect of both anticholinergic and sedative medicines in a quantitateive score • Increasing DBI has been associated with poorer physical function, falls, frailty, hospitalisation and mortality in studies of polypharmacy • A change of 0.5 in score is clinically significant
InteRAI-Long Term Care Facilities (InteRAI-LTCF) [2]	• Includes a wide array of cognitive performance, activities of daily living (ADL) using the InteRAI Hierarchy ADL scale [3] and health quality assessments. • The reliability of the inteRAI suite of assessment instruments has been tested and has been shown that all items tested met or exceeded standard cut-offs for acceptable reliability and a substantial proportion of items showed excellent reliability [4]. • It is a versatile, viable way of recording health information from routine practice in a way that permits aggregation of accurate, reliable, valid data, safe for use in health services research and pragmatic studies where randomised controlled trials are impossible [5].
EuroQoL-5 dimension-3 level (EQ-5D-3L) Quality of Life measure [6]	This measure will be used to monitor the participants' quality of life during the study and has been used in a number of interventional studies in this population. It allows for economic evaluation.
UKU Side effect rating scale (UKU-SERS) [7]	As we aim to deprescribe anticholinergic and sedative medicines (i.e. which include psychotropic medicines) and we expect our participants to be prescribed a large amount of these medicines inappropriately, it is pertinent to choose an adverse effect rating scale such as the UKU-SERS, which specifically reports on the unwanted adverse effects associated with the use of psychotropic medicines.

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Appendix 1: The Standard Protocol Items: Recommendations for Interventional trials (SPIRIT checklist)

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ✓ Title Page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ✓ Pg 2; Abstract ; trial registration
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier ✓ Pg 2; abstract; trial registration
Funding	4	Sources and types of financial, material, and other support ✓Pg 10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ✓ Title page
	5b	Name and contact information for the trial sponsor ✓Title page
	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 ✓ Pg10
	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) ✓ Pg 8
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 ✓ Pg 3; intro
	6b	Explanation for choice of comparators ✓ Pg 3; intro
Objectives	7	Specific objectives or hypotheses ✓ Pg 3; aims
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) ✓ Pg 3; study setting & design

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ✓ Pg 3; study setting & design
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) ✓ Pg 3-4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ✓ Pg 5; intervention
	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) ✓ Pg 6; step 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ✓ Pg 6; steps 4 & 5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ✓ Pg 6; step 4; line 21-22
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 ✓ Page 8; outcomes
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) ✓ Pg 5; intervention
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 Pg 9; power & sample size ✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ✓ Pg 9; power & sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions N/A

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 N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol ✓ Pg 7; Data collection
	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 ✓ Pg 9; lines 22-25
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 ✓ Pg 7; Data collection
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 ✓ Pg 9; statistical methods & analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) ✓ Pg 9; statistical methods & analysis; Figure 1
	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) ✓ Pg 9; statistical methods & analysis
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 ✓ Pg 8; paragraph 1

	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 ✓ Pg 8; data monitoring & safety
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 ✓ Pg 7; lines 6-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ✓ Pg 8; data monitoring & safety
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ✓ Pg 9; ethics & disemmination
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) ✓ Pg 9; ethics & disemmination
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ✓ Pg 4
	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 Appendices 2 & 3
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ✓ Pg 10
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 ✓ Pg 9; ethics & disemmination
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 ✓ Pg 9; ethics & disemmination
	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 ✓ Pg 9; ethics & disemmination

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ✓	Appendices 2 & 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Appendix 2: Patient information and consent forms for participants

Participant Information Sheet

Study title: Deprescribing anticholinergic and sedative medicines: A Feasibility study (DEFEAT-study) in residential aged care facilities

Locality: Timaru, NZ

Ethics committee ref.:

Lead investigator: Nagham Ailabouni

Contact phone number: 021-1226416

You are invited to take part in a study about Deprescribing. Deprescribing is the process of reducing and/or discontinuing medicines that may be inappropriate, harmful or no longer necessary. Whether or not you take part is your choice. If you do not wish to take part, you don't have to give a reason, and it won't affect the care you receive. If you wish to take part now, but change your mind later, you can withdraw from the study at any time.

This participant information sheet will help you decide if you wish to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. We expect this will take approximately 20 minutes. You may also want discuss the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 6 pages long, including the Consent Form. Please make sure that you have read all the pages.

Why are we doing the study?

Residents living in residential care aged care facilities are sometimes prescribed medicines they no longer need. The more medicines you take, the more susceptible you are to experiencing one or more negative health effects. These can include, for example, falling or experiencing uncomfortable drug side effects. Side effects can include having blurred vision, dry mouth, constipation or experiencing constant muscle pain or nightmares.

In particular, sedative and anticholinergic medicines, such as sleeping tablets or antidepressants tend to be overprescribed to older people. Side effects such as confusion, dizziness, poor quality of sleep and an increased number of falls have been reported with use of these medicines. This study aims to investigate whether it is feasible to reduce or discontinue these medicines and whether this will improve your quality of life and wellbeing.

In this study, a New Zealand registered pharmacist and PhD candidate from the University of Otago, Mrs. Nagham Ailabouni, will work alongside you and your general practitioner (GP) to review all medicines you are currently taking, in an attempt to discontinue or reduce anticholinergic and sedative medicines.

The study is being carried out by the following researchers:

- Dr Prasad Nishtala, Senior Lecturer, School of Pharmacy, University of Otago
- Professor Dee Mangin, Professor, University of Otago, Christchurch and David Braley Nancy Gordon, Chair in Family Medicine, McMaster University, Canada
- Nagham Ailabouni, PhD Candidate, School of Pharmacy, University of Otago

Nagham Ailabouni is conducting this study as the basis for the degree of Doctor of Philosophy at The University of Otago. This will take place under the supervision of Dr. Prasad Nishtala and Professor Dee Mangin.

This study is funded by an independent organization, the New Zealand Lotteries Health Research. Ethics approval to carry out this study has been granted, by the Human and Disability Human Ethics committee on this date xx/xx/xx (TBC).

If you have any questions regarding this project, you may contact the Principal investigator, Nagham Ailabouni, or any of the other principal researchers involved. Their details are listed on the page 7 of this document.

What would your participation involve?

If you choose to participate in this study, you will be asked to read this information sheet carefully and sign the consent form on page 8 of this document. In total, you will be asked to attend four main appointments with the pharmacist over a period of six months. You may wish to invite any of your relatives, family or whānau to this appointment and all future appointments. These appointments will include:

1) Initial appointment

Prior to this appointment, the pharmacist will thoroughly read your clinical notes and assess your medicine chart. With the help of the nurse, the pharmacist will schedule an appointment at a time that is convenient to you. At this appointment, the pharmacist will have an in-depth discussion with you about your current beliefs and ideas regarding your medicines, and any concerns you may have about any of your prescribed medicines. The purpose of this discussion is to ascertain any medicine(s) that you may be having trouble taking or would not like to continue taking.

In addition to this, the pharmacist will ask you, with the help of your chosen relative or friend to complete a survey. The survey will include a number of questions, for example, it will help to assess your current quality of life, and the appropriateness of all your medicines. The pharmacist will record this information alongside information from your medical notes in a secure and password protected computer database. This information will be de-identified and will be securely stored in such a way that only the principal researchers whose details are available on page 7, can

access it. The data monitoring committee of the study, consisting of another pharmacist and a biostatistician will also have access to this de-identified data in order for them to monitor the validity of the study data and the overall safety of the study.

The pharmacist will document the discussion that took place at this initial appointment in a purposive developed study document. You and your relative or family member will be provided with a hard copy of this document. If you are unhappy with any of the document's content, you have the right to request the pharmacist to change this.

2) Multi-disciplinary clinical review meeting

The pharmacist will submit recommendations to your GP based on the scientific evidence to reduce or discontinue the anticholinergic or sedative medicines that you may be prescribed. The pharmacist and your GP will discuss these recommendations. A meeting may be thought to be helpful to plan for you, and if so, you will be invited to attend this meeting with your chosen friend or relative. The registered nurse and general practitioner who are involved with your care, along with the pharmacist, will also be present at this meeting.

The recommendations that the pharmacist has made to your GP will be discussed. At any point, you have the freedom to refuse any of the recommendations that have been put forward.

An appropriate medication management plan (MMP) to reduce these medicines in a way that is safe and appropriate will be formulated. Certain monitoring might need to take place to ensure that you are healthy and fit. Standard blood tests will be ordered by your GP for monitoring.

After a medicine is reduced or discontinued, the pharmacist will follow up with you and review your wellbeing, twice a week. After two weeks, if you are stable and doing well, the dose will be further reduced or the next target medicine will be reduced. This process will continue until all target medicines are withdrawn and you are deemed to be stable. The pharmacist will then follow up with you, weekly for a further two visits and, if stable, no additional visits, besides those outlined above, will be conducted.

3) Three month appointment

At three months, the pharmacist will review all of your current medical information. The pharmacist will ask you about any medication side effects, in the presence of your relative or family member. This will be carried out in order to ascertain any changes to your health that could have resulted after reducing or discontinuing one or more of the medicines that you had been taking.

4) Six month appointment

At six months, the pharmacist will recollect all of your current medical information. She will carry out the same tests outlined above in the presence of your relative or family member. This will be carried out in order to ascertain any changes to your health that could have resulted after reducing or discontinuing one or more of the medicines you had been taking.

What are the possible benefits and risks to you of participating?

If you decide to participate in this study, you may experience one or more possible health benefits. You may feel better overall as you will have a reduced risk of suffering from the harmful effects your medicines. These include symptoms such as a dry mouth, blurred vision, confusion, agitation and even nightmares. You also may feel more mobile and active.

On the other hand, you may not experience any benefits from stopping any of your medicines. When reducing or stopping anticholinergic and sedative medicines (defined above), some patients

may be susceptible to developing adverse drug withdrawal effects (ADWEs). ADWEs occur because your body may have become used to the medicines after being prescribed them for a long period of time. To prevent ADWEs and reduce your risk of developing them, all target medicines will be slowly reduced or discontinued. In addition, you will be thoroughly monitored by the pharmacist and nursing staff. If any unexpected adverse effect is noted, or if you report to us that you are not feeling well, your GP will be immediately contacted for prompt medical attention.

The reason to why you have been feeling unwell will be ascertained, and explained to you. We will inform you that if the reason is likely to be as a result of reducing or discontinuing your medicines. If this is the case, you will be reminded of your option to withdraw from the study with no disadvantage being made to yourself. No payment or reimbursement will be provided for participants in this study.

What would happen if you were injured in the study?

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover. If you were injured in this study, which is unlikely, you would be eligible for compensation from Accident Compensation Corporation (ACC) just as you would be if you were injured in an accident at work or at home.

What are the rights of participants in the study?

If you decide to participate in the study, you will be assigned a specific study ID number. This will prevent your personal name being linked to any information that will be collected. All of the collected health information will be securely stored in a password-protected file, on a password-protected computer. This information will be backed up on a secure University of Otago network. Members of the research team (listed on page 6) are the only individuals who may access this information, during the course of the study.

Participation in this study is not obligatory. We expect that you might benefit from participating, however it is completely up to you whether you accept to participate or decline. You are also free to seek advice from your family member(s), relatives or friends about participating in this study. If you decide to participate in this study, you have the right to withdraw from the study and decline continuing to participate at any stage. You do not have to provide a full reason for why you do not wish to continue. However, this information would be very helpful and useful to the study.

During the outlined appointments or follow-ups the pharmacist will conduct during the study, you will be informed of any marked improvements to your health that could be attributed to your medicines being reduced or discontinued. You and your family member(s) or relative will also receive a copy of all formal documentation that may arise from meetings during the study. The pharmacist will explain these documents to you as necessary and you may ask her any questions you may have regarding these documents or the study. You have the right to request your health information to be deleted or altered. The pharmacist will amend your health information records according to your feedback, as appropriate.

As explained above, if you were to suffer from a harmful effect that is thought to be linked to stopping or reducing your medicines, the pharmacist or the GP will inform you of this. At this point, you will be reminded of your right to withdraw participation from the study. If you wish to withdraw,

no disadvantage will be made to you as a result. You will continue to receive your usual medical care by your GP and nursing staff.

What will happen after the study ends, or if you pull out?

No study intervention will occur after the conclusion of the study. Health information (i.e. study data) collected will be securely stored in such a way that only those researchers mentioned below will be able to gain access to it. At the end of the project, any personal information will be destroyed immediately except that any raw data on which the results depend will be retained in secure storage for ten years after which it will be destroyed.

Any reports about this project will contain information that is amalgamated for all the participants as a group, so it will not be possible to identify any individual in any of these reports. You are welcome to request a copy of the results of the project from the investigators.

The results of the project may be published in a peer-reviewed scientific journal. This may occur one to two years after the completion of the study. The publication will be emailed to the managers of the residential care aged facility. You may request for it to be emailed to yourself or designated family member(s) or relative.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any question or concerns about the study at any stage, you can contact:

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PO Box 56, Dunedin 9054
New Zealand
(03) 479 7321
nagham.ailabouni@otago.ac.nz

Dr Prasad Nishtala
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University of Otago
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Professor Derelie Mangin*
Co-supervisor
Dept of General Practice,
University of Otago,
Christchurch
David Braley
Chair in Family Medicine
McMaster University
Canada
mangind@mcmaster.ca

*School of Medicine, University of Otago, Christchurch

This information sheet is for you to keep. If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@hdc.org.nz

If you are concerned about the way this study is being conducted or you wish to make a formal compliant. Please contact the health and disability ethics committee (HDEC) that approved this study. Please quote the study title and protocol number.

Phone: xx xxx xxxx Email: xxx@moh.govt.nz

Consent Form

Declaration by participant:

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this study.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name:

Signature: Date:

Appendix 3: Patient information and declaration form for participants' enduring power of attorney (EPOA)

Participant Information Sheet

Study title: Deprescribing anticholinergic and sedative medicines: A Feasibility study (DEFEAT-study) in residential aged care facilities

Locality: Timaru, NZ

Ethics committee ref.:

Lead investigator: Nagham Ailabouni

Contact phone number: 021-1226416

Your relative/donor is invited to take part in a study about Deprescribing. Deprescribing is the process of reducing and/or discontinuing medicines that may be inappropriate, harmful or no longer necessary. Whether or not your relative/donor takes part is your choice. If you do not wish for them to take part, you don't have to provide a reason, and it won't affect the care that they receive. If you decide they may take part in the study, but change your mind later, you can withdraw your relative/donor from the study at any time.

This participant information sheet will help you decide if you wish for the relative/donor to take part. It sets out why we are doing the study, what their participation would involve, what the benefits and risks to them might be, and what would happen after the study ends. You may also want discuss the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree for your relative/donor to take part in this study, you will be asked to sign the declaration Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the declaration Form to keep.

This document is 6 pages long, including the declaration Form. Please make sure that you have read all the pages.

Why are we doing the study?

Residents living in residential care aged care facilities are sometimes prescribed medicines they no longer need. The more medicines they take, the more susceptible they are to one or more negative health effects. These can include, for example, falling or experiencing uncomfortable drug side effects. Side effects can include having blurred vision, dry mouth, constipation or experiencing constant muscle pain or nightmares.

In particular, sedative and anticholinergic medicines, such as sleeping tablets or antidepressants tend to be overprescribed to older people. Side effects such as confusion, dizziness, poor quality of sleep and an increased number of falls have been reported with use of these medicines. This study aims to investigate whether it is feasible to reduce or discontinue these medicines and whether this will improve your relative/donor's quality of life and wellbeing.

In this study, a New Zealand registered pharmacist and PhD candidate from the University of Otago, Mrs. Nagham Ailabouni, will work alongside you and your general practitioner (GP) to review all medicines you are currently taking, in an attempt to discontinue or reduce anticholinergic and sedative medicines.

The study is being carried out by the following researchers:

- Dr Prasad Nishtala, Senior Lecturer, School of Pharmacy, University of Otago
- Professor Dee Mangin, Professor, University of Otago, Christchurch and David Braley Nancy Gordon, Chair in Family Medicine, McMaster University, Canada
- Nagham Ailabouni, PhD Candidate, School of Pharmacy, University of Otago

Nagham Ailabouni is conducting this study as the basis for the degree of Doctor of Philosophy (PhD) at The University of Otago. This will take place under the supervision of Dr. Prasad Nishtala and Professor Dee Mangin.

This study is funded by an independent organization, the New Zealand Lotteries Health Research. Ethics approval to carry out this study has been granted, by the Human and Disability Human Ethics committee on this date xx/xx/xx (TBC).

If you have any questions regarding this project, you may contact the Principal investigator, Nagham Ailabouni, or any of the other principal researchers involved. Their details are listed on the page 7 of this document.

What would your relative/donor's participation involve?

If you agree for your relative/donor to take part in the study, they will be asked to attend in total four main appointments with the pharmacist over a period of six months. You may wish to invite any of your relatives, family or whānau to this appointment and all future appointments. These appointments will include:

1) Initial appointment

Prior to this appointment, the pharmacist will thoroughly read your relative/donor's clinical notes and assess their medicine chart. With the help of the nurse, the pharmacist will schedule an appointment at a time that is convenient to your relative. You are also welcome to attend this meeting. At this appointment, the pharmacist will have an in-depth discussion with you about your relative/donor's medicines, and discuss any concerns you may have about any of their prescribed medicines. The purpose of this discussion is to ascertain any medicine(s) that you might think your relative/donor doesn't need to continue taking.

In addition to this, the pharmacist will ask your relative/representative, with your help to complete a survey. The survey will include a number of questions to help to assess your relative/donor's current quality of life, and the appropriateness of all their medicines. The pharmacist will record this information alongside information from their medical notes in a secure and password protected computer database. This information will be de-identified and will be securely stored in such a way that only the principal researchers whose details are available on page 7, can access it. The data

monitoring committee of the study, consisting of another pharmacist and a biostatistician will also have access to this de-identified data in order for them to monitor the validity of the study data and the overall safety of the study.

The pharmacist will document the discussion that took place at this initial appointment in a purposive developed study document. You and your relative or family member will be provided with a hard copy of this document. If you are unhappy with any of the document's content, you have the right to request the pharmacist to change this.

2) Multi-disciplinary clinical review meeting

The pharmacist will submit recommendations to your relative/donor's GP based on the scientific evidence to reduce or discontinue the anticholinergic or sedative medicines that your relative/donor may be prescribed. The pharmacist and your GP will discuss these recommendations. A meeting may be thought to be helpful to plan the process for your relative/donor. If so, you will be invited to attend this meeting along with the registered nurse, the pharmacist and the general practitioner who are involved with your relative/donor's care.

The recommendations that the pharmacist has made to your GP will be discussed openly at this meeting. At any point, you have the freedom to refuse any of the recommendations that have been put forward.

An appropriate medication management plan (MMP) to reduce these medicines in a way that is safe and appropriate will be formulated. Certain monitoring might need to take place to ensure that your relative/donor are healthy and fit. Standard blood tests will be ordered by the GP for monitoring.

After a medicine is reduced or discontinued, the pharmacist will follow up with your relative/donor to review their wellbeing, twice a week. After two weeks, if your relative/friend are stable and are doing well, the dose of the medicine will be further reduced or the next target medicine will be reduced. This process will continue until all target medicines are withdrawn and your relative/donor are deemed to be stable.

3) Three month appointment

At three months, the pharmacist will review all of your relative/donor's current medical information. The pharmacist will carry out the same tests outlined above, in your presence if feasible. This will be carried out in order to ascertain any changes to your relative/donor's health that could have resulted after reducing or discontinuing one or more of the medicines that they had been taking.

4) Six month appointment

At six months, the pharmacist will recollect all of your relative/donor's current medical information. She will carry out the same tests outlined above. This will be carried out in order to ascertain any changes to your health that could have resulted after reducing or discontinuing one or more of the medicines they had been taking.

What are the possible benefits and risks to your relative/donor of participating?

If you agree for your relative/donor to participate in this study, they may experience one or more possible health benefits. They may feel better overall as they will have a reduced risk of suffering from the harmful effects caused by some of their medicines. They may also feel more mobile and active.

On the other hand, your relative/donor may not experience any benefits from stopping any of their medicines. When reducing or stopping anticholinergic and sedative medicines (defined above), some patients may be susceptible to developing adverse drug withdrawal effects (ADWEs). ADWEs occur because your body may have become used to the medicines after being prescribed them for a long period of time.

To prevent ADWEs and reduce your risk of developing them, all target medicines will be slowly reduced or discontinued. In addition, your relative/donor will be thoroughly monitored by the pharmacist and nursing staff. If any unexpected adverse effect is noted, their GP will be immediately contacted for prompt medical attention.

The reason to why your relative/donor may have been feeling unwell will be ascertained, and explained to them and yourself. We will inform you if the reason is likely to be as a result of reducing or discontinuing their medicines. If this is the case, you will be reminded of your option to withdraw your relative/friend from the study with no disadvantage being made to them or yourself. No payment or reimbursement will be provided for participants in this study.

What would happen if your relative/donor were injured in the study?

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover. If you were injured in this study, which is unlikely, you would be eligible for compensation from Accident Compensation Corporation (ACC) just as you would be if you were injured in an accident at work or at home.

What are the rights of participants in the study?

Your relative/donor will be assigned a specific study ID number. This will prevent their personal name being linked to any information that will be collected. All of the collected health information will be securely stored in a password-protected file, on a password-protected computer. This information will be backed up on a secure University of Otago network. Members of the research team (listed on page 6) are the only individuals who may access this information, during the course of the study.

Participation in this study is not obligatory. We expect that your relative/donor might benefit from participating, however it is completely up to you whether you accept for them to participate or decline this request.

You are also free to seek advice from your family member(s), relatives or friends about your relative/donor participating in this study. If you decide for your relative/donor to participate in this study, you have the right to withdraw from the study and decline continuing to participate at any stage. You do not have to provide a full reason for why you do not wish for your relative/donor to continue to participate in the study. However, this information would be very helpful and useful to the study.

During the outlined appointments or follow-ups the pharmacist will conduct during the study, you will be informed of any marked improvements to your health that could be attributed to your medicines being reduced or discontinued. You and your relative/donor will also receive a copy of all formal documentation that may arise from meetings during the study. The pharmacist will explain these documents to you as necessary and you may ask her any questions you may have regarding these documents or the study. You have the right to request your relative/donor's health information to be deleted or altered. The pharmacist will amend your health information records according to your feedback, as appropriate.

As explained above, if your relative/donor were to suffer from a harmful effect that is thought to be linked to stopping or reducing your medicines, the pharmacist or the GP will inform you of this. At this point, you will be reminded of your right to withdraw your relative/donor from participating in the study. No disadvantage will be made to your relative/donor as a result. They will continue to receive their usual medical care by their GP and nursing staff.

What will happen after the study ends, or if you pull out?

No study intervention will occur after the conclusion of the study. Health information (i.e. study data) collected will be securely stored in such a way that only those researchers mentioned below will be able to gain access to it. At the end of the project, any personal information will be destroyed immediately except that any raw data on which the results depend will be retained in secure storage for ten years after which it will be destroyed.

Any reports about this project will contain information that is amalgamated for all the participants as a group, so it will not be possible to identify any individual in any of these reports. You are welcome to request a copy of the results of the project from the investigators.

The results of the project may be published in a peer-reviewed scientific journal. This may occur one to two years after the completion of the study. The publication will be emailed to the managers of the residential care aged facility. You may request for it to be emailed to yourself or designated family member(s) or relative.

Where can you go for more information about the study, or to raise concerns or complaints?

If you have any question or concerns about the study at any stage, you can contact:

Mrs Nagham Ailabouni
PhD candidate
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University of Otago
PO Box 56, Dunedin 9054
New Zealand
(03) 479 7321
nagham.ailabouni@otago.ac.nz

Dr Prasad Nishtala
Primary supervisor
School of Pharmacy
University of Otago
PO Box 56, Dunedin 9054
New Zealand
(03) 479 4041
prasad.nishtala@otago.ac.nz

Professor Derelie Mangin*
Co-supervisor
David Braley Nancy Gordon
Chair in family medicine
McMaster University
Canada
mangind@mcmaster.ca

*School of Medicine, University of Otago, Christchurch

This information sheet is for you to keep. If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

If you are concerned about the way this study is being conducted or you wish to make a formal compliant. Please contact the health and disability ethics committee (HDEC) that approved this study. Please quote the study title and protocol number.

Phone: xx xxx xxxx Email: xxx@moh.govt.nz

Declaration Form

Declaration by enduring power of attorney (EPOA), on behalf of the participant:

I have read, or have had read to me in my first language, the participant information sheet, and I understand it. I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I have been given a copy of the Participant Information Sheet and Consent Form to keep.

I believe that this study might benefit my relative/donor, and would be in line with his/her interests:

Participant's name:

Signature: Date:

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant's EPOA, and have answered their questions about it.

I believe that the participant's EPOA understands the study and believes that the participation of his/her relative would be in line with their relative's interests.

Researcher's name:

Signature: Date:

Appendix 4: GP participant enrolment form

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Insert Date

Dear Dr X,

Please find below a list of the names of potential participants who are unable to provide their own consent and their EPOA have either agreed for them to take part in the study, or their EPOA have not yet responded.

Please indicate, by ticking the box next to the potential participant's name, if you agree that the deprescribing intervention, proposed in the study, might be beneficial to them. If you disagree for any potential participant to take part in the study, please indicate this in the designated box provided, along with a brief reason as to why the intervention would be unsuitable for them (e.g:. previous unsuccessful attempt at discontinuing medicines, resident receiving palliative care etc.)

Potential participants whose EPOAs have agreed for their resident to take part			**Potential participants whose EPOAs have not responded**		
Name	✓ / X	Reason for disagreeing to enrol participant	Name	✓ / X	Reason for disagreeing to enrol participant

GP signature: _____

Appendix 5: General practitioner invitation letter

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Insert Date

Dear Dr X,

I am writing to inform you of a study that is set to take place this year in three residential care homes in Timaru and Temuka. I would be most grateful if I can organise a fifteen-minute appointment over the next month, in order to discuss and explain the study's protocol in-depth, and address any of your question(s).

This study aims to test a method for reducing polypharmacy. I am a New Zealand (NZ) registered pharmacist and this study is a component of my doctoral studies at the School of Pharmacy, University of Otago. My PhD supervisors are Dr. Prasad Nishtala at the University of Otago, and Professor Dee Mangin from General Practice in Christchurch. The residential age care facilities (RACFs) that will be part of the study are The Croft and Margaret Wilson in Timaru, as well as the Wallingford Complex in Temuka. It is my understanding that you currently provide medical care for one or more of the residents residing in these RACFs. This letter will explain the purpose of the study, the intervention we intend to implement and the health outcomes we hope to achieve.

Deprescribing is the process of safely reducing or discontinuing medicines that are deemed to be inappropriate or no longer necessary. This study will involve deprescribing anticholinergic and sedative medicines, as these medicines are commonly prescribed in older people and are associated with many adverse effects including poor cognitive and physical functioning. Deprescribing has been associated with a lower annual acute hospital admission rate, an improvement in quality of life. No deprescribing studies have been conducted in NZ to indicate whether or not it is feasible.

If one or more of your residents would like to participate in the study, you will be notified of their names and dates of enrolment using your preferred method of contact as soon as possible. After reviewing the participant's medication regimen, drug-specific deprescribing protocols will be utilised to put forward suggestions to you as the participants' general practitioner of drugs that may be suitable to deprescribe (i.e. reduce or discontinue). The details of these recommendations will be summarised in a deprescribing medication review report and this will be emailed to you. Details of the intervention are outlined in-depth in the study protocol, attached to this letter.

We have registered this feasibility study in xxxxx. Testing this method and its effects may benefit you and your patients. It may also provide benefit to others if it proves feasible and successful. Ethical approval for this study has been obtained from the Human & Disability Ethics Committee (HDEC) board.

Yours sincerely,
Nagham Ailabouni, *PhD Candidate, RegPharm NZ, PGCertResPharm (Dist)*
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Contact email address: Nagham.ailabouni@otago.ac.nz

Appendix 6: Deprescribing drug protocols

Consider reducing if	Consider reviewing & reducing if	Consider resuming if	Consider reviewing & stopping if	Withdrawal effects/ Monitoring
Central Nervous System Antipsychotics (APS)				
Patient has dementia and experiences severe neuropsychiatric symptoms (NPS). Studies suggest that worsening of symptoms may occur when discontinuing antipsychotics (APS) in this group of patients [1].	Patient has been prescribed APS for > 3 months & has mild/moderate behavioural and psychological symptoms of dementia (BPSD). APS should be reviewed and tapering of dose should be trialled. Clinical trial evidence has shown no difference to patient's quality adjusted life years (QALY) when APS such as quetiapine, olanzapine & risperidone were discontinued compared to placebo [2]. However, the risk versus benefit of continuing APS's in older people is unfavourable [3] Specific symptom/target behaviour(s) need to be set for all patients initiating or continuing therapy. If the patient has been symptom/target behavior free for at least 3-6 months, then APS withdrawal should be considered [4].	Withdrawal of APS results in the recurrence/worsening of severe symptoms (e.g.: hallucinations, fixed delusions). Non-pharmacological options have failed and the patient is a threat to self or others [5].	- Prescribed for non-psychotic indications, unless patient is a threat to self or others [5, 6]. - There is no demonstrated benefit or there are un-due side effects [4]. - Reduce dose gradually (e.g. by 50% every two weeks or longer according to patient's response. Stop after the patient is stable on the minimum dose)	- Evidence suggests that the majority of older people with dementia can be withdrawn from long-term APS with no detrimental effects on their behaviour [1]. - Monitor recurrence or emergence of new target symptoms for several months after reducing/discontinuing APS as symptoms might relapse even after a longer period of time [1].

Antidepressants

Discontinuation of antidepressants:

1. If a patient is prescribed an antidepressant for a ≥ 6 weeks, this should be reduced gradually over at least four weeks or longer if withdrawal symptoms emerge [7]. There is less evidence for continuing antidepressant treatment in older people for a period ≥ 12 months [8, 9]
2. Rapid discontinuation may result in antidepressant discontinuation syndrome. This is associated with **F**lu-like symptoms, **I**nsomnia, **N**ausea, **I**mbalance, **S**ensory disturbances and **H**yperarousal (anxiety/agitation) (i.e.: FINISH). These usually appear a week after abrupt discontinuation of the antidepressant [10].
3. For patients with more severe symptoms, the original medicine dose may need to be restarted which results in the resolution of symptoms within 24 hours. Tapering can then be reinstated at a slower rate[11].
4. Patients should be monitored carefully as a high risk of suicide attempts exists during dosage changes and discontinuation[12].
5. **Antidepressants and dementia:**
   - Evidence suggests that antidepressants may not be effective for treating depression in dementia [13].
   - The use of antidepressants with anticholinergic properties may exacerbate cognitive decline [14].
   - When discontinuing antidepressants in those who have dementia, the Cornell scale of depression can help to determine the severity of depressive symptoms in these patients. Attaining a similar score to that attained while the patients were on the antidepressants indicates good tolerability to discontinuing therapy[15].

Consider continuing if	Consider reviewing & reducing if	Consider resuming if	Consider reviewing & stopping if	Withdrawal effects Monitoring
Tricyclic Antidepressants (TCAs)				
Patient has been suffering from moderate/severe depressive symptoms and antidepressants have been prescribed for < six months [16, 17]	Deemed necessary to be prescribed, reduce dose to <100mg per day[18].	Patient is suffering from worsening depressive syndromes or showing signs of potential suicidality [12].	Patient has: ➢ Dementia; as there is a risk of worsening cognitive impairment [14]. ➢ Cardiac conduction abnormalities (e.g: pro-arrhythmic effects)[19] ➢ ALT levels three times greater than the upper limit of normal, or has high bilirubin levels or experiences other signs/symptoms of hepatotoxicity [20] ➢ Prostatism or history of urinary retention [21].	➢ Should be withdrawn slowly (e.g: by 25% every four weeks) [10] ➢ Antidepressant discontinuation syndrome (explained above) [7] ➢ Depressive symptoms may re-occur

Selective Serotonin Reuptake Inhibitors (SSRIs)				
Patient has been suffering from moderate/severe depressive symptoms for a period lasting at least three months		Patient is suffering from worsening depressive syndromes or showing signs of suicidality [12]	➢ Co-prescribed with a non-steroidal anti-inflammatory drug (NSAID) or an antiplatelet drug due to an increased risk of upper gastrointestinal (GI) bleeding [22] ➢ Patient has any of the following factors, as they are at a high risk of developing hyponatremia [23]: - > 65 years, female - Low body weight - Concurrent use of medicines that contribute to hyponatremia (e.g.: thiazides, carbamazepine) - Prescribed fluoxetine as an SSRI [24] - Previous history of antidepressant-induced hyponatremia.	- Taper slowly (by 25%) every four to six weeks for medicines with a shorter half-life. Fluoxetine at low doses can be stopped abruptly and does not have to be tapered down, as it has a long half-life [10] - Mild self-limiting symptoms (listed above) could occur within a few days[11]. - These are more common with short-acting antidepressants such as paroxetine and immediate release venlafaxine[11]. - Could be a delay in the presentation of symptoms when fluoxetine is discontinued due to its longer half-life[11]. - Switching patients prescribed paroxetine or venlafaxine to fluoxetine, can decrease the severity of withdrawal symptoms. [25]

Consider continuing if	Consider reviewing & reducing if	Consider resuming if	Consider reviewing & stopping if	Withdrawal effects
Benzodiazepines (BZDs)/Non-benzodiazepines (Non-BZDs)				
	- Any high dose of BZD or non-BZDs (such as zopiclone) is prescribed. [5], as the risk of harm is dose-related. Although non-BZDs have been thought to be safer than BZDs, they have similar adverse effect profiles in older people[26]. A recent study showed that older men prescribed non-BZDs are more likely to have a fall than those prescribed a BZD[27]. - The patient has been prescribed the BZD or BZD-agonist for a period longer than 1-4 weeks, as the cumulative use of benzodiazepines for a few weeks has been shown to result in a greater risk of falls and developing withdrawal upon stopping [5, 28-30].		- Any BZD is prescribed as the risk of harm with BZD's has been found to be independent of the medicine's half-life [5]. - Patient experiences recurrent falls or has a history of a previous fracture. The highest risk for falls and fractures exists for older people who have recently been prescribed a high dose of BZD or non-BZD [31, 32].	Need to be withdrawn over a minimum period of 6 months in patients who have been treated long-term. - This reduces the chances of the patient experiencing "BZD withdrawal syndrome", characterised by insomnia, weight loss, sweating, tinnitus (ringing in the ears) and disturbances of perception [33]. - Appearance of this condition can vary from one day after stopping a short-acting BZD, up to three weeks after stopping a long-acting BZD. - Alternative methods to treating insomnia might need to be implemented such as sleep compression (reducing sleep hours to a fixed inadequate period each night, then gradually increasing the number of hours)[10]. - A suggested withdrawal protocol, which could take from 4 weeks up to one year, is as follows [33]: 1) Transfer the patient to the equivalent daily dose of diazepam (preferably taken at night). Equivalent doses for diazepam are listed in the New Zealand Formulary (NZF). 2) Reduce the diazepam dose every 2-3 weeks. If withdrawal symptoms start to appear, maintain the dose until symptoms

				start to improve. 3) Reduce the dose further, in smaller stops if necessary then stop completely.

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Appendix 7: Deprescribing medication use review form

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Deprescribing Medication Use Review Form

Date: xx/xx/xx

Study ID number: xxxxx
Full name: Mrs./Mr. X
NHI No: XXX123
GP: Dr. X

Your resident has consented to take part in a deprescribing feasibility study. I, Nagham Ailabouni, a New Zealand registered pharmacist and PhD candidate have conducted a deprescribing medication review, after completing an extensive clinical and medical history and having a discussion with the resident regarding their medicines.

The table below provides a summary of the potential medicines that would be appropriate for deprescribing. Please tick the relevant box to indicate whether or not you agree to the discontinuation (i.e. reducing or stopping) of these medicines. If you disagree to initiate discontinuation for any of these medicines in this patient, please state the reason in the far right column.

Medicines appropriate for deprescribing	Reasons for deprescribing	I, as the participant's GP		
		Agree	Disagree	Reasons for disagreeing to initiate discontinuation
1.				
2.				

GP signature: _____

Thank you for completing the table above. I will formulate a medicine management plan (MMP) for this resident within two weeks of receiving this form. This will guide deprescribing for this resident and will ensure deprescribing occurs in a safe manner. The MMP will only include those medicines you have agreed to deprescribe. A copy of this MMP will be emailed to you for approval, prior to providing a copy to the residential care staff or the resident.

Best wishes,

Nagham Ailabouni

PhD Candidate, RegPharm NZ, PGCertResPharm (Dist)

Appendix 8: Medication management plan (MMP) form

Deprescribing anticholinergic and sedative medicines: A Feasibility Trial (DEFEAT-study) in residential aged care facilities

Medication Management Plan

Date: xx/xx/xx

Study ID number: xxxxx
Full name: Mrs./Mr. X
NHI No: XXX123
GP: Dr. X

Mrs./Mr. X's GP has agreed to deprescribe some of Mrs./Mr. X's medicines. The recommended order in which the medicines are to be deprescribed accompanied by appropriate reasoning for deprescribing, is included in the table below.

Medicines	Reasoning for deprescribing	Deprescribing (reducing/stopping) instructions
1.		
2.		
3.		

When anticholinergic and/or sedative medicines are reduced or discontinued, adverse drug withdrawal effects (ADWEs) may develop in some participants. Therefore, it is important to slowly taper the dose of the medicine(s), and monitor the participants closely. We appreciate your help in monitoring the participants.

The following chart is a guide to what you can do, if you note that the resident is experiencing ADWEs.

These ADWEs require **immediate medical attention.**

If the resident develops any of these symptoms, please contact NA immediately (Ph: 021-1226416) and the resident's GP as soon as possible.

- Significantly increased aggressive behaviour
- Significantly increased anxiety
- Harm to one self or another resident/staff member
- Delirium
- Flushing
- Hand tremor
- Seizures
- Increased heart rate or blood pressure

These ADWEs **do not require immediate medical attention.**

If the resident develops any of these symptoms, please note them in the designated section below and notify NA (Ph: 021-1226416) or the resident's GP at the next GP visit.

- Unstable mood patterns
- Diminished appetite or weight loss
- Increased sleep disturbance

These ADWEs **do not require immediate medical attention.**

If the resident develops any of these symptoms, please note them in the designated section below and notify NA (Ph: 021-1226416) and the resident's GP at the next GP visit.

- Change in bowel motions
- Increased headaches
- Blurry vision
- Dry mouth

(Next page)

Notes:

_____

_____

_____

_____

Thank you for your valued cooperation and for monitoring the participants. If you would like to discuss any aspects of this study, please do not hesitate to contact any of the principal investigators whose details are listed below.

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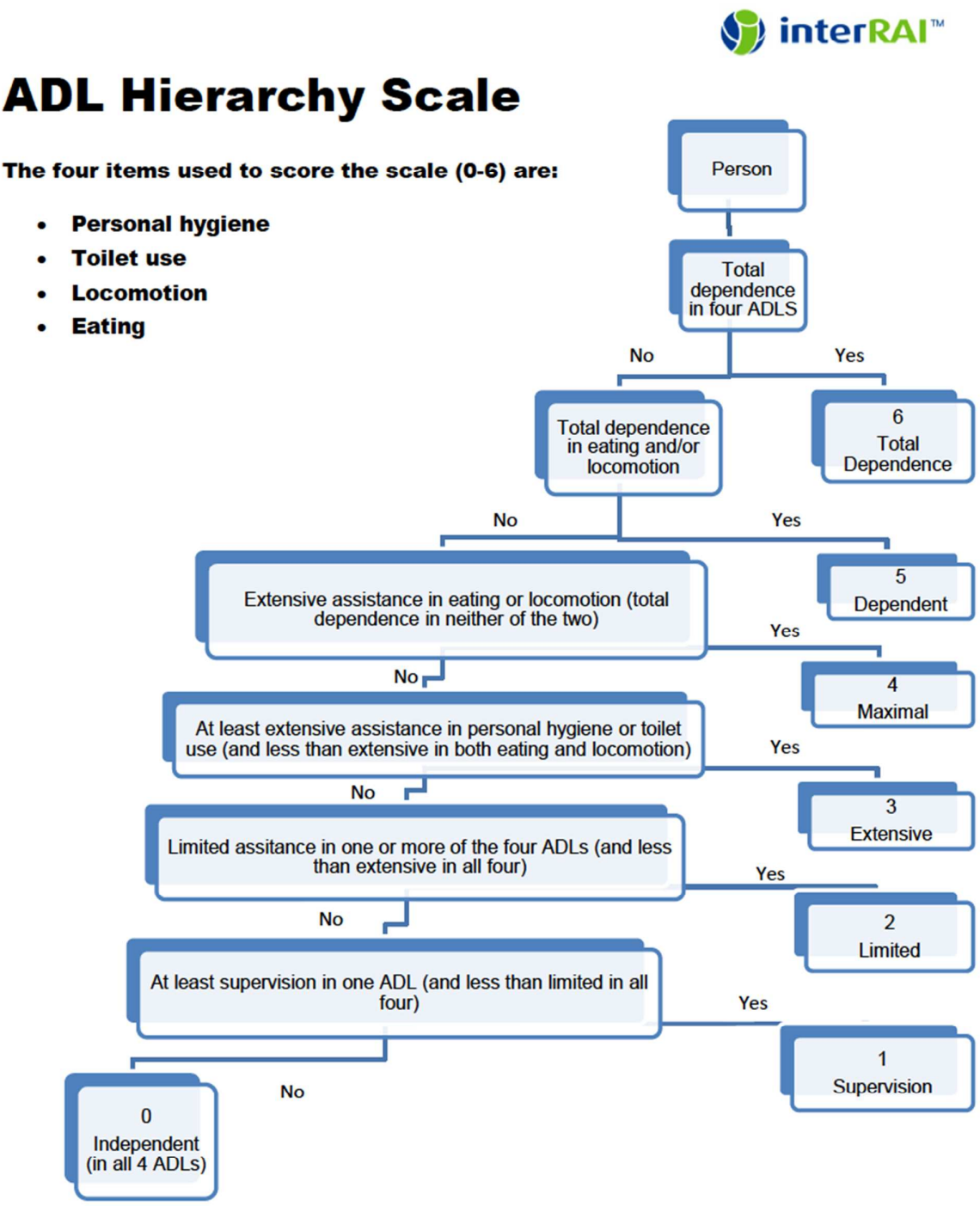
Appendix 9: Long Term Care Facilities (LTCF) InterRAI scales



Source: Morris JN, Fries BE, Morris SA. (1999) Scaling ADLs within the MDS. Journals of Gerontology: Medical Sciences 54(11):M546-M553.

Updated 9/2014

IADL Performance Scale

Score	IADLS
0–6	Meal preparation
0–6	Ordinary housework
0–6	Managing finances
0–6	Managing medications
0–6	Phone use
0–6	Stairs
0–6	Shopping
0–6	Transportation

Range: 0–48

Scoring in self-performance:

0 = Independent — No help, setup, or supervision

1 = Setup help only

2 = Supervision — Oversight/cuing

3 = Limited assistance — Help on some occasions

4 = Extensive assistance — Help throughout task, but performs 50% of task on own

5 = Maximal assistance — Help throughout task, but performs less than 50% of task on own

6 = Total dependence — Full performance by others during entire period

8 = Activity did not occur during entire period, Score = 6

Depression Rating Scale (DRS)

Score	Item
0-3	Made negative statements
0-3	Persistent anger with self or others
0-3	Expressions (including non-verbal) of what appear to be unrealistic fears
0-3	Repetitive health complaints
0-3	Repetitive anxious complaints/concerns (non-health related)
0-3	Sad, pained, worried facial expression
0-3	Crying, tearfulness

Range: 0-14

Scoring:

0 = No mood symptoms

14 = All mood symptoms present in last 3 days

Scores of 3 or greater indicate major or minor depressive disorders.

The Depression Rating Scale (DRS) is calculated by summing all seven input items after recoding each input item to a three-point (0, 1, 2) scale. For each input item, above, the first two levels, 0 and 1, are not recoded; level 2 is recoded to 1; and level 3 is recoded to 2.

Source: Burrows A, Morris JN, Simon S, Hirdes JP, Phillips C. (2000) Development of a Minimum Data Set-based Depression Rating Scale for Use in Nursing Homes. Age and Ageing 29(2): 165-172.

Changes in Health, End-Stage Disease, Signs, and Symptoms Scale (CHESS)

Score	Item
0–2, 8	Change in decision making
0–3	Change in ADL status
0–2, 8	Change in ADL status
0–4	Health condition — vomiting
0–4	Health condition — peripheral edema
0–3	Health condition — dyspnea
0,1	End-stage disease
0,1	Weight loss
0,1	Insufficient fluid
0,1	Dehydrated
0,1	Decrease in food or fluid
0,1	Fluid output exceeds input

Range: 0–5

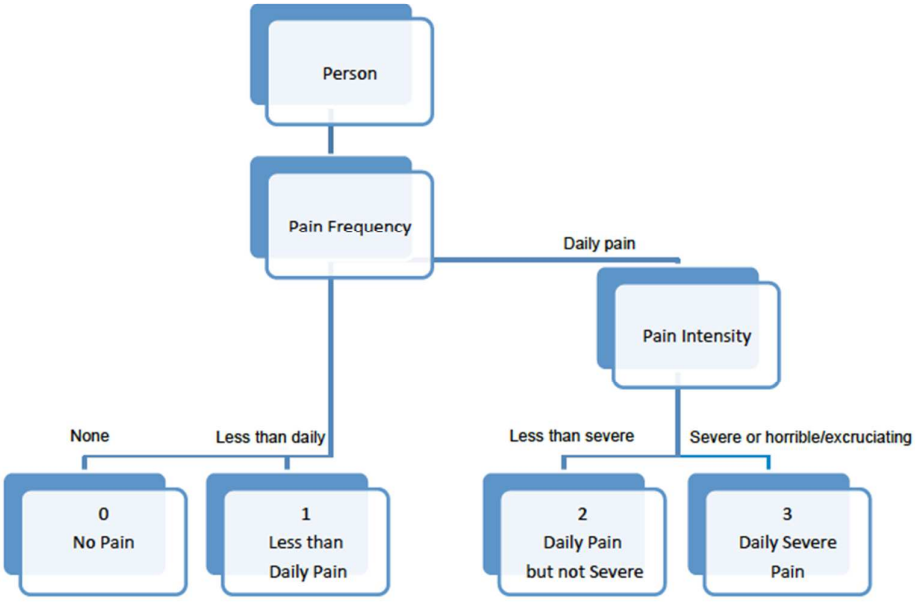
Scoring:

0 = No health instability
1 = Minimal health instability
2 = Low health instability
3 = Moderate health instability
4 = High health instability
5 = Very high health instability

The CHESS Scale is calculated by adding sign and symptom variables up to a maximum of 2, then adding three other variables (Change in decision making, Change in ADL status, and End-stage disease), giving a highest CHESS score of 5.

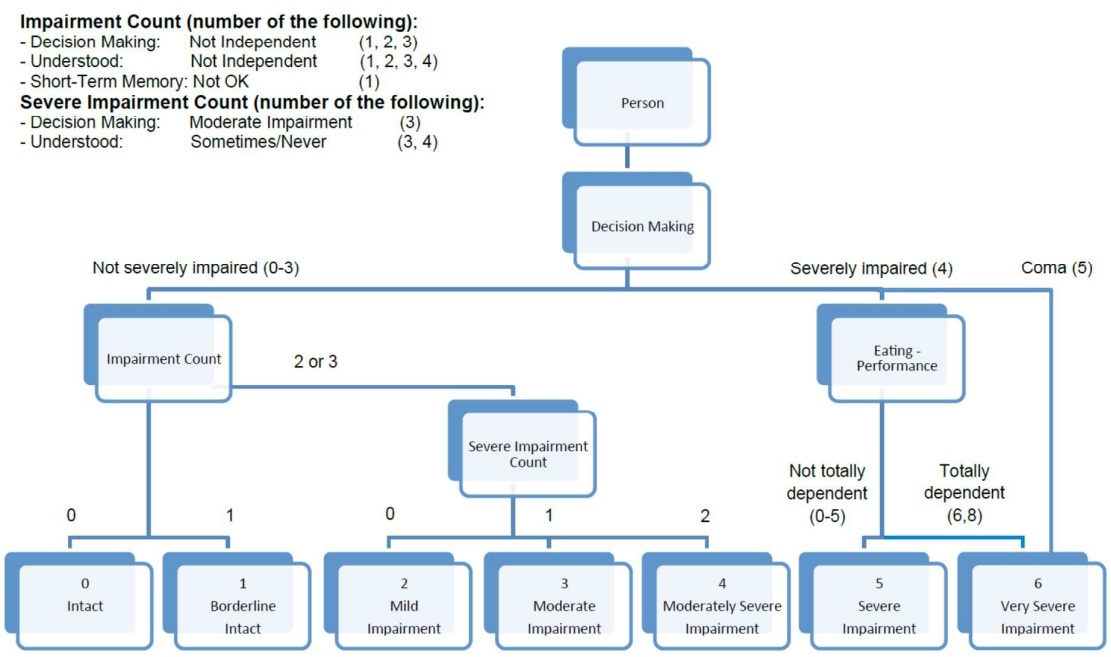
Source: Hirdes JP, Frijters D, Teare G. 2003.The MDS CHESS Scale: A New Measure to Predict Mortality in the Institutionalized Elderly. *Journal of the American Geriatrics Society* 51(1): 96–100.

Pain Scale

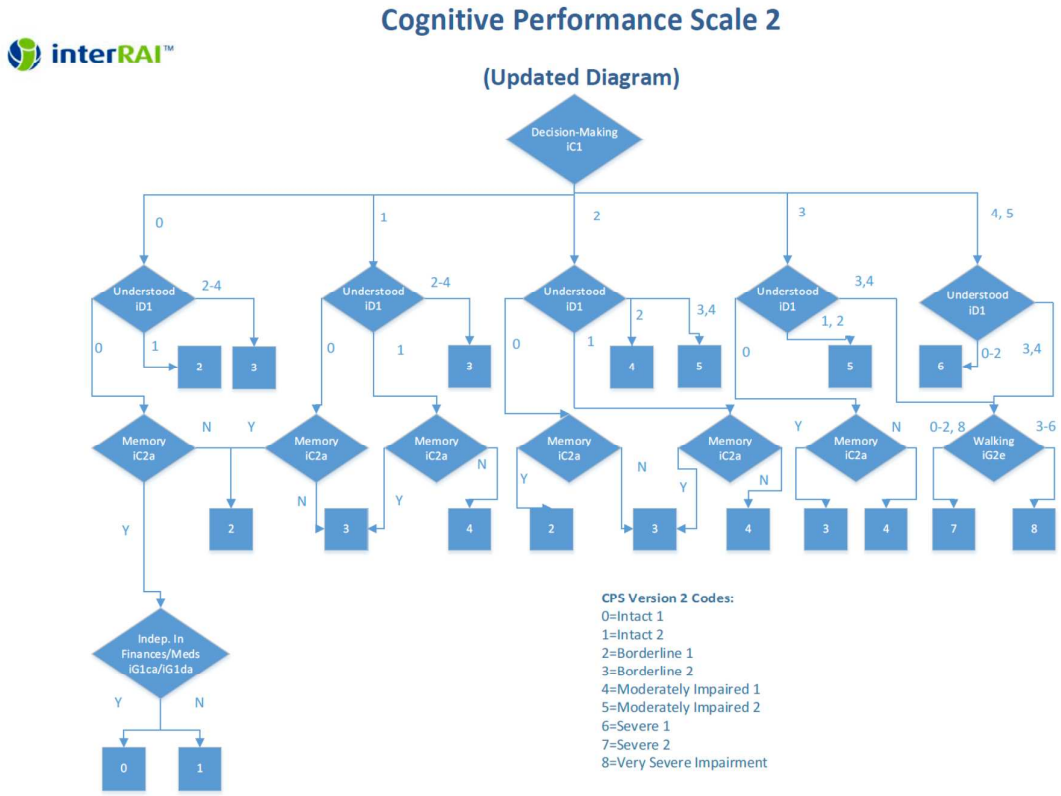


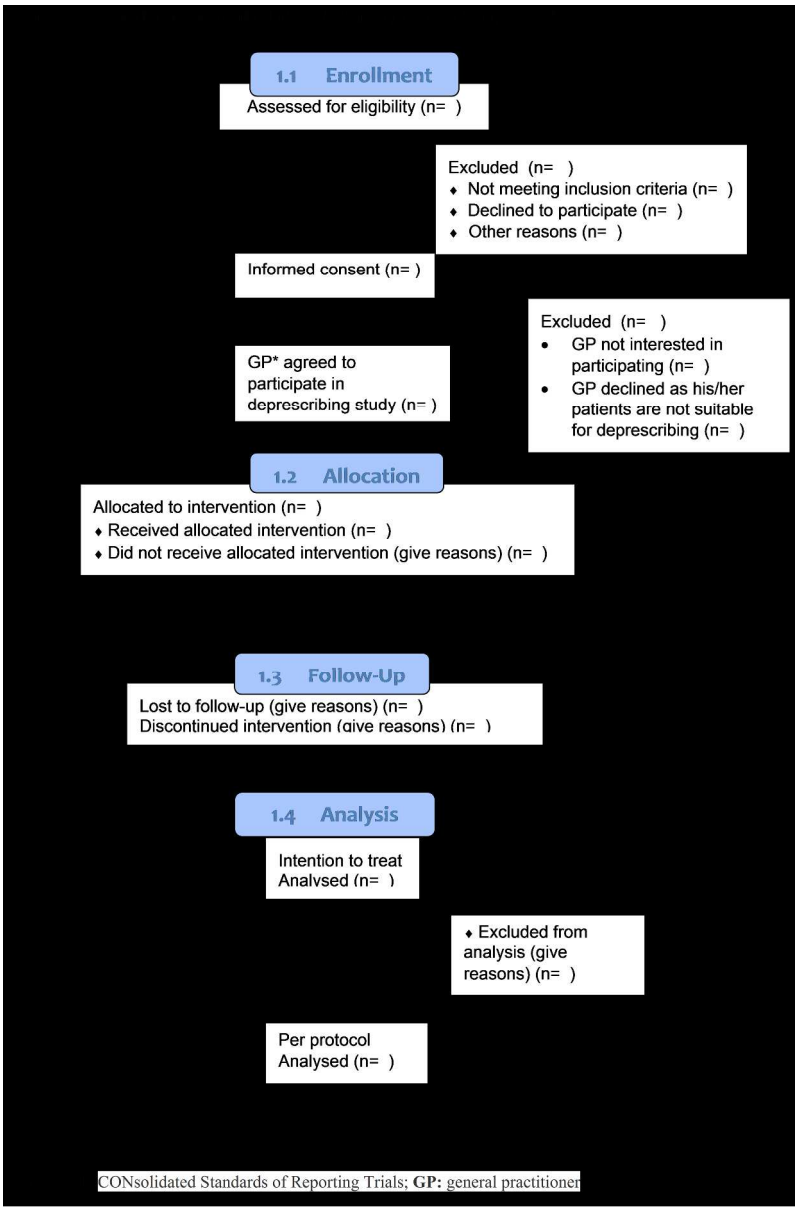
Source: Fries BE, Simon SE, Morris JN, Flodstrom C, Bookstein FL. 2001. Pain in U.S. Nursing Homes: Validating a Pain Scale for the Minimum Data Set. *Gerontologist* 41(2): 173–79.

Cognitive Performance Scale



Source: Morris JN, Fries BE, Mehr DR, Hawes C, Philips C, Mor V, Lipsitz L. (1994) MDS Cognitive Performance Scale. Journal of Gerontology: Medical Sciences 49 (4): M174-M182.





Flow diagram for the DEFEAT study using CONSORT

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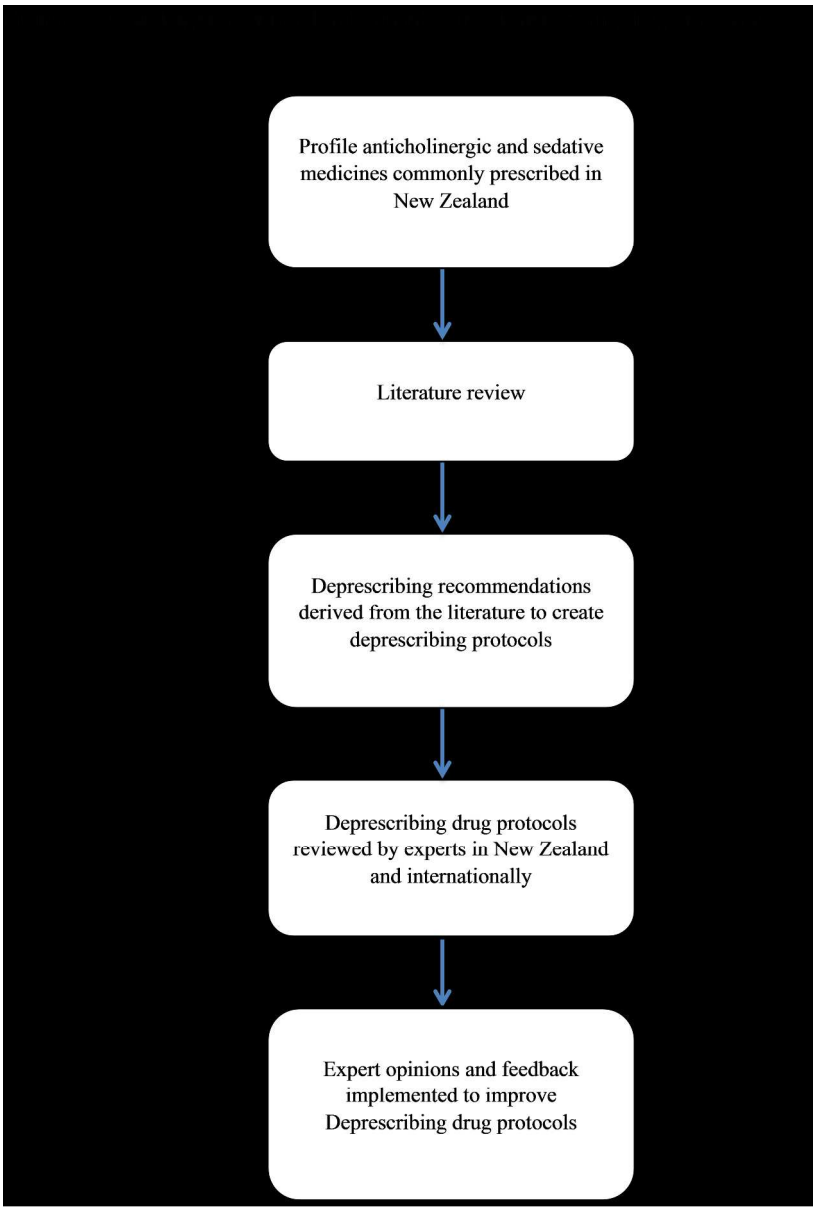

Flow diagram for the development of the deprescribing drug protocols

233x346mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym ✓ Title Page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry ✓ Pg 2; Abstract ; trial registration
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier ✓ Pg 2; abstract; trial registration
Funding	4	Sources and types of financial, material, and other support ✓ Pg 10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors ✓ Title page
	5b	Name and contact information for the trial sponsor ✓ Title page
	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 ✓ Pg10
	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) ✓ Pg 8
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 ✓ Pg 3; intro
	6b	Explanation for choice of comparators ✓ Pg 3; intro
Objectives	7	Specific objectives or hypotheses ✓ Pg 3; aims
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) ✓ Pg 3; study setting & design

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained ✓ Pg 3; study setting & design
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) ✓ Pg 3-4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ✓ Pg 5; intervention
	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) ✓ Pg 6; step 5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ✓ Pg 6; steps 4 & 5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial ✓ Pg 6; step 4; line 21-22
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 ✓ Page 8; outcomes
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) ✓ Pg 5; intervention
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 Pg 9; power & sample size ✓
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size ✓ Pg 9; power & sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions N/A

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 N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol ✓ Pg 7; Data collection
	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 ✓ Pg 9; lines 22-25
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 ✓ Pg 7; Data collection
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 ✓ Pg 9; statistical methods & analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) ✓ Pg 9; statistical methods & analysis; Figure 1
	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) ✓ Pg 9; statistical methods & analysis
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 ✓ Pg 8; paragraph 1

	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 ✓ Pg 8; data monitoring & safety
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 ✓ Pg 7; lines 6-9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor ✓ Pg 8; data monitoring & safety
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval ✓ Pg 9; ethics & disemmination
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) ✓ Pg 9; ethics & disemmination
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) ✓ Pg 4
	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 Appendices 2 & 3
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site ✓ Pg 10
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 ✓ Pg 9; ethics & disemmination
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 ✓ Pg 9; ethics & disemmination
	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 ✓ Pg 9; ethics & disemmination

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates ✓	Appendices 2 & 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.