Australian Government
Department of Health and Aged Care

University of South Australia

ReMInDAR – Reducing Medicine-induced Deterioration and Adverse Reactions Trial

Assessment report

Commercial in Confidence

31 March 2021

MSAC application no. TBC

Prepared by the Quality Use of Medicines and Pharmacy Research Centre, University of South Australia

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under MBS.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

The chief investigators for the ReMInDAR trial are Prof Elizabeth (Libby) E. Roughead (UniSA), A/Prof Nicole Pratt (UniSA), A/Prof Gaynor Parfitt (UniSA), Dr Renly Lim (UniSA), Prof Debra Rowett (UniSA), Dr Lisa Kalisch-Ellett (UniSA), Prof Luke Bereznicki (UTas), Prof Tracy Merlin (AHTA), Ms Megan Corlis (Helping Hand Inc), Ms Ai Choo Kang (Southern Cross Care SA, NT and Vic) and Mr Joseph Whitehouse (PharmIC). The project team, research partners, clinical governance groups and acknowledgements are listed in Appendix A.

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Contents

Tables

Boxes

Figures

Acronyms and Abbreviations

Acronym/Abbreviation	Meaning
ADE	Adverse drug event
ADL	Activity of Daily Living
AIHW	Australian Institute of Health and Welfare
ACFI	Aged Care Funding Instrument
BEH	behaviour
BMI	Body Mass Index
CHC	Complex Health Care
CI	confidence interval
EQ-5D	EuroQol 5 Dimension (health quality of life assessment tool)
GP	General Practitioner
HTA	health technology assessment
ITT	intention to treat
IQR	Interquartile Range
MBS	Medicare Benefits Schedule
MD	mean difference
MoCA	Montreal Cognitive Assessment
MSAC	Medical Services Advisory Committee
MVPA	Moderate and Vigorous Physical Activity
NEP	National Efficient Price
NNT	Number Needed to Treat
NWA	National Weighted Activity Unit
OR	Odds Ratio
OPD	Out Patient Department
PAS	Psychogeriatric Assessment Scale
PASC	PICO-confirmation Advisory Sub-Committee of the MSAC
PBS	Pharmaceutical Benefits Scheme
PICO	Population, Intervention, Comparator, Outcome
PIN	Patient Identification Number
PRN	*Pro re nata* “as needed”
RACF	Residential Aged Care Facility
RCT	Randomised Control Trial
RMMR	Residential Medication Management Review
RR	rate ratio
SA	South Australia
SACE	survivor average causal effect
SD	standard deviation
SE	standard error
Tas	Tasmania

Executive Summary

ReMInDAR - Reducing Medicine-induced Deterioration and Adverse Reactions Trial

This submission-based assessment examines the evidence to the support listing of a regular pharmacist-led service to reduce medicine-induced deterioration and adverse reactions on the Medicare Benefits Schedule (MBS). The service would be used in the Australian residential aged care facility setting for the prevention and management of medicine-induced deterioration and adverse reactions. The target population are elderly people who reside in residential aged care facilities and who are on 4 or more medicines or at least one medicine with anticholinergic or sedative properties, and have a cognition score (MoCA) of 18 or higher (corresponding to no or mild cognitive impairment), and a frailty index less than 0.4.

We propose that the successful listing of the pharmacist-led service in the target population and setting will lead to a reduction the rate of cognitive decline among residents in aged care over time and savings to the health care system.

ES.1. Alignment with agreed PICO Confirmation

The ReMInDAR trial was funded by the Australian Government Department of Health under the Sixth Community Pharmacy Agreement Pharmacy Trial Program. The trial proposal was reviewed by the PICO Advisory Sub-committee (PASC) of the Medical Services Advisory Committee.

This submission-based assessment of the Reducing Medicine-induced Deterioration and Adverse Reactions (ReMInDAR) trial addresses the required population, intervention, comparison and outcomes (PICO) outlined in the trial protocol.

ES.2. Proposed Medical Service

The proposed service is a pharmacist-led service to prevent medicine-induced deterioration and adverse medicine reactions among residents in aged care facilities. Pharmacists trained in the detection of signs and symptoms of medicine-induced deterioration review targeted residents in aged care facilities every eight weeks. The review includes assessment of resident or carer reported changes in health, assessment of changes in cognition, physical activity, strength, sleep, and review of the resident care assessment record to identify any signs of medicine-induced deterioration or adverse medicine events. Recommendations concerning medication management are made to the resident's general practitioner, residents themselves or facility care staff in order to prevent or mitigate harm from medicines.

The proposed pharmacist service in aged care facilities is currently not available in any private or public setting in Australia. It is proposed that it be offered in addition to usual care for the defined subgroup of the population of residents in aged care facilities.

ES.3. Proposal for Public Funding

The proposal for funding is:

- A pharmacist service to prevent medication-related decline in residents of aged care facilities. At least 8 weeks must elapse between services for the same resident.

The program funding mechanism for the proposed service and fee structure would require negotiation between the relevant government department and industry stakeholders.

ES.4. Population

The proposed service will be provided to residents of aged care facilities who are taking 4 or more medicines or at least one medicine with anticholinergic or sedative properties; and who have a cognition score (MoCA) of 18 or higher (corresponding to no or mild cognitive decline) and a frailty index less than 0.4.

ES.5. Comparator Details

The comparator for assessment of the proposed service is 'usual care' as currently provided to residents in all Australian residential aged care facilities. Residents are entitled to a Residential Medication Management Review by a pharmacist.

ES.6. Clinical management algorithm

Residents will receive the proposed pharmacist-led service every eight weeks in addition to 'usual care'. The service is comprised of regular pharmacist-led assessments of residents in aged care to detect signs and symptoms of medicine-induced deterioration and adverse events. Recommendations concerning medication management will be made to the resident's general practitioner, residents themselves and facility care staff in order to prevent or mitigate harm from medicine-induced deterioration and adverse reactions (Figure ES-2).

In the absence of the proposed pharmacist-led service for eligible populations 'usual care' as currently provided to residents in all Australian residential aged care facilities would remain in place.

Text alternative for Figure ES-1 and ES-2

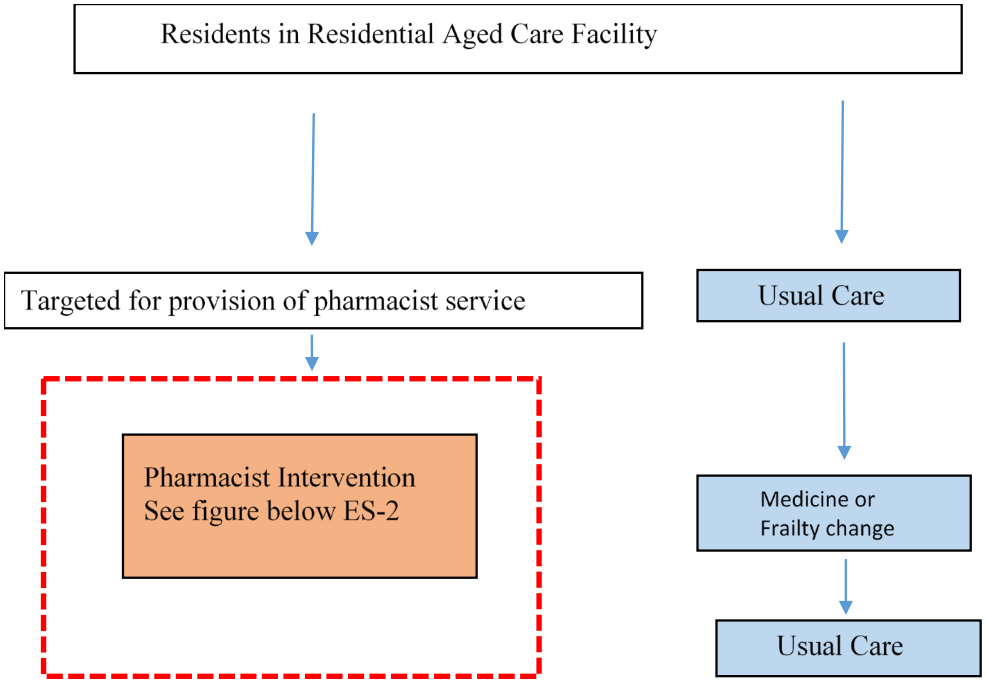


Figure ES-1: Flow chart indicating the clinical algorithm proposed for the new service in comparison to the clinical algorithm for the comparator of usual care.

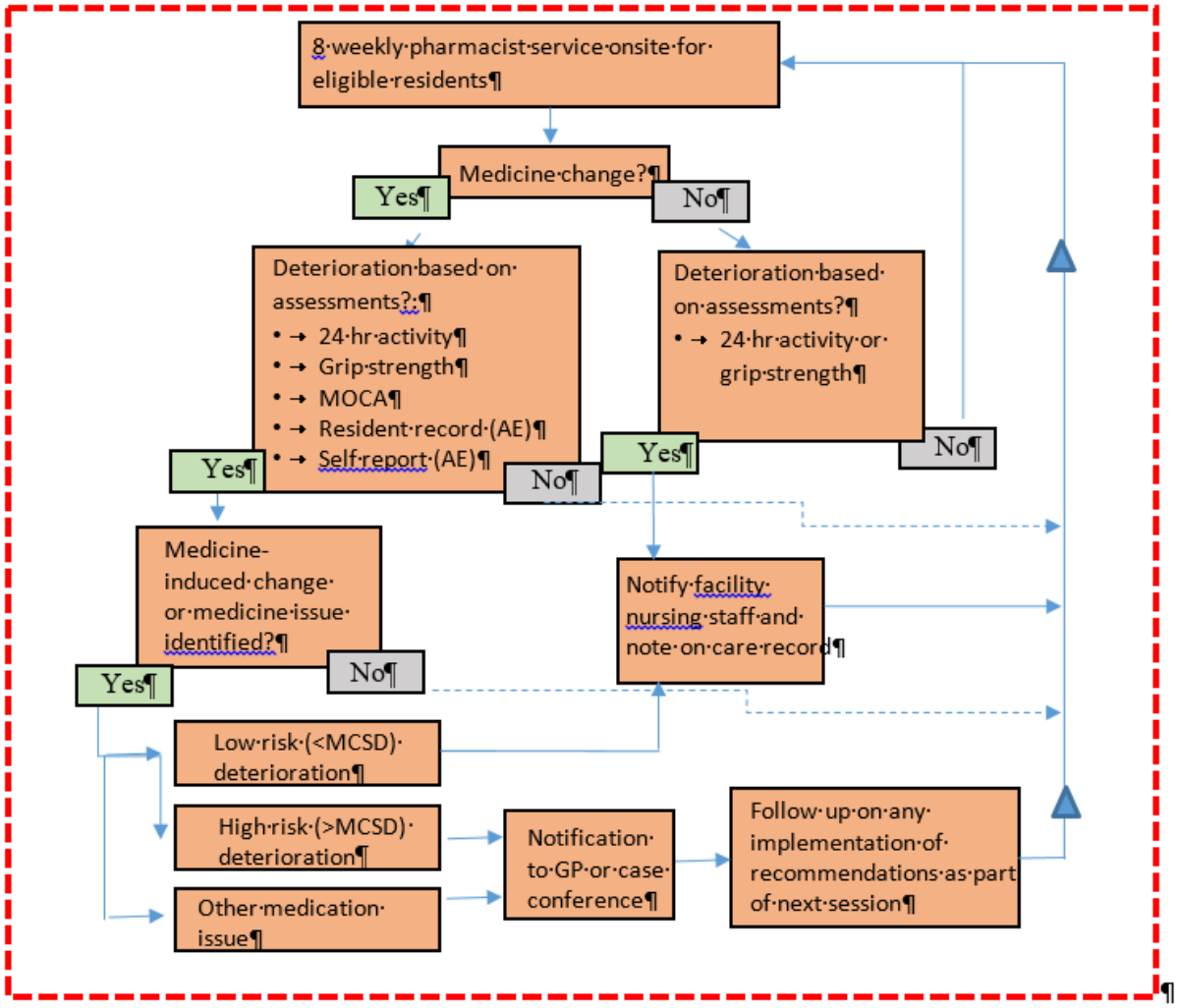


Figure ES-2: Flow chart indicating the clinical algorithm proposed for the new service.

Abbreviations: AE – adverse event, MCSD = minimum clinically significant difference.

ES.7 Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator

The key difference of the proposed service to the comparator of usual care is the addition of the pharmacist-led service that has a particular focus on detecting and avoiding harms from medicines, rather than usual care which has a focus on resolving medication related problems. The service is comprised of pharmacist-led assessments every eight weeks of residents in aged care to detect signs and symptoms of medicine-induced deterioration and adverse events. The review includes assessment of resident or carer reported changes in health, assessment of changes in cognition, physical activity, strength, sleep, and review of the resident care assessment record to identify any signs of medicine-induced deterioration or adverse medicine events. Recommendations concerning medication management are

made to the resident's general practitioner, residents themselves and facility care staff in order to prevent or mitigate harm from medicine-induced deterioration and adverse reactions.

ES.8 Clinical Claim

The clinical claim is that the pharmacist-led intervention is more effective than usual care for reducing medicine induced deterioration in persons resident in aged care who have a cognition score 18 or higher (corresponding to no or mild cognitive impairment) and a frailty index score of 0.4 or less as evidenced by maintenance of cognition.

ES.9 Results

ES.9.1 Effectiveness

The ReMInDAR trial was a multicentre, open-label randomised controlled trial of a pharmacist-led service with 12 month follow-up undertaken in 39 aged care facilities in South Australia and Tasmania. In total, 282 participants were randomised, with 248 completing the trial. Twelve month data were collected for 97 intervention and 111 control participants. Groups were similar at baseline with the exception of weight and cognition.

In total 575 pharmacist sessions with intervention participants were undertaken. In total 112 (97%) of the 115 people who received the service had at least one medicine related problem or symptom report identified. In total, pharmacists identified 673 medicine related problems or symptom reports; (averaging six per person adjusted for follow-up time). The proportion of people with a problem or symptom report at each session was consistently above 60%, ranging from 79% in the first two sessions down to 64% by the sixth session. Fifty percent of residents had five or more problems or symptoms identified across the study period (range 1 to 29). Over 50% of the population had an adverse reaction or toxicity problem, 50% over or under-treatment, 57% required education or information for the resident or staff and for over 80% pharmacists made symptom reports. Analysis of the time to develop a new problem found that 50% of the population had developed a new problem by the next session and 75% had a new problem by the subsequent session, this suggests the time between pharmacist reviews was appropriate at intervals of eight weeks. At the level of the individual, pharmacists made recommendations to reduce medicine use for 61% of the population, while recommendations to increase use were made for 29%. The classes accounting for over 60% of the recommendations for reduced use were opioids antipsychotics, sedative medicines, antidepressants, anti-Parkinson agents, proton pump inhibitors, diuretics (predominantly furosemide), and statins.

With regards to the primary outcome of a change in frailty scores, no significant difference was found between groups.

There was a statistically significant result for cognition, with an observed mean difference of 1.36 point change at 12 months. A *post hoc* analysis identified that in the intervention arm an additional 12% of residents avoided clinically significant cognitive decline in 12 months. This represents a NNT (number needed to treat/provide intervention to) of 8.33; i.e. for every 8.33 residents that pharmacists reviewed every eight weeks over a year, it would be expected that one would avoid a clinically-relevant cognitive decline.

Weight was also found to be statistically significantly different, with the control arm gaining more weight than the intervention arm. (1.34 kg). However, a post hoc subgroup analysis indicated that this was variable across the subgroups making it less clear if this was an intervention effect. The secondary outcomes analysed for physical activity and sleep utilised data from the GENEActiv accelerometers. No significant results were found, however, the point estimates favoured the intervention arm for overall amount of time spent in moderate activity, the length of each bout of time of moderate or vigorous activity, sedentary behaviour and sleep efficiency. Clinically, the expectation of trajectory in this population is towards a decline in function (1), so a trend improved function could be viewed as a favourable outcome. No significant difference was observed for quality of life.

During the trial, 1978 adverse events were recorded for trial participants. The majority of these adverse events were for falls or fracture, bleeding or bruising, or gastrointestinal symptoms. No significant difference was observed in the rate of adverse events. Of the adverse events, 583 were judged to be possible, probable or definite adverse medicine events, of which 83% were considered possibly or probably preventable. This equates to approximately 20% of residents experiencing one preventable adverse medicine event each month. Statistical analyses indicated no difference between the trial arms for the rate of adverse medicine events (AME) or the rate of preventable adverse medicine events.

More than half the participants had their 12 month follow-up measures assessed during the COVID-19 restrictions which appears to have affected the results at 12 months. The point estimates for the primary outcome at 6 and 12 months were larger after excluding or imputing post COVID-19 measurements, however, they did not reach statistical significance.

On the basis of the evidence provided, relative to the comparator, the intervention is superior efficacy with regards to cognition, and is non-inferior for frailty, physical activity, grip strength, and quality of life.

ES.10 Translation Issues

The health economic analysis was pre-specified as a trial-based analysis, using both outcome and cost data directly measured in the clinical trial. No additional data sources were utilised, nor was data extrapolated. Therefore, no significant translation issues apply as the clinical trial, alone, directly informs the analysis. Given that some administrative cost data were not available for the whole trial population, the applicability of the study sub-group for whom Commonwealth Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS) costs was available was assessed - this sub-group was found to be representative of the broader trial population.

ES.11 Economic Evaluation

The base case result of the trial-based analysis includes pharmacist intervention costs, PBS costs, MBS costs and inpatient and emergency department (ED) hospitalisation costs (Table ES-1). Overall, a net total incremental healthcare cost of $1,841 per resident over 12 months was associated with the intervention arm. However, the association of the net cost difference with the intervention was highly uncertain. Aside from the intervention, none of the cost differences were statistically significant and there is a high risk of confounding due to unrelated imbalances in underlying health conditions across the arms, and therefore the analysis results should be interpreted with caution.

Descriptor	Intervention	Control	Increment
Proposed pharmacist review	$586		$586
Pharmaceuticals (PBS costs)	$2,840	$3,504	-$664
Medical services (MBS costs)	$2,637	$2,357	$280
Hospital costs - admissions	$2,192	$623	$1,569
Aged Care subsidies	$56,023	$55,953	$70
TOTAL	**$64,278**	**$62,437**	**$1,841**

Table ES-1: Average healthcare costs per patient over 12 months for each study arm (adjusted trial-based cost analysis): base case

The observed difference in pharmaceutical costs was in the opposite direction to all other resource use, and showed reduced pharmaceutical costs in the intervention arm. This finding is consistent with the findings of previous studies and is considered more likely to be directly associated with the intervention. If only the pharmacist and pharmaceutical costs are analysed, the intervention is associated with a net saving of $78 per resident per year.

Exploratory trial-based cost-effectiveness analysis around clinically significant cognitive decline estimated a trial-based incremental cost-effectiveness ratio of $15,342 per resident

avoiding clinically significant cognitive decline, in one year. If only pharmacist and pharmaceutical costs were considered relevant, the exploratory analysis results in the intervention being dominant; preventing clinically significant cognitive decline and resulting in a net saving due to reduced pharmaceutical expenditure.

ES.12 Estimated Extent of Use and Financial Implications

An epidemiological approach has been used to estimate the financial implications of the introduction of pharmacist-led intervention among residents in aged care facilities. Based on projected numbers of people in residential care, estimated intervention eligibility and uptake rates, the pharmacist service may be expected to cost between $5-6 million per year.

If PBS savings are associated with the intervention, as suggested by the clinical trial and consistent with the literature, the pharmacist intervention costs would be fully offset by reduced PBS expenditure and may deliver net savings of approximately $1 million per year (Table ES-2).

Descriptor	2021-22	2022-23	2023-24	2024-25	2025-26
No. people in residential aged care	249,441	251,651	253,860	256,070	258,280
No. people eligible on the basis of medications and cognition (7.7%) and uptaking service (50%)	9,647	9,732	9,818	9,903	9,989
Estimated number of services (5 per patient)	48,233	48,660	49,088	49,515	49,943
Estimated government pharmacist expenditure ($107.07 per service)	**$5,164,254**	**$5,210,026**	**$5,255,799**	**$5,301,571**	**$5,347,343**
Potential reduction in PBS expenditure	−$6,405,276	−$6,462,048	−$6,518,820	−$6,575,592	−$6,632,364
Net cost if PBS savings realised	**−$1,241,022**	**−$1,252,022**	**−$1,263,021**	**−$1,274,021**	**−$1,285,021**

Table ES-2: Projected people in residential aged care who would be eligible for the proposed pharmacist review over five years

Section A: Context

This submission-based assessment of the Reducing Medicine-induced Deterioration and Adverse Reactions (ReMInDAR) trial is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The University of South Australia has undertaken a health services intervention trial of a pharmacist-led service to reduce medicine-induced deterioration and adverse reactions in the aged care population. The trial was funded through the Department of Health Pharmacy Trial Program. Appendix A provides a list of the people involved in the development of this assessment report.

A.1. Items in the agreed PICO Confirmation

The proposed pharmacist-led service to reduce medicine-induced deterioration and adverse reactions in residents in Australian residential aged care was outlined in the population, intervention, comparator and outcomes (PICO) document (Appendix D) that was reviewed by the PICO Confirmation Advisory Sub-Committee (PASC) as part of the Sixth Community Pharmacy Agreement Pharmacy Trial Program (3 February 2017).

This submission-based assessment of the Reducing Medicine-induced Deterioration and Adverse Reactions (ReMInDAR) trial addresses the required PICO elements outlined in the trial protocol.

A.1.1. Proposed Medical Service

The proposed service is a pharmacist-led service to reduce medicine-induced deterioration and adverse reactions among residents of Australian residential aged care facilities. Pharmacists trained in the detection of signs and symptoms of medicine-induced deterioration reviewed targeted residents in aged care facilities every eight weeks. The review included assessment of resident or carer reported changes in health, assessment of changes in cognition, physical activity, strength, sleep, and review of the resident care assessment record to identify any signs of medicine-induced deterioration or adverse medicine events. Recommendations concerning medication management were made to the

resident's general practitioner, residents themselves or facility care staff in order to prevent or mitigate harm from medicines.

The proposed pharmacist service in aged care facilities is currently not available in any private or public setting in Australia. It is proposed that it be offered in addition to usual care for the defined subgroup of the population of residents in aged care facilities.

Pharmacists providing the service will need to undertake training in order to have the knowledge and skills required to recognise and manage medicine-induced deterioration and adverse reactions. The training is further outlined in Section F3.

A.1.2. Other Indications

None.

A.1.3. Current funding arrangements

The pharmacist service trialled in ReMInDAR is not currently funded in Australia. Residential medication management reviews (RMMRs) are the existing services to support appropriate medicine use for residents of aged care facilities.(2) The RMMR is a comprehensive medication review conducted by an accredited pharmacist following a referral from the resident's GP. Accredited pharmacists are funded to conduct an RMMR every 12 to 24 months, or where there has been a significant change in the residents' condition or medication regimen.(3) During the majority of the time that the ReMInDAR trial was underway, this ruling applied for a sole review. In November 2019, additional funding was provided to enable up to two follow-up visits to resolve medication related problems noted at the initial review if required.(2)

A.2. Proposal for Public Funding

The proposal for funding is:

- A pharmacist service to prevent medication-related decline in residents of aged care facilities. At least 8 weeks must elapse between services for the same resident.

The program funding mechanism for the proposed service and fee structure would require negotiation between the relevant government department and industry stakeholders.

A.3. Proposed population

The proposed service will be provided to residents of aged care facilities who are taking 4 or more medicines or taking at least one medicine with anticholinergic or sedative properties;

and who have a cognition score (MoCA) of 18 or higher (corresponding to no or mild cognitive impairment) and a frailty index less than 0.4.

The intervention targets persons at risk of medicine-related decline who have not yet suffered significant decline in cognition or frailty. This population aligns with the study population and is expected to be the population most likely to benefit from the service.

A.3.1. Rationale

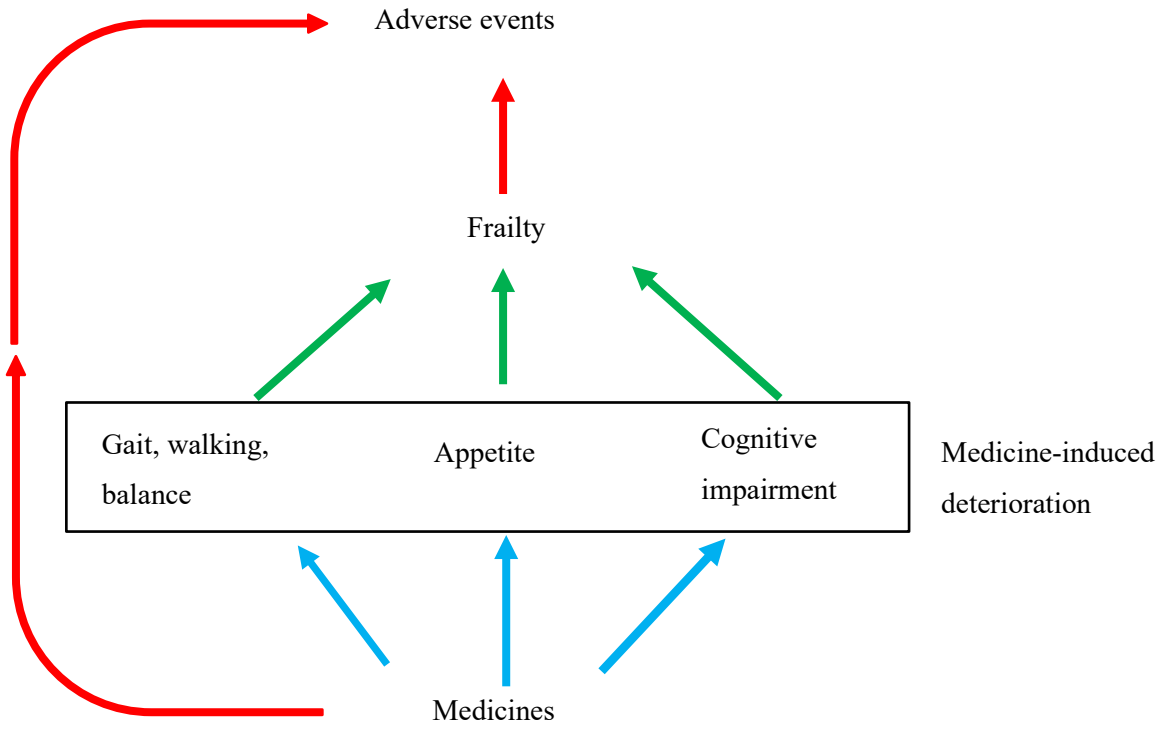
Harm from medicines is the most frequent and the most avoidable harm in health care. Residents of aged care are particularly vulnerable to the harmful effects of medicines. International evidence suggests, every month up to one in 10 residents in aged care experience an adverse event due to their medicines.(4-6) The majority of these adverse events are serious, life-threatening or fatal.(7, 8) In Australia, this equates to over 250,000 serious, life-threatening or fatal adverse medicine events in aged care each year. More than half of this harm is preventable.(7, 8)

In addition to recognised adverse medicine events, many medicines often have what might be considered “minor side effects” which are difficult to detect and frequently unrecognised. These side effects, particularly if the cumulative effects build over time, may be misattributed as geriatric syndromes, frailty or “changes due to aging”. These cumulative effects, which can be described as medicine-induced deterioration,(9) encompass symptoms including cognitive and functional impairment, the latter which may be due to muscle weakness, neuropathy or sedation. All these symptoms may reduce physical activity or increase risk of falls. Additional symptoms that can be medicine-induced include loss of appetite, changes in urinary function and bowel function, changes in respiration, and changes in activity or sleep patterns. While these symptoms may occur independently of medicine use, many medicines have side effect profiles that may cause or contribute to these symptoms. Medicine-induced deterioration can be further exacerbated where medicines with differing indications but similar or overlapping side effect profiles are used concurrently.

Medicines can affect a range of physiological systems including cognition and physical function, both of which are components of frailty.(10) This may partially explain the reason why there is significant evidence demonstrating that medicine use is associated with frailty.(11-13) Frailty is a risk factor for adverse events including falls, delirium and hospitalisation,(14) and frail individuals have worse health outcomes than non-frail individuals.(11, 12, 15) Emerging longitudinal evidence suggests that medicines may worsen frailty, with longitudinal evidence showing that the cumulative load of anticholinergic and sedative medicines is associated with increased risk of developing pre-frail states.(16)

Once frail, individuals are also more vulnerable to adverse drug reactions.(17) An Irish study demonstrated that the odds of developing an adverse reaction in frail persons was double that of a non-frail person (29% compared to 17% respectively, odds ratio OR 2.1 (95% confidence interval CI 1.5 – 3.0).(17) Reducing medicine-induced deterioration would therefore reduce the potential for people to develop frailty and, thus, reduce the potential for adverse medicine events (see Figure A-1).

Figure A-1: The relationship between medicines, medicine-induced deterioration, frailty and adverse events.



A.3.2. Exclusion criteria

The trial did not include very frail or cognitively impaired residents, thus, evidence is lacking for the effectiveness of the service in these groups and for this reason, the proposed exclusion criteria are:

i) residents with significant existing frailty, defined as a score of 0.40 or above using the Frailty Index; (15)
ii) residents with moderate or severe dementia, measured using the Psychogeriatric Assessment Scales (18) or Montreal Cognitive Assessment (MoCA) tool; and
iii) residents receiving palliative care or respite care.

A.4. Comparator Details

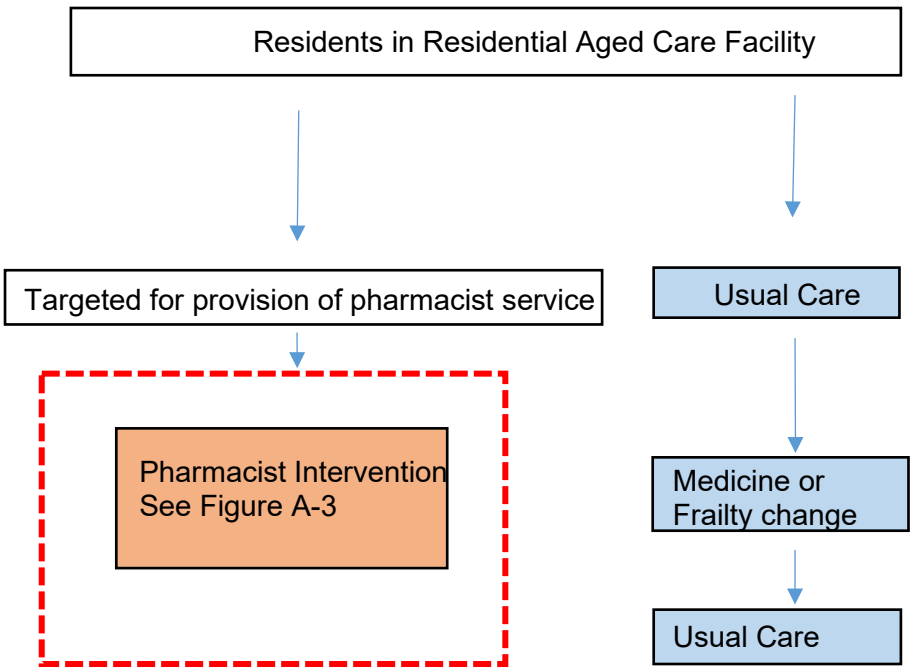
The comparator group is usual care provided to Australian aged care residents. The proposed service would be in addition to usual care for a defined subgroup of the population of residents in aged care facilities.

A.5. Clinical management Algorithms

As detailed in the clinical care algorithm shown in Figures A-2 and A-3, residents will receive the proposed pharmacist-led service in addition to 'usual care'. The service is comprised of regular pharmacist-led assessments of residents in aged care to detect signs and symptoms of medicine-induced deterioration and adverse events. Recommendations concerning medication management will be made to the resident's general practitioner, residents themselves and facility care staff in order to prevent or mitigate harm from medicines (Figure A-3).

In the absence of the proposed pharmacist-led service for eligible populations 'usual care' as currently provided to residents in all Australian residential aged care facilities would remain in place. The key difference of the proposed service to the comparator of usual care is the additional pharmacist-led service.

Figure A-2: Clinical management algorithm for the proposed pharmacist service in comparison to usual care



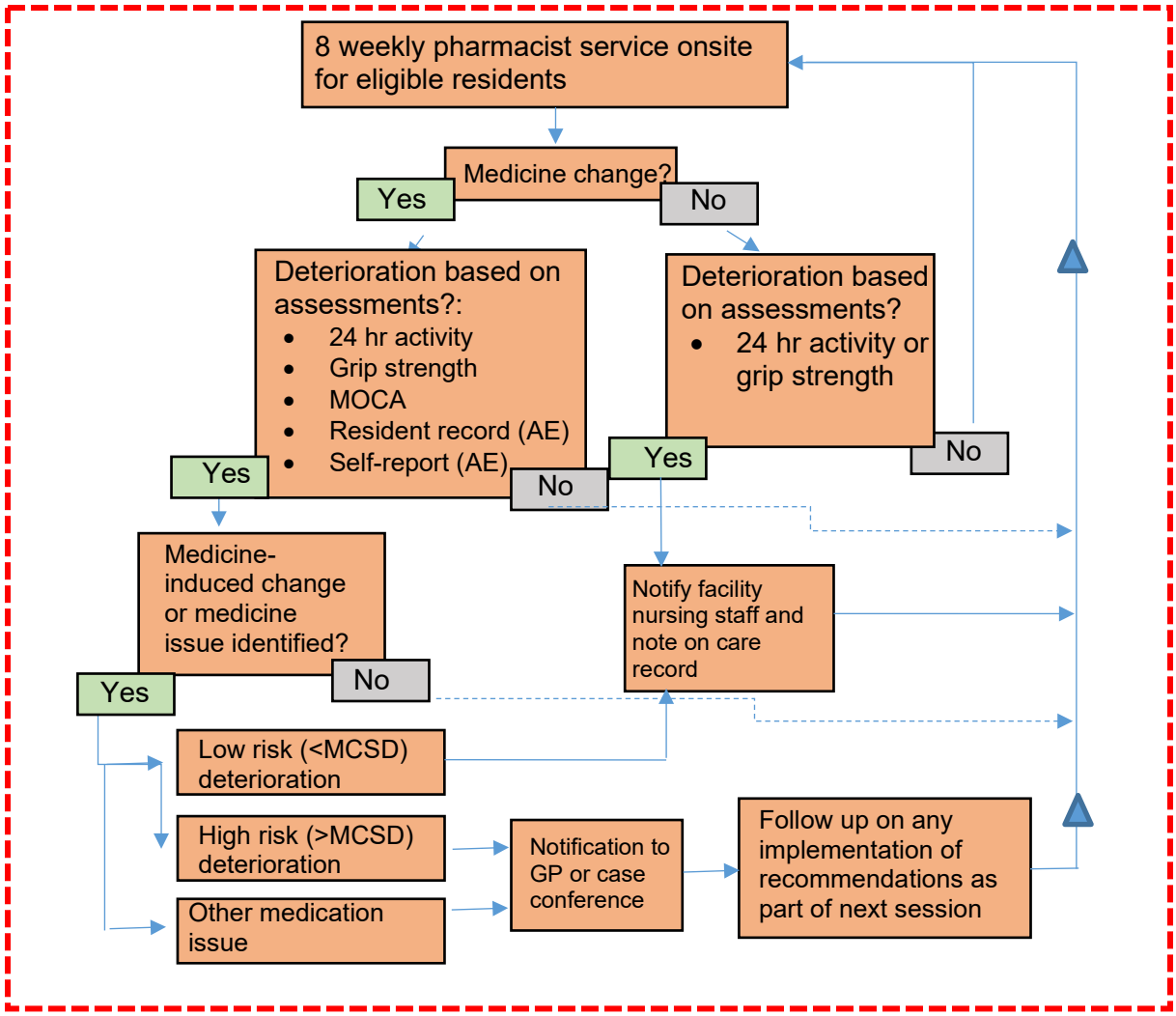


Figure A-3: Clinical management algorithm for proposed pharmacist service.

Abbreviation: A= adverse event, MCSD = minimum clinically significant difference.

A.6. Clinical Claim

The clinical claim is that the pharmacist-led intervention is more effective than usual care for reducing medicine induced deterioration in persons resident in aged care who have a cognition score 18 or higher (corresponding to no or mild cognitive impairment) and a frailty index score of 0.4 or less as evidenced by maintenance of cognition.

A.7. Summary of the PICO

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1.(Appendix D)

Box 1 Criteria for identifying and selecting studies to determine the safety of a pharmacist-led service in persons resident in aged care taking four or more medicines or at least one medicine with anticholinergic or sedative properties

Selection criteria	Description
Population	Residents of aged care residential facilities who: • Are taking four or more medicines or at least one medicine with anticholinergic or sedative properties; and • have a cognition score (MoCA) of 18 or higher (corresponding to no or mild cognitive impairment); and • have a frailty index less than 0.4.
Intervention	Regularly delivered (every eight weeks) pharmacist-led service for preventing medicine-induced deterioration and adverse reactions
Comparator	Usual care
Outcomes	• Cognition Note: additional outcomes assessed in the trial included • Frailty • Physical Activity • Grip strength • Weight • EQ-5D • Adverse medicine events
Systematic review question	Are pharmacist-led services in aged care to reduce medicine induced deterioration and adverse medicine events effective?

Section B: Clinical Evaluation

B.1. Literature Sources and Search Strategies

The medical literature was searched on 7 February 2021 to identify relevant studies and systematic reviews published during the period 1991 to January 2021. Searches were conducted of the databases and sources (See Appendix B). To source unpublished or grey literature, reference lists and publications of key authors in the field were manually searched to identify relevant full-text articles across the same time period.

Consistent with the PICO criteria the search aimed to identify controlled trials that included:

- A population (P) that was aged care residents treated with medicines;
- An Intervention (I) that involved a pharmacist service that included multiple visits for the same person and medication review or assessment of medicine appropriateness or medicine induced harm;
- Comparison (C) was standard care; and
- Outcomes (O) were reduction in medicine-induced deterioration from baseline to end of intervention, change in cognition scores, change in body weight or change in rate of adverse medicine events.

Medication review was defined as any kind of systematic assessment of a patient medication with an aim to evaluate and optimize the pharmaceutical treatment. We included randomised controlled trials (RCT) and restricted the publications to English. Studies in which the medication review was focused on a specific condition or a specific class of drug were excluded. Ongoing studies or protocols were not included in the review, but their references were examined to detect any relevant studies.

Elements of clinical question, as well as specific search terms are described in Table B-1.

Element of clinical question	Does the pharmacy service have impact on cognition, adverse events, falls and mortality in older adults living in aged care facilities?
Population	“aged” OR “aging” OR “elderly” OR “resident” OR “senior”
Intervention	(“randomized controlled trial”) OR (“randomised clinical trial”) AND ((“residential aged care”) OR (“nursing home”) OR (“aged care”) OR (“long term”) OR (“care home”)) AND ((“pharmacy service”)
Comparator (if applicable)	Control (usual care)
Outcomes (if applicable)	“cognition” OR “cognitive” OR (“Montreal Cognitive Assessment”) OR “MoCA” OR (“Cognitive Assessment Screening Instrument”) “frail” OR “frailty” OR "frailness" OR "frails" “frailty index” “weight” OR “weight body” OR “weights and measures” OR “weighting” OR “weights” "adversely" OR “medication error” “misadventure” OR “medication incidence” OR “”medication safety” OR ‘’adverse drug reaction” OR ”hospitalisation” OR "adverse" AND ("event" OR "events" OR "events")

Limits	Studies published from 1990 until January 2021 English language

Table B-1 Search terms used (literature search platform)

Data screening and extraction

Studies were selected independently by a single reviewer with a random sample receiving independent assessment by a second reviewer. Discrepancies in judgement were discussed among the reviewers to reach consensus about final decision.

Additional pre-specified criteria for excluding studies included:

- interventions limited to the community or home setting;
- interventions for residents transitioning from hospital setting;
- single clinical pharmacist review;
- the intervention was provided by a health professional other than a pharmacist;
- lack of comparative data for both groups, e.g. only baseline data or data for only one group; and
- Systematic or narrative reviews (all were screened for relevant primary studies).

The application of the study selection criteria included in the PRISMA checklist was used to guide reporting. (19) (See Appendix B)

B.2. Results of Literature Search

The search criteria resulted in 1792 potentially relevant records; 316 were duplicates and 1353 were deemed as irrelevant after screening of the title or abstract level. A full-text analysis was completed for 123 studies, of which four RCTs (20-23) met the inclusion criteria.

A PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart (Figure B-1) provides a graphic depiction of the results of the literature search. The most common reason for excluding studies was wrong setting, wrong intervention, single review only. Among the excluded studies, 16 were protocols only. Two studies performed a single medication review for aged care residents during the trial (24, 25), and nine studies compared intervention effect of training non-pharmacy professionals.(26-35) All references from excluded studies were examined to identify any further relevant studies. Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as excluded studies.

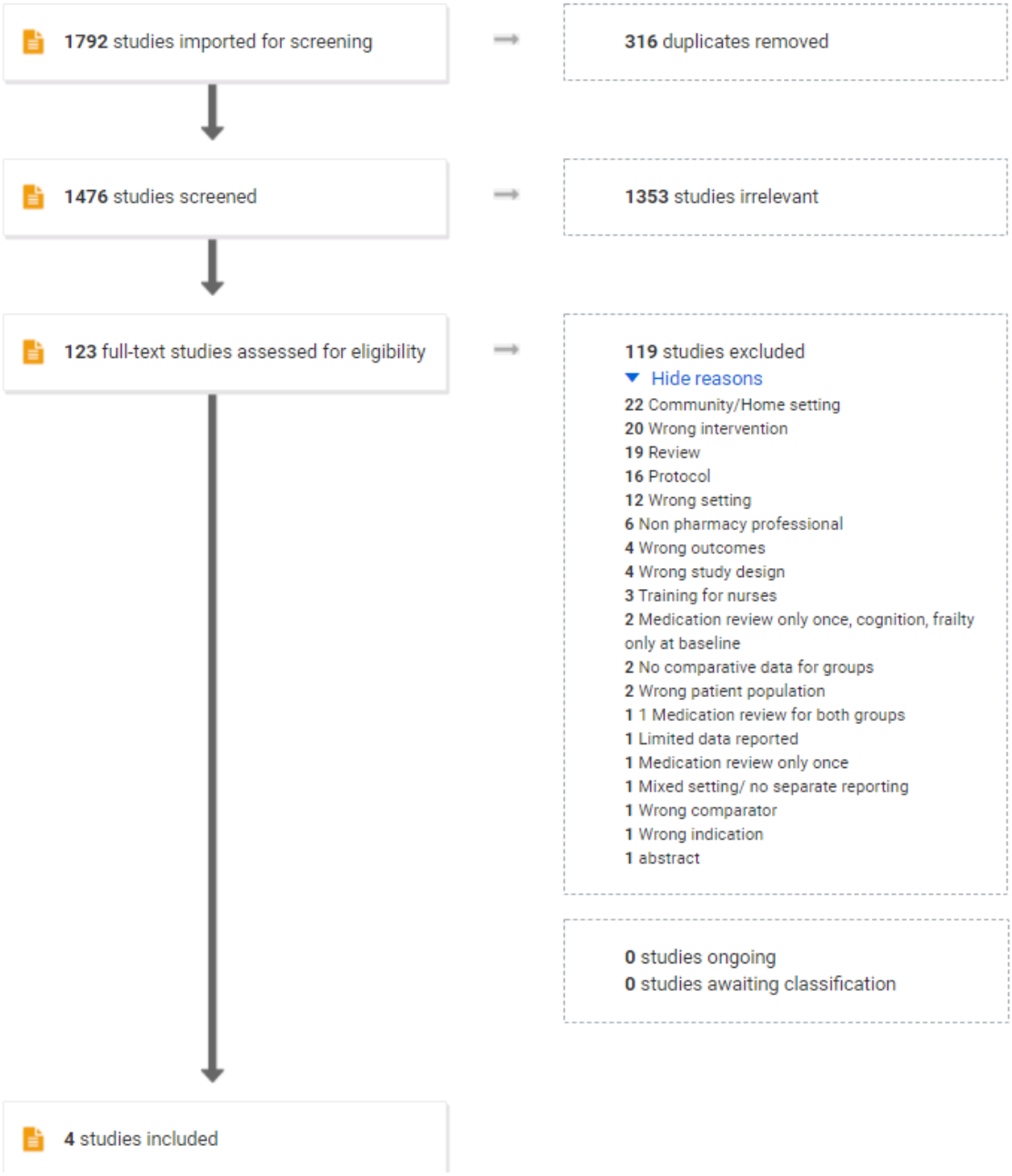


Figure B-1 Summary of the process used to identify and select studies for assessment

Four studies met the inclusion criteria.

Furniss *et al*., tested the effectiveness of a single medicine review with a follow-up visit at three weeks. Outcomes were assessed at four and eight months. (21)

Frankenthal *et al*., tested the effectiveness of a pharmacist intervention comprising 2 visits over a 6 month period. (20) The pharmacists used the Stop/Start criteria as part of their intervention. Follow-up was at 12 months.

Patterson *et al*., tested the effectiveness of monthly pharmacist services to aged-care residents with a focus on reducing use of psychoactive medicines. (23) Pharmacists were

supported with an algorithm adapted from a previous study. "[Pharmacists] *assessed the pharmaceutical care needs of each resident by interviewing the residents, their named nurses and their family members or caregivers. Potential and actual medication-related problems were identified, and recommendations for intervention were recorded. An algorithmic approach adapted from a previous study was used as a guide for study pharmacists to ascertain whether participating residents were receiving inappropriate psychoactive medication".* Intervention participants were followed up monthly. Follow-up was at 12 months.

Lapane *et al*., tested the effectiveness of an algorithm generated from the clinical record to support pharmacists undertaking medicine reviews. (22) Pharmacists visited the facility monthly, with algorithms generated for all residents newly admitted as well as for all residents with a recent fall or case of delirium. Mandated medicine reviews occurred quarterly or yearly as required. The usual care group received a similar number of interventions as the intervention group, thus this intervention is really testing the additional benefit of the algorithm rather than the pharmacist service.

None of these studies were limited to the aged-care population with mild cognitive impairment. Thus, the ReMInDAR trial forms the basis of the evidence for this submission. A full summary of the results of the four studies is provided in Appendix B.

B.3. Results of the Systematic Literature review

We located no previous research that aimed to assess the effect of ongoing pharmacist assessment to prevent deterioration due to medicine use in persons in aged care who were not cognitively impaired or frail. Further, no previous research aimed to prevent mild cognitive impairment or used assessment tools to detect mild cognitive impairment. The limitation of prior research is that cognitive assessment tools used would only detect major changes in cognition. No previous published studies used the Montreal Cognitive Assessment (MoCA). The MoCA is validated for detecting mild cognitive impairment in older people.(36) Thus, the ReMInDAR trial forms the basis of the evidence for this submission.

B.3.1. Methodology of the ReMInDAR trial

Ethics and dissemination

The trial was conducted in accordance with principles of the World Medical Association Declaration of Helsinki (37) and the Australian National Statement of Ethical Conduct in Human Research.(38) Ethics approvals were obtained from the Human Research Ethics Committee, University of South Australia (ID: 0000036440); the Tasmania Health and Medical Human Research Ethics Committee, University of Tasmania (ID: H0017022); the

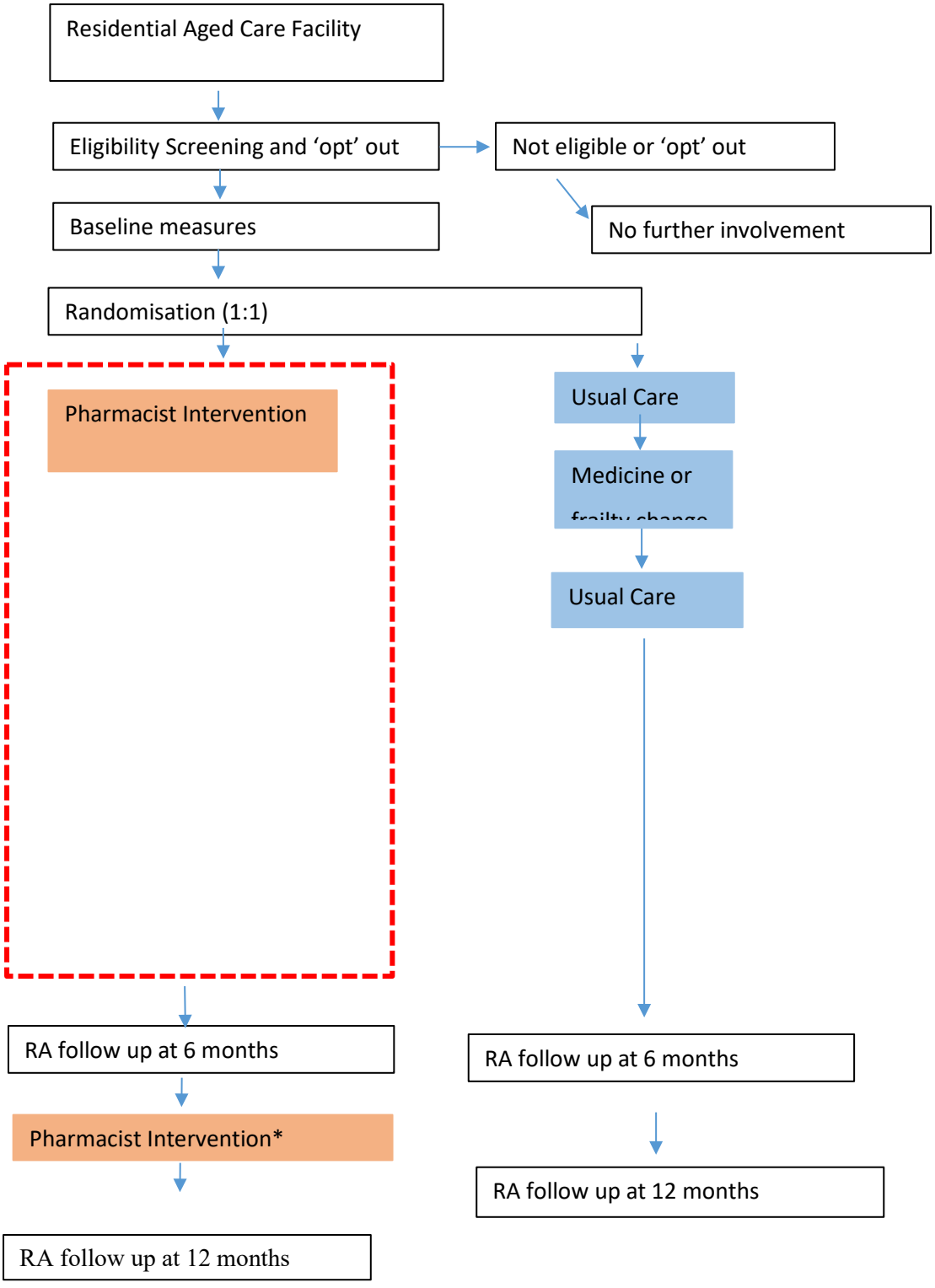
Services Australia External Request Evaluation Committee (ID: RMS0124); and SA Department for Health and Wellbeing (DHW) Human Research Ethics Committee (ID: HREC/19/SAH/83).

The trial was registered with the Australian and New Zealand Trials Registry (ACTRN12618000766213).

Trial design and setting

The Reducing Medicine-induced Deterioration and Adverse Reactions (ReMInDAR) trial was a multicentre, open-label, randomised controlled trial involving 39 aged care facilities with a 12 month follow-up period (Figure B-2). The intervention occurred between August 2018 and July 2020.

Figure B-2: ReMInDAR recruitment and trial delivery flow chart.



Randomisation

Residents were randomised in a 1:1 ratio (Figure B-2). Randomisation was stratified at the level of the individual and not at the level of the facility to avoid confounding by facility related factors such as gym and exercise programs that may affect the outcome. A list of resident randomisation codes and unique participant identification numbers (PIN) was generated electronically for each facility. Residents were screened and residents meeting eligibility criteria were enrolled and assigned to a treatment arm and allocated a PIN based on the next randomised allocation. Due to the nature of the intervention (delivery of an in person pharmacist service), it was not possible to conceal allocation during the trial period.

The statistician responsible for the main outcome analysis was provided with the PIN only and was blinded to the intervention arm allocation. No data on the number of services provided or clinical data collected during the course of the trial was provided to the statistician to maintain blinding of intervention arm allocation.

Eligibility criteria

Residents were included if they were using four or more medicines at the time of recruitment, or were taking at least one medicine with anticholinergic or sedative properties. Residents were excluded if they:

i) had significant existing frailty, defined as a score of 0.40 or above using the Frailty Index,(15)
ii) had moderate or severe dementia, measured using the Psychogeriatric Assessment Scales (18) (PAS < 12/21) or Montreal Cognitive Assessment tool (MoCA ≤ 17/30) ,
iii) were receiving palliative care or respite care, or
iv) were involved in another research project that affected their participation in this trial.

Studies have shown that medicine changes such as anticholinergic cessation do not improve cognitive function in people who have dementia.(39, 40) Additionally there was an ethical requirement of the trial for participants to self-consent. Therefore, we excluded residents with moderate or severe dementia. In addition, residents with significant existing frailty burden, defined as Frailty Index score ≥ 0.40, were excluded because frailty index appears to reach a plateau by 0.6 (41), meaning medicine changes affecting frailty may be harder to detect in residents who have a frailty index above 0.40. The exclusion criteria meant that the proportion of residents who could be involved in the trial was low. More than 50% of residents living in aged care facilities in Australia have dementia(42) and between 50% and 90% of aged care residents are frail.(43)

Recruitment

Aged care resident recruitment

Trial participants were recruited from 39 aged care facilities across two Australian states, South Australia and Tasmania. Facilities were recruited to the trial by purposeful selection. Data on facility demographics and the bed numbers were collected to assess whether the facilities were representative of RACF in Australia. The trial adopted an “opt out approach”, as requested by the residential aged care facilities and consumer advisors. In compliance with the National Statement of Ethical Conduct in Human Research section 2.3.6, flyers were displayed at all participating residential aged care facilities at least one month prior to recruitment to inform the residents, family members and staff of the introduction of the pharmacist service. In addition, flyers were provided to all potential residents. The flyer explained the pharmacist service, information on what to do if the residents did not wish to participate and informed the residents that they could opt out at any time throughout the study period.

The trial excluded persons with moderate or severe dementia, as determined by the last facility recorded Psychogeriatric Assessment scale (PAS) or through administration of the Montreal Cognitive assessment (MoCA) tool during eligibility screening, meaning that the eligible residents had the capacity to decline participation if they wish to do so. Participants who enrolled in the trial could withdraw from the trial for any reason or without having to give a reason.

Pharmacist recruitment

The pharmacists were purposively recruited from community pharmacy or the pool of accredited pharmacists associated with the individual facilities. Initially, the community pharmacy providing the supply services to the aged care facility was invited to provide the pharmacist intervention. Where there was not capacity among the pharmacists at the community pharmacy, alternative pharmacists were sought, with accredited pharmacists associated with aged care facilities being approached. The 28 pharmacists who participated were experienced community pharmacists or accredited pharmacists. One hospital pharmacist was also recruited.

Pharmacists who agreed to provide intervention services under the trial were provided a three-hour one on one initial training session prior to commencement of the service. The training covered identification of medicine-induced deterioration, use of the assessment tools, data collection and interpretation of measures. Standard operating procedure and training manuals were supplied for the pharmacists to ensure consistency in trial operation (See section F3).

To ensure the intervention was integrated into existing work flows, the clinical research pharmacists provided the intervention pharmacists with further on-site support during the first sessional visit. The on-site support aimed to ensure consistency in adherence to trial protocol and ensure pharmacist competence in using the standardised tools in the aged care setting. Additional on-site support and training sessions were provided on request or where necessary. Pharmacists independently delivered the intervention once the clinical research leader was confident in their capacity to implement the intervention as planned. Clinical experts acted as mentors and were available to assist the pharmacists to interpret the results. Pharmacist discussion groups were convened every two months to provide mentoring and discuss solutions to any identified issues. A staged roll-out was employed to allow sufficient time for testing of work-flows and incorporation of feedback from all stakeholders, participants and trial pharmacists.

The training program was reviewed and accredited by the Pharmaceutical Society of Australia for delivery of Group 2 continuing professional development points. The full training manual and accreditation notification are included in Section F3.

General Practitioner recruitment

General practitioners (GPs) were not actively recruited to the trial. The general practitioners providing services to the aged care facilities received a letter introducing the ReMInDAR trial prior to participant recruitment. If the participants were assigned to either trial group, GPs caring for the participants received a follow-up letter informing them of their patients' trial allocation, and pharmacists made contact with the general practitioner as appropriate.

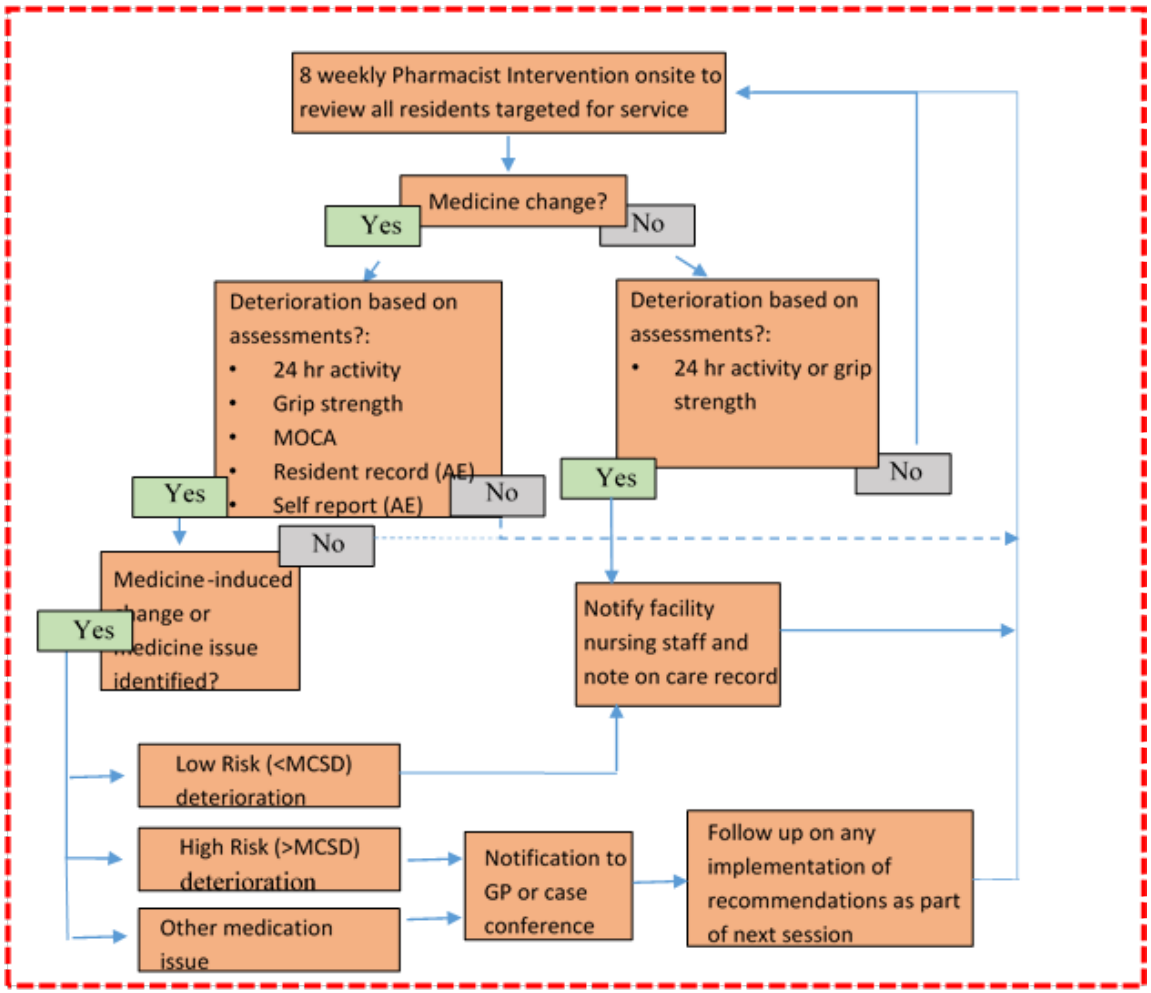
Intervention

The intervention group received a sessional pharmacist service that occurred approximately every eight weeks over 12 months (Figure B-3). The eight week period was chosen as analysis of data from aged care facilities showed that, on average, there were seven medication changes per resident per year; approximately one every two months. Australian evidence also shows that the majority of adverse events occur within the first four weeks of starting a medicine, (44) thus visits every 8 weeks were considered most likely to detect adverse events in a timely manner.

All pharmacist interventions across the 12-month period were conducted by the same pharmacist assigned to the specific site where possible. Exceptions included pharmacists moving interstate, change of pharmacy contracts with the aged care facility or alterations to pharmacist availability.

Text Alternative for Figure B-2

Figure B-3: Flow chart for sessional pharmacist visit.



Abbreviations: AE - adverse event, MCSD - Minimal clinically significant difference

The pharmacist service included assessment for adverse medicine events and medicine-induced deterioration. The pharmacists reviewed electronic or hard copy resident care records to identify any new illnesses or conditions present since the last assessment, including any adverse events (e.g. falls, delirium events, bowel or urinary changes, weight loss) or any signs or symptoms noted in the care record that could be indicative of adverse events (e.g. changes in nutritional status, pain). The pharmacists also reviewed the medication chart to identify any medication changes that had occurred since the last visit. The pharmacist met with the resident and care staff to discuss and identify any concerns that they may have and to assess changes in activity and cognition. The assessment of participant cognition was undertaken using the Montreal Cognitive Assessment tool (MoCA)) (45), 24-hour movement behaviour including sleep was assessed using Activinsights Bands, Activinsights Ltd, Cambridgeshire, UK, and hand grip strength was assessed using a dynamometer, Jamar, Illinois, USA. The Activinsights accelerometer was chosen because it was a health professional grade accelerometer with wireless communication function that did

not require charging for up to a year. Pharmacists recorded their findings in intervention documentation (example shown in Appendix C1).

The pharmacists compared the results for the 24-hour movement behaviour, MoCA test, grip strength and weight with the most recent previous assessment and with baseline data to identify immediate and cumulative changes in a person's condition. Where medicine-induced deterioration was detected and considered clinically significant, the pharmacists liaised with the participants' GPs to discuss the participants' condition and provide recommendations on medication-related problems. After the pharmacists communicated recommended actions, they subsequently followed-up with the GP and facility staff. The pharmacists reassessed the participant at the next sessional visit to determine if medicine-induced deterioration or adverse events had resolved and documented this in their progress notes.

Implementation of the Activinsights accelerometer was not maintained across the trial, due to limited wireless communication in some facilities and inconsistencies with the devices' data collection at low activity and the Bluetooth upload of the data.

The final months of the trial were affected by the COVID-19 pandemic which delayed, modified or stopped some pharmacist sessions for some facilities. Variations to the delivery of the pharmacist intervention during the COVID-19 pandemic were approved by the Commonwealth Pharmacy Trials Program and the Human Research Ethics Committees of University of South Australia and University of Tasmania. The variations allowed for remote data review and interview by telehealth where possible when access to residential aged care sites by 'non-essential' staff was prohibited due to COVID-19; a period that spanned April to June 2020. Pharmacists were able to review medication charts and a summary of progress notes and adverse events remotely, however, intervention data including grip strength and MoCA could not be collected remotely by the pharmacist. Variations to the data collection for each participant at each session were logged to inform trial analysis.

Usual care

Residents in the aged care facilities were eligible to receive residential medication management reviews (RMMRs)(2), and where required as part of usual care during the trial period, this occurred for participants in both intervention and control group. The RMMR is a comprehensive medication review conducted by an accredited pharmacist following a referral from the resident's GP.(2) Accredited pharmacists are funded to conduct an RMMR every 12 to 24 months, or where there has been a significant change in the residents' condition or medication regimen.(3) No intervention other than usual care was provided to participants in the control group.

Primary outcome

The primary outcome was the reduction in medication-induced deterioration from baseline to twelve months, as measured by change in the frailty index.(15)

Because medicine-induced deterioration is not limited to a single event, but can occur in either the physical, medical or psychological domains (for example loss of physical function or poorer cognition), an outcome measure that captured multiple domains was required. For this reason, the frailty index, which captures physical, medical, psychological, and social domains, was used as a surrogate measure of medicine-induced deterioration. The Frailty Index (15) is a 39-item instrument. Measures within the physical domain of the Frailty Index include ability to undertake the physical activities of daily living, while the medical domain includes morbidities. The psychological domain includes measures of cognitive function. The frailty index has been validated in the population recruited for the Australian Longitudinal Study of the Ageing, where it was shown to have good predictive ability for adverse events of falls and hospitalisations.(15, 46)

Frailty assessment is increasingly being used in the clinical setting. For example, it is part of the standard risk assessment records collected on admission to hospitals in South Australia. Measures of frailty have consistently been shown to be predictive of adverse events, (15, 47-58). The rate of death within three to five years in frail persons compared with non-frail persons is double; hazard ratios (HR) range between 1.9 and 2.4 (49, 52, 53). Frail older people are more likely to have disability at follow-up than non-frail older people; odds ratios (OR) range from 2.8-5.2 (47, 53). Further, there is a two to three fold increased risk of hospitalisations (15) and a twofold increased risk of falls (15) in the frail population compared to non-frail population.

Secondary outcomes

The secondary outcomes were:

i) Change in cognition scores

Changes in cognition were assessed using the Montreal Cognitive Assessment (MoCA) test(45). This is the same tool that was used in the pharmacist intervention, and which is validated for screening in mild cognitive impairment.(59) All participants were able to complete the MoCA at enrolment, if during enrolment, participants cognition had declined to such an extent that they were not able to complete the MoCA, a score of 4 was applied which corresponds to commencement of severe cognitive impairment on the MoCA scale (equivalent to 16/21 on PAS).

ii) Change in 24-hour movement behaviour

Change in 24-hour movement behaviour was assessed using the GENEActiv accelerometer, a research-grade activity tracker that has been validated in adults for physical activity(60) and for sedentary behaviour.(61) The GENEActiv was initialised to collect unfiltered, triaxial acceleration data at a sampling rate of 80Hz. Output data included number of sedentary and active bouts, sleep, and active time using previously established age appropriate cut-points. (62) Participants in both the intervention and control group wore the GENEActiv on the wrist for a seven-day period at each data collection point.

iii) Change in grip strength

Grip strength was measured using a handheld dynamometer (Jamar, Illinois, USA) using the dominant hand. The best measurement of three scores was used. Cut off points for grip strength that are considered reflective of sarcopaenia are 27 kg for men; 16 kg for women (63). Measures categorised as 'weak' based on thresholds for men not in residential aged care between 70 -99 years are <21.3kg and <14.7 kg for women of the same age not in residential aged care.(64)

iv) Change in weight

Data on the weight of participants were extracted from the resident serial weight chart, which forms part of the Resident Care Assessment Record.

v) Percentage robust, pre-frail, and frail

The proportion of participants who were frail, pre-frail or robust was measured using the frailty phenotype.(65) The frailty phenotype comprises five criteria: unintentional weight loss, low grip strength, self-rated exhaustion, low walking time and low physical activity. In the frailty phenotype, individuals were classified as frail if they meet three or more of the five criteria, and pre-fail if they have one or two attributes. Individuals who meet none of the criteria are classified as robust. Due to access limitations with data collection at 12 Months, frailty phenotype was not reported in the final analysis.

vi) Rate of adverse medicine events.

The rate of adverse medicine events was measured as a composite outcome of adverse medicine events judged by a clinical panel to be possibly, probably or definitely medicine induced. Adverse events were extracted from the care record and include events such as falls (non-injurious and injurious including fractures), bleeding and bruising, delirium, confusion, dizziness, faecal impaction. An independent clinical panel subsequently judged

the events to be medicine related or not. The number of adverse medicine events per 100 resident months is reported.

vii) Change in health related quality of life.

Health related quality of life was assessed using the EQ-5D. The EQ-5D is a simple generic health related quality of life measure which provides utility weights enabling cost-effectiveness analysis.(66) The questionnaire contains five dimensions (mobility, self-care, usual activities, pain or discomfort, anxiety or depression) and a visual analogue scale (range 0 to 100) representing current health state.

The EQ-5D-5L defines a total of 3125 health states, which are converted into a single index using the Index Value Calculator developed by the EuroQol Group.(67) Reference data for the Australian population have not been generated, thus, the interim scoring for EQ-5D-5L from the cross-walk value set of the United Kingdom is the recommended comparator and was used for this analysis. (67)

viii) Change in health resource use, including costs and net costs/savings associated with the intervention.

Data were collected on intervention-associated resource use, including pharmacist, doctor, nursing and care staff time, changes in medication and non-medication management and resource use associated with any adverse events. Data were obtained on health resource use based on administrative billing data for Pharmaceutical Benefits Scheme, Medicare Benefits Schedule and public hospital services. The Aged care Funding Instrument was used to inform aged care costs.

Follow up

All participants undertook follow-up assessments at six and twelve months.

Stakeholder satisfaction

Stakeholder interviews or focus groups with 7 trial participants, 4 residential aged care staff, 4 general practitioners and 6 pharmacists were undertaken to determine participant satisfaction with the service, barriers and enablers to participation and potential for application of the service more widely. In addition, all pharmacists were provided with a survey to evaluate the training for the intervention, and 56% responded.

Consent to link data

Written consent was obtained from residents to access their Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data from Services Australia. Consent

was obtained or a waiver for consent was approved to obtain state hospital data through the respective state health data custodians.

Data collection and storage

Table B-2 outlines the data that were collected throughout the trial period. Research assistants at the aged care facilities or independent to the facilities were responsible for collecting data for all participants at baseline, six months and twelve months. Data were entered into a custom-built web-based data management information system.

The research assistants received training on the protocol and procedures, administration of trial measures and completion of the electronic case report forms. Standard operating procedure manuals were supplied for the research assistants to ensure consistency in trial operation.

The pharmacists were responsible for collecting data on medicine changes, medicine-induced deterioration and adverse events during the sessional pharmacist visits. Data are stored in secure settings at the Quality Use of Medicines and Pharmacy Research Centre, University of South Australia. All trial data are stored securely in a de-identified format.

Task	Screening & baseline	Pharmacist service	Outcome measures
Timeline (month)	At trial entry	Every 8 weeks	6 & 12 months
Assess eligibility to enter trial	x		
Demographics, medical history, Resident Care Assessment Record	x		
Randomisation	x		
Frailty index	x		x
EQ-5D	x		x
Health resource use	x		x
Activity tracker - GENEActiv	x		x
Weight	x	x	x
MoCA	x	x	x
Dynamometer	x	x	x
Activity tracker – Activinsights (intervention group only)	x	x	x
Identification of medication change		x	
Identification of adverse events		x	x
GP report if high risk of deterioration		x	
Reassess participant if medicine-induced deterioration or adverse event has resolved		x	

Table B-2: Assessment and pharmacist service schedule.

Outcome measures and assessment tools: Activinsights: Health professional grade activity tracker (partial collection only); Dynamometer: instrument to measure grip strength; EQ-5D: 5-item questionnaire and a visual analogue scale to measure quality of life; Frailty index: 39-item multidimensional questionnaire to assess frailty; GENEActiv: Research grade activity tracker fitted for one week at baseline, 6- and 12-months; MoCA: Montreal Cognitive Assessment, a 30-point assessment for multiple cognitive domains. X denotes the task was conducted during the visit.

Data classification

Medication related problems identified by the pharmacists were classified according to eight categories in the Document classification.(68) Development of the Document classification system is based on the types of medication related problems identified by Hepler and Strand (69) and the Pharmaceutical Care Network Europe (PCNE) (70) classification system. The Document system is a validated classification system to categorise drug-related problems and clinical interventions performed in community pharmacy.(68)

Problems identified by the pharmacists were extracted and classified by two independent researcher pharmacists for a random sample of 108 participants' records. Cohen's kappa to quantify the level of agreement between identification and classifications was used.(71) The computation of kappa values was performed using the vcd package for open-source R Studio Version 1.2.1335 (R Development Core team, 2009).(72)

Adverse events were assessed to determine the extent of medication related harm in aged care and the preventability of that harm. Adverse events that were collected during the ReMInDAR trial were classified according to an abbreviated set of validated assessment criteria for each event. The assessments were limited to abbreviated sets of criteria, as not all required data were available or collected for the residents.

Adverse events were independently coded by two researcher pharmacists using an abbreviated Naranjo assessment criteria to classify them for causality as an adverse medicine event. (73) If an agreement on positive causality was determined then the adverse event was considered a potential adverse medicine event and referred to a multi-disciplinary panel of three clinicians for further review. Where there was disagreement on causality, the adverse event was assessed by a third pharmacist with the majority decision deciding allocation. The clinical panel made a final determination of the causality of all potential adverse events. Where likelihood of causality was determined to be 'possible' or greater that the adverse event was classified as medicine induced. The clinical panel assessed the event for its preventability (using an abbreviated set of abbreviated Schumock-Thornton criteria (74), and considered any if there were precipitating (potentially modifiable) or contributing factors. Severity was not assessed due to insufficient collection of clinical information.

Source data documentation and monitoring

To ensure accurate data entry a member of the research team checked data entered by each research assistant. Data for the first 50 participants entered into the electronic case report forms were cross-referenced to the original source information by two members of the research team. Additionally, two members of the research team performed on-going source data verification (10% random sample of participants' data) and review to confirm that the source data (e.g. progress notes, medication chart, outcome measures) entered by the research assistants into the electronic case report forms was accurate, complete and verifiable from the source documents. Medication data was dual coded to ensure accuracy. An audit trail was created of data validation, with each entry time-stamped when created or modified. The statistician conducted quality assurance and applied validation and consistency rules to ensure the integrity of the trial data.

Analysis plan

Sample size calculation

The sample size calculation for the trial was based on the primary outcome, change in frailty over twelve months. The estimated change was based on data from the Australian Longitudinal Study of Ageing.(75) The intervention was assumed to prevent medicine-induced frailty by half a deficit, with the treatment effect being a change in the frailty index of 0.015 with a standard deviation of 0.06.(76)

Assuming a correlation in the frailty index over twelve months of 0.7, a sample size of 302 was estimated to provide 80% power with two-sided $\alpha=0.05$ to detect a difference in the change in the frailty index over twelve months of half a deficit. Allowing for a loss to follow-up of 17% based on a study of twelve-month death rates in Australian aged care residents with mild to moderate frailty,(77) the total estimated sample size required was 354.

Health economic analysis

The primary economic analysis proposed was a trial-based cost comparison from the perspective of the Australian healthcare system (public and private funded healthcare costs). The primary economic outcome is average change in total health resource expenditure (net costs/ savings) associated with the pharmacist intervention per resident over a one year time horizon. Costs were collected during the trial and were also informed by administrative data obtained from Services Australia, and the respective state health department data custodians.

The health economic analysis utilised participant data on an 'intention to treat' (ITT) basis. Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS)

administrative claims data, as well as administrative claims data for hospital admissions was linked to the clinical effectiveness data collection set and used to inform the economic evaluation. The health economics plan is in Appendix C3.

Governance

The Trial Steering Committee, comprising representatives from all research partners, governed the trial. This committee reviewed and agreed to all trial planning documents and monitored the progress of the trial. A Trial Management Plan was the master planning document outlining all requirements for successful implementation and completion of the trial. A Communications Management Plan, Data Management Plan, Quality Management Plan and Intellectual Property Management Plan supported the master planning document. Standard Operating Procedures were established to operationalise aspects of all plans. A Risk Register and Intellectual Property Register was maintained and reviewed regularly.

Resident, Public, Staff and Resident Engagement

We established a consumer advisory group and a stakeholder advisory committee to ensure that the intervention met stakeholder needs.

The consumer advisory group included membership representing the: Consumer Health Forum of Australia; Health Consumers Alliance of SA; Primary Health Network (PHN) Adelaide Consumer Group; Helping Hand Inc. consumer group; Southern Cross Care SA, NT and Vic consumer group; Southern Cross Care Tasmania consumer group; and Aged Rights Advocacy Service. The consumer advisory group was convened prior to the trial commencing and met 4 times throughout the trial. Residents and carers were engaged to provide a consumer perspective on the trial activities during the promotion of the trial onsite, and their feedback incorporated into the recruitment and data collection process.

Representatives from key healthcare professional and peak body organisations, including the: Pharmaceutical Society of Australia; Pharmacy Guild of Australia; Australian Medical Association; Royal Australian College of General Practitioners; Primary Health Network - Adelaide; Primary Health Network - Tasmania; Southern Cross Care Tasmania; Leading Aged Services Australia; and Aged and Community Services Australia formed the membership of a stakeholder advisory committee which met 4 times across the life of the trial.

B.4. Risk of Bias Assessment

The ReMInDAR trial was a multicentre, open-label, randomised controlled trial involving 39 aged care facilities. The intervention occurred between August 2018 and July 2020. Assessment of the potential risks of bias are described in Table B-3.

Type of bias	Description
Selection bias: random sequence generation and allocation concealment	Residents were randomised in a 1:1 ratio. Randomisation was stratified at the level of the individual and not at the level of the facility to avoid confounding by facility related factors, such as gym and exercise programs, that may affect the outcome.
Performance bias: blinding of personnel	ReMInDAR was a blinded trial in which neither the principal investigator nor statistical staff knew the residents treatment assignment. A list of resident randomisation codes and unique participant identification numbers was generated electronically for each facility. Residents were screened and residents meeting eligibility criteria were enrolled and assigned to a treatment arm and allocated a participant identification number (PIN) based on the next randomised allocation. The statistician responsible for the main outcome analysis was provided with the PIN only and was blinded to the intervention arm allocation. No data on the number of services provided or clinical data collected during the course of the trial was provided to the statistician to maintain blinding of intervention arm allocation. Participating pharmacists were aware of intervention allocation.
Attrition bias: incomplete outcome data	**Intent-to-treat population** All residents who were randomised were included in the intent to treat population. Residents who prematurely discontinued from the study for any reason were excluded consistent with ethics. **Per-Protocol population** The Per-Protocol Population included all residents in the intent to treat population who did not withdraw. Efficacy analyses performed using the Per-Protocol Population were considered supportive.
Hawthorne bias of participants	Potentially there might be an issue with Hawthorn Effect given the residents live in a closed community receiving a service and participants may potentially behave differently due to the fact that they are aware that they were being observed. Due to the nature of the intervention (delivery of an in person pharmacist service), it was not possible to conceal allocation during the trial period.
Survivor bias	Due to an imbalance in the number of deaths between the intervention and control arms, the potential for bias due to a survivor effect was assessed in sensitivity analyses for the primary outcome, weight and MoCA.
Other sources of bias	No other sources of bias were identified.

Table B-3: Assessment of risk of bias for ReMInDAR trial.

B.5. Characteristics of the ReMInDAR trial cohort

B.5.1. ReMInDAR trial baseline cohort

Residential aged care facilities in ReMInDAR.

In total, 39 residential aged care facilities were recruited for the ReMInDAR trial. The characteristics of the facilities are presented in Table B-4.

Characteristic	Type of Difference	No. of Facilities	% of Facilities
Facility Type	Village or Cottage	3	7.7
	Traditional	36	92.3
Facility building age	Range: 2 months to 125 years Median: 21.5 years	-	-
Size (bed numbers)	Range: 29 to 184 beds per RACF Median: 92 beds per RACF	-	-
Location[1]	Inner Regional	4	10.3
	Major Metropolitan	35	89.7
Average ACFI cost ($)[2]	Range: $132.90 – $222.58 Median: $182.93	-	-
Profit Status	Not-for-profit	38	97.4
	For-profit	1	2.6
RACF provider type	Single, privately owned	2	5.1
	Part of chain or group	37	94.9
Socio-economic Disadvantage [3]	1 (highest disadvantage)	5	12.8
	2	12	30.8
	3	9	23.1
	4	11	28.2
	5 (least disadvantage)	2	5.1
Resident Age	Range: 48 -107 years old	-	-
Resident sex ratio	Range: 26% - 93% female Median: 79% female	-	-
Specialist space or services	Access to outside space	39	100.0
	Access to communal space	39	100.0
	Access to gym	18	46.2
	Access to wellness/lifestyle activities	39	100.0
	Access to allied health staff	39	100.0

Table B-4: Characteristics of residential aged care facilities and resident populations in the 39 ReMInDAR trial RACF sites. ABS Remoteness classification[1]; July 2018 - June 2019 ACFI subsidy rates for time of facility recruitment to trial[2]; ABS Index of Socio-economic Disadvantage[3]

ReMInDAR trial consort

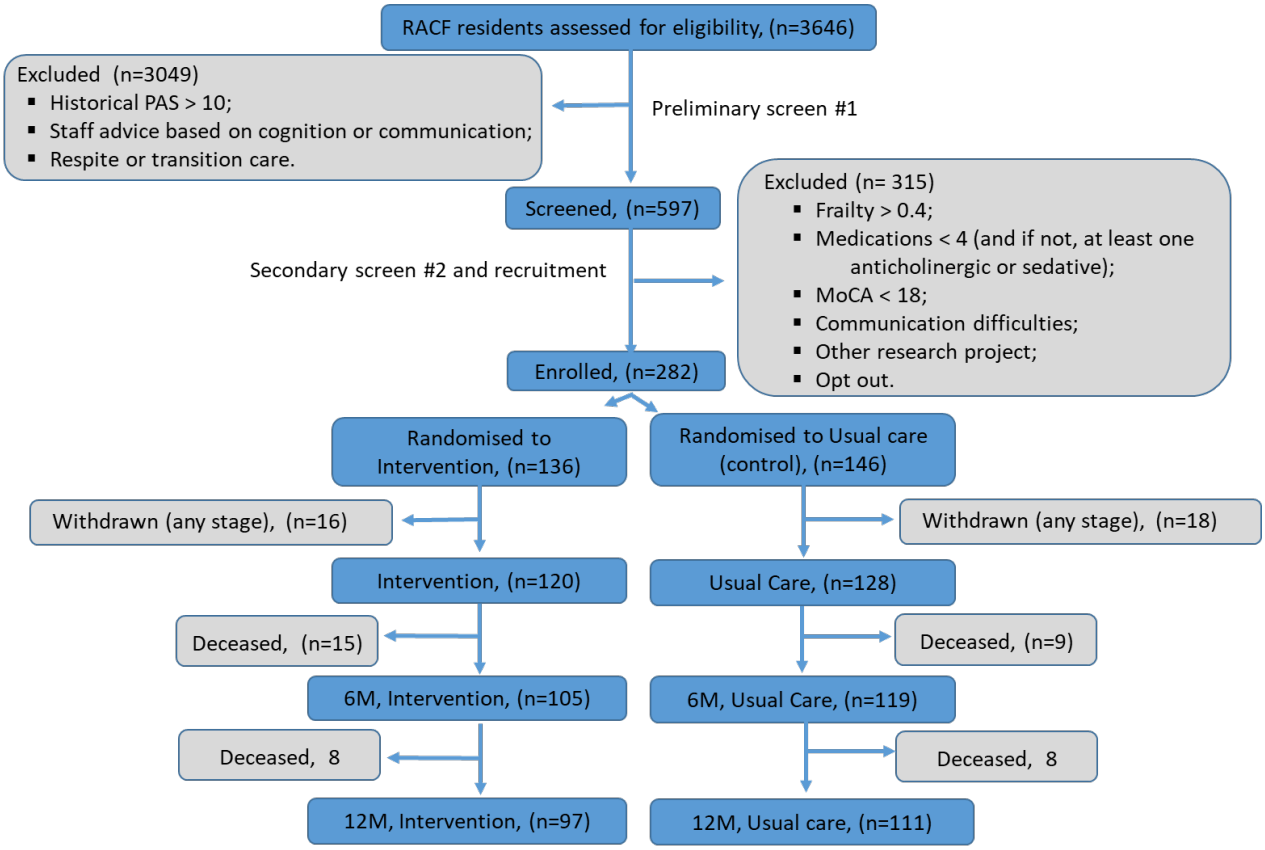
The 39 RACFs that were involved in the trial had 3,646 residents at the commencement of the trial (Figure B-4). Overall, 3,049 were excluded based on one or more of the following reasons: 1) having a historical psychogeriatric scale score on the RACF client files of greater than 10 (where a score of 10 or less is considered the threshold for capacity for self-consent); 2) staff advice regarding the residents limitations, cognition or capacity for communication; or 3) being in respite or transition care. The remaining 597 residents were screened by interview. A further 315 were excluded based on one or more of the following reasons: 1) having a frailty index greater than 0.4; 2) being on less than 4 medications (if one was not a sedative or anti-cholinergic medication); 3) scoring less than 18 in the MoCA administered during screening (corresponding to PAS of >10); 4) significant communication difficulties; 5) already in a research project that wasn't at a facility-wide level; or 6) resident opted out.

[1] https://itt.abs.gov.au/itt/r.jsp?ABSMaps

[2]https://webarchive.nla.gov.au/awa/20191107022039/https://agedcare.health.gov.au/funding/schedule-of-subsidies-and-supplements-from-20-september-2018

[3]https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/2033.0.55.001~2016~Main%20Features~IRSD%20Interactive%20Map~15

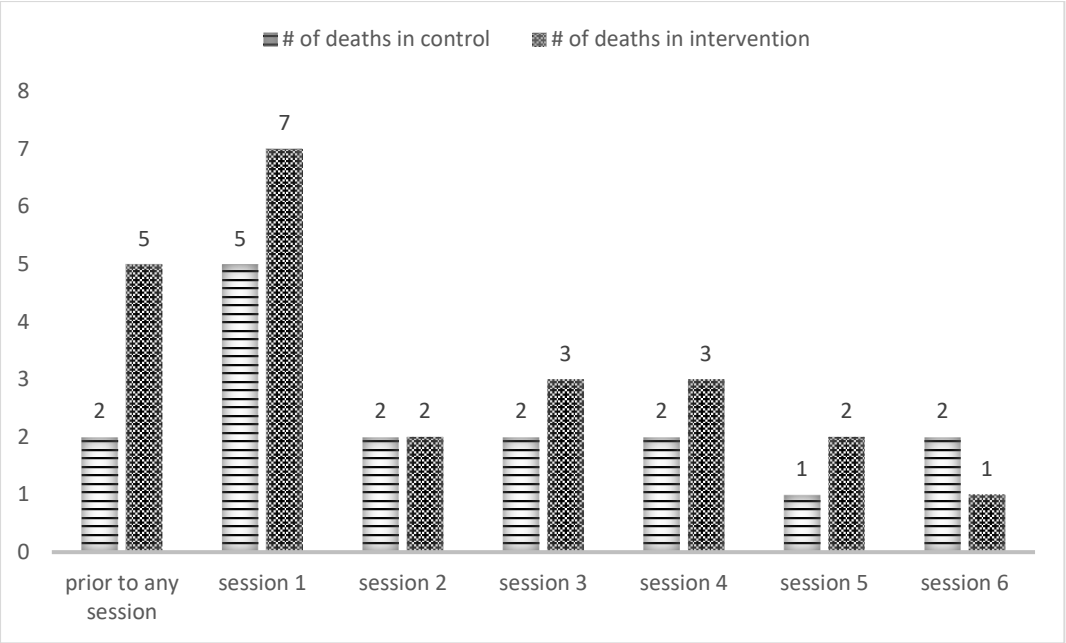
Figure B-4: ReMInDAR consort diagram illustrating the numbers and flow of residents in RACF who were screened, excluded, enrolled, randomised and followed up at each time-point.



Consideration of death rates between trial arms

There was an imbalance in the number of deaths between the two treatment arms during the 12 month follow-up. The imbalance in deaths predominantly occurred prior to the intervention commencing (i.e. prior to the first pharmacist session 1) with 5/120 deaths (4%) for intervention arm and 2/128 deaths (2%) for the control group occurring in this time (Figure B-5). The number of deaths before the time of Session 2 was 12 and 7 respectively.

Figure B-5: Deaths in ReMInDAR cohort by trial arm aligned to timing of pharmacist session.



*** Death date of residents in control arm of trial were imputed based on the pharmacist session dates for their intervention arm counterparts at each facility.**

ReMInDAR trial consort characteristics

A total of 282 participants were enrolled in the trial and of these 136 were randomised to the intervention arm of the trial and 146 were randomised to the comparison arm. Withdrawals included 16 from the intervention arm and 18 withdrew from the comparison arm. Excluding those who died left a total of 97 participants for analysis of the primary outcome at 12 months for the intervention arm and 111 for the comparison arm.

Baseline characteristics by trial arm are presented in Tables B-5a and b. The trial cohort characteristics were similar at baseline with the exception of weight, body mass index and cognition (MoCA), with intervention participants being slightly heavier and having slightly better cognition scores. The median age was 87 years and 40% were men. At baseline, the ReMInDAR cohort were taking a median of 15 unique medicines, inclusive of a median of 5 'as needed' medicines. Overall, 46% of both arms were taking a median of 3 or more sedative medicines at baseline.

Baseline Descriptor	Intervention arm	Intervention arm proportion (%) or Standard Deviation (SD)	Comparison arm	Comparison arm proportion (%) or Standard Deviation (SD)
Total number (n) in trial cohort post randomisation (excl. withdrawn)[1]	120		128	
Gender = Male, n (%)	41	34.2%	39	0.5%
Weight* (kg), overall, (mean SD)	**75.60 kg**	**(16.44)**	**71.72 kg**	**(19.18)**
Male weight* (kg), (mean SD)	**83.54 kg**	**(15.24)**	**81.03 kg**	**(17.22)**
Female weight* (kg), (mean SD)	**71.47 kg**	**(15.58)**	**67.65 kg**	**(18.64)**
Height (cm), (mean, SD)	164.73 cm	(9.33)	164.85 cm	(8.23)
BMI*, (mean, SD)	**27.55**	**(5.53)**	**26.42**	**(7.34)**
Frailty Index (mean, SD)	0.27	(0.07)	0.27	(0.08)
Number of comorbidities in frailty index, (mean, SD)	4.60	(1.77)	4.78	(1.88)
Number of difficulties in frailty index, (mean, SD)	4.30	(2.16)	4.27	(2.3)
Frailty subgroup (frailty index >= 0.25), n (%)	71	59.2%	77	60.2%
Highest Grip Strength (kg), (mean, SD)	16.94 kg	(6.9)	17.39 kg	(7.93)
Grip Strength Male (kg), (mean, SD)	21.84 kg	(7.11)	24.26 kg	(8.55)
Grip Strength Female (kg), (Mean, SD)	14.40 kg	(5.25)	14.37 kg	(5.39)
Calculated Montreal Cognitive Assessment (MoCA) score*, (score between 0-1), (mean, SD)	**0.76**[1]	(0.11)	**0.74**[1]	(0.11)
EQ-5D-5L single index (mean, SD)	0.68	(0.26)	0.65	(0.26)
Accelerometer data				
GENEActiv - average sleep time per day, mins (mean, SD)	545.00 minutes	(80.19)	546.54 minutes	(83.09)
GENEActiv - calculated sleep efficiency (%),(mean, SD)	76.04%	(18.47)	78.00%	(15.11)
GENEActiv - average sedentary time per day, mins (mean, SD)	750.67 minutes	(87.15)	743.11 minutes	(109.67)

Baseline Descriptor	Intervention arm	Intervention arm proportion (%) or Standard Deviation (SD)	Comparison arm	Comparison arm proportion (%) or Standard Deviation (SD)
GENEActiv - average light activity time per day, mins (mean, SD)	97.86 minutes	(54.87)	96.12 minutes	(51.24)
GENEActiv - moderate activity time per day, mins (mean, SD)	45.06 minutes	(46.08)	50.58 minutes	(48.72)
GENEActiv - average moderate and vigorous activity (MVPA) time per day, mins (mean, SD)	45.09 minutes	(46.14)	50.67 minutes	(48.90)
GENEActiv Moderate Vigorous Physical Activity Bout Length, mins (mean, SD)	2.91 minutes	(1.16)	2.90 minutes	(1.10)
GENEActiv number of Moderate Vigorous Physical Activity Bouts (mean, SD)	14.3	(11.4)	15.8	(11.2)

Table B-5a: ReMInDAR baseline cohort, clinical descriptors for participants by intervention arm.

*** indicates variation between trial arms**

[1] corresponds to a MoCA (0-30) score of 23/30 for Intervention arm and 22/30 for control arm.

Baseline Medicine Descriptor	Intervention arm	Intervention arm proportion (%) or Standard Deviation (SD)	Comparison arm	Comparison arm proportion (%) or Standard Deviation (SD)
Number of PRN medicines, n (mean, SD)	5.34	(3.17)	5.05	(3.22)
Number of unique* medicines, n (mean, SD)	15.23	(5.71)	14.33	(5.58)
Number of unique** medicines, n (mean, SD)	2.48	(1.8)	2.38	(1.87)
Number of sedatives categorised				
# sedatives, n= 0, n (%)	16	13.3%	21	16.4%
# sedatives, n=1-2, n (%)	52	43.3%	52	40.6%
# sedatives, n=3+, n (%)	52	43.3%	55	43.0%
Anticholinergic load (mean, SD)	2.16	(2.33)	1.93	(2.29)

Baseline Medicine Descriptor	Intervention arm	Intervention arm proportion (%) or Standard Deviation (SD)	Comparison arm	Comparison arm proportion (%) or Standard Deviation (SD)
Anticholinergic load categorised, n (%)				
n= 0, n (%)	40	33.3%	50	39.1%
n=1-2, n (%)	32	26.7%	39	30.5%
n=3+, n (%)	48	40.0%	39	30.5%

Table B-5b: ReMInDAR baseline cohort, medicine descriptors for participants by intervention arm.

***Medicines are unique at the level of generic name (ATC code)**

B.6. Outcome Measures and Analysis

B.6.1. Outcomes

The primary outcome was the reduction in medication-induced deterioration from baseline to twelve months, as measured by change in the frailty index.(15)

Secondary outcomes

The secondary outcomes were:

i. Change in cognition scores assessed using the Montreal Cognitive Assessment (MoCA) test(45);
ii. Change in 24-hour movement behaviour assessed using the GENEActiv accelerometer;
iii. Change in grip strength assessed as the best measurement of three scores measured using a handheld dynamometer (Jamar, Illinois, USA) using the dominant hand;
iv. Change in weight, which was extracted from the resident serial weight chart, which forms part of the Resident Care Assessment Record;
v. Rate of adverse medicine events; and
vi. Change in health related quality of life assessed using EQ-5D.

B.6.2. Quantitative analysis

The trial analysis followed a pre-specified statistical analysis plan. Participants were analysed according to the treatment to which they were randomised using an intention-to-treat approach.

Analyses used mixed-effects repeated measures models to account for correlated measurements from the same individual over time. Although frailty index and other measures such as weight and MoCA had non-normal distributions, the modelled outcomes were changes from baseline, which were assumed to be normally distributed. To test whether the outcomes differed between the intervention groups, models included fixed effects for treatment group, time point and an interaction term between treatment group and time point. Treatment effects were reported separately at six and twelve months post randomisation and statistical significance was assessed at the two-sided 0.05 level. Both unadjusted and adjusted analyses were performed, with the adjusted analyses including the randomisation stratification variables (aged care facility and gender) as covariates. If adjusting for a covariate prevented models from converging (for example, from small facilities), the covariate was excluded and this was noted in the reporting. Continuous outcomes were adjusted for baseline values. Conclusions on group differences were based on the adjusted analyses. Planned subgroup analyses of the primary outcome included gender, baseline frailty phenotype, and use of sedative and anticholinergic medications.

For continuous outcomes, linear regression models were used with no planned data transformations. For ordinal categorical outcomes, proportional odds models were used. Poisson or negative-binomial regression models were used for the count outcomes, as appropriate. If the mixed models failed to converge, generalised estimating equations were used instead. The normality assumption was assessed using the model residuals. Sensitivity analyses for defined subgroups, potential survivor bias, bias due to deaths and post-hoc imputation of results after COVID-19 lockdowns are further described in the respective analyses below and in Appendix E. The full statistical analysis plan is in Appendix C2.

B.7. Results of the ReMInDAR trial

B.7.1. Intervention delivery

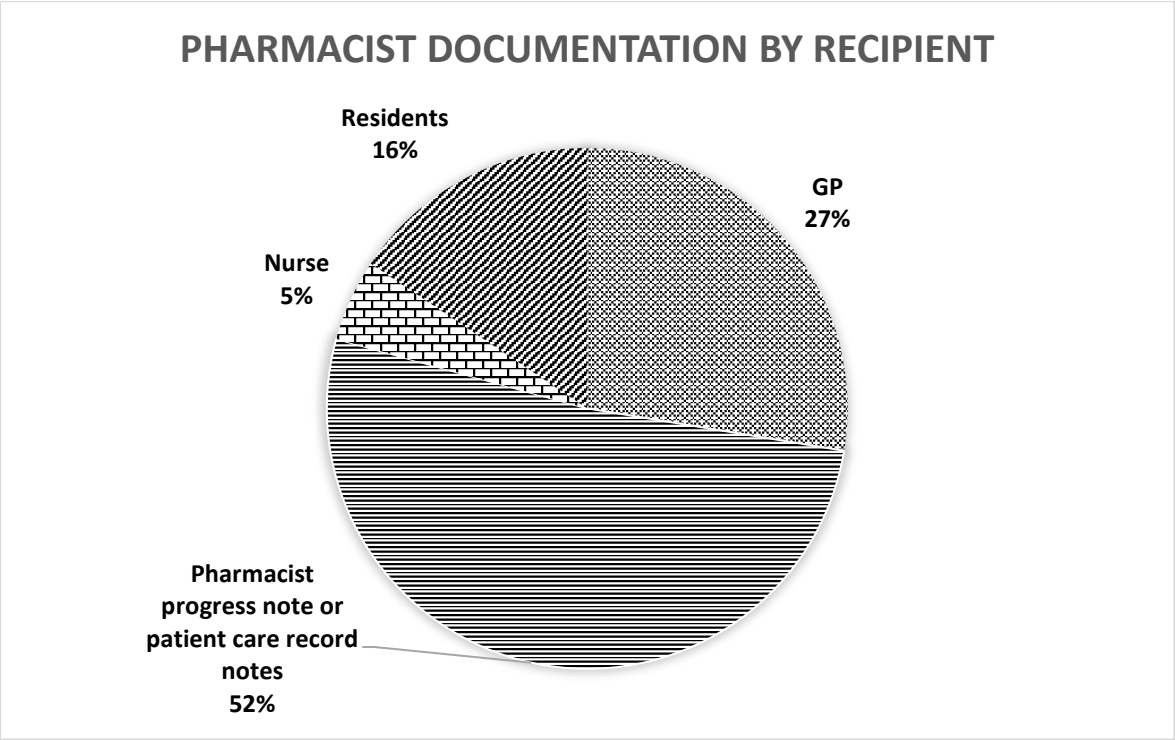
A total of 120 participants were randomised to the intervention arm of ReMInDAR, however 5 participants died prior to commencement of the delivery of their service, leaving 115 participants who received pharmacist services. Pharmacists attempted to visit all participants for each of the planned sessions every 8 weeks over 1 year, however participant numbers

varied due to death and *ad hoc* unavailability of the participant, as well as the inability to access facilities in person or via telephone during COVID-19 restrictions.

Overall, 88 planned visits with intervention participants were affected by the COVID-19 restrictions, with 25 delayed, 7 undertaken via telephone, 21 constrained to a review of medication chart and care records only (no participant interview) and 35 unable to be undertaken. Delays have the potential to result in insufficient time for resolution of problems during the trial period.

Overall, 575 individual pharmacist visits with residents were undertaken across the life of the trial; a median of 6 pharmacist sessions per person. For 572 of the 575 sessions, pharmacists recorded documentation (See Appendix C1 for example of pharmacist documentation record). The documentation included notes on communications directed to the general practitioner, the nursing home staff or the resident as well as progress notes for the pharmacist's ongoing review or inclusion in the resident care record (Figure B-6).

Figure B-6: Pharmacist documentation by recipient.



B.7.2. Medication related problems

In total 112 (97%) of the 115 people who received the service had at least one medicine related problem or symptom report identified (Table B-6). In total, pharmacists identified 673 medicine related problems or symptom reports; (averaging six per person adjusted for follow-up time). The proportion of people with a problem or symptom report at each session was consistently above 60%, ranging from 79% in the first two sessions down to 64% by the sixth session) (Figure B -7). Fifty percent of residents had five or more problems or symptoms identified across the study period (range 1 to 29). During the majority of sessions one or two problems or symptom reports per person were identified (Figure B-8).

Session number	1	2	3	4	5	6
Number of people who received a session	115	107	105	96	91	55
Percent with a problem or symptom report	79%	79%	75%	73%	65%	64%

TableB-6: Proportion of persons with a problem or symptom report at each session

We analysed time to develop a new problem after session one and found that 50% had developed a new problem by the next session and 75% had a new problem by the subsequent session, this suggests the time between pharmacist reviews was appropriate at intervals of eight weeks.

Over 50% of the population had an adverse reaction or toxicity problem, 50% over or under-treatment, 57% required education or information for the resident or staff and for over 80% pharmacists made symptom reports (Figure B-9).

Alternative text for figures

Figure B-7: Number of problems or symptom reports per person per session

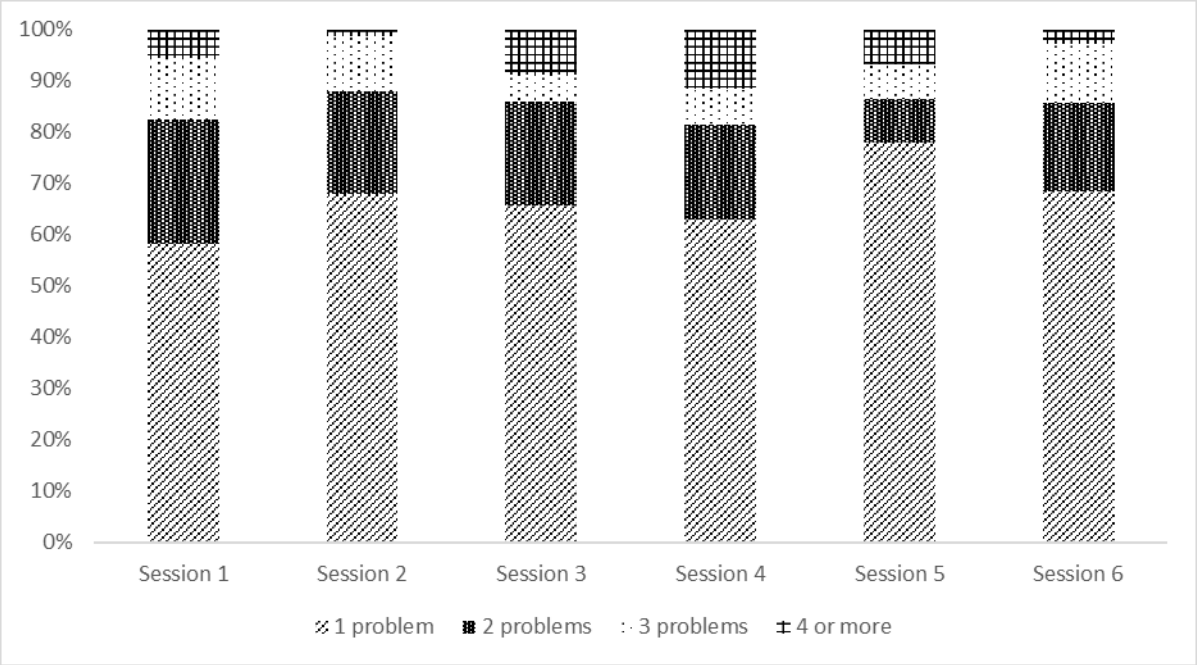


Figure B-8 Probability to develop a new medicine related problem, by session

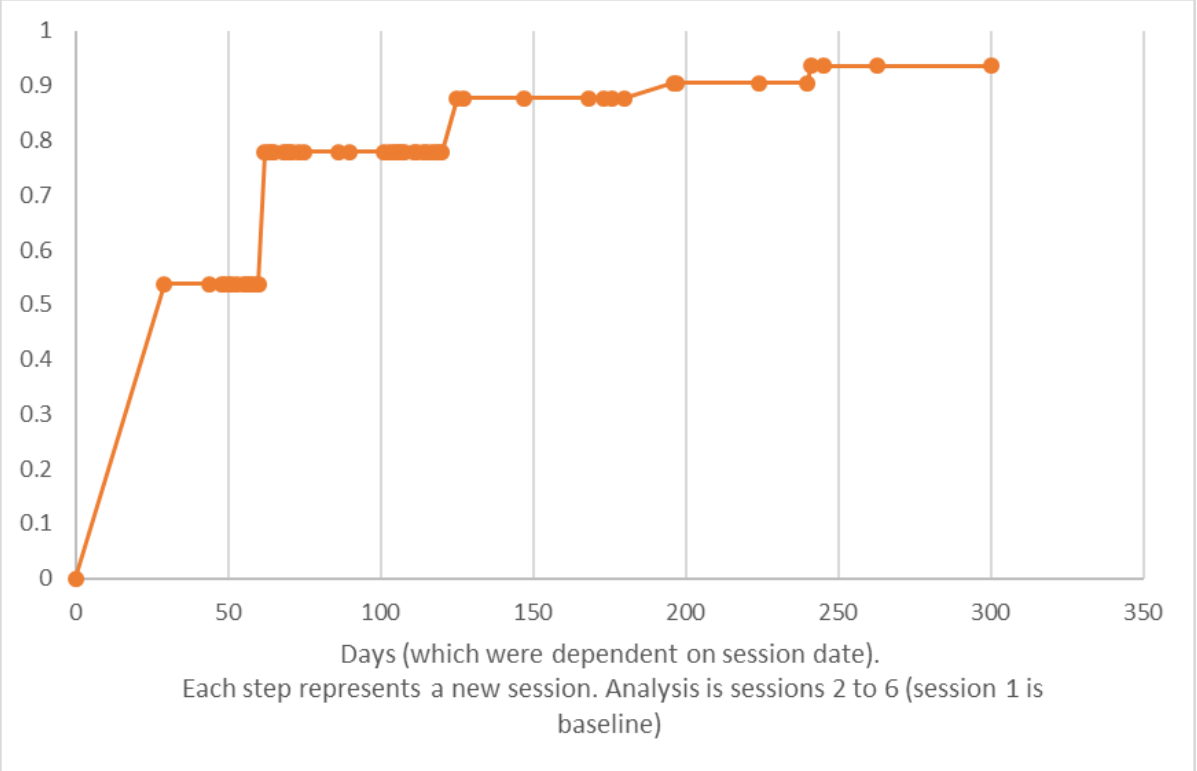
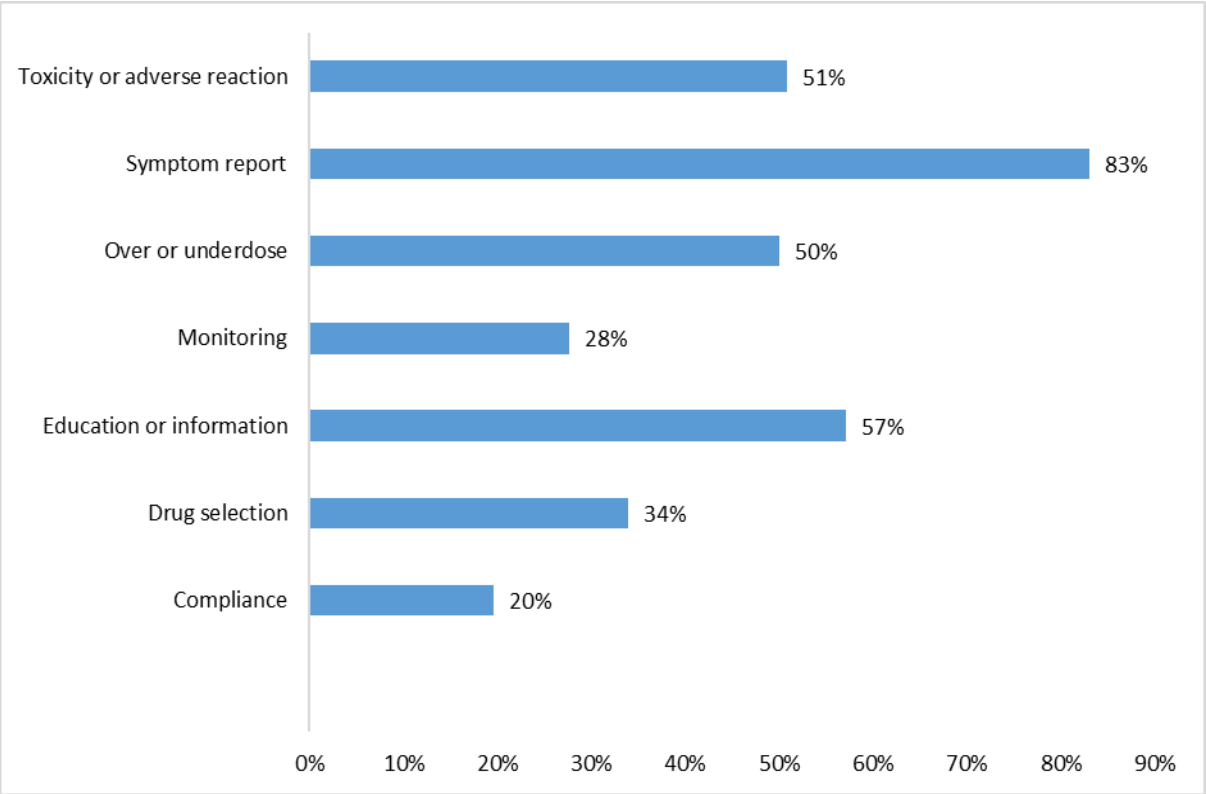


Figure B-9: Proportion of the population with medicine related problems identified.



B.7.3. Pharmacist recommendations

Pharmacists made 309 recommendations to change or monitor a medicine use with a view to change it at a future session. On 53% of occasions, the recommendation was to decrease the dose or cease use, while on 17% of occasions it was to monitor with a view to change. On 18% of occasions, a recommendation was made to increase medicine use and on 11% of occasions to stay the same. At the level of the individual, pharmacists made recommendations to reduce medicine use for 61% of the population, while recommendations to increase use were made for 29% (Figure B 10). The classes accounting for over 60% of the recommendations for reduced use were opioids antipsychotics, sedative medicines, antidepressants, anti-Parkinson agents, proton pump inhibitors, diuretics (predominantly frusemide), and statins.

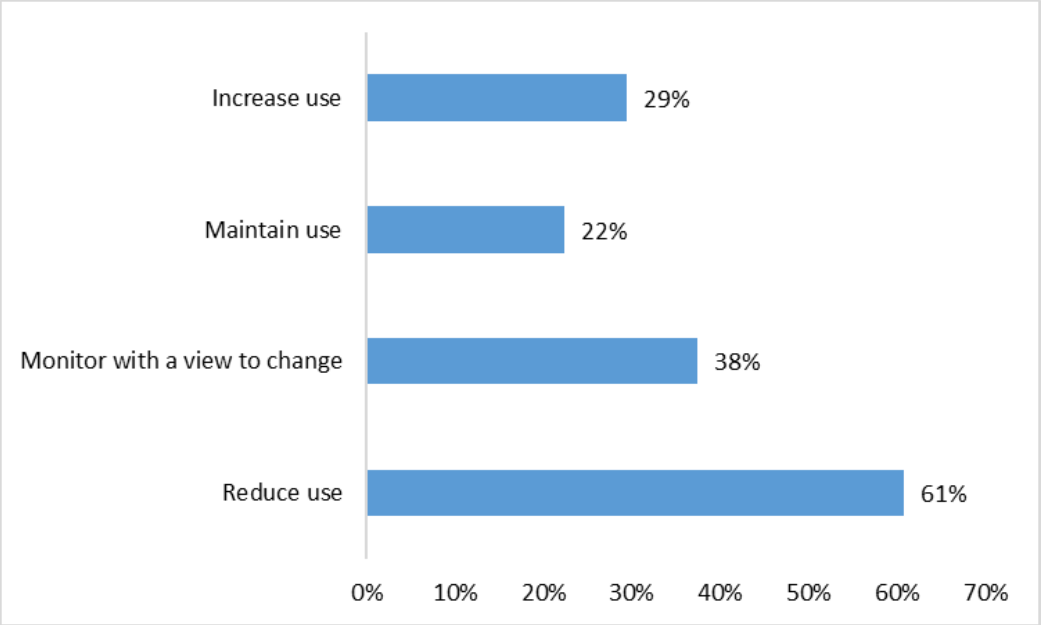
Examples of pharmacist recommendations and judgements include:

"Nocturia is a likely contributing factor to poor sleep which may be manifesting as decreased cognitive function." Since the recent increase in Frusemide could be contributing to disrupted sleep time (nocturia)", pharmacist recommends review, which is accepted by GP.

In response to significant cognitive decline the pharmacist noted, *"Likely worsening of Parkinson's - possible dementia associated with Parkinson's"*. This patient was also taking

quetiapine, which could be implicated in cognitive decline. However, the pharmacist noted *"Although quetiapine is not ordinarily suitable for long-term use in the elderly for treatment of behavioural and psychological symptoms of dementia, the attempted dose reduction a few weeks ago was not successful, and for the time being, it is likely to be best to leave patient at the current quetiapine dose, particularly as patient reports sleeping well and feeling better".*

Figure B-10: Proportion of the population with recommendations to change medicines.



B.7.4. Case studies of pharmacist sessions

While individual sessions contributed to changes, the consistent sessional nature of the pharmacist service also provided opportunity for monitoring and change. Qualitative case studies over the provide insights into the types of improvements in medication management and quality of life that the residents who participated in the ReMInDAR trial experienced over the course of the trial (names and circumstances have been changed but clinical issues are actual issues). Two case studies are briefly summarised below. Eight full case studies are presented in detail in Section F1.

Barbara

Barbara had returned from the hospital after recently have a stroke with a large number of new medications. Barbara was still feeling very unwell after her stroke and could no longer complete the cognitive assessments for the ReMInDAR trial, which she had been able to complete prior to her stroke. Her mood was very low.

The ReMInDAR pharmacist reviewed and reconciled Barbara's medicine and identified medicines which had been ceased in the hospital but were still on the medication chart in the facility.

The pharmacist discussed Barbara's concerns and the issue of gagging with her GP and as a result Barbara was taken off many of her tablets, the dose was reduced for some medications and some of her medications were changed to liquid forms. **Barbara's spirit improved and she was once again able to complete the cognitive assessments.**

Betty

The ReMInDAR pharmacist noted that Betty's dose of pregabalin was increased from 225 mg twice a day to 300 mg twice a day due to pain in her right foot. She had also been given temazepam (10mg at night) to aid with sleep. ***Betty felt dizzy and complained of weight gain.*** Her weight had increased by 5.5 kg within a month. The pharmacist discussed with Betty the potential for pregabalin to cause these side effects and the possibility of reducing the pregablin dose, however Betty was reluctant to reduce the dose due to her pain.

Betty started to have falls. Four weeks later, Betty had a fall. Within six days, Betty had another fall in the bathroom and was admitted to the hospital. Betty had had two further falls and stated she was 'losing strength' in her legs. She was still on same medicine regimen; in addition, she had started perindopril 40mg daily.

Upon the pharmacist's recommendation, the doctor decreased Betty's pregabalin dose from 300mg twice a day to 250 mg twice a day. **Betty had not had any falls and her pregabalin dose was further reduced to 75mg twice a day**. Betty indicated she would like to further decrease the pregabalin dose if she can, as long as her pain is under control.

B.7.5. Is it effective?

B.7.5.1 Effectiveness Outcome 1 (primary) – Frailty

The primary outcome for the trial was mean change in frailty index from baseline. Table B-7 and Figure B -11 show the model estimates, which were not statistically significant, across the two arms at 6 and 12 months.

Outcome*	Trial Stage	Intervention group***, Observed Mean Change	Intervention group, Observed Standard deviation (SD)	Control group, Observed Mean Change	Control group**** Observed Standard Deviation (SD)	Modelled Estimate = Intervention - Control	Modelled Estimate = Intervention - Control (95% CI)	P-value
Frailty** Index	6 Months	0.040[1]	0.064	0.044	0.062	-0.005	-0.023, 0.013	0.606
Frailty**Index	12 Months	0.080[2]	0.076	0.089	0.082	-0.009	-0.028, 0.009	0.320

Table B-7: Frailty outcome, change from baseline.

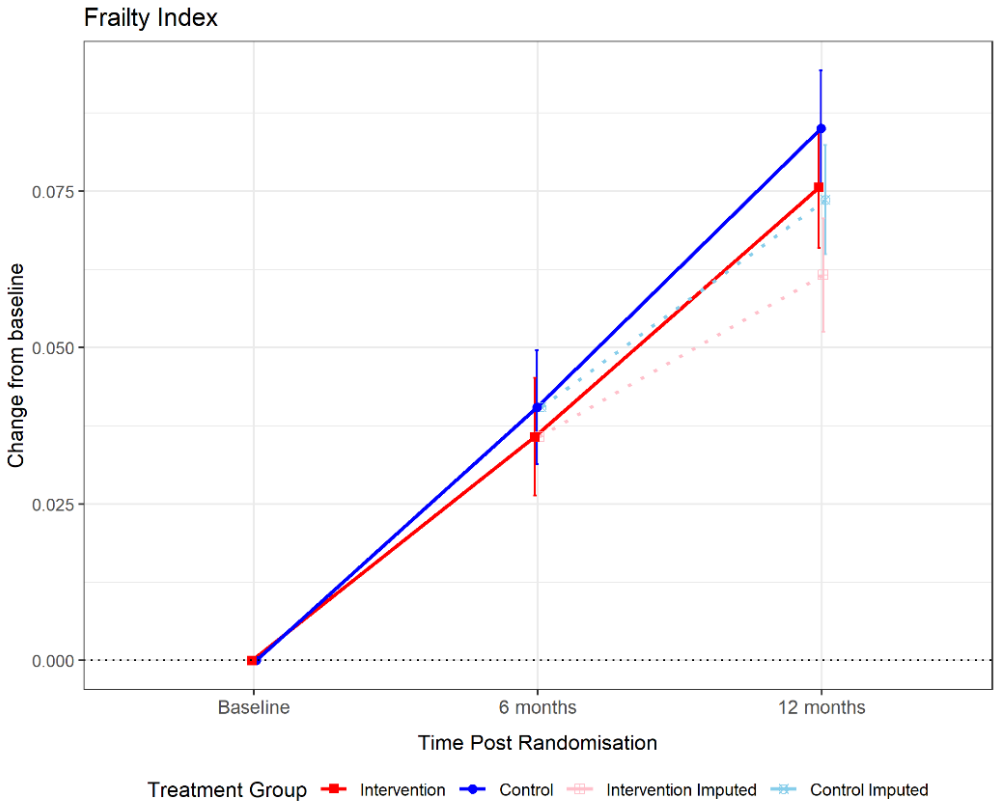
***Change from baseline, adjusted for baseline, gender and facility. Observed values are mean (SD).**

**** The Frailty index primary outcome measure is based on a 39 point assessment tool, where the sigmoidally distributed outcome scale ranges from 0 (not frail) to 1.0 (extreme frailty).**

*****The number (n) used to calculate the mean for the intervention arm is n=105 for 6 months[1], and n= 97 for 12 months[2].**

******The number (n) used to calculate the mean for the control arm is n=119 for 6 months[3], and n= 111 for 12 months[4].**

Figure B-11: Modelled* mean change in Frailty Index from baseline in intervention and control arms.



***80% confidence intervals for each group are displayed for comparison purposes for the intervention and control arms. (78)**

The imputed results for Frailty outcome accounting for impacts of COVID-19 (Table B-8) have been overlaid for visual comparison purposes only and may have slight statistical inaccuracies.

Impact of COVID-19 access restrictions

From 20 March 2020, access to residential aged care facilities were restricted due to COVID-19 and pharmacists were unable to implement the intervention. These restrictions may have affected the difference in frailty trajectories between the two groups at the 12 month time point. To estimate the effect of the intervention on the primary outcome if COVID-19 restrictions had not occurred, a sensitivity analysis was conducted, imputing frailty index measurements taken after COVID-19 restrictions (see full methodology and analysis in Appendix E).

The point estimates for the primary outcome at 6 and 12 months were larger after excluding or imputing post COVID-19 measurements (Table B-8). 95% confidence intervals were narrower after imputation, but still contained zero. However, the point estimate at 12 months after accounting for COVID-19 restrictions (-0.012) is close to the effect size of -0.015 used

in the sample size calculation. The imputed results for the frailty outcome accounting for impacts of COVID-19 have been overlaid for visual comparison purposes only in Figure B-11. These results suggest that the treatment effect would have been closer to that expected from the intervention if COVID-19 restrictions had not been implemented.

Outcome*	Intervent-ion** Observed mean	Intervent-ion variation (SE)	Intervention number (n)	Control*** Observed mean	Control, variation (SE)	Control number (n)	Intervention-Control variation	Intervention-Control (95% CI)	P-val-ue
Frailty Index, all participants	0.080	(0.076)	97	0.089	(0.082)	111	-0.009	(-0.028, 0.009)	0.320
Frailty Index, excluding post COVID	0.045	(0.065)	30	0.062	(0.077)	32	-0.012	(-0.039, 0.016)	0.410
Frailty Index, post COVID imputed	-			-			-0.012	(-0.033, 0.009)	0.270

Table B-8: Imputation of Frailty measurements after COVID-19 access restrictions.

***Change from baseline to 12 months, adjusted for baseline, gender and facility.**

B.7.5.2 Effectiveness Outcomes (secondary outcomes)

The values for secondary outcomes for the trial are presented in Table B-9a. There was a statistically significant result for cognition, with an observed mean difference of 1.36 point change at 12 months. The guide to clinical interpretation of the assessment measures for the outcomes is provided in Table B-9b. The estimated change in MoCA that is clinically significant is 2 point change (79). The change in MoCA in the control group was over 3 points, a clinically significant decline, while the change in the intervention group less than 2 points. The change in weight was also statistically significantly different, with the control arm gaining more weight than the intervention arm, (1.34 kg). Subgroup analysis indicated that the change in weight was variable across the subgroups and therefore, unlikely to be a clinical effect of the intervention. The modelled change from baseline for both outcomes are shown graphically (Figure B-11 and Figure B-12).

The secondary outcomes analysed for physical activity and sleep utilised data from the GENEActiv accelerometers. No significant results were found, however, the point estimates favoured the intervention arm for overall amount of time spent in moderate activity, the length of each bout of time of moderate or vigorous activity, sedentary behaviour and sleep efficiency. Clinically, the expected trajectory in this population is towards a decline in function (1), so a trend upwards in function is favourable. More than half the participants had their 12

month follow-up measures assessed during the COVID-19 restrictions which may have affected this result at 12 months.

Outcome	Trial Stage	Intervention group** (A) Observed Mean Change	Intervention group (A) Standard Deviation (SD)	Control Group** (B) Mean Change	Control Group (B) Standard Deviation (SD))	Modelled Estimate A-B	Modelled Estimate A-B Variation (95% CI)	P-value
MoCA (0-30) *	6 Months	**-0.63**	**(4.07)**	**-1.46**	**(3.73)**	**0.84**	**(-0.46, 2.13)**	**0.204**
	12 Months	**-1.89**	**(4.87)**	**-3.16**	**(5.88)**	**1.36**	**(0.01, 2.72)**	**0.048**
Weight*	6 Months	**-0.13 kg**	**(3.47)**	**1.14 kg**	**(4.10)**	**-1.31 kg**	**(-2.54, -0.07)**	**0.039**
	12 Months	**-0.21 kg**	**(5.57)**	**0.85 kg**	**(5.22)**	**-1.34 kg**	**(-2.60, -0.09)**	**0.035**
Grip Strength*	6 Months	0.17 kg	(3.91)	0.32 kg	(3.51)	-0.37 kg	(-1.44, 0.70)	0.495
	12 Months	0.53 kg	(4.53)	-0.15 kg	(4.07)	0.47 kg	(-0.71, 1.66)	0.433
EQ-5D*	6 Months	-0.118	(0.304)	-0.063	(0.304)	-0.043	(-0.121, 0.035)	0.280
	12 Months	-0.199	(0.339)	-0.159	(0.329)	-0.023	(-0.110, 0.050)	0.566
Sleep Efficiency*	6 Months	-2.82%	(20.80)	-3.10%	(19.14)	1.30%	(-5.03, 7.62)	0.682
	12 Months	4.49%	(17.86)	0.01%	(16.05)	2.66%	(-4.92, 10.24)	0.484
Sleep Time*	6 Months	-15.75 mins	(75.23)	-22.68 mins	(86.40)	5.24 mins	(-20.88, 31.37)	0.689
	12 Months	-9.66 mins	(59.65)	-7.99 mins	(79.38)	-1.84 mins	(-32.72, 29.03)	0.905
Sedentary Time*	6 Months	11.82 mins	(75.43)	21.54 mins	(89.28)	-12.38 mins	(-48.21, 23.45)	0.492
	12 Months	-7.68 mins	(90.93)	-5.04 mins	(85.20)	-4.96 mins	(-45.83, 35.91)	0.809
Light Activity*	6 Months	-5.19 mins	(21.07)	-2.79 mins	(32.32)	-6.04 mins	(-20.87, 8.80)	0.419
	12 Months	1.70 mins	(37.14)	4.71 mins	(39.78)	-4.71 mins	(-22.12, 12.70)	0.590
Moderate Activity*	6 Months	0.16 mins	(23.54)	-1.62 mins	(29.81)	2.16 mins	(-11.29, 15.61)	0.749
	12 Months	5.64 mins	(39.30)	-3.90 mins	(35.77)	7.06 mins	(-8.23, 22.35)	0.359
Moderate Vigorous	6 Months	0.16 mins	(23.54)	-1.66 mins	(29.81)	2.20 mins	(-11.26, 15.66)	0.745

Outcome	Trial Stage	Intervention group** (A) Observed Mean Change	Intervention group (A) Standard Deviation (SD)	Control Group** (B) Mean Change	Control Group (B) Standard Deviation (SD))	Modelled Estimate A-B	Modelled Estimate A-B Variation (95% CI)	P-value
Physical Activity*	12 Months	5.68 mins	(39.39)	-3.91 mins	(35.86)	7.08 mins	(-8.22, 22.39)	0.358
MVPA bout length*	6 Months	0.01 mins	(0.78)	0.01 mins	(0.95)	0.23 mins	(-0.13, 0.58)	0.200
	12 Months	0.06 mins	(0.88)	0.04 mins	(0.76)	0.20 mins	(-0.21, 0.61)	0.338
# of MVPA bouts*	6 Months	0.13	(4.78)	-0.80	(6.57)	0.20	(-2.76, 3.16)	0.894
	12 Months	0.85	(8.29)	-0.57	(6.74)	0.58	(-2.80, 3.96)	0.731

Table B-9a: Secondary outcomes

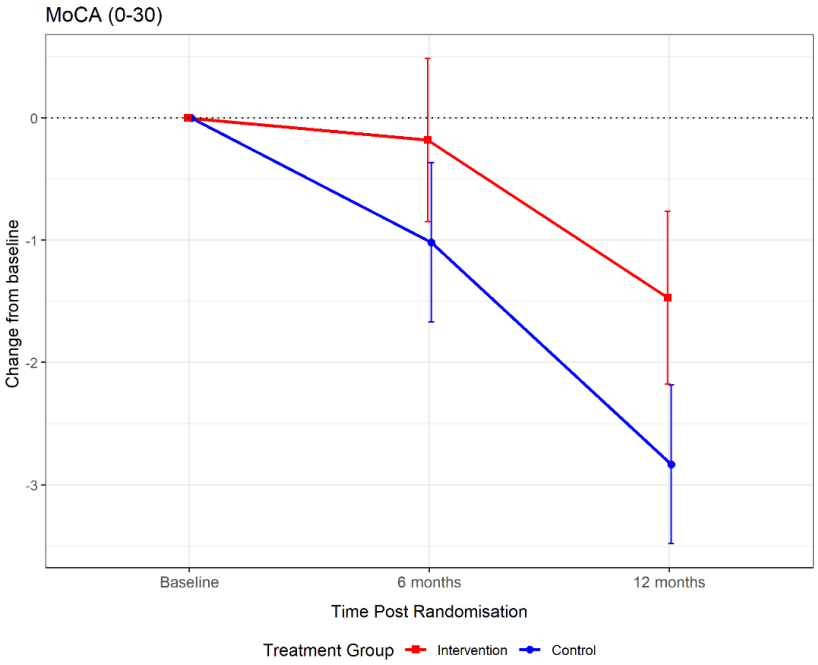
***Change from baseline, adjusted for baseline, gender and facility. Observed values are mean (SD)**

****The sample number (n) varied for each intervention arm and each outcome. The full table with corresponding sample size numbers for each result are shown in Appendix E.**

Outcome	Scale	Favourable Direction	Minimum Clinically Significant Difference	Clinically important changes
MoCA	0 -30 or 0 – 22 (modified), converted to 0 -1.0	+ve	2 point change on 30 point scale (~ 0.067)	Ref (79)
Weight	Total kg, unlimited	unknown	unknown	
Grip Strength	Total kg, unlimited	+ve	~ 20% change; 0.84kg-2.69kg	Measures categorised as 'weak' based on thresholds for males or females not in residential aged care between 70 -99 years are <21.3kg, and <14.7 kg respectively. Refs (64, 65)
EQ-5D	<0.0: worse than death; 0.0: death; 1.0: full health (maximum)	+ve	unknown	https://euroqol.org/publications/user-guides/ Ref (80)
Sleep Efficiency	0 – 100%	+ve	unknown	
Sleep Time	Total mins, unlimited	+/-ve	6-8 hrs	Ref (81)
Sedentary Time	Total mins, unlimited	-ve	30 mins	10% increase in sedentary time increased frailty risk by 55% (82, 83); 1 hour increase in sedentary time increases death by 19% (82); 30 minutes increase in sedentary time increases rate of mobility disability by 10%.(84)
Light Activity	Total mins, unlimited	+ve	30 mins	500 steps gives15% decrease in major mobility disability. (67)
Moderate Activity	Total mins, unlimited	+ve	10 mins	10 min increase leads to 10% decrease in mortality risk. (85)
Moderate Vigorous Physical Activity	Total mins, unlimited	+ve	10 mins	10 min increase leads to 10% decrease in mortality risk.(85)
MVPA bout length	Total mins, unlimited	+ve	No minimum	Any bouts of activity are accumulatively beneficial. (85)
# of MVPA bouts	Total counts, unlimited	+ve	unknown	

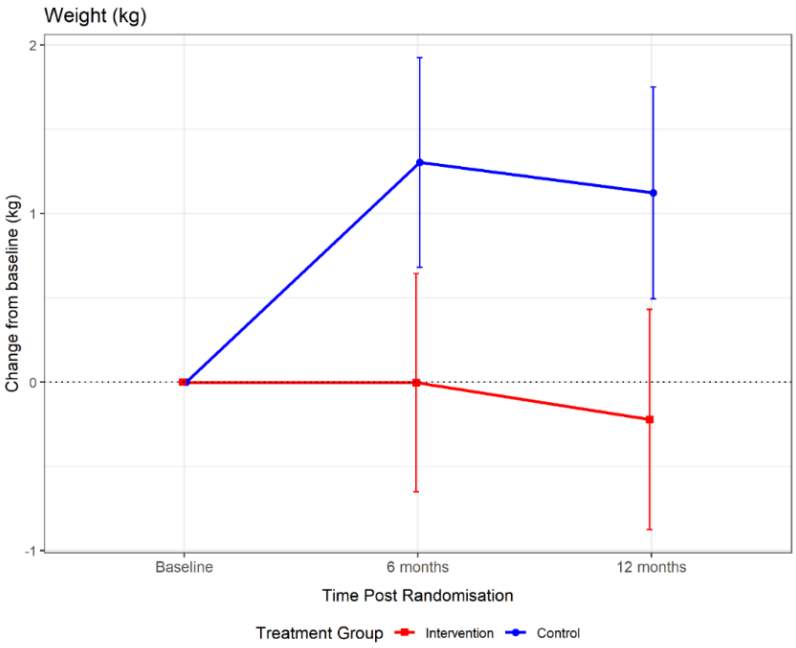
Table B-9b: Clinical interpretation of secondary outcomes

Figure B-12: Modelled* mean change in MoCA from baseline in intervention and control arms.



***80% confidence intervals for each group are displayed for comparison purposes. (78)**

Figure B-13: Modelled* mean change in weight from baseline in intervention and control arms.



***80% confidence intervals for each group are displayed for comparison purposes. (78)**

Post-Hoc Exploratory analysis and Sensitivity analyses for secondary outcomes

Given a statistically significant difference was found between groups for weight and cognition an assessment for potential survivor bias was undertaken (Appendix E). No difference in results was found for weight or MoCA at baseline by withdrawal status, for either the control or intervention arms, indicating that there was a low likelihood of survivor bias. Post hoc subgroup analysis for weight when grouped into two categories above and below the median weight showed the direction of the result, while not significant, was variable across the subgroups, thus, making it uncertain if the weight result was a clinical effect of the intervention. Post hoc subgroup analysis for MoCA when grouped into two categories above and below the median score showed the direction of the result, while not significant, was consistent for all subgroups, suggesting the result for MoCA is likely to be an intervention effect.

Post-hoc exploratory analysis of cognition (MoCA) examined the difference in the proportion of residents with a clinically significant MoCA decline of 2 or more points from baseline between the intervention and control arms. While not statistically significant, point estimates (Table B-10) indicate that approximately 11% more residents in the intervention arm avoided a clinical decline of 2 points.

Trial Stage	Intervention ** Observed Proportion, Mean	Intervention, Variation in Observed Proportion, (SE)	Control***, Observed Proportion, Mean	Control, Variation in Observed Proportion, (SE)	Estimated Difference in Proportions, Intervention-Control	95% Confidence Interval	P-value
6 months	0.37[1]	(0.48)	0.50[3]	(0.50)	-0.11	-0.25, 0.02	0.09
12 months	0.46[2]	(0.50)	0.57[4]	(0.50)	-0.12	-0.26, 0.02	0.10

Table B-10: Exploratory analyses of a 2-point MoCA decline between intervention and control arms

***adjusted for gender, facility, MoCA at baseline and anticholinergic score at baseline**

****The number (n) used to calculate the mean for the intervention arm is n=101 for 6 months[1], and n= 87 for 12 months[2].**

*****The number (n) used to calculate the mean for the control arm is n=111 for 6 months[3], and n= 107 for 12 months[4].**

Adverse events

During the trial, 1978 adverse events were recorded for trial participants. The majority of these adverse events were for falls or fracture, bleeding or bruising, or gastrointestinal

symptoms. No significant difference was observed in the rate of adverse events (Table B-11).

Outcome*	Trial Stage	Intervention***, Observed rate per month, Mean change	Intervention, Observed rate per month ,change error (SE)	Control***, Observed rate per month, Mean change	Control, Observed rate per month change error (SE)	Modelled Estimate Intervention/ Control	Modelled Estimate A/B variation (95% CI)	P-value
Adverse events RR A/B**	6 Months	0.510	0.607	0.541	0.667	0.97	0.71, 1.32	0.827
	12 Months	0.758	1.093	0.685	0.881	1.11	0.77, 1.58	0.583
Falls/Fracture RR A/B	6 Months	0.108	0.200	0.113	0.253	0.97	0.57, 1.66	0.912
	12 Months	0.187	0.593	0.180	0.423	1.06	0.49, 2.28	0.877

Table B-11: Adverse events.

***Change from baseline, adjusted for baseline, gender and facility. Observed values are mean (SE)**

****Adjusted for gender, weight and MoCA at baseline. Estimate is Rate Ratio (RR) for Intervention/Control. Adjusted for gender, weight and MoCA at baseline. Observed values are n (%) at each time point. Estimate is observed rate for a less frail category for Intervention/Control**

Adverse medicine events

Of the adverse events, 583 were judged to be possible, probable or definite adverse medicine events, of which 83% were considered possibly or probably preventable (Figure B-14). This equates to approximately 20% of residents experiencing one preventable adverse medicine event each month.

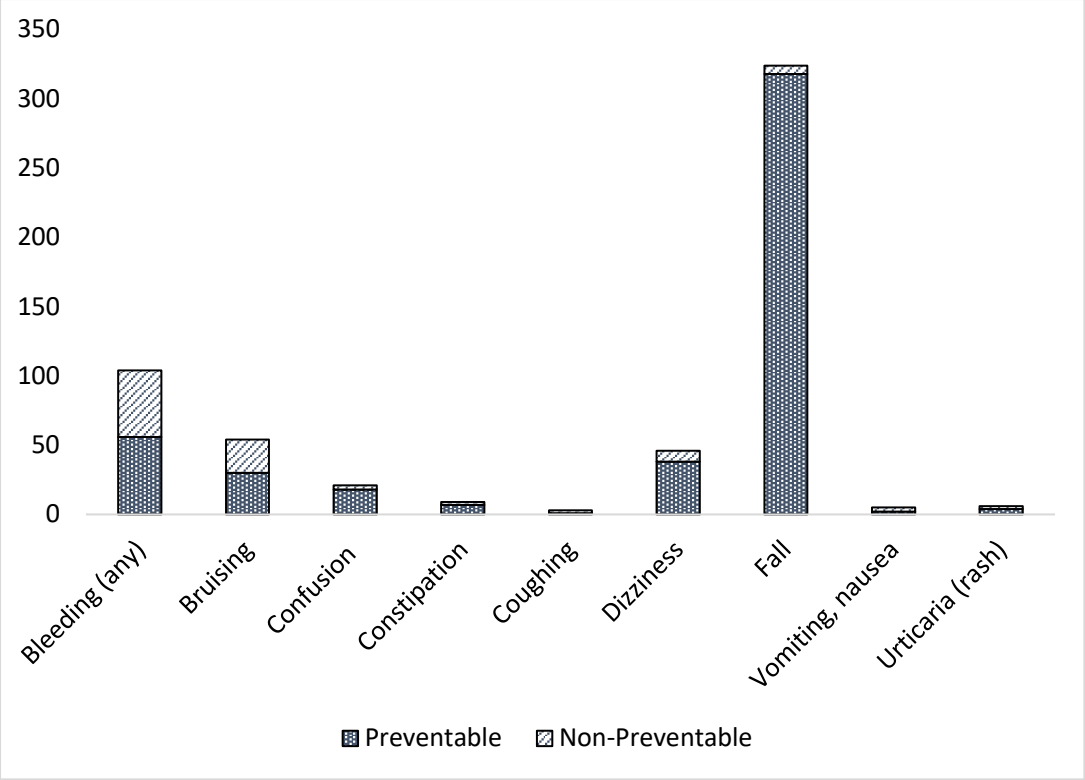


Figure B-14 Preventability characterisation of adverse medicine events

Statistical analyses of the adverse medicine event data indicated no difference between the trial arms for the rate of adverse medicine events (AME), and similarly, no difference between the trial arms for the rate of preventable adverse medicine events (Table B-12).

Outcome	# Residents, Intervent-ion	Intervent-ion, Mean observed Rate/ month	Intervent-ion Variation in observed Rate/ month (SE)	# Residents, Control	Control, Mean observed Rate/ month	Control, Variation in observed Rate/ month (SE)	Estimated Rate Ratio, Intervention/ Control	95% Confidence Interval	P-value
AME rate 0-365 days	120	0.23	(0.32)	128	0.20	(0.36)	1.12	0.78, 1.61	0.55
Preventable AME rate 0-365 days	120	0.19	(0.31)	128	0.17	(0.32)	1.17	0.77, 1.76	0.47

Table B-12: Comparison of differences in adverse drug events for each trial arm.

Falls were the most frequent adverse event and a *post-hoc* subgroup analysis was undertaken to determine the numbers of people who had a fall. Within the intervention arm, the proportion of persons with a fall fell, while the proportion of persons with a fall in the control arm increased over time (Table B-13). This result did not reach statistical significance (Rate Ratio 0.80, 95%CI 0.53, 1.21, p=0.29).

Outcome*	Time from randomis-ation	Intervent-ion (N)	N Fall, Intervent-ion	Fall %, Intervent-ion	Control (N)	N Fall, Control	Fall %, Control
Residents with any fall ADE	0-182 days	120	38	32%	128	30	23%
	183-365 days	106	27	25%	119	40	34%
Residents with any preventable fall ADE	0-182 days	120	38	32%	128	30	23%
	183-365 days	106	27	25%	119	38	32%

Table B-13 Comparison of differences in falls for each trial arm

To determine which residents were most at risk of adverse events, we assessed the relationship between the resident characteristics collected at base-line and their subsequent first adverse event. Factors collected at baseline that were found to be independently predictive of adverse medicines events included male sex (Odds Ratio (OR), 2.6; 95% CI, 1.4-5.0), number of sedative medications (OR, 1.2; 95% CI, 1.02-1.4), and use of anticoagulants (OR, 2.9; 95% CI, 1.3-6.2). The factors found to be independently predictive of preventable adverse medicine events were male sex (OR, 2.5; 95% CI, 1.3-4.7), number of sedative medications (OR, 1.2; 95% CI, 1.01-1.4), use of medications to treat diabetes (OR, 2.6; 95% CI, 1.2-5.7) and use of antipsychotics (OR, 3.0; 95% CI, 1.2-7.1).

While the changes in adverse medicine events and falls were not statistically significant, the majority of the pharmacists' recommendations were for reducing sedative and anticholinergic medicines (Section B.6.1). The predictive models showed that sedative medicines were a predictor of adverse medicine events. This is consistent with the hypothesis underpinning the ReMInDAR trial, which was that medicine use could affect cognition, gait or activity, resulting in medicine-induced deterioration, which would subsequently lead to adverse events (Figure A-1). To explore the potential for medicines to affect the changes observed, we used multivariate, multilevel regression models to examine the relationship between sedative and anticholinergic medication load and activity as measured by the GENEActiv accelerometer at baseline and 12-month follow-up.

The results are plotted in Figure B-15. The predicted changes in activity across time for incremental changes to medication load are plotted relative to expected changes in activity for a stable medication load of 2 (i.e., relative to the situation where medication load = 2 at both time points). The analysis shows that if sedative load is increased from 2 to 4, the change in sedentary behaviour (green line) over the 12-month period is predicted to be +26 min/d, while sleep, light and moderate activity all decline.

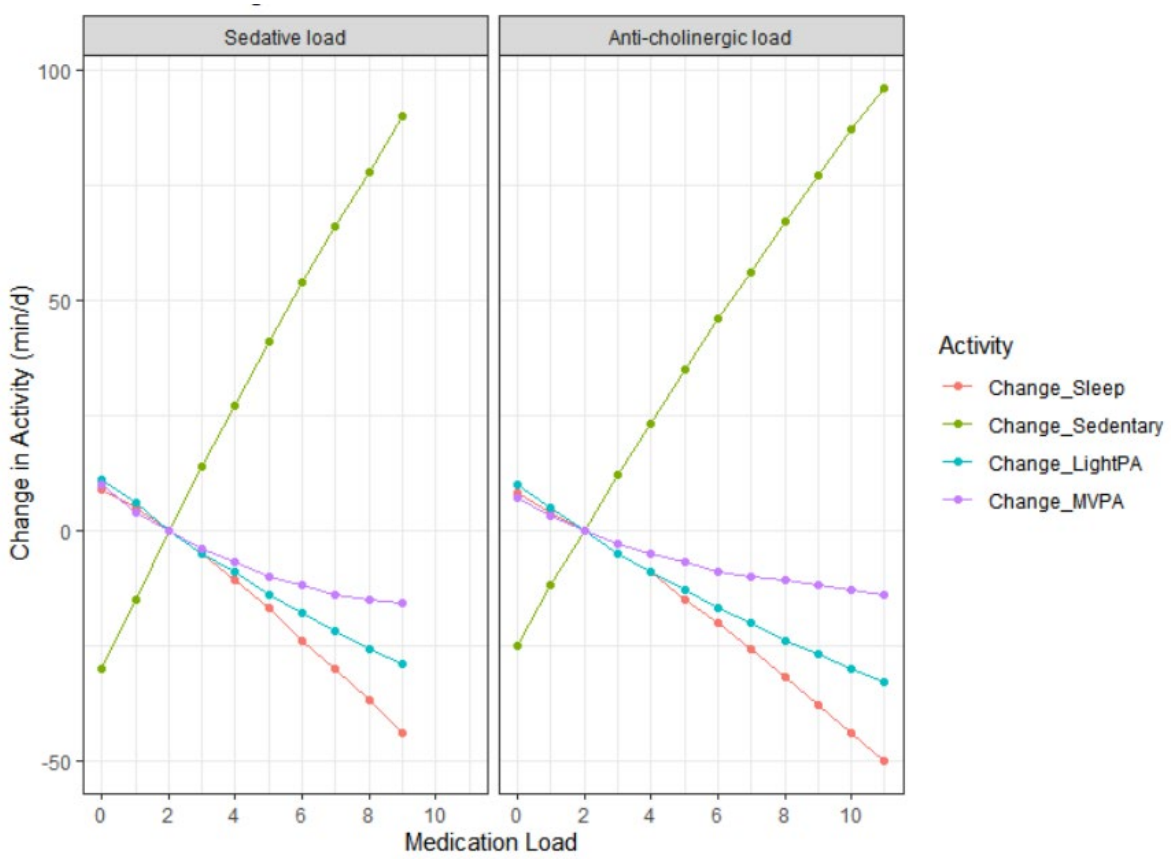


Figure B-15. Predicted changes in activity across a 12-month period when medication loads are changed.

Changes in activity are considered relative to no change in medication load (i.e., medication load = 2 at both time points).

B.7.6. Stakeholder Evaluation

Evaluation of the residential clients' and healthcare professionals' experience of the pharmacist service in the form of stakeholder feedback was solicited from ReMInDAR stakeholders over the trial period. This was undertaken to discern the need and acceptability of this type of pharmacy service to the different stakeholder groups and to the factors that would promote success. Feedback was sought from the residents, their GPs, the RACF staff and the pharmacists' trialling the service. Stakeholder interviews or focus groups with 7 trial participants, 4 residential aged care staff, 4 general practitioners and 6 pharmacists were undertaken to determine participant satisfaction with the service, barriers and enablers to participation and potential for application of the service more widely. In addition, all pharmacists were provided with a survey to evaluate the training for the intervention, and 56% responded.

Overall, all stakeholder groups thought that the ReMInDAR pharmacy service was a much needed and valuable service, with the feedback overwhelmingly positive. Pharmacists reported gaining additional skills and experience, the GPs reported some of the recommendations useful in improving medication management for their patients, and the residents enjoyed having regular visits. The essential elements for a successful pharmacist service that were identified by stakeholders were:

- Training and peer support of the pharmacists in new tools, communication skills and making clinical recommendations;
- Early engagement with General Practitioners;
- Establishment of productive working relationships with residents, GPs and residential aged care staff;
- Integrated communication and coordination among the multidisciplinary team, including nurses, care staff, the GP, and the pharmacist.

Stakeholders noted the need for pharmacists to communicate regularly with staff and build relationship and the need for pharmacists to be seen as a resource to and integrated as a full member of the team.

Further consideration of the use of tools to identify medication induced-deterioration.

- Cognition tools were poorly received by residents, grip strength measurements were well received and the use of activity trackers might be acceptable if they were reliable, comfortable and attractive.

Residents who participated in the ReMInDAR trial were overwhelmingly welcoming of having a pharmacist service as they recalled minimal previous opportunities to speak with a pharmacist since they had entered the facility:

- "I have never seen a pharmacist since coming here, and I've been here for 5 years, so thank you for doing this.";

- "It's about time we have pharmacists here";
- "Nobody here can help me with my medicines. Nobody explains to me why I need to pay for these medicines. Can you please help?".

In terms of opportunities to expand the service delivery, stakeholders were supportive of the need to continue to provide medication review services to residents in aged care. Logistical issues such as frequency of service; co-location of pharmacists; and expanding the service to other target groups within aged care, as well as into the community were identified issues to be resolved.

The themes arising from feedback collected from the different stakeholder groups are presented in greater detail in Section F2 for each stakeholder group.

B.8. Extended Assessment of Harms

No harms were reported from the trial.

B.9. Interpretation of the Clinical Evidence

On the basis of the evidence provided, relative to the comparator, the intervention has superior efficacy with regards to cognition, and is non-inferior for frailty, physical activity, grip strength, weight and quality of life.

Section C: Translation Issues

C.1. Overview

The primary economic analysis is a trial-based cost comparison from the perspective of the Australian healthcare system (public and private funded healthcare costs). The primary economic outcome is the incremental difference in average total health resource expenditure (net costs/savings) per resident over a one year time horizon. The healthcare resource use/costs are determined using the data collected in the clinical trial or provided by the Services Australia or state health department data custodians.

The health economic analysis will utilise participant data on an 'intention to treat' (ITT) basis. External Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS) administrative claims data, as well as external administrative claims data for hospital admissions has been linked on a per patient basis to the clinical trial data collection set and used to inform the economic evaluation. The evaluation plan for the health economics analyses is located in Appendix C3.

A trial-based cost effectiveness analysis has not been presented because the study did not meet its primary clinical outcome objective of identifying a reduction in medicine-induced frailty.

Potential translation issues with respect to the economic analysis are identified and addressed below.

C.2. Applicability translation issues

C2.1 Is the costing data acquired from administrative claims data applicable?

Not all study participants provided the additional consent that was required for the release of MBS, PBS and hospital cost data, therefore the average per patient MBS, PBS and hospital costs are derived from a subset of the trial population. It is necessary to confirm that the study participants for whom cost data was available are representative of the broader study participants.

The complete set of study participants (excluding withdrawals but including patients who died during the study period) comprised 248 aged care residents. Of these, state hospital data was obtained for 170 South Australian and 39 Tasmanian study participants (i.e. approximately 85% of the study participants) which should therefore be reliable representation. In addition 168 (approximately 68%) provided additional consent to allow

retrieval of their MBS and PBS cost data from the Commonwealth government (Services Austalia). A comparison of the baseline characteristics of the ITT study group and the 67% of participants who provided MBS and PBS data is shown (Tables C1 and C2).

The comparison of available demographics and baseline characteristics between each sub-group and the full trial set suggests that the sub-groups for whom costing data is available are representative of the study population overall. The sub-groups closely reflected their respective trial arms with respect to age, frailty score, MoCA score, number of medicines, ACFI subsidy rate and self-rated health. There were some minor numerical differences with respect to gender and BMI, but these were not significant and not expected to affect the applicability of the economic analysis.

Descriptor	Intervent-ion, ITT trial arm (n=120)	Intervent-ion, ITT trial arm, Proport-ion (%) or Variation [IQR]	Intervent-ion, MBS costs sub-dataset (n=80)	Intervent-ion, MBS costs sub-dataset Proport-ion (%) or Variation [IQR]	Control, ITT trial arm (n=128)	Control, ITT trial arm Proportio n (%) or Variation [IQR]	Control, MBS costs sub-dataset (n=88)	Control, MBS costs sub-dataset Proport-ion (%) or Variation [IQR]
Age (years) at Baseline, (median [IQR])	87 years	[81.75, 90.00]	88 years	[81.74, 90.46]	87 years	[81.75, 90.00]	87 years	[80, 90]
Gender = Male, n (%)	41	34.2%	24	30%	39	30.5%	26	30%
BMI, (median [IQR])	27.02	[24.65, 30.85]	26.23	[24.61, 30.77][a]	25.06	[22.27, 30.13]	25.31	[21.75, 31.03][b]
Frailty Index (median [IQR])	0.26	[0.22, 0.31]	0.26	[0.22, 0.30]	0.28	[0.21, 0.33]	0.28	[0.21, 0.32]
Calculated Montreal Cognitive Assessment (MoCA) score (score between 0-1), (median [IQR])	0.77	[0.67, 0.87]	0.78	[0.67, 0.87]	0.73	[0.66, 0.81]	0.73	[0.67, 0.83]
Number of unique** medicines,(median)	15.25		15.13		14.41		14.14	
Daily ACFI supplement at baseline (mean)	$145.47[c]		$142.89[d]		$154.85[e]		$154.27[f]	

Descriptor	Intervent-ion, ITT trial arm (n=120)	Intervent-ion, ITT trial arm, Proport-ion (%) or Variation [IQR]	Intervent-ion, MBS costs sub-dataset (n=80)	Intervent-ion, MBS costs sub-dataset Proport-ion (%) or Variation [IQR]	Control, ITT trial arm (n=128)	Control, ITT trial arm Proportio n (%) or Variation [IQR]	Control, MBS costs sub-dataset (n=88)	Control, MBS costs sub-dataset Proport-ion (%) or Variation [IQR]
Baseline utility (mean)*	0.68		0.71		0.65		0.63	0.63
Self-rated EQ-5D Health Scale (1-100), (median [IQR])	75.00	[60.00, 85.00]	75	[64, 86]	75.00	[60.00, 80.00]	75	[60, 80]

Table C-1: Comparison of demographics and baseline data for the ITT study population and the sub-groups with MBS administrative costing data.

*** based on responses to EQ-5D-5L questionnaire transformed to utility weights (UK preferences) using crosswalk method (67) – see Section C.4.**

The sample size for each arm or sub-group is indicated in the table. However, sample size for BMI outcome is [a] n = 51, [b] n = 59 and for Daily ACFI supplement is [c]n=116, [d]n=78, [e]n=123, [f]n=85.

Descriptor	Intervent-ion, ITT trial arm (n=120)	Intervent-ion, ITT trial arm Proport-ion (%) or Variation [IQR]	Intervent-ion, PBS costs sub-dataset (n=78)	Intervent-ion, PBS costs sub-dataset Proport-ion (%) or Variation [IQR]	Control, ITT trial arm (n=128)	Control, ITT trial arm Proport-ion (%) or Variation [IQR]	Control, PBS costs sub-dataset (n=85)	Control, PBS costs sub-dataset Proportion (%) or Variation [IQR]
Age (years) at Baseline, (median [IQR])	87 years	[81.75, 90.00]	87 years	[82, 90]	87 years	[81.75, 90.00]	87 years	[80, 90]
Gender = Male, n (%)	41	34.2%	24	31%	39	30.5%	24	28%
BMI, (median [IQR])	**27.02**	**[24.65, 30.85]**	**26.23[a]**	**24.61, 30.77] [a]**	**25.06**	**[22.27, 30.13]**	**25.41 [b]**	**[21.81, 31.34][b]**
Frailty Index (median [IQR])	0.26	[0.22, 0.31]	0.26	[0.22, 0.30]	0.28	[0.21, 0.33]	0.28	[0.21, 0.32]
Calculated Montreal Cognitive Assessment (MoCA) score (score between 0-1), (median [IQR])	**0.77[1]**	**[0.67, 0.87][1]**	**0.78**	**[0.68, 0.87]**	**0.73**	**[0.66, 0.81][1]**	**0.73**	**[0.67, 0.83]**
Number of unique** medicines, n (median [IQR])	15.25	15.25	15.17	15.17	14.41	14.41	14.31	14.31
Daily ACFI supplement at baseline (mean)	$145.47[c]		$142.85[d]	$	$154.85[e]		$155.82[f]	
Baseline utility (mean)*	**0.68**	**0.68**	**0.71**	**0.71**	**0.65**	**0.65**	**0.63**	**0.63**
Self-rated EQ-5D Health Scale (1-100), (median [IQR])	75.00	[60.00, 85.00]	75	[61, 89]	75.00	[60.00, 80.00]	75	[60, 80]

Table C-2: Comparison of demographics and baseline data for the ITT study population and the sub-groups with PBS administrative costing data.

** based on responses to EQ-5D-5L questionnaire transformed to utility weights (UK preferences) using crosswalk method (67) – see Section C.4.*

*** based on unique ATC code*

The sample size for each arm or sub-group is indicated in the table header. However, sample size for BMI outcome is a n = 51, b n = 5 and for Daily ACFI supplement is cn=116, dn=76, en=123, fn=82.

Some differences in baseline EQ-5D derived utility were noted with respect to the sub-groups; where the intervention group cost data sub-group reported slightly higher average utility than the overall intervention arm and the control cost data subgroup had slightly lower average utility than the overall control arm. Also, a difference in baseline utilities between the arms was noted. With respect to the economic analysis, if a trial-based cost-utility analysis was conducted an adjustment for the difference in baseline utilities would be necessary; however on the basis of the primary outcome results a cost-utility analysis will not be conducted. Overall the slight differences in baseline characteristics between the groups run in opposite directions (favourable utility and MoCA scores in the intervention group, but less favourable frailty scores) and do not raise significant concern of bias or applicability for the economic evaluation.

C.3. Extrapolation translation issues

The economic evaluation is a trial-based analysis. It is derived entirely on data observed within the trial period (approximately one year). There are no extrapolations included in the economic analysis.

C.4. Transformation issues

No economic outcome transformations are required

The study did not identify a difference in the primary clinical outcome, nor the pre-specified secondary outcomes of economic interest (adverse medicine events or quality of life to inform quality-adjusted life years), therefore the primary economic analysis is a cost analysis.

However in Section B8 a clinical claim of superiority is made, based on the statistically significant observed difference in MoCA scores that showed reduced cognitive decline in the intervention arm. As cost-effectiveness analysis can only be justified with patient relevant outcomes the *post hoc* analysis presented in Table B6-10 is the most relevant analysis of effect on cognitive function for economic analysis purposes. This analysis identified that in the intervention arm an additional 12% of residents avoid clinically significant cognitive decline in 12 months. This estimated outcome difference is used as the basis of an exploratory cost-effectiveness analysis.

Section D Economic Evaluation

D.1. Overview

The clinical evaluation suggested that relative to standard care the pharmacist intervention has superior safety and superior effectiveness in terms of preventing cognition decline based on the evidence profile given in Table D-1.

Table D-1 sets out the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake (if any) in this Section.

The economic analysis plan pre-specified that a trial-based cost-comparison and a cost-effectiveness analysis identifying incremental cost per adverse event avoided would be conducted if the primary study outcome or change in adverse events was identified. However, the study did not produce a significant result with respect to frailty or adverse events; therefore, the primary trial-based analysis is a cost analysis.

The finding of clinical superiority with respect to cognition decline has been used for a further exploratory cost-effectiveness analysis identifying the incremental cost per resident who avoids a significant cognitive decline (over a 12 month time horizon).

	Comparative effectiveness - Inferior	Comparative effectiveness - Uncertain[a]	Comparative effectiveness – Non-inferior	Comparative effectiveness - Superior
Comparative safety - Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Comparative safety - Uncertaina	Health forgone possible: need other supportive factors	**?** **1. Trial-based cost analysis (base case)**	?	? Likely CEA/CUA
Comparative safety - Non-inferior	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Comparative safety - Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA **2. Exploratory CE analysis**

Table D-1. Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

b An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

D.2. Populations and settings

The population for the trial-based economic analysis is based directly on the study population for whom economic data were available. It represents aged care residents in Australia who are at high risk of adverse medication events (as identified by them taking 4 or more medicines or taking at least one medicine with anticholinergic or sedative medicine) but have not yet suffered extensive decline. These residents have a cognition score (MoCA) of 18 or higher (corresponding to no or mild cognitive impairment) and a frailty index less than 0.4, as detailed in Section A.3 and B.4.2.

A summary of the characteristics of the study participants is presented in Section B.4. In Section C.2 the characteristics of the study sub-group for whom external administrative costing data was available is assessed alongside the broader study population. The population with costing data is identified to be representative of the broader study population.

Like the primary study, the setting of the trial-based cost analysis is in the Australian aged care setting and the perspective of the analysis is the Australian Healthcare system.

D.3. Structure and rationale of the economic evaluation

A summary of the key characteristics of the economic evaluation is given in Table D-2.

Perspective	Australian healthcare system, including aged care funding
Comparator	Usual practice (no additional pharmacist intervention)
Type of economic evaluation	Base case: cost-analysis Exploratory analysis: cost-effectiveness analysis
Sources of evidence	ReMInDAR clinical trial
Time horizon	1 year (consistent with clinical study follow-up)
Outcomes (base case cost outcome only)	Change in total health resource expenditure (net costs/ savings) per resident, associated with the pharmacist intervention. Exploratory analysis: residents avoiding clinically significant cognitive decline
Methods used to generate results	Trial-based analysis – data collected directly within study combined with Commonwealth and state health department administrative data

Discount rate	Not relevant (1 year time horizon)
Software packages used	Excel

Table D-2 Summary of the economic evaluation

D.3.1 Literature review

A literature search was conducted to identify studies published that analysed costs comparing pharmacist-led medication reviews with usual care in the setting of residential aged care facilities. The search found seven studies, of which one was a cost-utility analysis, and the remainder were cost analyses. All studies limited the costs considered to pharmaceuticals and the pharmacist service, none included comprehensive costs of the patient care. All studies, except the cost-utility analysis (86) reported cost savings as a result of pharmacist-led medication reviews. A summary of the existing economic literature is presented in Table D-3.(86-92).

Only one study, Roberts *et al*. (2001) (90), is Australian, and this is relatively historic. This study evaluated a year-long clinical pharmacy program in nursing homes involving development of professional relationships, nurse education on medication issues, and individualized medication reviews. It found medication use in the intervention group was reduced by 14.8% relative to the controls, which at that time translated to a saving of $64 on annual prescription costs per resident.

The available evidence appears limited in that the perspective of costs was limited to pharmaceuticals, the Australian data is not current and the pharmacist intervention was not as targeted and defined as the proposed intervention, nevertheless the results of the Roberts et al., (90) study will be considered in the light of the pre-existing literature.

Study, Location	Study Details	Duration (months)	Medication review type	Results
Zermansky *et al*. (2006) UK	Design: RCT No. of residents: 661 No. of homes: 65	6	Clinical medication review by pharmacist	Cost of drugs per patient per 28 days: Intervention: £42.24 Control: £42.94
Jodar-Sanchez *et al*. (2014) Spain	Design: Prospective No. of residents: 332 No. of homes: 15	12	pharmacotherapy follow-up	ICER: 1st Scenario: usual care dominated 2nd Scenario: €3,899/QALY 3rd Scenario: €6,574/QALY
Chia *et al*. (2015) Singapore	Design: Retrospective No. of residents: 480 No. of homes: 3	6	Clinical medication review by pharmacist	Total cost savings: Pre: SGD 388.30 Post: SGD 876.69
Brulhart *et al*. (2011) Switzerland	Design: Retrospective costs No. of residents: 329 No. of homes: 10	36	Prescription review by pharmacist	Intervention: annual decrement of drug costs: 14.6% Control: 0.1% decrement
Christensen et al. (2004) USA	Design: pre-post review No. of residents: 9,208 No. of homes: 253	3	Prescription review by pharmacist	Mean drug cost savings: $30.33 per patient per month
Furniss *et al*. (2000) UK	Design: Prospective Trial No. of residents: 330 No. of homes: 14	8	Clinical medication review	Average total costs per resident: Intervention: £314.89 Control: £492.98
Roberts *et al*. (2001) Australia	Design: Clustered RCT No. of residents: 3,230 No. of homes:52	12	Clinical review by multidisciplinary team with pharmacist	Annual prescription saving of AUD 64 per resident

Table D-3 Published literature comparing the costs of pharmacist-led medication reviews with usual care among older adults in aged care facilities.

D.3.2. Structure of the economic evaluation (Cost Analysis)

The primary economic analysis for this trial-based cost comparison is from the perspective of the Australian healthcare system (public and private funded healthcare costs). The primary economic outcome will be; total average healthcare costs per patient per day based on data collected in the clinical trial, adjusted for baseline differences in aged care subsidy rates. Total costs per cohort arm and average costs per patient per cohort arm will be presented, however as differing numbers of residents died in each arm, and at differing times, the total number of resident-days being costed over the trial period differs between the arms. Therefore the per arm cohort costs and average per patient costs should be interpreted with caution; as a calculation step; only the average per patient per day cost is meaningful in a comparative sense.

The health economic analysis is conducted using the 'intention to treat' principle (ITT) (i.e. patients allocated to the intervention arm are analysed in this arm regardless of whether they received the intervention or not), but the analysis is not conducted with the full ITT population. This was because additional participant consent steps were required to enable release of the external Services Australia and hospital data records to the study investigators and not all participants completed these. The representativeness of the patients with external economic data to the whole study is assessed in Section C.2.

Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS) administrative claims data, as well as administrative claims data for hospital admissions were linked to the clinical effectiveness data collection set and used to inform the economic evaluation.

The economic analysis is a simple trial-based cost analysis. Microsoft Excel was used to calculate average and aggregate cost estimates. No modelling techniques or modelling software were used.

The following healthcare resources and their associated costs were identified as relevant to a health economic evaluation in this study setting:

- pharmacist reviews (the study intervention);
- medical (Services Australia) services and all items claimed via the MBS;
- PBS medicines;
- hospital costs – both inpatient, outpatient and emergency department presentations;
- aged care subsidies related to the level of care required (ACFI daily subsidy rates);
- ambulance services;
- additional allied healthcare services (not claimable through the MBS).

For the intervention, pharmacist reviews were organised and reimbursed on a 'sessional basis' (3-4 patients at a single Aged Care facility, reviewed over 3-4 hours). For the purpose of this conventional health economic evaluation, the costs have been calculated on a 'per patient' basis, but if the proposed intervention were to be publically funded then the expected service delivery pattern and optimal funding structure would require further negotiation by stakeholders.

Medical services (funded through the MBS), PBS-funded medicines and public hospital costs are routine components in Australian health economic evaluations. The costs associated with MBS, PBS and public hospital for residents in the study were measured by matching residents to the external databases used for administrative claims purposes – i.e. the Services Australia databases (for MBS and PBS use) and the state government hospital costing records. As per the healthcare system perspective, government costs and patient co-payments are included in the base case analysis. Over-the-counter medicines were not able to be reliably costed and included in the analysis.

When designing the trial, ambulance services were considered a relevant health resource given that in the residential aged care setting they are directly associated with the provision of off-site health services, and are essential and in routine use. The study design was to use third-party administrative data on ambulance costs linked to study patients, if approval for this was received from all relevant bodies. However at the conclusion of the study, when lodging the data request with the 3rd party, it was found that the necessary patient-linked costing data could not be provided in a timely manner, therefore ambulance costs are not included in the base case analysis. The study data collection form did record ambulance use as apparent from clinical records and a scenario analysis using these data is presented.

Although not always included in health economic analysis from the Australian healthcare system perspective, it was considered that costs associated with non-MBS funded allied healthcare services are relevant to consumers and may be significant in the area of aged care. Data on resident use of any allied health services was collected from participants' residential care records, including specifically; acupuncture, chiropractic, dental (general/specialist), dietetics, exercise physiology, myotherapy, naturopathy, occupational therapy, optical, osteopathy, physiotherapy, podiatry, psychology, remedial massage, speech therapy and wound care. Health resource use associated with non-publically funded allied healthcare services from the trial is analysed and costed. This is not included in the base case but is included in a sensitivity analysis.

Finally, the cost of aged care, in particular Commonwealth aged care funding instrument (ACFI) subsidies associated with increasing levels of care, were identified as directly related

to the broader purpose of the study. ACFI subsidies are determined by residents' care needs across the areas of:

1. Activities of daily living (ADL);
2. Behaviour (BEH);
3. Complex Health Care (CHC).

Given that the clinical outcomes of interest relate to frailty and age-related deterioration (including cognition) the effectiveness of the intervention may directly affect resident's care needs based on their abilities to perform activities of daily living, their behaviour and complex health requirements and therefore directly impact aged care funding requirements.

The analysis determines the average per patient cost over the 12 months. Only costs incurred within 12 months of follow-up are included. In the case of medicines, the analysis measures medicine costs rather than medicine consumption, therefore where a resident is using medicines that were purchased before commencing in the study, these are not included in the study costs. Likewise medicines dispensed toward the end of the study period are included, even if not all consumed within the study period.

Separate average costs were calculated for type of health-related resource. Total costs over the study cohort were not able to be meaningfully combined since not all patients have data on all resource types.

D.4. Inputs into the economic evaluation

D.4.1 Resource use data and pricing

A summary of the unit price (and source) for the resources included in the cost analysis are presented (Table D-4). The quality of the resource use and pricing data for each resource is discussed following.

Type of resource	Value	Data Description / Source
Pharmacist review	Equivalent to $107.07 per person	Derived from professional sessional fees as provided to community pharmacists in the trials. Described in detail below.
Pharmaceuticals (PBS)	Direct cost ($) to PBS and patient contribution	Expenditure value from patient-linked confidential PBS Information Report compiled by Services Australia. Pricing and patient contributions Data provided by Services Australia $ value (PBS Schedule at time of dispensing)
Medical Services (MBS)	Direct cost ($) to MBS and patient contributions	Expenditure value from patient-linked confidential MBS Information Report compiled by Services Australia. Pricing and patient contributions. (Item fees represent MBS Schedule at time of service)
Hospitalisation - inpatient and emergency department costs (public hospitals)	$5,134 per NWAU (NEP 2020)	Hospitalisation data for South Australian residents was obtained through a data linkage request to SA Health and patient data from inpatient and emergency admissions databases provided. For Tasmanian residents, a summary patient record of hospital admissions and emergency presentations were provided on a 'per resident' level. All resident hospital costs are calculated by multiplying all recorded National Weighted Activity Unit (NWAUs) by the National Efficient Price (NEP).The Independent Hospital Pricing Authority, National Efficient Price Determination 2019-20[1].
Public hospital outpatient costs	Based on assigned NWAU and NEP - varied by clinic type; see Appendix F	Compiled hospital outpatient records were not available for South Australian residents from SA Health, however outpatient clinic visit records were reported in Tasmanian resident hospital files. This outpatient data was provided with a clinic description only (no NWAU or cost value). Therefore a cost was calculated for each outpatient service, based on the described type of service (used to inform the clinic code) (assuming no adjustments for patient or hospital characteristics). "non-admitted_2019-20_nwau_calculator.xls"[2]
Aged Care Subsidies	Variable – see below	Each patient had their ACFI care levels recorded at baseline, 6 months and 12 months. Total government residential care subsidies are calculated by multiplying the daily subsidy rate (for each care level) x number of days (that resident is classified at that care level). ACFI rates as per Schedule from 1 July 2019 are shown in Table D-5 below, and published[3]
Allied Health costs		
MBS	(as per MBS)	Study researchers recorded allied health services from the residents' case notes.
	Variable:	
Non-MBS	$143.90	
Audiologist/hearing	$53.50	MBS funded allied health services were removed from study-collated allied health dataset to remove duplicate costing as these services and costs would also be included in the MBS dataset.
Dental care	$102.90	
Dietetics	$76.00	
Nurse practitioner		
Occupational Therapy	$129.22	Non-MBS funded allied health services were allocated costs (on a per service basis), obtained from advertised prices, sourced on-line from a variety of Australian providers; these are listed in Attachment H.
Physiotherapy	$65.00	
Podiatry	$71.40	
Psychology	$112.40	
Remedial Massage	$110.00	
Social Worker	$80.05	
Speech therapist	$148.87	

TableD-4 Summary of the data collection and valuation sources used to estimate healthcare resource costs

1 https://www.ihpa.gov.au/publications/national-efficient-price-determination-2019-20

2 https://www.ihpa.gov.au/publications/national-efficient-price-determination-2019-20 (accessed 12/01/21)

3 https://www.health.gov.au/resources/publications/schedule-of-subsidies-and-supplements-for-aged-care

Pharmacist intervention costs

In the study the pharmacist intervention was provided on a 'sessional' basis where the pharmacist was renumerated ($300) for a block of time (3-4 hours), and in that time reviewed numerous residents and reported results. Initially while pharmacists were learning the process, fewer patients were reviewed per session, however in the last 6 months of the study, an average of 2.8 patients were reviewed per session and the average 'pharmacist review' cost per patient was $107.07. This per review cost is used to calculate the average expected annual cost per resident, assuming that reviews are conducted six times per year. If in practice review are conducted less frequently, or remuneration is provided on a sessional basis and more residents are able to be reviewed in a session then this cost estimate may overestimate the costs associated with the service.

MBS and PBS costs

MBS and PBS resource data were provided to the research group as individual patient costs; the dollar cost value of each item was pre-assigned, based on the actual service, pharmaceutical fee or price at the time of supply (i.e. the MBS Schedule or PBS Schedule current at date of supply). Of the 174 residents consenting to release of their MBS and PBS data, MBS data was available for 169, and PBS data was available for 164. Consenting residents for whom no MBS or PBS data were identified were assumed to have alternative funding mechanisms for medical services and pharmaceuticals (e.g., Department of Veteran's Affairs, private funding arrangements etc) and were excluded from the resident /exposure count for their respective arm. Overall, the MBS and PBS cost data are considered highly reliable.

Hospital costs

Hospital data within the study follow-up period were available for residents with appropriate consents. This identified any inpatient admissions and emergency department visits to South Australian or Tasmanian public hospitals (depending on State of residence). The hospital inpatient data reported estimated National Weighted Activity Units for each admission, and for the cost analysis these are priced using the National Efficient Price 2019-2020 ($5,134 per unit). Total admissions are costed for each patient to enable an estimate of average

inpatient hospital costs over 12 months per patient. In South Australia, data linkage to centralised and processed SA Health inpatient and emergency hospital data was achieved for 170 of 172 consented SA residents (out of a total of 198 SA residents); of which all hospital data records appeared complete and had assigned National Weighted Activity Unit (NWAU) estimates. Overall the SA Health hospital cost data are considered to be highly reliable. The Tasmanian hospital data were collected on an individual record basis, rather than via data linkage with the state government administrative system. Summary admission or presentation records were retrieved for 39 of the 49 Tasmanian residents. Of the 39 hospital records retrieved only 13 reported NWAU values within the study period, and numerous hospital entries were incomplete and had not been assigned NWAU values. Only inpatient and emergency department entries for which an NWAU was allocated were included in this cost analysis study data. Overall, the Tasmanian hospital data (as received for the study) did not appear to complete or reliable, therefore the base case cost analysis uses only the SA Health data to estimate average resident hospital costs, and a sensitivity analysis is presented where the Tasmanian data are included to form the estimate.

Outpatient use data were only available for Tasmanian aged care residents. No per patient data on outpatient clinic use or costs were available for South Australian study participants in time for inclusion in the cost analysis study. A limited record of hospital outpatient clinic visits was provided for the Tasmanian aged care residents. For these patients during the economic analysis an Out Patient Department (OPD) clinic classification code was allocated based on the hospital case note summary description. The base NWAU for the OPD clinic code was then calculated using the "non-admitted_2019-20_nwau_calculator.xls"[4] assuming no funding adjustment factors were applicable for any study participant (i.e. increased funding is allocated for various patient characteristics), which is likely to underestimate real outpatient costs. A summary of the clinics and costs allocated to each attendance is provided in Appendix F. Given the small number of study participants for whom OPD data were available and the reliance on non-administrative manual coding, the average outpatient cost estimates are quite uncertain and therefore a sensitivity analysis is presented where this cost is excluded.

[4] Available at https://www.ihpa.gov.au/publications/national-efficient-price-determination-2019-20

Aged Care health-related government subsidies

The government aged care daily subsidy is variable and based on the level of care a resident requires in each of the following areas; activities of daily living, behaviour and complex health care. For each category a patient may require nil, low, medium or high levels of assistance, and the government subsidy increases accordingly. The rates associated with each category area and level of care are shown in Table D-5:

Level	Activities of daily living	Behaviour	Complex Health Care
Nil	$0.00	$0.00	$0.00
Low	$37.68	$8.61	$16.71
Medium	$82.05	$17.85	$47.61
High	$113.67	$37.21	$68.74

Table D-5: Residential Aged Care Subsidies and Supplements, basic daily ACFI subsidy rates

ACFI = Aged Care Funding Instrument

These rates are applicable from 1 July 2019 to 30 June 2020.

ACFI patient data (ACFI classifications and supplements and dates of reclassification) were sought from aged care facility records at 6 monthly intervals (baseline, 6 months and 12 months) by the study research team. It was noted, surprisingly, that there was significant incomplete data in patient care records and there were inconsistencies in the research data entered with respect to ACFI level assessments and assessment dates. To resolve these issues with the data, the following approaches and assumptions regarding costing based on ACFI care levels were made:

residents with blank or unknown levels at baseline were excluded;

where 6 or 12 month data were missing, the ‘last observation carried forward’ was applied;

where revised subsidy levels were reported at the 6 month or 12 month observation period, the change was assumed to occur at the central point of the observation period. (This assumption is unlikely to be correct in any individual resident’s case, but in the absence of reliable data on each resident’s re-assessment date, the approach was considered reasonable to apply across the cohort as a whole to estimate average costs, and it does not inherently favour one arm over the other.);

supplementary subsidies (oxygen, enteral feeding etc.) were excluded from the analysis due to incomplete and unreliable data.

Ideally, for the trial-based analysis to identify an effect on ACFI costs, each resident’s total ACFI costs would be estimated by multiplying the resident’s daily subsidy rate for the number of days that subsidy applied to them in the study period (and the subsidy would, on average, be the same across arms, until a treatment effect occurred). However, the baseline

characteristics of the study arms are compared In Section C.2 and it is apparent that the average ACFI subsidy per patient is different between the arms when entering the study; the intervention group commences the study with a daily subsidy rate of $145.47, whereas the average daily rate in the comparator arm is $154.85. If not adjusted for this initial difference the total ACFI costs would be $3,426 greater in the control arm (for the study period (one year) without any intervention or intervention effect. Therefore, an adjustment to equate baseline ACFI subsidy rates is required to remove this bias in the raw cost data.

The actual and relative change in ACFI subsidies observed over the study are reported below (Table D-6), including the disaggregated average subsidy components for each arm at each time point, and the change relative to baseline.

Time and Measure	Pharmacist Intervention	Comparator	Pharmacist Intervention	Comparator	Pharmacist Intervention	Comparator
Baseline - ADL	$76.844	$81.412			Adjusted for baseline difference	
Baseline - BHL	$13.713	$17.218				
Baseline - CHCL	$54.908	$56.221				
Baseline Total	$145.466	$154.851	Weighted average: $150.30	Weighted average: $150.30	$150.30	$150.30
6 months - ADL	$77.117	$82.747	Change Relative to Baseline		Applied to weighted average	
6 months - BHL	$13.700	$17.361				
6 months - CHCL	$56.109	$56.987				
6 months - Total	$146.927	$157.095	1.010	1.014	$151.81	$152.47
12 months - ADL	$81.659	$86.321	Change Relative to Baseline		Applied to weighted average	
12 months - BHL	$14.957	$17.713				
12 months - CHCL	$58.287	$58.690				
12 months -Total	$154.903	$162.723	1.065	1.051	$160.05	$157.94

Table D-6: Daily health-related ACFI subsidy rates observed in each arm and adjusted for baseline difference

ADL = activities of daily living, BHL = Behavioural health level, CHCL = complex health care level.

In addition, the number of resident days across arms differed significantly, therefore total ACFI costs associated with each arm of the study should not be directly compared. To remove the effect of the different exposure time that occurred between arms in the study, a simple modelled approach was applied. As stated above, it is assumed that the change in subsidy between observed time points occurs in the middle of the observation period, therefore using the 6 month and 12 month rates adjusted for baseline differences, the total annual subsidy for a resident alive for a year in each arm is calculated as:

(((‘baseline daily rate’ + ‘6 month daily rate’)/2)*365/2) + (((‘6 month daily rate’+’12 month rate’)/2)*365/2)

Significant uncertainty in the ACFI data is acknowledged, and the analysis is presented both with and without inclusion of this resource.

Allied Health Care (non-MBS)

A record of the allied health services each resident used during the study period (by date and type of service) was made by a clinical study research assistant who reviewed each study participant’s residential care case files at 6 months and 12 months. The internally collected study data were cross-checked against the externally provided Commonwealth MBS claims data to ensure duplicate counting of allied health services that are MBS funded did not occur; a revised data set of ‘non-MBS funded allied health services’ was generated by removing those services for which there was an MBS claim for the same patient for the same allied health service on the same day. Prices were allocated to non-MBS-funded services based on various published fee schedules (listed in Appendix F).

The overall estimate of the costs of non-MBS allied health services in each arm is highly uncertain because:

1) The pricing assigned to allied health services is highly uncertain;
   a) Within each allied health profession, multiple services are available and pricing depends on the specific service provided. Generally there was insufficient detail on the service provided (e.g. whether it was an initial assessment or follow-up or short or long duration consult etc.) to accurately identify and assign a service price; and
   b) There is likely to be variation in pricing (of equivalent services) between different private allied health providers. Specific provider information and pricing was not available and it is unknown whether the published price reflects the price of the private provider used by the resident during the study period.
2) The non-MBS funded allied health service use data may be incomplete. Research assistants reported difficulty in finding the required information in the residential care facility case files; therefore, it is likely that some omissions occurred in data collection.

Overall, compared to MBS, PBS, hospital and ACFI costs, the non-MBS allied health costs are relatively inconsequential. Given this, coupled with the uncertain reliability of the data

and prices, it was decided that these costs should not be included in the base case analysis, but they are presented in a scenario analysis.

Resource use

A summary of the 'per resident' resource use that occurred in the study follow up period (excluding daily ACFI-subsidised care) is presented in Table D-7.

The reported number of pharmacist reviews and the hospital activity units are used directly in the analysis. The number of medical services and pharmaceutical dispensings are presented for information purposes only, as direct cost data for MBS services and PBS dispensings was provided and used. The allied health service numbers are aggregated for information purposes only also as these are individually costed by the type of service.

Descriptor	Intervention (n) in dataset	Intervention # services/ activity units recorded	Intervention Average # per patient	Control, (n) in dataset	Control, # services/ activity units recorded	Control, Average # per patient
Pharmacist reviews	115	575	5	-	-	-
Medical services (MBS items)	80	4032	50.40	88	4079	46.35
Pharmaceuticals (PBS dispensings)	78	7677	98.42	85	7662	90.14
Hospitalisation – Inpatient NWAUs	100	57.22	0.572	109	16.26	0.149
Hospitalisation – Outpatient NWAUs	21	2.02	0.096	18	0.46	0.025
Allied Health services	120	349		128	225	

Table D-7: Number of healthcare services provided over 12 months for each study arm (disaggregated base case)

D.4.2 Health Outcomes

The health outcome where a significant difference between arms was demonstrated in the study was cognitive decline, as shown in Table B9a. To be interpretable in the context of value for money, health outcome differences in a cost-effectiveness analysis should be societally or patient relevant. Therefore, for economic purposes the *post hoc* analysis presented in Table B-10 is the most relevant to quantify patient-relevant effects on cognitive function. This analysis identified that in the intervention arm an additional 12% of residents avoided clinically significant cognitive decline in 12 months. This represents a NNT (number needed to treat/provide intervention to) of 8.33. I.e for every 8.33 residents that pharmacists

reviewed 8 weekly over a year, it would be expected that one would avoid a clinically-relevant cognitive decline.

D.5. Results of the economic evaluation

Disaggregated Cost Results

Pharmacist intervention

115 residents in the intervention arm received 575 pharmacist reviews over a total of 38,342 study follow-up days. Costing reviews at an average of $107.07 each, represents an expenditure of $61,565 over the cohort, or $535.35 per resident in the intervention arm. However, because average follow-up in the intervention arm was only 333 days (due to the fact that some residents died before 1 year), all cost estimates will be adjusted to an estimate of costs over a 365 day period to enable a comparison to be made to the usual care arm.

This adjustment (calculation of an average cost of $1.61 per day, and multiplying it by 365) results in an estimate of the intervention cost to be on average $586 per resident per year.

MBS costs and PBS costs

Total MBS use and PBS use over the 12 month follow-up period for each patient are reported separately (Tables D-8 and D-9), with the calculations of the average cost per patient and the average cost per day also presented. The costs reported below are total healthcare system costs (i.e. include both public benefits paid and also patient contributions). The public funding perspective (i.e. based on public expenditure only) is presented in the sensitivity analysis.

MBS Costs	Intervention, Denominator	Intervention, Costs	Control, Denominator	Control, Expenditure	Increment
Per trial arm		$209,028		$206,047	$2,982
Av cost per person	80	$2,613	88	$2,341	$271
Av cost per day	28,937	$7.22	31,908	$6.46	$0.77
Av cost per year (adj)		**$2,637**		**$2,357**	**$280**

Table D-8: Medicare Benefits Schedule (MBS) costs in each arm of the study

A slightly higher increase in MBS expenditure was observed in the pharmacist intervention arm of the trial, with and without adjustment for resident follow-up, but the difference is small (approximately 10%) and not statistically significant (p = 0.24 using 2 tailed t-Test).

PBS Costs	Intervention, Denominator	Intervention, Costs	Control, Denominator	Control, Expenditure	Increment
Per trial arm		$219,500		$295,832	-$76,332
Av cost per person	78 people	$2,814	85 people	$3,480	-$666
Av cost per day	28,207 days	$7.78	30,813 days	$9.60	-$1.82
Av cost per year (adj)		**$2,840**		**$3,504**	**-$664**

Table D-9: Pharmaceutical Benefits Scheme (PBS) costs in each arm of the study

PBS expenditure per patient was observed to be lower in the intervention arm than the usual care arm, and this observation holds when adjusted for follow-up time. The adjusted annual difference of $664 represents a 23% reduction in annual prescription costs. Although a substantial difference in costs, the difference was not statistically significant (p = 0.5 using 2 tailed t-Test), however, the study was not powered to detect differences in costs. This finding is consistent with the findings in the literature (Section D.3), where 6 of the 7 economic studies identified cost savings in pharmaceutical expenditure associated with pharmacist interventions.

Hospital costs

The hospital cost data for consenting residents obtained from various systems through SA Health and Tasmania Health are presented as raw and adjusted data for each jurisdiction before calculating an overall estimate (Table D-10).

The difference between the average hospital cost per resident is not statistically significant. Only the SA Health costs will be used in the base case results of the analysis given the unreliability of the Tasmanian hospital data. It is also noted that there was one resident in the intervention arm that was an outlier in that they had extremely high hospital costs ($81,323, representing 53% of the overall hospital costs in that arm). The effect of removing the outlier from the analysis is presented as a sensitivity analysis.

	Hospital Costs	Intervention, Denominator	Intervention, Costs	Control, Denominator	Control, Costs	Increment
Total SA Health	Per trial arm		**$153,754**		**$53,935**	**$99,819**
	Av cost per person	79 people	$1,946	91 people	$593	$1,354
	Av cost per day	25,600 days	$6.01	31,612 days	$1.71	$4.30
	Av cost per year (adj)		**$2,192**		**$623**	**$1,569**
	Excluding outlier		$1,045		$623	$422

	Hospital Costs	Intervention, Denominator	Intervention, Costs	Control, Denominator	Control, Costs	Increment
Total Tas Health	Tas Health IPD		$140,027		$29,521	$110,506
	Tas Health OPD		$10,379		$2,350	$8,029
	Per trial arm		**$150,407**		**$31,871**	**$118,535**
	Av cost per person	**21**	$7,162	18	$1,771	$5,392
	Av cost per day	**7,665 days**	$19.62	6,570 days	$4.85	$14.77
	Av cost per year (adj)		**$7,162**		**$1,771**	**$5,392**
Pooled SA and Tas hospital data	**Total costs for arm**		**$304,161**		**$85,806**	**$218,355**
	Av cost per person	100	$3,042	109	$787	$2,254
	Av cost per day	33265	$9.14	381182	$2.25	$6.90
	Av cost per year (adj)		$3,337		$820	$2,517

Table D-10: Hospital costs over 12 months in each arm.

Adj- adjusted

Residential Care health-related care costs (ACFI subsidies)

Estimates of total ACFI subsidies allocated to the care facility residents to assist with health-related costs of care were based on the resident's ACFI assessments in the areas of Activities of Daily living, Behavioural and Complex Health requirements. Subsidies are provided as a daily rate, and it was identified that the average daily subsidy rate was slightly different between the arms at baseline. Although this difference is small, when applied over a year it is significant, therefore to enable a fair comparison of the potential effect of the intervention on total ACFI subsidy related costs over a year an adjustment to equalise baseline subsidy rates was made and the subsidies over the year estimated based on the relative change in the daily rate from baseline. The total projected subsidies per patient in each arm are also adjusted to estimate one year of subsidisation (Table D-11). This analysis of the subsidy rates observed in the study suggests there was no significant change in ACFI-health related subsidies associated with the intervention.

Timeframe	Intervention	Control	Increment
In first 6 months	$27,567	$27,628	-$61
In months 6-12	$28,456	$28,325	$131
Total	$56,023	$55,953	$70

Table D-11: Estimated health-related ACFI subsidies per resident incorporating observed changes to the average daily rate in each arm, applied over one year (adjusted for baseline difference).

Allied Health Services costs

Estimates of allied healthcare services that are not funded though MBS were also made (Table D-12. Although nominally incurred by the patient, where supported through private health insurance rebates, these services are partially indirectly funded as government funding supports the private health insurance industry. In either case, an argument to include these costs in analysis from a healthcare systems perspective could be made. However, in this case, the data collected during the trial was deemed too uncertain to reliably inform the base case and so allied healthcare costs will only inform a scenario analysis.

Allied Health Costs	Intervention, Denominator	Intervention, Costs	Control, Denominator	Control, Expenditure	Increment
Per trial arm		$27,921		$17,479	$10,442
Av cost per person	120 people	$233	128 people	$137	-$96
Av cost per day	39,212 days	$0.71	44,071days	$0.40	$0.32
Av cost per year (adj)		**$260**		**$145**	**$115**

Table D-12: Allied health services costs in each arm of the study

Cost and Incremental cost analysis

For the base case analysis, the average per resident healthcare costs adjusted to equally reflect 12 months of survival in each arm (as calculated in the disaggregated results above) is shown below (Table D-13), with the incremental cost difference between arms shown for each resource and calculated for the total healthcare costs. The base case analysis includes pharmacist intervention costs, PBS costs, MBS costs, and inpatient and emergency department hospitalisation costs based on the more reliable SA Health data, and identified a net total incremental healthcare cost of $1,841 per resident over 12 months associated with the intervention arm.

Descriptor	Intervention	Control	Increment
Proposed pharmacist review	$586		$586
Medical services (MBS costs)	$2,637	$2,357	$280
Pharmaceuticals (PBS costs)	$2,840	$3,504	-$664
Hospital costs - admissions	$2,192	$623	$1,569

Descriptor	Intervention	Control	Increment
Aged Care subsidies	$56,023	$55,953	$70
TOTAL	$64,278	$62,437	$1,841

Table D-13: Average healthcare costs per patient over 12 months for each study arm (adjusted trial-based cost analysis): base case

The trial-based economic analysis adjusted for differences in baseline costs and survival differences, does not show a reduction in total healthcare costs associated with the intervention. However, with the exception of the cost of the proposed pharmacist service, none of the differences in other resource costs were statistically significant, and it is likely that random differences in underlying health conditions between residents in each arm at the time of randomisation contributed to the difference in overall healthcare costs and confounded the results. This explanation is also consistent with the increased number of deaths, unrelated to the intervention, that were observed in the intervention arm. It is not likely that the differences observed in MBS costs, hospitalisation, ACFI subsidy were unrelated to the pharmacist intervention.

However it is noted that the observed difference in pharmaceutical costs was in the opposite direction to all other resource use, and showed reduced pharmaceutical costs in the intervention arm. This finding is consistent with the findings of previous studies and may possibly be directly associated with the intervention, given pharmacist recommendations on medications included suggestions to cease some medications and to reduce the dose of some medications.

Exploratory cost-effectiveness analysis

As calculated in Section D4.2, based on the results of the clinical trial, for every 8.33 resident years of intervention, one resident avoids a clinically significant decline in cognition. For the base case analysis, the observed average per resident incremental healthcare cost adjusted to reflect one year was $1,841. For 8.33 residents, the incremental cost is $15,342.

This equates to a trial-based incremental cost-effectiveness ratio of $15,342 per resident avoiding clinically significant cognitive decline.

This analysis is highly uncertain given the study was not adequately powered to show statistical significance for this outcome analysis (although the difference in average cognitive decline between groups was statistically significant), and the cost differences were not statistically significant and appeared to be highly confounded by residents' unrelated health conditions.

D.6. Sensitivity Analysis

Considering only pharmacist and pharmaceutical costs

If the observed differences in other resource use are attributed to confounding due to underlying health differences between the study arms and excluded, but pharmaceutical expenditure is considered most likely to be directly affected by the intervention, then it is noted the difference in average 12 month pharmaceutical expenditure between arms was greater than the cost of the pharmacist intervention. I.e. the intervention (after paying for itself) potentially saves an additional $77.92 per patient per year (Table D-14). This may be an underestimate of the cost-saving if confounding due to differences in underlying health between the arms was increasing pharmaceutical costs in the intervention arm, consistent with other medical costs.

Descriptor	Intervention	Control	Increment
Proposed pharmacist review	$586		$586
Pharmaceuticals (PBS costs)	$2,840	$3,504	-$664
TOTAL	**$3,426**	**$3,504**	**-$78**

TableD-14: Average healthcare costs per patient over 12 months for each study arm (adjusted trial-based cost analysis): base case

The finding of cost-savings in pharmaceuticals associated with pharmacist review is consistent with the literature, however it is acknowledged that, given the apparent imbalance in costs generally between arms, any conclusion or attribution of effect is highly uncertain.

If the exploratory cost-effectiveness analysis only considers pharmacist and pharmaceutical costs the intervention would be considered dominant, as it has a positive health outcome; preventing a clinically significant cognitive decline in one resident for each 8.33 residents assessed regularly over a year, while concurrently delivering a net cost-saving of $650.

Other trial-based scenario analysis

Additional scenario analysis of cost differences between arms in the trial-based data are presented below in Table D-15.

Description	Intervention, total costs	Control, r total costs	Increment
Including only MBS and PBS costs	$6,063	$5,861	$202
Including all base case costs + SA Hospital cost data excluding outlier	$63,131	$62,437	$694
Including all base case costs +Allied Health Costs	$64,538	$62,582	$1,956
Including all base case costs + All Hospital cost data	$65,423	$62,634	$2,789

Table D-15: Scenario analysis of the trial-based analysis

Section E Financial Implications

An epidemiological approach has been used to estimate the financial implications of the introduction of a pharmacist-led intervention among residents in aged care facilities.

E.1. Justification of the Selection of Sources of Data

Table E-1 summarises the parameters and data sources used in the financial analysis.

Description	Value used	Source
Number of people who received permanent residential aged care 2015-16 – 2019-20	239,379−244,363	Reports on the Operation of the *Aged Care Act 1997*, (2015-16, 2016-17, 2017-18, 2018-19, 2019-20)
Number of people who received permanent residential aged care 2020-21 – 2025-26	247,231−258,280	Projections based on a linear extrapolation of the 2015-16 to 2019-20 data.
Proportion of residents meeting eligibility criteria	7.7%	282 of 3,646 residents screened were eligible for study participation, as per Section B.4 of this report.
Uptake of pharmacist review by aged care residents	50%	Assumption
Number of pharmacist reviews per eligible resident	5	Observed average number of services per resident in the ReMInDAR trial
Cost per pharmacist review	$107.07	Section D.4 – Approximate estimate – further negotiation re fees and payment methods would be required with key stakeholders.
Change in PBS costs per patient who takes up pharmacist review	−$664.00	Section D.5

Table E-1: Data and sources used in the financial analysis

E.2. Use and Costs of ReMInDAR

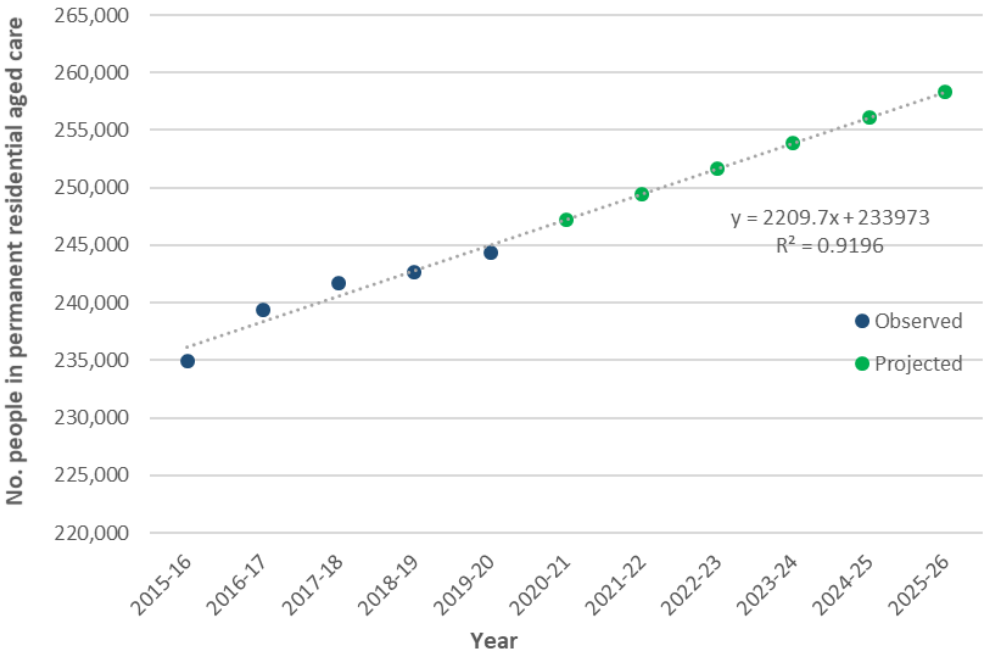
The number of people who received permanent residential aged care in Australia is reported annually by the Department of Health. Table E-2 presents the number of people who received permanent residential aged care in Australia in 2015-16 to 2019-20. A linear projection of this data was used to estimate the number of people estimated to receive permanent residential aged care to 2025-26 (Figure E-1).

Description	2015–16	2016–17	2017–18	2018–19	2019–20
People who received permanent residential aged care	234,931	239,379	241,723	242,612	244,363

Table E-1: Number of people who received permanent residential aged care, 2015-16 to 2019-20

Source: Reports on the Operation of the Aged Care Act 1997, (2016-17, 2017-18, 2018-19, 2019-20)

Figure E-1: Number* of people in permanent residential aged care, projected to 2025-26.



**Source: Observed data from Reports on the Operation of the Aged Care Act 1997, (2016-17, 2017-18, 2018-19, 2019-20), projections created using linear extrapolation for this analysis.*

Based on the rate of eligibility of aged care residents to enter the clinical trial, approximately 7.7% of aged care residents would be expected to meet the cognitive and frailty criteria required for eligibility for the pharmacist review. Of those meeting the eligibility criteria, the likely uptake of the proposed service is highly uncertain, but for the purposes of this report is estimated at approximately 50%. Each resident that takes up the pharmacist-led intervention is assumed to receive five services per year, based on the average number of services observed in the clinical trial. The average cost per service was estimated to be approximately $107.07 during the clinical trial, however this value is approximate and the exact funding methods and costs would require further consultation with key stakeholders. For the purposes of this report, the cost per service of $107.07 was used to estimate total government expenditure if the service was to be government funded.

The number of people estimated to uptake pharmacist review, the expected number of services and cost to the MBS is presented in Table E-3.

	2021-22	2022-23	2023-24	2024-25	2025-26
No. people in residential aged care (Figure E-2)	249,441	251,651	253,860	256,070	258,280
No. people eligible on the basis of medications, frailty and cognition (7.7%)	19,293	19,464	19,635	19,806	19,977
No. people that uptake proposed pharmacist review (50%)	9,647	9,732	9,818	9,903	9,989
Estimated number of services (5 per patient)	48,233	48,660	49,088	49,515	49,943
Estimated government pharmacist expenditure ($107.07 per service)	**$5,164,254**	**$5,210,026**	**$5,255,799**	**$5,301,571**	**$5,347,343**

Table E-3: Projected people in residential aged care who would be eligible for the proposed pharmacist review over five years

E.3. Changes in Use and Cost of Other Medical Services

Although the clinical trial-based cost analysis identified differences in annual MBS costs across the different arms of the study, it concluded that these are unlikely to be associated with the intervention. Therefore, these are not included in the base-case financial analysis and no real change to MBS expenditure as a result of the pharmacist intervention is anticipated.

E.4. Financial Implications for Government Health Budgets

The clinical trial-based economic evaluation did identify a difference in PBS expenditure that was considered possibly associated with the intervention, as PBS expenditure was more likely to be directly influenced by pharmacist recommendations, and the finding of reduced pharmaceutical expenditure was consistent with previous studies reported in the literature. Therefore, the financial analysis assumes that a reduction of PBS pharmaceutical expenditure of $664 per person, as observed in the trial may be associated with the intervention.

The financial implications to Commonwealth health budgets resulting from the proposed listing of pharmacist intervention are summarised in Table E-4.

	2021-22	2022-23	2023-24	2024-25	2025-26
No. people that uptake proposed pharmacist review	9,647	9,732	9,818	9,903	9,989
Net cost of pharmacist intervention program	**$5,164,254**	**$5,210,026**	**$5,255,799**	**$5,301,571**	**$5,347,343**
Change in use of other affected Commonwealth services					
Change in PBS expenditure (−$664 per person)	−$6,405,276	−$6,462,048	−$6,518,820	−$6,575,592	−$6,632,364
Net cost to Commonwealth health services	**−$1,241,022**	**−$1,252,022**	**−$1,263,021**	**−$1,274,021**	**−$1,285,021**

TableE-4: Total costs to Commonwealth health budgets associated with pharmacist intervention

E.5. Identification, Estimation and Reduction of Uncertainty

The uncertainty associated with various parameters is assessed in the sensitivity analyses presented (Table E-5).

Scenario	Costing	2021-22	2022-23	2023-24	2024-25	2025-26
Base case	**Net cost of pharmacist intervention program**	**$5,164,254**	**$5,210,026**	**$5,255,799**	**$5,301,571**	**$5,347,343**
	Net cost to Commonwealth health budgets	**−$1,241,022**	**−$1,252,022**	**−$1,263,021**	**−$1,274,021**	**−$1,285,021**
Proportion eligible on the basis of medications, frailty and cognition, 5% (base case: 7.7%)	Net cost of pharmacist intervention	$3,338,443	$3,368,155	$3,397,599	$3,427,311	$3,456,755
	Net cost to Commonwealth health budgets	−$802,261	−$809,401	−$816,477	−$823,617	−$830,693
Proportion eligible on the basis of medications, frailty and cognition,	Net cost of pharmacist intervention	$6,676,885	$6,736,041	$6,795,198	$6,854,354	$6,913,510
	Net cost to Commonwealth health budgets	−$1,604,523	−$1,618,739	−$1,632,954	−$1,647,170	−$1,661,386

Scenario	Costing	2021-22	2022-23	2023-24	2024-25	2025-26
10% (base case: 7.7%)						
Proportion that uptake proposed pharmacist review, 40% (base case: 50%)	Net cost of pharmacist intervention	$4,131,403	$4,168,021	$4,204,639	$4,241,257	$4,277,875
	Net cost to Commonwealth health budgets	−$992,818	−$1,001,617	−$1,010,417	−$1,019,217	−$1,028,016
Proportion that uptake proposed pharmacist review, 60% (base case: 50%)	Net cost of pharmacist intervention	$6,197,105	$6,252,031	$6,306,958	$6,361,885	$6,416,812
	Net cost to Commonwealth health budgets	−$1,489,227	−$1,502,426	−$1,515,626	−$1,528,825	−$1,542,025
Number of pharmacist services per resident, 6 (base case: 5)	Net cost of pharmacist intervention	$6,197,105	$6,252,031	$6,306,958	$6,361,885	$6,416,812
	Net cost to Commonwealth health budgets	−$208,171	−$210,017	−$211,862	−$213,707	−$215,552
Cost of per pharmacist review service, $117.20 (base case: $107.07)	Net cost of pharmacist intervention	$5,652,849	$5,702,952	$5,753,055	$5,803,158	$5,853,261
	Net cost to Commonwealth health budgets	−$752,427	−$759,096	−$765,765	−$772,434	−$779,103
Cost of per pharmacist review service, $91.01 (base case: $107.07)	Net cost of pharmacist intervention	$4,389,616	$4,428,522	$4,467,429	$4,506,335	$4,545,242
	Net cost to Commonwealth health budgets	−$2,015,660	−$2,033,526	−$2,051,391	−$2,069,257	−$2,087,122

Table E-5 Sensitivity analyses around the financial implications to the MBS and Commonwealth health budgets

The net costs of the potential pharmacist intervention program were moderately sensitive to the changes explored, in particular the proportion of residents considered eligible for the pharmacist-led intervention. The net costs to Commonwealth health budgets were similarly affected, however analyses exploring increases in cost of pharmacist-led interventions substantially reduced the estimated cost-savings, in particular the increase in the average number of services from five to six reduced the cost savings from $1.2 million per year to $0.2 million per year.

Section F Other relevant considerations

F.1. Case studies

Case studies have been produced with consent from trial participants. *The clinical vignette represents each case, however, names and circumstances have been changed,

Case study – Barbara*

“My medicines are making me ‘gag’!”

Barbara was born in regional Australia where she has lived most of her life. Barbara now lives in the local residential aged care facility. She uses 11 regular medications to manage her multiple comorbidities including hyperlipidaemia, hypertension, diabetes, congestive heart failure, renal failure and depression. She also has 8 medicines prescribed for use when necessary. She has been a very active member of the facility, an avid reader and is passionate about completing cross words.

Barbara recently had a stroke and returned from the hospital with a large number of new medications. Despite being back in the facility, **Barbara was still feeling very unwell after her stroke and could no longer complete the cognitive assessments for the ReMInDAR trial, which she had been able to complete prior to her stroke**. Her mood was very low.

The pharmacist asked Barbara “What bothers you the most?” to which Barbara expressed real concern about her medications and said that all her medications were making her feel really nauseous. Barbara said she was **“most terrified of the sound of the nurses pushing the medication trolley to her room each day”.**

As Barbara could not swallow her medications after her stroke, the nursing staff have been crushing the medications and the mixture was very unpalatable and made her “gag”. The ReMInDAR pharmacist reviewed and reconciled Barbara’s medicine and identified medicines which had been ceased in the hospital but were still on the medication chart in the facility.

The pharmacist discussed Barbara’s concerns and the issue of gagging with her GP and as a result Barbara was taken off many of her tablets, the dose was reduced for some medications and some of her medications were changed to liquid forms.

Barbara’s spirits improved, her cognition improved.

During subsequent pharmacist sessions, Barbara’s spirits had greatly improved and she was once again able to complete the cognitive assessments. Barbara was visibly much happier

and was very grateful to the pharmacist for intervening on her behalf. The pharmacist's advocacy on her behalf significantly improved Barbara's outlook and quality of life.

Case study – Mary*

Too scared to say I'm bleeding

88-year-old Mary has been living in residential aged care for almost a year. Mary, who has several children, is a widow of many years. She dotes on her grandchildren.

Mary is quite active, with a keen interest in craft. She is on medicines to manage her atrial fibrillation and hypertension. She has never smoked and doesn't drink. She has cataracts which are affecting her ability to do craftwork.

Mary feared the worst so kept her problems to herself.

The ReMInDAR pharmacist spent time with Mary, and during the first session discovered that Mary was concerned that she sometimes has bright red blood in her stool. Mary had kept this to herself because she feared needing to undergo a colonoscopy and "suspected the worst". However, based on a review of Mary's medications, the pharmacist suspected the bleeding might be due to the apixaban (5mg twice daily). The pharmacist notified the nurse regarding the blood in the stool and asked for the general practitioner (GP) to review.

During subsequent visits, the pharmacist noted that Mary was still experiencing blood in her stool once or twice a week. Mary was not constipated or straining while using the toilet. It didn't appear that a GP review to address Mary's concern had been undertaken. Mary's vital signs including weight, age and laboratory results indicating kidney function (CrCl =0.66mg/dL) were checked by the pharmacist. Considering Marys' weight (<60kg) and age (>80 years old), the pharmacist contacted the GP again and recommended a reduction in the apixaban dose to 2.5mg. The GP did not think that the bleeding could be due to apixaban and therefore no changes were made.

Persistence in GP communications pays off.

The pharmacist continued to stress Mary's concerns about the bleeding to the GP and by the fourth pharmacist session, the GP finally agreed to trial reducing apixaban from 5mg twice daily to 2.5mg twice daily.

During follow up at the fifth pharmacist session, Mary told the pharmacist that the blood in stool had stopped recently and that she no longer had bruising. By the sixth session, Mary confirmed that her bleeding problems had resolved completely.

In this case study, the pharmacist continued to serve as an advocate for Mary and made sure that her concerns about her condition were followed up by the GP and resolved.

Case study – Harry*

Finally in my own bed!

Harry is an 82-year-old client of residential aged care. In his working life, he was a town planner for the local council, and an active chess player. He is married and enjoys visits from his wife and their beagle. Harry moved into aged care because of his illnesses, which include incontinence, osteoarthritis, amnesia, obesity, obstructive sleep apnoea, transient cerebral ischaemic attacks, atrial fibrillation, cancer, dementia, depression, anxiety and hypertension; he has also been experiencing recurrent falls.

Harry has been sleeping in his chair for the last six months

Harry has been sleeping in his arm chair for the last six months, as he found his bed was too narrow and he was fearful he would fall out. Harry had swollen ankles and back pain, which was most probably from sleeping in his chair. Harry also thought his speech and mobility were declining. Harry was on 18 regular and eight "when required" medicine, which he was unhappy about, particularly the **"big orange tablets that catch his throat and irritates him for a few hours"** (Allopurinol 300mg).

Harry didn't like living in the aged care facility. He was bored. His mental health was poor and he spent almost all day in the same arm chair. Harry appeared to willingly self-isolate; refusing to leave his room, and did not engage in any wellness or social activities because they were "not interesting". He also did not engage with the facility care staff, but he did look forward to the visits from his wife and his dog.

The REMINDAR pharmacist spent time with Harry and reviewed his medicines. The pharmacist discussed Harry's issues with his doctor after the second session. Subsequently, some of Harry's medicines were removed, or substituted for smaller alternatives and the dose was reduced for few medications. At the same time, based on concerns expressed to the staff by the pharmacist, the Lifestyle co-ordinator made additional weekly one on one visits to Harry to try and find activities to improve his social engagement.

At the ReMInDAR pharmacist's third visit, Harry expressed pleasure with these outcomes, especially **not having to take any more "orange pills"**, however, he was still not leaving his room. Despite this, the small 'win' by the pharmacist helped establish a new relationship based on trust. Harry continued to open up to the pharmacist about his problems and revealed that he had previously fallen out of his bed (unreported to staff) hence his anxiety about sleeping in the current bed.

The pharmacist told Harry she was **"concerned for him and would talk with the staff about the issue of the bed"** and encouraged him to get out of his room. The pharmacist

continued to advocate with the facility staff on Harry's behalf about the importance of getting him a new bed.

At the fourth pharmacy visit the pharmacist learned that Harry had purchased a recliner chair that enabled him to lay further back and elevate his feet; this reduced the swelling in his legs. **More promisingly a new wider bed was on order for him.**

By the fifth session (conducted by phone during COVID -19 access restrictions), the pharmacist noted that Harry had remarkably improved. "In the past he was negative about the nursing care he got but now seemed quite complimentary about the staff. Even when talking about a fall, he didn't want to dwell on it and look back. It seemed very different to his attitude on previous visits".

Harry is now doing exercises by himself, and even going for a walk down the corridor.

Although the swelling in his legs has not improved significantly, he is able to sleep for longer blocks in the chair overnight. He is very much looking forward to being able to use his new bed.

The REMINDAR trial has shown that pharmacist's engagement including communication and trust building was crucial to identify and imply necessary changes affecting Harry's quality of life, not just in terms of his improved sleep, but also the positive impact on his mental health and engagement in social activities.

Case study – Jack*

Now I know I have medicines for when I need them.

Jack is an 84-year-old man who grew up in Tasmania. He moved into his residential nursing home in October 2016 so that he could be around more people and "be taken care of". Jack's wife visits him regularly, and he enjoys participating in the wellness and social activities at the facility.

I just put up with it.

Jack has been experiencing episodes of vertigo following a stroke, which had been an issue from time to time and was something he just "puts up with".

The ReMInDAR pharmacist noted that GP had a betahistine order 'when necessary', however when the pharmacist asked Jack about it, Jack said that he had not heard of it, nor had he taken any. There were several other medications charted for use when required. Jack was not aware of any of them. Jack said, **"the carers did not offer me anything when I complained of being dizzy".**

During a ReMInDAR session, the pharmacist explained to Jack what each of his medications were and what he could ask to use when each symptom occurred. The pharmacist typed up a list of his medications for Jack and gave them to him as a reference (coloxyl and senna, maxolon, movicol, paracetamol, betahistine, triamcinolone, ibuprofen and voltaren gel) with the names of the medications, their dose and explanation of what the medicines are used for.

Jack had an active mind and was very interested in the medicines and **felt empowered by knowing what was available to him.** The pharmacist reminded Jack to ask the nursing staff for assistance if he required any of the "when required" medicines and also reminded the staff that Jack had prn orders for his conditions.

Case Study – Grace*

*withdrawn but specific permission from participant was given to use her case study despite her withdrawal.

Don't question the prescribing

Grace is an active 91-year old who resides in a metropolitan aged care facility. She looked after her daughter as a stay at home mum, and still continues to 'worry about her' even though she is grown up now.

Grace had a previous heart attack and coronary artery bypass graft surgery in the past. Grace currently suffers from a number of medical conditions, including cancer, diabetes, hypertension, hyperlipidemia, varicose veins, incontinence, temporomandibular joint dysfunction, gallbladder stone, hiatus hernia and peptic ulcer. Her conditions are managed with 13 regular medicines and three medicines for use when required.

Grace expressed a concern about the number of tablets she was on and informed the pharmacist that she wanted to cease esomeprazole and magnesium which she had been using long term. The pharmacist supported Grace's decision and reassured Grace that he would contact the GP by letter to discuss this.

The GP was unreceptive to the pharmacist's recommendation and instead told Grace that "she did not need to have a pharmacist review her medications" and instructed her to take all her medications. Consequently, Grace continued to take all her medications and withdrew from the ReMInDAR trial.

The challenge of effective communication between healthcare professionals impeded the opportunity for Grace's medication preferences to be enabled for medicine optimisation and

for potential improvement of Graces' health outcomes. Grace continued to use magnesium and esomeprazole long-term without any indication for their use.

Case Study – Anita*

No more swollen legs

Anita is an 80 year old retired school teacher who she has been residing in aged care for almost 18 months. She has two sons. Anita is a very social woman who previously enjoyed having visitors to her home and going out with her friends.

Anita has a history of cancer, anxiety and depression, gastro-oesophageal reflux disease (GORD) and arthritis.

During the initial pharmacist review, ankle oedema and ongoing constipation were identified as additional issues for Anita. The pharmacist considered the ongoing constipation might be attributed to amlodipine or buprenorphine.

At the second session eight weeks later, Anita's lower leg oedema was still an issue, and quite concerning for her. The pharmacist identified amlodipine as the likely culprit medicine, however, complicating any recommendation surrounding cessation of amlodipine was Anita's blood pressure which was elevated in recent measurements.

The pharmacist contacted Anita's general practitioner (GP) and suggested a trial cessation of amlodipine, with possible replacement with a beta-blocker or moxonidine if the blood pressure was not managed sufficiently. The pharmacist suggested adding regular docusate and senna to manage the on-going constipation. **The GP agreed to cease the amlodipine.**

In the medical review one month later, **the GP noted that Anita had significantly less ankle oedema.** The GP was unsure if it was due to cessation of amlodipine but there did not appear to be any other changes that contributed to it. The constipation remained an issue; and the pharmacist noted buprenophrine could be the contributing factor.

Anita continued to have significantly less ankle oedema at the subsequent visits with the ReMInDAR pharmacist.

During the fifth visit, the pharmacist noted several potential medicine-related problems. There was now duplication of proton-pump inhibitor therapy; Anita was already on rabeprazole but pantoprazole was added to the medication chart. The pharmacist contacted the GP to suggest removing duplicate pantoprazole (proton pump inhibitor, PPI) from the medication chart and increasing the dose of rabeprazole if necessary. The dose of buprenorphine dose had increased from 10mcg/h to 15mcg/h recently. Anita appeared visibly tired, which the pharmacist considered might be due to the combination of

buprenorphine and diazepam, the latter which Anita was on to manage her anxiety. Anita indicated that she would like to try not taking diazepam to see if her tiredness reduced.

The pharmacist discussed with the GP the opportunity to reduce the dose of diazepam from 5mg to 2 mg, and to cease the medicine eventually. Pantoprazole was removed from Anita's medication chart due to duplication of PPI. All recommendations were implemented by the GP and Anita reported to the pharmacist that she feels much better; however, constipation remained to be an ongoing issue for Anita.

Case Study – John*

Spirits lifted and no more weeping legs

John is a 91 year old man who entered residential aged care due to his medical conditions including glaucoma, macular degeneration, constipation, short-term memory loss, hypertension, and hyperlipidaemia, ankle oedema, back pain, arthritis, gout, and an enlarged prostate.

John complained to the ReMInDAR pharmacist about his ankle oedema and said he felt depressed due to his worsening condition.

When the ReMInDAR pharmacist visited John, she noted that John's health had declined over the past few weeks, and his ankle oedema was significantly worse with fluid seeping from his calves. His cognitive function (assessed using the Montreal Cognitive Assessment) and grip strength had both decreased significantly when compared to his baseline values recorded during his enrolment in the trial. John had also developed shortness of breath with a cough, potentially secondary to retention of fluids in his lungs, which was not present during the pharmacist's previous visit.

John told the pharmacist repeatedly "if my oedema does not further improve, I will cease all my medicines and just wait to die".

The pharmacist suspected that the worsening oedema could be due to felodipine or pregabalin, and was extremely concerned for John's worsening mental state. The pharmacist attempted to contact John's GP to suggest a trial cessation of those medicines. However, the GP was overseas, so the pharmacist communicated with the facility nurse instead. In addition, the pharmacist spoke to a locum GP who stated that he could see John "early next week". Despite the pharmacist stressing the urgency of reviewing John, he was not reviewed immediately. The pharmacist continued to make several attempts to contact the locum GP and John's GP, managing to get in touch with John's GP two weeks later. **The pharmacist suggested that a trial cessation of felodipine or pregabalin should be**

undertaken. The GP was welcoming and supportive of the trial. Although the GP was not convinced that oedema was medication-related, the GP agreed to trial a decrease in pregabalin (25mg) from 3 times a day to twice daily once John's infection cleared to see if this would improve his condition.

Persistence pays off!

A follow-up was scheduled by the pharmacist to further monitor John's oedema and general health. During the third session, the pharmacist noted that John's health had significantly improved since the last session and that **his oedema had improved since the pregabalin was reduced**. John had started exercising regularly which allowed him to lose weight slowly and improve his oedema. The pharmacist continued to monitor his condition and reinforced the importance of exercise to help with the oedema.

Case Study – Betty*

No more falls: reducing the sedative dose does it.

Betty is an 80-year old woman who has been a resident in her aged care facility for the past two years. She never married and had lived with her sister until her sister's death.

Betty had been recently hospitalised for congestive cardiac failure. In addition, Betty suffers from diabetes, obesity, hyperlipidaemia chronic back pain, sciatica, cognitive impairment, double vision, poor balance, necrobiosis lipoidica, peripheral arterial disease, peripheral neuropathy, recurrent chronic leg ulcers, anxiety, dementia, depression, and incontinence.

In the first session, the ReMInDAR pharmacist noted that Betty's dose of pregabalin was increased from 225 mg twice a day to 300 mg twice a day due to pain in her right foot. She had also been given temazepam (10mg at night) to aid with sleep.

Betty felt dizzy and complained of weight gain

Betty was satisfied with her pain management, however she indicated to the pharmacist that she felt dizzy and disliked the weight gain since the increased dosing of the pregabalin. Her weight had increased by 5.5 kg within a month. Pregabalin may cause drowsiness, impaired balance, confusion and weight gain. The pharmacist discussed with Betty the potential for pregabalin to cause these side effects and the possibility of reducing the pregablin dose, however Betty was reluctant to reduce the dose due to her pain.

Betty started to have falls

Four weeks later, Betty had a fall and she stated that she was feeling tired for a week before her fall. Betty acknowledged the risks associated with losing her balance; however, she was still reluctant to reduce the dose of pregabalin. The pharmacist reiterated the benefits of

reducing the medicine. In addition, the ReMInDAR pharmacist discussed her concerns with the aged care staff to ensure they provided the care necessary for Betty. Within six days, Betty had another fall in the bathroom and was admitted to hospital.

At the subsequent pharmacist review visit, Betty had had two further falls and stated that she was 'loosing strength' in her legs. She was still on same medicine regimen; but in addition, she had started perindopril 40mg daily. The ReMInDAR pharmacist noted that this medicine could cause hypotension, which could also contribute to her falls.

The pharmacist discussed these issues with the Registered Nurse (RN) as Betty's doctor was on holidays. A follow-up communication with the RN occurred within a month and the doctor decreased Betty's pregabalin dose from 300mg twice a day to 250 mg twice a day.

By the fifth pharmacist review session, Betty had not had any falls and at this time Betty's pregabalin dose was further reduced to 75mg twice a day. Betty indicated she would like to further decrease the pregabalin dose if she can, as long as her pain is under control. The pharmacist noted to review and monitor Betty closely.

F.2. Stakeholder feedback

Feedback was solicited from ReMInDAR stakeholders to discern the need and acceptability for the pharmacy service from the different stakeholder viewpoints and to identify the critical success factors.

Feedback from pharmacists was sought through a purposeful pharmacist focus group discussion session as well as informally during pharmacist bi-monthly training and discussion sessions held over the lifespan of the trial implementation. In addition, a brief pharmacist training evaluation survey was undertaken.

Feedback from intervention-arm participants, their general practitioners and RACF staff was sought via purposeful one-to-one stakeholder phone interviews and through informal discussion sessions during implementation of the trial.

Overall, all stakeholder groups thought that the ReMInDAR pharmacy service was a much needed and valuable service, with the feedback overwhelmingly positive. Pharmacists reported gaining additional skills and experience, the GPs reported some of the recommendations useful in improving medication management for their patients, and the residents enjoyed having regular pharmacist visits.

The essential elements for a successful pharmacist service that were identified by stakeholders were:

- training and peer support of the pharmacists in new tools, communication skills and making clinical recommendations
- early engagement with General Practitioners
- establishment of productive working relationships with residents, GPs and residential aged care staff
- Iintegrated communication and coordination among the multidisciplinary team, including nurses, care staff, the GP, and the pharmacist
- the need for pharmacists to communicate regularly with staff and build relationship and the need for pharmacists to be seen as a resource to and integrated as a full member of the team.

The pharmacists and trial participants noted there was a need for further consideration of the use of tools to identify medication induced-deterioration. The residents did not like using the cognition tools. Grip strength measurements were well received and the use of activity trackers might be acceptable if they were reliable, comfortable and attractive.

In terms of opportunities to expand the service delivery, stakeholders were supportive of the need to continue to provide pharmacist services to residents in aged care. Issues such as the frequency of the service; co-location of pharmacists; and expanding the service to other target groups within aged care, as well as into the community were all discussed.

The themes arising from feedback collected from the different stakeholder groups are presented in greater detail below.

F2.1 RACF resident (participant) feedback

Out of the 97 aged care residents who were participants in the intervention arm at the 12 month time point, 7 were interviewed by phone (due to COVID-19 restrictions) towards the end of the trial.

Participants were overwhelmingly welcoming of having a pharmacist service as they recalled minimal previous opportunities to speak with a pharmacist since they had entered the facility:

- “I have never seen a pharmacist since coming here, and I’ve been here for 5 years, so thank you for doing this”
- “It’s about time we have pharmacists here”
- “Nobody here can help me with my medicines. Nobody explains to me why I need to pay for these medicines. Can you please help?”

Feedback about the perceived benefits of the service was overwhelmingly positive, including the use of the grip strength assessment tool:

- “Overall, participating in this intervention has been good experience.”
- “The one I like most was the grip strength, knowing how good my strength is.”
- “Yes, I like all the tests undertaken by the pharmacist, and those tests may detect any adverse drug reactions and that was beneficial.”.

During the enrolment and intervention visits, many participants were initially keen to try wearing an activity band and could see the potential benefits of monitoring their activity and sleep quality, and seeing how this interacted with their medicines. Interviewed participants were questioned on their perceived tolerance to wearing similar activity monitors in future, and whilst there were mixed opinions it seemed that many would at least consider it:

- "That was not good, sometimes it irritates and was not comfortable"
- "If it is lighter than the one use in this research, which should be fine to wear it all the time. The band used in this research was too heavy and sometimes itchy to the skin"
- "Not a problem to wear the band on my wrist. Good to get print out to see that it worked."

The intervention pharmacists had previously provided notes that indicated that the intervention participants were often very interested in their assessment results and keen to know if there had been any changes to their results since the previous assessment.

- "Resident was really pleased to know that grip strength had improved as he has been going to the gym and could see that this has helped with his results"
- "Resident was pleased (clearly very delighted) to know that her cognition score was the same as previous, as her family are expressing concerns that she is more 'forgetful' lately".

For many interviewed residents, it was the opportunity to have someone to talk with or to ask questions:

- "Good to have the chance to ask questions"
- "… it was nice to have someone to talk to and discuss any problems with. I am so lucky in that I'm healthy and don't need to see the doctors very often, but it's nice to have someone to chat about my health".

Every participant interviewed said that they would like to keep going with the service themselves, and that their fellow RACF residents would also benefit. They did not identify any aspects of the current service delivery that they would change. Their suggestions about the frequency of a potential service ranged from fortnightly to every 6 months:

- "Yes, and I would also recommend others to get similar services"
- "In most cases it would help the health and well-being of people, and it is a wonderful idea to do this for a lot of residents"
- "I would like to continue to get this service".

F2.2 Pharmacist feedback

Overall pharmacist feedback was overwhelmingly positive about the value of the service and its capacity to meet an unmet need for RACF residents.

All pharmacists appreciated the opportunity to trial a new pharmacist service in residential aged care which is an area where as a profession they feel pharmacists are under-

represented but definitely needed and liked the opportunity of a service that enabled follow-up:

- "Every RACF has regular visits from allied health except pharmacists! RMMR visits are so infrequent"
- "Currently pharmacists are not part of the allied health team supporting aged care and they can and should be"
- "Liked the trial because able to follow up with residents. Had good relationship with GP. Had good success with implementation of recommendations".

Pharmacists felt that the main benefit to participants was having someone to talk to and follow up regularly:

- I feel the activity gave the residents an outlet to discuss issues that often slip through undetected. I feel the repeated visits gave a great chance to follow through and improve outcomes more than a one off review."
- "..engaging with the resident and talking to them was, in my opinion, a crucial part of the activity".

Specific examples were given highlighting positive improvements that were achieved for residents' health and well-being due to actions taken by the pharmacist:

- "If she hadn't been in this trial she would have given up, deteriorated and died quickly." [pharmacist able to recommend to reduce large numbers of medications post hospitalisation following stroke where participant was gagging on tablets]
- "She looks really good, looks like a different lady" [regarding resident after cessation of medication]
- "The resident didn't know they had these PRN and the staff were not giving it to him. So with the doctor's permission I wrote a chart for the resident to help him understand what each PRN was for and what it did so that he knew that he could ask for it".

Nearly all pharmacists felt that the trial required new skill development and that training to undertake the service was essential for this specialty service, especially focusing on communication, and writing reports and recommendations.

- Mentoring valuable – Took away fear and anxiety at the start"
- "Want to say it should be accredited even though I'm not"
- "Communication with GP is the additional skill that is missing"
- "Don't agree that all trained pharmacists have capacity to do this as have seen examples of key knowledge lacking in some pharmacists".

Pharmacists were questioned in the group interview about the usefulness of the tools in assisting clinical decision making. Apart from Grip Strength, tools were considered by the group as a conversation starter rather than being helpful or used often. Interview and clinical judgement was seen as the most useful assessment 'tool', but that the frequency would be critical to be able to make clinical comparisons regarding any changes.

- “Didn’t use much with GP conversations, just judgement and experience”
- “Would need to use all the time to be able to rely on it for deterioration”
- “Tools could be useful in some circumstances”.

The cognitive assessment tool (MoCA) was reported to be a deterrent to a good interview as it was poorly received by residents:

- “Used MoCA sometimes, but noticed that the timing of administration needed to be consistent because the scoring changed during the day (late afternoon always poorer)”
- “Didn’t use MoCA as residents were intimidated and called it “that memory test””
- “MoCA was exhausting and residents didn’t like it, so only used it if really necessary. Sometimes deterioration was so obvious that it wasn’t needed and the resident couldn’t have completed it anyway”.

Early General Practitioner (GP) engagement was identified as a key factor for the uptake of recommendations.

- “One bad thing was not having enough time to develop relationships with the doctor as I was not at site often enough to get access to the GPs regularly”
- “One of the things I'm aware of is the lack of involvement or collaboration with the GPs that I'm encountering. This just means I'm a little reluctant to contact them with trivial issues”.

Methods to improve GP engagement and get recommendations implemented included:

- Early engagement to develop a relationship prior to commencing reviews, especially when meetings were undertaken face-to-face
- Holistic recommendations based on the overall resident’ health and history
- Framing recommendations in patient-centric terms
- Offering solution-focused, actionable and concise evidence-based recommendations
- Starting with small or simple recommendations and leveraging from previous ‘wins’
- Following up recommendations in a timely manner
- Involving onsite nursing staff in advocating for changes or in communicating identified problems
- Tailoring communication methods and timing to suit the individual GP preferences.
- “I took the opportunity to introduce myself to GPs when I was onsite and they were there”
- “If you have built up a good relationship this will help lay a good foundation if you need to raise something a bit more challenging”
- “Empower nurses to advocate for residents based on recommendations”
- “Slowly working to reduce medications over time to get the GP to be comfortable in taking up suggestions”
- “Just sending a written recommendation is not a good approach”
- “Ensure you give them advice they can actually use”
- “I learnt to send my GP reports to the RACF and not to the GP clinics. GPs onsite are focused on RACF clients”.
- “There is a lot of effort and coordination involved between all health professionals (GPs, nurses, pharmacists, care workers, physiotherapists) to achieve optimal health outcomes for residents. Therefore it is important to have a good understanding of each discipline and their role within the health care team to best utilise their area of expertise”.

Approaches that helped with staff engagement included:

- understanding the work structure, work-flow and schedules of the facility in terms of times for best access to staff and electronic record;
- identifying key staff familiar with the care of residents;
- utilising onsite communication methods to report and record pharmacist visits, concerns and recommendations as well as a verbal or email hand over to key care staff;
- reciprocating and offering value to the staff in terms of provision of medicines expertise.

Relationships with residents was also critical. The pharmacists agreed that it took time to build relationships with the residents they reviewed, but could see that the time spent developing this paid off in terms of improving the pharmacists' capacity to help and advocate for the resident in the future:

- "Sometimes it was hard to establish relationships with some of the residents, for example they were hard of hearing or grumpy, but relationships improved over time"
- "Building a good relationship with my residents has allowed deeper insight into their thoughts and feelings of how they are being managed by their GP"
- "Asking open ended questions – what bothers you the most?"

Pharmacists explored some of the components that would need to be considered for a national service (Figure F-1). In considering service frequency, a regular facility service was the favoured model. They felt an infrequent presence onsite led to many challenges. For example, impeding establishment of relationships, impairing coordinated communications, and difficulty with software access. A sessional visiting service or being regularly based at a facility was proposed with the advantage that pharmacists being onsite regularly enables ongoing monitoring of adverse effects in residents and allows concerns to be addressed pro-actively. Finally, the pharmacists agreed that ongoing peer support was helpful and useful, and a digital platform to obtain and exchange information would be a valuable resource.

Based on previous feedback received from the pharmacist group discussion it was clear that, in the pharmacists' opinions, some residents needed the service and some didn't. The group agreed that a service should be open to everyone to get a baseline assessment and then provided more frequently for the residents who need it. The group stressed that very stable residents, those on respite, and self-medicating residents still need to be seen and given support, otherwise it may be too late for early prevention of any issues.

- "Don't exclude the healthy residents! Had cases where residents were relatively well but one had difficulty swallowing large tablets (recommended crushing) and one had a rash due to Norspan patch (alternate sites and steroid cream) and these things made a huge improvement to their quality of life even though they might not seem major to others"
- "A lot of time spent on education, explanation and advocacy especially with more cognitively able residents who do not have opportunity to see a pharmacist. In the community they would have been asking pharmacists questions regularly"
- ".. people in the community can ask all their 'little questions' to a pharmacist regularly, whereas in facility they will not see pharmacist and don't want to bother GP with these".

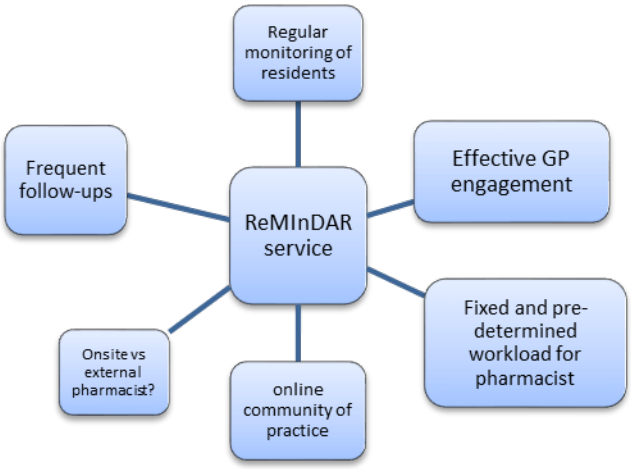


Figure F-1.Pharmcist recommended components for the service.

F2.3 General Practitioner feedback

Four interviews were undertaken by telephone with GPs. The GPs serviced 11 of the 39 ReMInDAR trial sites.

Overall, the GPs were supportive and indicated the service was beneficial.

- "Yes, I had patients talking to me about the pharmacists visit but can't recall any details"
- "… needs and expectations were met. The importance and presence of clinical pharmacists' attendance and input is acknowledged. I received feedback which was useful for my practice"
- "The intervention was very useful and beneficial for my residents"
- ".. liked the reviews and recommendations I received from the pharmacy reviews. The pharmacist picked up the drug interaction and could potentially identify and prevent a medication related problem".

Throughout the service delivery, some intervention pharmacists directly received positive feedback to their recommendations from the GPs.

- "Thanks heaps for input. His condition has changed. I have started him on [alternative medication recommended by pharmacist] today".

When considering a hypothetical future national model, GPs were asked to consider the structure, feasibility, enablers and barriers. According to the GPs interviewed, it would be useful and feasible for bigger practices to have up to two pharmacists attached for one or two days a week. GPs emphasised that the best way to implement such programs would be for the pharmacist to attend RACFs together with the GP. This could happen when GPs have rounds in the facilities. Doing so would facilitate communication and implementation of interventions. In the GPs' viewpoint, proper documentation and presentation by the pharmacist of any issue related to residents would also facilitate implementation of interventions.

- "..liked the intervention as it was implemented and would for example engage the pharmacists working in nursing homes for drug related issues"
- "In future, I would prefer to receive recommendations in the form of a more structured feedback and more specific in regard to the problem my resident was having"
- "This service could be implemented as a pharmacist being attached to bigger practices for 1-2 days per week".

GPs also felt that it would be useful if the program could be extended to the community beyond RACFs. GPs indicated there are many people who live in their own homes who take multiple medications and do not get medication review services, and that they thought the program would benefit them if the service was extended in these areas. GPs also suggested it would be beneficial if the service could be expanded to regional and rural areas.

- "..In my opinion, this type of service would be of benefit to those who are residing in rural areas and have limited access to GPs and clinics."

F2.4 RACF staff feedback

Six interviews were undertaken by telephone with RACF staff based at different facilities. RACF staff were asked what they consider to be the most difficult issues they experience with medication management in RACFs. The most common feedback was about the numbers of medications administered to residents and concerns about the potential harms of some types of medications:

- "Overprescribing - residents are on too many medications"
- "We need regular reviewing and de-prescribing of some medications whenever we can"
- ".. reducing medication related incidents- that has always been a major challenge"
- "Prescribing of medications without detailed assessment if something wrong is happening with residents".

Upon questioning the staff as to whether the trialed pharmacy service met their needs and their residents' needs, they had limited feedback on any benefits they felt their residents may have gained. The infrequency of the service meant many struggled to recall specific details:

- "Can't comment on any specifics as don't recall"
- "It has been time consuming but good for pharmacists to interact with residents and see where they do struggle, such as in their progression in memory and dexterity"
- "Not aware if recommendations were made or improved resident health"
- "Know that the pharmacist talked to GP and to care manager (but I wasn't involved) about one resident, but after the discussion they decided not to change anything".

RACF Staff were asked to consider what types of pharmacist service they would like. The majority of those interviewed emphasised their desire for additional medication reviews:

- "Medication reviews - get them done as required not having to wait a long time for them"

- "Psychotropic reviews are every 3 months as per government requirements, but more frequent pharmacist support would be appreciated (advice on titration, types of medicines to watch for, dosing issues)"
- "Extra person communicating with doctor and giving their medical point of view certainly backs something that we want - to get GPs to change medications and de-prescribe some of those medications"
- "RMMRs do not seem to have been done as frequently as they used to, and I think this is another way of getting that review".

Additionally, the need for pharmacist support in providing a resource for RACF staff for medication education and support was regularly mentioned during the stakeholder telephone interviews:

- "Recommendations and support about medication administration, crushing etc. As speech pathologists just report about difficulty with swallowing etc. and say as per appropriate administration but then there is no one to ask advice about that"
- "Ideal would be a pharmacist onsite once a week as a resource to ask questions"
- "Often need recommendations re tapering"
- "Have access to information regarding what a medication does and possible side effects and related updates, especially if there is a new medication in the market".

Finally, RACF staff were asked what issues could be addressed to improve any future pharmacist service provided to aged care, and communication between the various stakeholder groups was the main barrier identified:

- "Barriers are GPs in terms of acceptance. Same as for RMMRs (some like it, some don't)"
- "Communications gaps not only from the pharmacists but also from GPs are major barriers for most services in ACFs"
- "Facilities need to be engaged"
- "Lack of effective communication with family members in relation to medication changes is also a major barrier".

RACF staff were asked what sort of features a future service might have in terms of frequency and availability, with a range of suggestions made:

- "Not needed full time"
- "Have a visiting pharmacist"
- "Regular person to build a relationship with"
- "Need to be part of the team".

They were also asked about the residents who they believed would benefit from additional review:

- "Residents that are frequent fallers"
- "For residents who self-administer it would be good to be able to ring pharmacist. Provide resource and reassurance"
- "Residents with dementia and those who take anti-psychotropic would have benefited most; and those with complex pain"

- “All residents should get it”.

F.3. Pharmacist training manual and accreditation

See attachment ‘MSAC Section F3a_ ReMInDAR Training Manual_FINAL_Accessible’ for the training manual.

See attachment ‘MSAC Section F3b_ReMInDAR training accreditation letter_CX20034’ confirming accreditation of training by the Pharmaceutical Society of Australia

Appendix A: Project team, research partners, clinical governance and acknowledgements

The ReMInDAR trial was funded by the Australian Government Department of Health as part of the Sixth Community Pharmacy Agreement Pharmacy Trial Program.

This trial was implemented through the efforts and guidance of many people:

A.1 Chief Investigator Team

Prof Elizabeth E. Roughead (UniSA), A/Prof Nicole Pratt (UniSA), A/Prof Gaynor Parfitt (UniSA), Dr Renly Lim (UniSA), Prof Debra Rowett (UniSA), Dr Lisa Kalisch-Ellett (UniSA), Prof Luke Bereznicki (UTas), Prof Tracy Merlin (AHTA), Ms Megan Corlis (Helping Hand Inc), Ms Ai Choo Kang (Southern Cross Care SA, NT and Vic) and Mr Joseph Whitehouse (PharmIC).

A.2 Project team and staff

Project team

- UniSA: Dr Rebecca Bilton, Dr Lan Kelly, Dr Gerel Dorj, Dr Andre Andrade, Dr Imaina Wigado, Ms Annette Paschke, Ms Monica Vnuk, Ms Kristin Clark, Mr Ryan Higgins, Dr Danielle Post, Ms Alison Barratt, Dr Dot Dumid and Ms Ciana Dearcy;
- University of Tasmania: Mr Justin Cousins, Dr Mackenzie Williams, Mr Jackson Crawn, and Dr Endalkachew Alamneh;
- Adelaide University: Ms Camille Schubert and Mr Andrew Holton.

Research partners

- Ms Michelle Hogan (Helping Hand Inc) and Ms Stacey Torode (Southern Cross Care SA, NT and Vic)

Research assistants

- UniSA – Ms Jacqui Amadi, Ms Anthea Freeman, Mr Daiki Kasai, Ms Anne Whitehouse, Ms Heather Cockram, Dr Gizat Kassie, Dr Tesfahan Eshitie, Ms Ju Ni Ho and Mr Adrian Marchesano;
- Helping Hand – Ms Tessa Caporale and Ms Veronica Ogilvy;
- Southern Cross Tas – Ms Georgina Nugent;
- Southern Cross SA – Ms Ai Choo Kang and Ms Stacey Torode.

A.3 Aged Care Research Partners

- Southern Cross Care (SA, NT and Vic)
- Southern Cross Care (Tas)

- Helping Hand Inc
- AnglicareSA
- UnitingSA
- Queen Victoria Care
- Allity
- Rembrandt Living
- Gloucester Residential Care
- St Basil's
- Kalyra Communities.

A.4 Consumer Advisory Group

The ReMInDAR Consumer Advisory Group included representatives or nominees from:

- Consumers Health Forum of Australia;
- Health Consumers Alliance of South Australia;
- Primary Health Network (PHN) Adelaide Consumer Group;
- Helping Hand Inc. consumer group;
- Southern Cross Care SA, NT and Vic consumer group;
- Southern Cross Care Tasmania consumer group; and
- Aged Rights Advocacy Service.

A.5 Stakeholder Advisory Committee

The ReMInDAR Stakeholder Advisory Committee included representatives from:

- Pharmaceutical Society of Australia;
- Pharmacy Guild of Australia;
- Australian Medical Association;
- Royal Australian College of General Practitioners;
- Primary Health Network – Adelaide;
- Primary Health Network – Tasmania;
- Southern Cross Care Tasmania;
- Leading Aged Services Australia; and
- Aged and Community Services Australia.

A.6 Trial pharmacists

Twenty eight pharmacists from both South Australia and Tasmania were involved in the delivery of the ReMInDAR trial.

A.7 Thank you

The project team would like to thank the clients in aged care facilities who agreed to participate, the management and care staff and families of our contributing aged care trial sites, and the community pharmacists providing dispensary services to aged care sites. Without their ongoing contributions and assistance over the life of the trial, it would not have been possible.

A.8 Noted conflicts of interest

There were no conflicts of interest.

Appendix B: Literature Review

Literature Sources and Search Strategies

The medical literature was searched on 7 February 2021 to identify relevant studies and systematic reviews published during the period 1991 to January 2021. Searches were conducted of the databases and sources listed. To source unpublished or grey literature, reference lists and publications of key authors in the field were manually searched to identify relevant full-text articles across the same time period.

Consistent with the PICO the search aimed to identify controlled trials that included:

- A population (P) that was aged care residents treated with medicines;
- An Intervention (I) that involved a pharmacist service that included multiple visits for the same person and medication review or assessment of medicine appropriateness or medicine induced harm;
- Comparison (C) was standard care; and
- Outcomes (O) were reduction in medicine-induced deterioration from baseline to end of intervention, change in cognition scores, change in body weight or change in rate of adverse medicine events.

Medication review was defined as any kind of systematic assessment of a patient medication with an aim to evaluate and optimize the pharmaceutical treatment. We included randomised controlled trials (RCT) and restricted the publications to English. Studies in which the medication review was focused on a specific condition or a specific class of drug were excluded. Ongoing studies or protocols were not included in the review, but their references were examined to detect any relevant studies.

Elements of clinical question, as well as specific search terms are described in Table App B-1.

Element of clinical question	Does the pharmacy service have impact on cognition, adverse events, falls and mortality in older adults living in aged care facilities?
Population	“aged” OR “aging” OR “elderly” OR “resident” OR “senior”
Intervention	(“randomized controlled trial”) OR (“randomised clinical trial”) AND ((“residential aged care”) OR (“nursing home”) OR (“aged care”) OR (“long term”) OR (“care home”)) AND ((“pharmacy service”)
Comparator (if applicable)	Control (usual care)
Outcomes (if applicable)	“cognition” OR “cognitive” OR (“Montreal Cognitive Assessment”) OR “MoCA” OR (“Cognitive Assessment Screening Instrument”) “frail” OR “frailty” OR "frailness" OR "frails" “frailty index” “weight” OR “weight body” OR “weights and measures” OR “weighting” OR “weights”

	"adversely" OR “medication error” “misadventure” OR “medication incidence” OR “”medication safety” OR ‘’adverse drug reaction” OR ”hospitalisation” OR "adverse" AND ("event" OR "events" OR "events")
Limits	Studies published from 1990 until January 2021 English language

Table App B-1 Search terms used (literature search platform)

Data screening and extraction

Studies were selected independently by a single reviewer with a random sample receiving independent assessment by a second reviewer. Discrepancies in judgement were discussed among the reviewers to reach consensus about final decision.

Additional pre-specified criteria for excluding studies included:

- interventions limited to the community or home setting;
- interventions for residents transitioning from hospital setting;
- single clinical pharmacist review;
- the intervention was provided by a health professional other than a pharmacist;
- lack of comparative data for both groups, e.g. only baseline data or data for only one group; and
- Systematic or narrative reviews (all were screened for relevant primary studies).

The application of the study selection criteria included in the PRISMA checklist was used to guide reporting. (19)

Section	Topic	#	Checklist item	Reported on page #
TITLE	Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title/page 1
ABSTRACT	Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract/page 1
INTRODUCTION	Rationale	3	Describe the rationale for the review in the context of what is already known.	Background/page 2-3
	Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Last paragraph of the background section/page 3
METHODS	Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	First paragraph of method section/page 4

Section	Topic	#	Checklist item	Reported on page #
	Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods: Study Selection /page 4
	Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	-Methods: Data sources &search strategy section/page 4 -Search Strategy, Additional file 2.
	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Search Strategy, Additional file 2.
	Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	-Methods: Study selection Page 4 -Results: Figure1/page 6.
	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods: Data extraction and quality assessment/page 5
	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods: page 4-6.
	Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods: Assessment of risk of bias page 5, Risk of bias in included studies page 11, Figures 2&3 -Additional file 3 (funnel plots).
	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods: Statistical analysis section/page 5.
	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods: Statistical analysis section/page 5.

Table AppB-2 Application of PRISMA selection criteria

Results of Literature Search

The search criteria resulted in 1792 potentially relevant records; 316 were duplicates and 1353 were deemed as irrelevant after screening of the title or abstract level. A full-text analysis was completed for 123 studies, of which four RCTs (20-23) met the inclusion criteria.

A PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart (Figure App B-1) provides a graphic depiction of the results of the literature search. The most common reason for excluding studies was wrong setting, wrong intervention, single review only. Among the excluded studies, 16 were protocols only. Two studies performed a single medication review for aged care residents during the trial, and nine studies compared intervention effect of training non-pharmacy professionals. All references from excluded studies were examined to identify any further relevant studies. After review, four studies met the inclusion criteria.

None of these studies were limited to the aged-care population with mild cognitive impairment. Thus, the ReMInDAR trial forms the basis of the evidence for this submission.

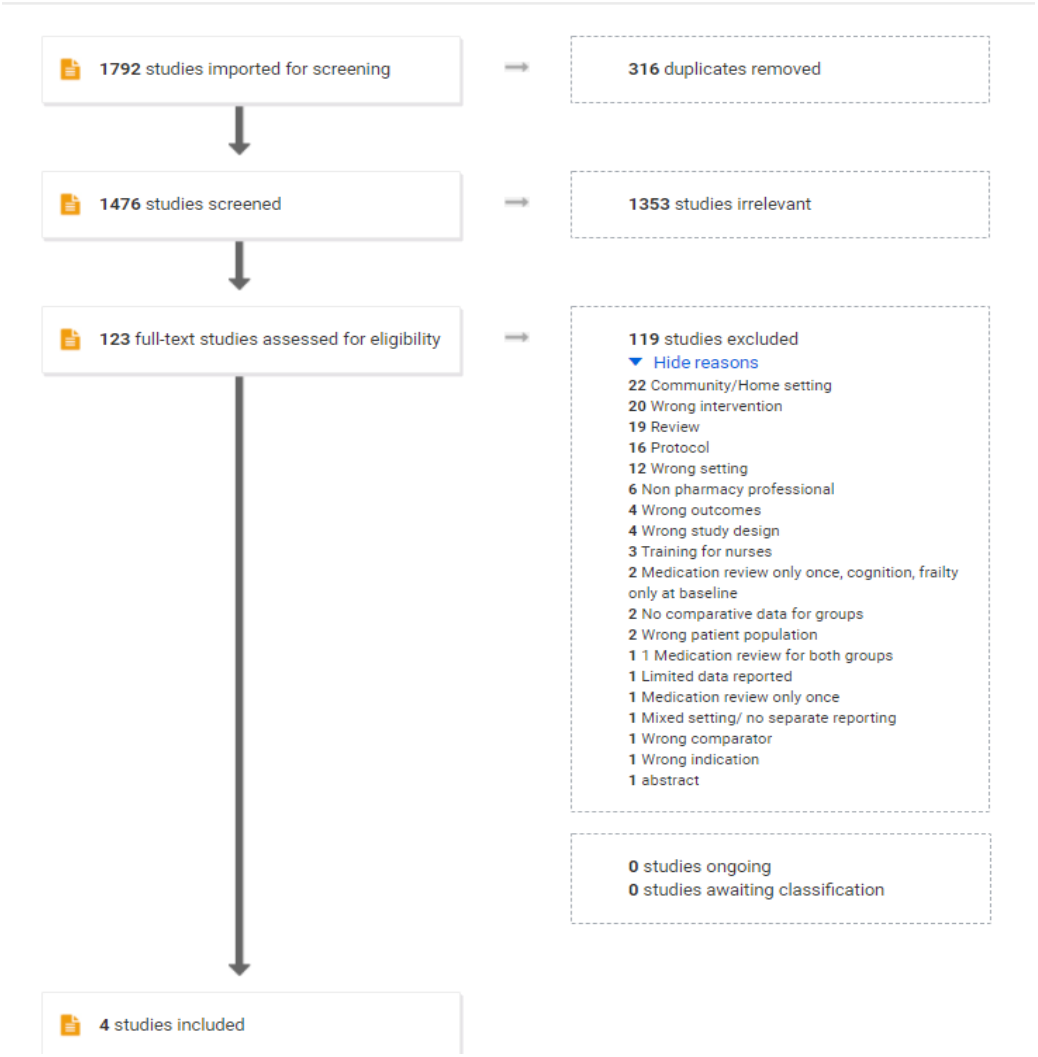


Figure AppB-1 Summary of the process used to identify and select studies for assessment

Appraisal of the evidence

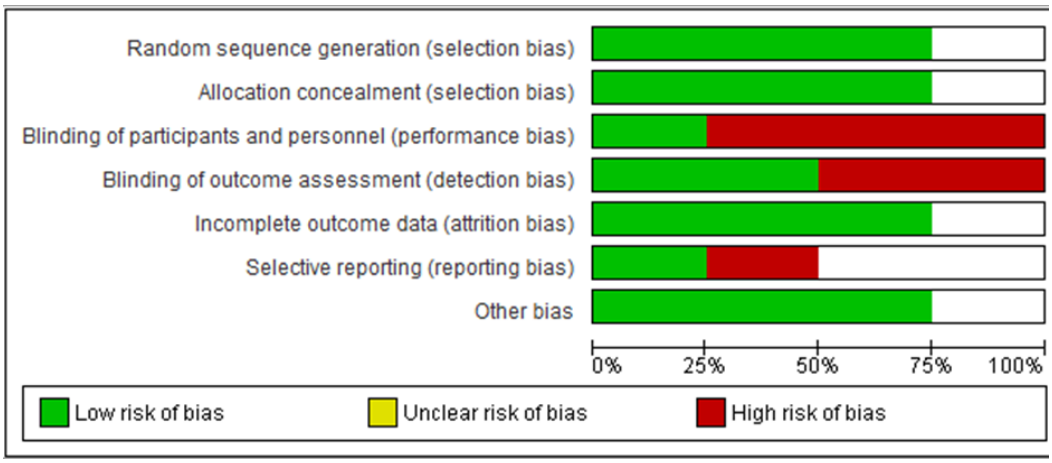
Appraisal of the evidence was conducted in four stages:

- Stage 1: Appraisal of the risk of bias within individual studies included in the review. Some risk of bias items were assessed for the study as a whole, while others were assessed at the outcome level.
- Stage 2: Extraction of pre-specified outcomes for this assessment, synthesising (a narrative synthesis) to determine an estimate of effect per outcome, a determining the assumed baseline risk.
- Stage 3: Rating the overall quality of the evidence per outcome across studies based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was undertaken to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice.
- Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the content of Australian clinical practice.

Risk of Bias Assessment

Evidence quality for each outcome of included RCTs was assessed using the Cochrane Collaboration Risk of Bias tool.(93) The standard list of criteria included: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other sources of bias.

The majority of the studies had performance bias, with detection bias also present.



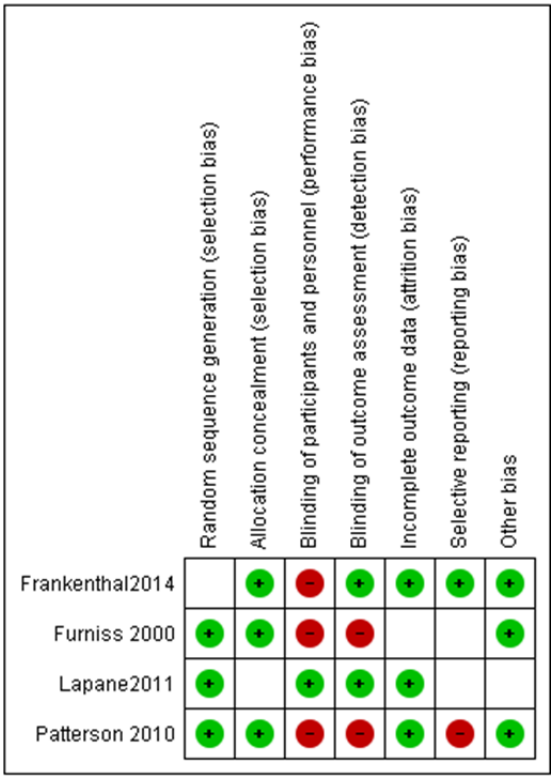


Figure AppB-2 Summary of risk of bias, assessed with Cochrane's Risk of Bias tool (generated by Review Manager (RevMan) v5.3)

Characteristics of the Evidence Base

Key features of the studies are provided in Table AppB-3.

Furniss *et al*., (21) tested the effectiveness of a single medicine review with a follow-up visit at three weeks. Outcomes were assessed at four and eight months.

Frankenthal *et al*., (20) tested the effectiveness of a pharmacist intervention comprising 2 visits over a 6 month period. The pharmacists used the Stop/Start criteria as part of their intervention. Follow-up was at 12 months.

Patterson *et al*., (23) tested the effectiveness of monthly pharmacist services to aged-care residents with a focus on reducing use of psychoactive medicines. Pharmacists were supported with an algorithm adapted from a previous study. "[Pharmacists] *assessed the pharmaceutical care needs of each resident by interviewing the residents, their named nurses and their family members or caregivers. Potential and actual medication-related problems were identified, and recommendations for intervention were recorded. An algorithmic approach adapted from a previous study was used as a guide for study pharmacists to ascertain whether participating residents were receiving inappropriate psychoactive medication."* Intervention participants were followed up monthly. Follow-up was at 12 months.

Lapane *et al*., (22) tested the effectiveness of an algorithm generated from the clinical record to support pharmacists undertaking medicine reviews. Pharmacists visited the facility monthly, with algorithms generated for all residents newly admitted as well as for all residents with a recent fall or case of delirium. Mandated medicine reviews occurred quarterly or yearly as required. The usual care group received a similar number of interventions as the intervention group, thus this intervention is really testing the additional benefit of the algorithm rather than the pharmacist service.

Trial/Study	Country	Total, No of participants	No of nursing homes	Design/ duration	Patient population	Key outcome(s)
Frankenthal 2014	Israel	359 183 intervention 176 control	1	RCT, 12mnths	Residents aged over 65 years	Appropriateness of medication use, hospitalisation, adverse event
Furniss 2000	UK	300 158 intervention 142 control	14	RCT, 4 mnths	Residents aged over 65 years	No of prescribed medicines, MMSE, hospitalisation, adverse event, death

Trial/Study	Country	Total, No of participants	No of nursing homes	Design/ duration	Patient population	Key outcome(s)
Lapane 2011	USA	3321 1769 intervention 1552 control	25	RCT, 12 mnths	Residents aged over 65 years	Mortality, hospitalisation potentially due to adverse drug events, cognition RAI_MDS
Patterson 2010	Ireland	334 173 intervention 161 control	11	cRCT, 12mnths, pharmacist review every month	Residents aged over 65 years	Proportion of residents with inappropriate psychoactive medications, no of falls

Table AppB-3 Key features of the included evidence comparing the Intervention and Control group

RCT=randomise control trial; mnths= months; MMSE=Mini-Mental State Examination; RAI_MDS= Resident Assessment Indicator-Minimum Data Set>

Outcome Measures and Analysis

Outcomes extracted from all relevant studies are consistent with those identified in the PICO. Assessment of cognitive function of participants in two groups was completed in all studies.(20-23). The prevalence of adverse events was compared in all studies, however, Patterson *et al* reported residents who had falls during the intervention.

One study assessed integration of an electronic tool to reduce the incidence of potential delirium, falls due to adverse drug events.(22)

Cognitive function

No studies assessed mild cognitive impairment.

Furniss *et al*., (21) applied the Mini-Mental State Examination (MMSE) (n=4) to identify the cognitive function of the participants. MMSE is a validated clinical tool for grading cognitive deterioration, often used in the elderly. A decrease of 1-2 points in MMSE score is considered to be minimal clinically significant.(94)

Lapane assessed delirium using the validated Nursing Home Confusion Assessment Method (NH-CAM).(22)

Falls

Three RCTs compared the occurrence of falls experienced by residents in the intervention and control groups (20, 22, 23). Due to inconsistent reporting we performed a meta-analysis for only two studies.(22, 23) Lapane *et al* reported repeat measurements for newly administered residents, and these were included in the analysis.(22)

Hospitalisation

Hospitalisation was reported as an outcome in two studies: Frankenthal *et al*., (20) who reported all cause hospital admissions, and Lapane *et al*.(22), who reported both all cause hospitalisation and hospitalisation due to potential adverse medicine events.

Mortality

Three RCTs reported mortality rates for 3,621 residents in 39 aged care facilities.(20-22) Studies assessed the mortality with Kaplan-Meier survival curves and the Cox proportional hazards model to compare survival in the intervention and control groups.

Frankenthal *et al* estimated mortality as number of deaths over 12-months.(20) Furniss *et al* reported it over 8- months. Lapane et al provided repeated measurements for average percentage of mortality per 1000 person-months.(22)

Results of the Systematic Literature review

We located no previous research that aimed to assess the effect of ongoing pharmacist assessment to prevent deterioration due to medicine use in persons in aged care who were not cognitively impaired or frail. Further, no previous research aimed to prevent mild cognitive impairment or used assessment tools to detect mild cognitive impairment. The limitation of prior research is that cognitive assessment tools used would only detect major changes in cognition. No previous published studies used the Montreal Cognitive Assessment (MoCA). MoCA is validated for detecting mild cognitive impairment in older people and was the tool used in the ReMInDAR trial.(36) Thus, the ReMInDAR trial forms the basis of the evidence for the submission.

Cognition

Furniss *et al* used MMSE to assess cognition of 330 elderly residents in the UK.(21) At baseline more than 70% of the cohort had cognitive impairment with more of the intervention group have cognitive impairment (mean MMSE 13.8) than in the control group (mean MMSE 15.6). The intervention did not affect cognition. (21)

Delirium

Onset of potential delirium was measured by Lapane *et al*. (22), Overall the intervention had no effect on delirium, (adjusted HR 0.93, 95%CI 0.80–1.09) however, in persons newly admitted to aged care a statistically significant reduction was observed. (Adjusted HR=0.42, 95% CI=0.35– 0.52).

Hospitalisation

Two RCTs assessed hospitalisation as an outcome. Neither found no difference in hospitalisations (all cause) or potential adverse medicine event related hospitalisations.

Falls

Three studies investigated falls experienced by 4014 residents living across 37 nursing homes.(20, 22, 23) None of the studies reported a difference.

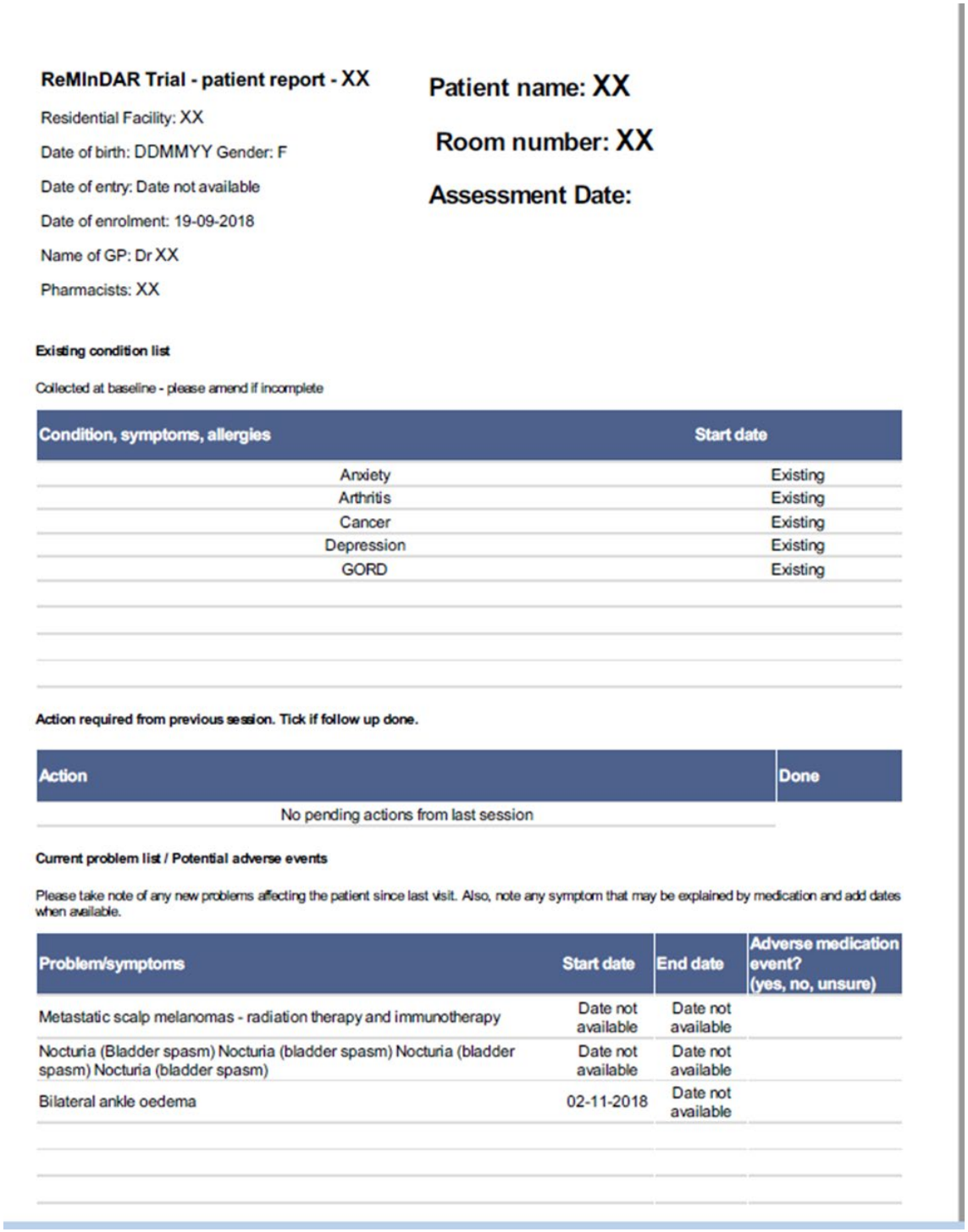
Mortality

Frankenthal *et al* (20) and Lapane *et al*., (22), both reported death as an outcome, with neither showing a significant difference.

Appendix C: Supplementary methodology documentation

C.1 Pharmacist intervention documentation record

Alternative Text for Figure APP C-1



ReMInDAR Trial - patient report - XX

Residential Facility: XX

Date of birth: DDMMYY Gender: F

Date of entry: Date not available

Date of enrolment: 19-09-2018

Name of GP: Dr XX

Pharmacists: XX

Patient name: XX

Room number: XX

Assessment Date:

Existing condition list

Collected at baseline - please amend if incomplete

Condition, symptoms, allergies	Start date
Anxiety	Existing
Arthritis	Existing
Cancer	Existing
Depression	Existing
GORD	Existing

Action required from previous session. Tick if follow up done.

Action	Done
No pending actions from last session	

Current problem list / Potential adverse events

Please take note of any new problems affecting the patient since last visit. Also, note any symptom that may be explained by medication and add dates when available.

Problem/symptoms	Start date	End date	Adverse medication event? (yes, no, unsure)
Metastatic scalp melanomas - radiation therapy and immunotherapy	Date not available	Date not available	
Nocturia (Bladder spasm) Nocturia (bladder spasm) Nocturia (bladder spasm) Nocturia (bladder spasm)	Date not available	Date not available	
Bilateral ankle oedema	02-11-2018	Date not available	

Recent relevant lab results

Please include measurement unit in the results (i.e. mg/ml, IU/ml)

Test name	Date	Results
Creatinine		

Medication

Cross reference with conditions and current problems to ensure completeness. Please include dates.

Ingredients	Formulation	Route	Frequency	Start date	Cease date	Notes
Valsartan 80 mg Hydrochlorthiazide 12.5 mg	tablet	Oral	morning	02-11-2018		
Buprenorphine 10 mcg	Transdermal patch	Topical	once a week		12-09-2018	10
Vemurafenib 480 mg	tablet	Oral	twice a day			
Cholecalciferol 25 mcg		Oral	morning			
Valsartan 80 mg	tablet	Oral	morning		01-11-2018	
Rabeprazole 10 mg	tablet	Oral	morning			
Vitamin D 1000 IU		Oral	morning			
Paracetamol 1330 mg	tablet	Oral	3 times a day		08-11-2018	
Paracetamol 1000 mg	tablet	Oral	once a day in the afternoon			
Diazepam 5 mg	tablet	Oral	night			
Mirtazapine 15 mg	tablet	Oral	night			
Amlodipine 5 mg Atorvastatin 40 mg	tablet	Oral	once a day			
Aspirin 100 mg	tablet	Oral	once a day			
Oxybutynin 5 mg	tablet	Oral	night			
Eye drop 1	eye drop	Eye drop	3 times a day			
Buprenorphine patch 10 mcg/hr	transdermal patch	transdermal	once a week			Increased from 5mcg/hr on 13/09/18
Metochlopramide 10 mg	tablet	Oral	as needed			
Polyethylene glycol-400 1 Propylene glycol 0	eye drop	Eye drop	as needed			Prescribed as Systane

Cognitive assessment scores (MoCA)

Please perform this test if there has been a medication change or signs of deterioration.

Note: patient has not finished high school (add 1 point)

Score	Date of measurement	Clinically significant change if decrease by >2 pts	Due to medicine change? (yes, no, unsure)	Due to new condition? (yes, no, unsure)
24	13-11-2018			
23	19-09-2018			

Weight

Weight	Date of measurement	Due to change in appetite? (yes, no, unsure)	Due to medicine change? (yes, no, unsure)	Due to new condition? (yes, no, unsure)
64.18 kg	06-11-2018			
65 kg	19-09-2018			

Physical activity - Summary

If not wearing a band, please ask participant about activity and sleep and sleep pattern changes as per SOP.

Start date	Last measurement	Sedentary time	Number of moderate exercise sessions	Daily steps	Sleep Duration	Number of sleep active sessions
		Clinically significant change if increased by >30 min	Clinically significant change if decrease by >5 sessions per day	Clinically significant change if decreased by >500 steps, per day		
04-12-2018	18-12-2018	6:31	65	442	8:40	30
20-11-2018	04-12-2018	7:43	43	347	6:44	24
19-11-2018	01-01-2019	7:00	172	418	7:53	23
06-11-2018	19-11-2018	7:08	96	548	7:27	20
23-10-2018	05-11-2018	0:46	0	316	0:00	2

Grip strength

Hand position: Right (Setting: 2)

Please assess at all sessions. To compare sessions, consider the highest of 3 measurements.

Measurement 1	Measurement 2	Measurement 3	Date of measurement	Clinically significant? (20% change)	Due to medicine change? (yes, no, unsure)	Due to new condition? (yes, no, unsure)
8.1	8.0	7.7	13-11-2018			
9.2	9.9	**11.4**	19-09-2018			

Subjective findings

Example: fatigue, uncontrolled pain, restlessness

Is there evidence of a new or worsening problem that could explain the deterioration? If a condition is likely to explain deterioration, advise facility staff and record in notes

Objective findings

Is there evidence of clinically significant change? (based on objective measurements e.g. MoCA, grip strength)	☐
Is there evidence of medicine or dosage change that could explain the deterioration? Check that medication has been used as prescribed over the period of change (ie taken, not taken, crushed etc)	☐

Overall evaluation

Emergency and hospital visit notes

Actions

Example: Recommend tapering dose of medication

1 -
2 -
3 -
4 -
5 -
6 -

9 -

10 -

If deterioration present but not considered due to medicines, record in notes and advise facility nurse

If medication induced side effects and clinically significant, develop report and recommendations for patient's general practitioner

Pharmacist session notes, 06-11-2018

Weight:64.18

Missed pre-existing conditions were Metastatic scalp melanoma (radiation therapy and immunotherapy) and Nocturia (bladder spasm). Resident indicated that activity had remained the same over the past several months. Sleep has been poor for a number of years and this continues. Only sleeps for a short period of time. Bilateral ankle oedema= Unsure if related to adverse mediation event, may be due to amlodipine and/or vemurafenib. BP - 28/10/2018 - 145/73 07/08/2018 - 180/67 09/11/2018 - Self-medicating from Webster packs. Resident reports always feeling tired. Resident reports osteoarthritis in the hips and knees. Had 3 doses of immunotherapy but now ceased. As there was a medicine change (hydrochlorothiazide added to treat ankle oedema), the MoCA and grip strength test were performed. Grip strength change: clinically significant?Yes; Due to medicine change? Unsure; Due to new condition? Unsure

FIGURE APP C-1: pharmacist report template example

C.2 Statistical analysis plan

See attachment ‘MSAC Section C2_ ReMInDAR Statistical analysis plan’.

C.3 Health economics analysis plan

See attachment ‘MSAC Section C3_ ReMInDAR Health Economics analysis plan’

C.4 ReMInDAR contracted performance indicators

Summary of success for the ReMInDAR trial as evidence by contract performance indicators is demonstrated by:

- Evidence of resident or consumer collaboration in trial design and throughout its operation (Table C1);
- Expanded pathways of service delivery by pharmacists that improve documented resident health outcomes to inform a cost-effective analysis (Tables C2 and C3); and
- Cost-effective, expanded pathways of service delivery by community pharmacy that improve resident health outcomes (Reported in March 2021).

C.4.1 Resident and Consumer Collaboration

In addition to the engagement with residents and families prior to the recruitment process onsite at each of the trial facilities, the ReMInDAR trial collaborated with the Consumer Advisory Group that was established to formally consult with consumer representatives and improve trial design based on their feedback (Table App C1).

Objective	**'Resident or consumer collaboration in trial design and throughout its operation'**
Measure	• Numbers of residents or consumers who engage with the trial during trial design and operation (Note: this does not include recruitment)
Definition & Rationale	• Resident and consumer collaboration with the trial will improve trial design • Resident and consumer collaboration with the trial will improve participation rates • Resident and consumer collaboration will ensure that if the trial objectives are successful the program could be better implemented in pharmacy and aged care practice at a national level
Frequency	• Ongoing measure
Indicator & Status	• Consumer Advisory Group collaboration – The consumer advisory group included representation from the following consumer groups Consumer Health Forum of Australia; Health Consumers Alliance of SA; Primary Health Network (PHN) Adelaide Consumer Groups representative; Helping Hand consumer representative; Southern Cross Care SA & NT consumer group; Southern Cross Care Tasmania consumer representative; and the Aged Rights Advocacy Service. ○ The Terms of Reference for the advisory group were agreed at the first meeting held on 2 July 2018; ○ Subsequent meetings were held on 6 March 2019, 8 April 2020, 7 October 2020 and a joint meeting of both stakeholder groups on 19 March 2021. • Resident and family engagement – There was engagement with residents and family members for each of the 39 trial sites, either through resident and family meetings or through flyers distributed to potentially eligible residents. Engagement with resident and family members commenced on 19 June 2018 and was completed on 26 June 2019 after final recruitment. Feedback from

Objective	'Resident or consumer collaboration in trial design and throughout its operation'
	early meetings was used to inform the improvement of communication messages and documentation. • Interviews with 7 residents who participated in the trial to gain feedback on trial implementation

Table App C-1: Contracted Performance Indicator 1 – demonstration of resident and consumer engagement.

C.4.2 Expanded pathways of pharmacist service delivery

A total of 28 pharmacists with between 2 and 35 or more years' experience were engaged to deliver the ReMInDAR service (Tables App C2 and App C3). The "Detection of Medication Induced Deterioration' training program for pharmacists for the ReMInDAR trial was developed and subsequently accredited by the Pharmaceutical Society of Australia (CX20034). This training program delivered 23 initial training sessions outlining medicine-induced deterioration and the use of the assessment tools to facilitate detection and reporting. The training was re-enforced through delivery of 33 one-on-one on-site peer support sessions for the pharmacists, and 6 peer discussion sessions which occurred every two months.

Objective	'Expanded pathways of service delivery by pharmacists that improve documented resident health outcomes to inform a cost-effective analysis'
Measure	• Pharmacist agreement to undertake service delivery • Pharmacist training • Pharmacist satisfaction with service delivery process • Improvements in documented resident health outcomes (end of trial)
Definition & Rationale	• The proposed pharmacist-led 'prevention service for medicine-induced deterioration and adverse events' in aged care is currently not available in any private or public settings in Australia. The pharmacist service will provide a platform for a new standard of care which is likely to be easily integrated into existing practice, and which is readily accessible to residents in aged care settings.
Frequency	• Bi-annually (or at trial completion)
Indicator & Status	• Service agreements signed with all pharmacists • Training of pharmacists • Pharmacist retention during trial (minimal changes to intervention pharmacists during service delivery) • Pharmacist participation in discussion panels every two months • Pharmacists interviewed to provide feedback and evaluation of training. The ReMInDAR final report provides the evidence of improved cognition as a result of the expanded pharmacy service. The service resulted in a statistically significant difference in cognition scores in favour of the intervention group. The

Objective	'Expanded pathways of service delivery by pharmacists that improve documented resident health outcomes to inform a cost-effective analysis'
	analysis identified that in the intervention arm an additional 12% of residents avoided clinically significant cognitive decline in 12 months. This represents a NNT (number needed to treat/provide intervention to) of 8.33. i.e for every 8.33 residents that pharmacists reviewed 8 weekly over a year, it would be expected that one would avoid a clinically-relevant cognitive decline.

Table App C2: Contracted Performance Indicator 2 – demonstration of expanded pathways of pharmacist service delivery that improve documented resident health outcomes to inform a cost effectiveness analysis.

Training and engagement of pharmacists	n
Total pharmacists engaged	28
Accredited pharmacists	14
Community pharmacists	20
Hospital pharmacists	1
Total number of training sessions for pharmacists in protocol and standard operating procedures	23
Total number of sessions of onsite peer support and training of pharmacist in protocol (incl. follow up sessions)	33
Number of peer group discussion sessions delivered every 2 months	6

Table App C3: Summary table of engagement and training activities for pharmacists for ReMInDAR trial.

C.4.3 Cost effective, expanded pathways of service by community pharmacists

Objective	'Cost effective, expanded pathways of service by community pharmacy that improve patient health outcomes'
Measure	• Incremental cost or saving per adverse medicine event avoided (end of trial) • Improvements in documented patient health outcomes (end of trial)
Definition & Rationale	• The economic analysis will be a trial-based cost-effectiveness evaluation, with the intention to identify and report the incremental cost or saving per adverse medicine event avoided as the primary economic outcome of interest. The perspective of the analysis is the healthcare system.
Frequency	• End of project
Indicator & Status	• Resource use: – data collection recorded time involving other health professionals (doctors, nurses, allied health), and other resource use identified in Residential Care Assessment Records (eg medication changes, health services, hospitalisations etc). Data collection commenced from July 2018 and will conclude in June 2020. • Health Economic analysis (see Sections C, D and E) • The health economic analysis showed the service equates to a trial-based incremental cost-effectiveness ratio of $15,342 per resident avoiding clinically significant cognitive decline. • If the exploratory cost-effectiveness analysis only considers pharmacist and pharmaceutical costs the intervention would be considered dominant, as it has a positive health outcome; preventing a clinically significant cognitive decline in one resident for each 8.33 residents assessed regularly over a year, while concurrently delivering a net cost-saving of $650. • Implementation of the service in the identified population would be expected to be deliver overall cost savings in the order of $0.2million to $1.2 million per year.

Table App C4: Contracted Performance Indicator 3 – demonstration of expanded pathways of pharmacist service delivery that improve documented resident health outcomes to inform a cost effectiveness analysis.

Appendix D: ReMInDAR PICO

See attachment ‘MSAC Appendix D_PICO Confirmation_ReMInDAR’

Appendix E: Sensitivity and Post Hoc analyses

E.1 Sensitivity analyses of potential survivor bias on death, weight and MoCA

There was an imbalance in the number of deaths between the two treatment arms during the 12 month follow-up. Although up to 15-20% of the population was expected to die during the 12 month follow-up period (82),the larger proportion of deaths in the intervention group (23/120, 19%) than in the control group (17/128, 13%) was investigated as a potential cause of bias due to a survivor effect. This sensitivity analysis was pre-specified in the Statistical Analysis Plan (Appendix C2) using the survivor average causal effect (SACE) (95) SACE estimates the effect of treatment in the subgroup of participants who would not have died in either treatment group.

SACE analysis was pre-planned for the primary and health economic outcomes; however, we considered the primary outcome, weight and MoCA in our sensitivity analyses.

Timing of deaths

We investigated the timing of deaths relative to that for the intervention visits, to determine how many deaths would have occurred regardless of treatment assignment. Deaths before the first intervention visit to the facility cannot be due to any treatment difference, while deaths occurring soon after the time of the first (and possibly the second) intervention may not be attributable to any intervention effect. It is reasonable to expect that there would be a time lag in a pharmacist being able to instigate changes to care that may reduce likelihood of death.

In the intervention group, 5/120 deaths (4%) occurred before the first intervention visit, while in the control group 2/128 deaths (2%) occurred before the first pharmacist visit to the facility. If these deaths are excluded, the proportion of deaths was 18/120 (15%) and 15/128 (12%) in the intervention and control groups, respectively. The number of deaths before the time of the second intervention visit was 12 and 7 respectively, and after excluding these, the proportion of deaths reduced to 13/120 (11%) and 10/128 (8%) in the intervention and control groups. Furthermore, the proportion of deaths occurring between 6 and 12 months in the intervention and control groups was the same: 7/120 (6%) and 8/128 (6%).

Tests for potential survivor bias

Evidence for potential survivor bias was pre-specified in the SAP (Appendix C2), whether the death rate differed by treatment group or that baseline frailty index differs between treatment groups when deaths were excluded ($p<0.2$ for any of the log-rank statistic, hazard ratio with death as the outcome or mean difference in baseline frailty index). Results for these analyses were log-rank test $p=0.24$, Hazard Ratio $p=0.25$ and Wilcoxon test for difference in frailty index at baseline excluding deaths, $p=0.201$ (Figure AppE-1). Further details are presented in the SAP.

Tests for differences in MoCA and weight at baseline after excluding deaths did show differences between the groups; however these differences were present at randomisation. Further analysis of differences in baseline values between survivors, deaths and withdrawals within each group separately such no difference.

According to these pre-specified tests and further investigations, there was low risk of bias due to a survivor effect. However, we performed the SACE analysis to confirm our risk assessment.

Survivor Average Causal Effect analysis

A detailed description of the SACE sensitivity analyses is in the SAP. SACE is estimated as a sum of the estimated treatment difference and a bias term, calculated using clinically plausible sensitivity parameters.

The results can be summarised as follows:

- The bias term varied between positive and negative for all three outcomes
- The point estimate for the frailty index was always negative and all 95% CIs contained 0
- Point estimates for weight were negative in 49/50 scenarios and the 95% CI contained 0 in 23/50

All point estimates for MoCA were positive and in 13/18 scenarios the 95% CI was above 0

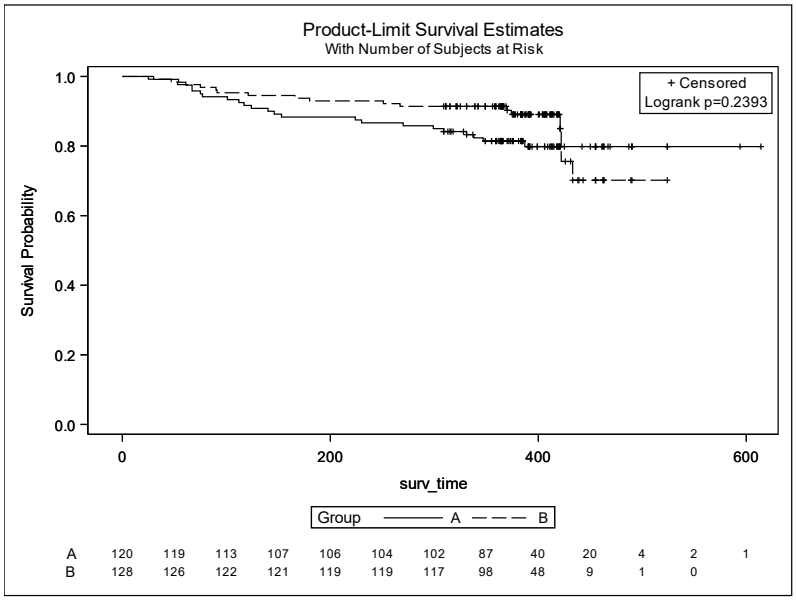
Conclusion: The imbalance in deaths between the intervention and control groups occurred before 6 months when there would have been little, if any, effect of the intervention on death. The proportion of residents who died between 6 and 12 months was the same for both groups (6%). It is possible that the increased number of deaths in the intervention group was due to chance.

According to pre-specified tests, the risk of survivor bias in the frailty index was low. Sensitivity analyses confirmed this, since all point estimates favoured the intervention arm and inference using the confidence intervals did not change (all 95% CIs contained 0). 95% of the point estimates in the modelled scenarios for weight were in the same direction as the estimated treatment difference, however in 23/50 scenarios the 95% confidence interval contained 0. For MoCA, point estimates for all scenarios favoured the intervention group and the majority of 95% CIs did not contain 0. However, the upper range on the sensitivity parameters were larger than the estimated treatment difference, which may be implausibly high.

Tests for survivor bias

Kaplan Meier curves for mortality

Figure AppE-1: Test for survivor bias using the Kaplan Meier curve for mortality.



Log-rank test p=0.24

Cox proportional hazards model for mortality:

Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Intervention	1	0.37404	0.32301	1.008	1.3410	0.2469	1.454	0.772	2.738

Table App-E1. Cox proportional hazards model for mortality

Analysis of Maximum Likelihood Estimates with Sandwich Variance Estimate. Hazard ratio p=0.25

Difference in frailty index at baseline between groups, excluding or including deaths and post-randomisation withdrawals

Frailty index was balanced between Intervention and Control arms when withdrawals and deaths were included (Table App-E3) or excluded (Table App-E2).

Chi-Square	1.6350
DF	1
Pr > Chi-Square	0.2010

Table App-E2. Kruskal Wallis Test indicating difference in frailty at baseline between groups, excluding deaths and post-randomisation withdrawals

Chi-Square	0.3141
DF	1
Pr > Chi-Square	0.5752

Table App-E3. Kruskal Wallis Test indicating difference in frailty at baseline between groups, when withdrawals and deaths are included

Weight

Difference in weight at baseline between treatment groups, excluding or including deaths and post-randomisation withdrawals

No difference in weight at baseline in Control or intervention arms, by withdrawal status (Table App-E4 and 5).

Chi-Square	4.3879
DF	1
Pr > Chi-Square	0.0362

Table App-E4. Kruskal Wallis Test indicating difference in weight at baseline between groups, when withdrawals and deaths are excluded.

Chi-Square	4.8616
DF	1
Pr > Chi-Square	0.0275

Table App-E5. Kruskal Wallis Test indicating difference in weight at baseline between groups, when withdrawals and deaths are included

MoCA

Difference in MoCA at baseline between treatment groups, including or excluding deaths and post-randomisation withdrawals

No difference in MoCA at baseline in Control or intervention arms, by withdrawal status (Table AppE-6 and 7).

Chi-Square	3.0769
DF	1
Pr > Chi-Square	0.0794

Table App-E6. Kruskal Wallis Test indicating difference in MoCA at baseline between groups, when withdrawals and deaths are excluded

Chi-Square	5.8190
DF	1
Pr > Chi-Square	0.0159

Table App-E7. Kruskal Wallis Test indicating difference in MoCA at baseline between groups, when withdrawals and deaths are included

Survivor Average Causal Effect

Although the pre-defined tests showed there was no requirement for the survivor average causal effect, a sensitivity analysis was performed for the frailty index, weight and MoCA. The method described by Chiba and Vander Weele was used (95), without assuming monoticity (i.e. we did not assume that assignment to the control group could not have prevented deaths). A bias term was estimated using a range of plausible clinical sensitivity parameters (beta0 and beta1), which were assumed to be a proportion of the treatment effect size at 12 months. The parameters p0 and p1 were the proportion of deaths in the control and intervention arms, respectively, and the parameter pi01 was the proportion of residents who would have survived if they were in the control but not the intervention group. Beta0 and beta1 are the treatment differences between a less and more healthy population and the sign for these parameters was chosen to reflect this (positive for the frailty index and negative for MoCA, while weight varied between positive and negative).

According to Chiba and Vander Weele, Beta0 “contrasts the average outcomes under the control condition between 1) the population that would have survived under control but not under treatment and 2) the population that would have survived under both treatment and control”. Beta1 “contrasts the average outcomes under treatment between 1) the population that would have survived under treatment but not under control and 2) the population that would have survived under both treatment and control.” (95)

The survivor average causal effect was based on the estimates of treatment differences at 12 months, including those measured after COVID-19 restrictions. Then the bias term was added to the point estimate, as well as the upper and lower confidence limits, to produce the SACE estimates and confidence intervals.

Parameters:

- pi01 was 0.02 or 0.04;
- beta0 and beta1 for the frailty index varied between ¼ and ½ a deficit and were negative (ie 0.015 and 0.0075);
- beta0 and beta1 for weight varied between -2 and +2 kg;

- beta0 and beta1 for MoCA were -2, -1 and 0.

Results for the modelled scenarios are shown in the following tables (Table App-E9 and 10).

Frailty Index

pi01	p1	p0	beta0	beta1	bias	SACE	SACE_lower	SACE_upper	ci
0.02	0.192	0.133	0.0000	0.0000	0.000	-0.009	-0.028	0.009	-0.009 (-0.028, 0.009)
0.04	0.192	0.133	0.0000	0.0000	0.000	-0.009	-0.028	0.009	-0.009 (-0.028, 0.009)
0.02	0.192	0.133	0.0000	0.0075	-0.003	-0.013	-0.031	0.006	-0.013 (-0.031, 0.006)
0.04	0.192	0.133	0.0000	0.0075	-0.004	-0.013	-0.032	0.005	-0.013 (-0.032, 0.005)
0.02	0.192	0.133	0.0000	0.0150	-0.006	-0.016	-0.034	0.003	-0.016 (-0.034, 0.003)
0.04	0.192	0.133	0.0000	0.0150	-0.008	-0.017	-0.036	0.001	-0.017 (-0.036, 0.001)
0.02	0.192	0.133	0.0075	0.0000	0.001	-0.008	-0.027	0.010	-0.008 (-0.027, 0.010)
0.04	0.192	0.133	0.0075	0.0000	0.002	-0.007	-0.026	0.011	-0.007 (-0.026, 0.011)
0.02	0.192	0.133	0.0075	0.0075	-0.002	-0.011	-0.030	0.007	-0.011 (-0.030, 0.007)
0.04	0.192	0.133	0.0075	0.0075	-0.002	-0.011	-0.030	0.008	-0.011 (-0.030, 0.008)
0.02	0.192	0.133	0.0075	0.0150	-0.005	-0.014	-0.033	0.004	-0.014 (-0.033, 0.004)
0.04	0.192	0.133	0.0075	0.0150	-0.005	-0.015	-0.034	0.004	-0.015 (-0.034, 0.004)
0.02	0.192	0.133	0.0150	0.0000	0.002	-0.007	-0.026	0.011	-0.007 (-0.026, 0.011)
0.04	0.192	0.133	0.0150	0.0000	0.005	-0.005	-0.024	0.014	-0.005 (-0.024, 0.014)
0.02	0.192	0.133	0.0150	0.0075	-0.001	-0.010	-0.029	0.008	-0.010 (-0.029, 0.008)
0.04	0.192	0.133	0.0150	0.0075	0.001	-0.009	-0.027	0.010	-0.009 (-0.027, 0.010)
0.02	0.192	0.133	0.0150	0.0150	-0.004	-0.013	-0.032	0.005	-0.013 (-0.032, 0.005)
0.04	0.192	0.133	0.0150	0.0150	-0.003	-0.013	-0.031	0.006	-0.013 (-0.031, 0.006)

Table App-E8. Results for modelled scenarios for survivor causal effect for Frailty Index

Weight

pi01	p1	p0	beta0	beta1	bias	SACE_weight	SACE_lower	SACE_upper	ci
0.02	0.192	0.133	-2	-2	0.52	-0.82	-2.08	0.43	-0.82 (-2.08, 0.43)
0.04	0.192	0.133	-2	-2	0.43	-0.91	-2.17	0.34	-0.91 (-2.17, 0.34)
0.02	0.192	0.133	-2	-1	0.11	-1.23	-2.49	0.02	-1.23 (-2.49, 0.02)
0.04	0.192	0.133	-2	-1	-0.09	-1.43	-2.69	-0.18	-1.43 (-2.69, -0.18)
0.02	0.192	0.133	-2	0	-0.30	-1.64	-2.90	-0.39	-1.64 (-2.90, -0.39)
0.04	0.192	0.133	-2	0	-0.60	-1.94	-3.20	-0.69	-1.94 (-3.20, -0.69)
0.02	0.192	0.133	-2	1	-0.71	-2.05	-3.31	-0.80	-2.05 (-3.31, -0.80)
0.04	0.192	0.133	-2	1	-1.12	-2.46	-3.72	-1.21	-2.46 (-3.72, -1.21)
0.02	0.192	0.133	-2	2	-1.12	-2.46	-3.72	-1.21	-2.46 (-3.72, -1.21)
0.04	0.192	0.133	-2	2	-1.63	-2.97	-4.23	-1.72	-2.97 (-4.23, -1.72)
0.02	0.192	0.133	-1	-2	0.67	-0.67	-1.93	0.58	-0.67 (-1.93, 0.58)
0.04	0.192	0.133	-1	-2	0.73	-0.61	-1.87	0.64	-0.61 (-1.87, 0.64)
0.02	0.192	0.133	-1	-1	0.26	-1.08	-2.34	0.17	-1.08 (-2.34, 0.17)
0.04	0.192	0.133	-1	-1	0.21	-1.13	-2.39	0.12	-1.13 (-2.39, 0.12)
0.02	0.192	0.133	-1	0	-0.15	-1.49	-2.75	-0.24	-1.49 (-2.75, -0.24)

pi01	p1	p0	beta0	beta1	bias	SACE_weight	SACE_lower	SACE_upper	ci
0.04	0.192	0.133	-1	0	-0.30	-1.64	-2.90	-0.39	-1.64 (-2.90, -0.39)
0.02	0.192	0.133	-1	1	-0.56	-1.90	-3.16	-0.65	-1.90 (-3.16, -0.65)
0.04	0.192	0.133	-1	1	-0.82	-2.16	-3.42	-0.91	-2.16 (-3.42, -0.91)
0.02	0.192	0.133	-1	2	-0.97	-2.31	-3.57	-1.06	-2.31 (-3.57, -1.06)
0.04	0.192	0.133	-1	2	-1.33	-2.67	-3.93	-1.42	-2.67 (-3.93, -1.42)
0.02	0.192	0.133	0	-2	0.82	-0.52	-1.78	0.73	-0.52 (-1.78, 0.73)
0.04	0.192	0.133	0	-2	1.03	-0.31	-1.57	0.94	-0.31 (-1.57, 0.94)
0.02	0.192	0.133	0	-1	0.41	-0.93	-2.19	0.32	-0.93 (-2.19, 0.32)
0.04	0.192	0.133	0	-1	0.52	-0.82	-2.08	0.43	-0.82 (-2.08, 0.43)
0.02	0.192	0.133	0	0	0.00	-1.34	-2.60	-0.09	-1.34 (-2.60, -0.09)
0.04	0.192	0.133	0	0	0.00	-1.34	-2.60	-0.09	-1.34 (-2.60, -0.09)
0.02	0.192	0.133	0	1	-0.41	-1.75	-3.01	-0.50	-1.75 (-3.01, -0.50)
0.04	0.192	0.133	0	1	-0.52	-1.86	-3.12	-0.61	-1.86 (-3.12, -0.61)
0.02	0.192	0.133	0	2	-0.82	-2.16	-3.42	-0.91	-2.16 (-3.42, -0.91)
0.04	0.192	0.133	0	2	-1.03	-2.37	-3.63	-1.12	-2.37 (-3.63, -1.12)
0.02	0.192	0.133	1	-2	0.97	-0.37	-1.63	0.88	-0.37 (-1.63, 0.88)
0.04	0.192	0.133	1	-2	1.33	-0.01	-1.27	1.24	-0.01 (-1.27, 1.24)
0.02	0.192	0.133	1	-1	0.56	-0.78	-2.04	0.47	-0.78 (-2.04, 0.47)
0.04	0.192	0.133	1	-1	0.82	-0.52	-1.78	0.73	-0.52 (-1.78, 0.73)
0.02	0.192	0.133	1	0	0.15	-1.19	-2.45	0.06	-1.19 (-2.45, 0.06)
0.04	0.192	0.133	1	0	0.30	-1.04	-2.30	0.21	-1.04 (-2.30, 0.21)
0.02	0.192	0.133	1	1	-0.26	-1.60	-2.86	-0.35	-1.60 (-2.86, -0.35)
0.04	0.192	0.133	1	1	-0.21	-1.55	-2.81	-0.30	-1.55 (-2.81, -0.30)
0.02	0.192	0.133	1	2	-0.67	-2.01	-3.27	-0.76	-2.01 (-3.27, -0.76)
0.04	0.192	0.133	1	2	-0.73	-2.07	-3.33	-0.82	-2.07 (-3.33, -0.82)
0.02	0.192	0.133	2	-2	1.12	-0.22	-1.48	1.03	-0.22 (-1.48, 1.03)
0.04	0.192	0.133	2	-2	1.63	0.29	-0.97	1.54	0.29 (-0.97, 1.54)
0.02	0.192	0.133	2	-1	0.71	-0.63	-1.89	0.62	-0.63 (-1.89, 0.62)
0.04	0.192	0.133	2	-1	1.12	-0.22	-1.48	1.03	-0.22 (-1.48, 1.03)
0.02	0.192	0.133	2	0	0.30	-1.04	-2.30	0.21	-1.04 (-2.30, 0.21)
0.04	0.192	0.133	2	0	0.60	-0.74	-2.00	0.51	-0.74 (-2.00, 0.51)
0.02	0.192	0.133	2	1	-0.11	-1.45	-2.71	-0.20	-1.45 (-2.71, -0.20)
0.04	0.192	0.133	2	1	0.09	-1.25	-2.51	-0.00	-1.25 (-2.51, -0.00)
0.02	0.192	0.133	2	2	-0.52	-1.86	-3.12	-0.61	-1.86 (-3.12, -0.61)
0.04	0.192	0.133	2	2	-0.43	-1.77	-3.03	-0.52	-1.77 (-3.03, -0.52)

Table AppE-9. Results for modelled scenarios for survivor causal effect for Weight

MoCA

pi01	p1	p0	beta0	beta1	bias	SACE_moca	SACE_lower	SACE_upper	ci
0.02	0.192	0.133	-2	-2	0.52	1.88	0.53	3.24	1.88 (0.53, 3.24)
0.04	0.192	0.133	-2	-2	0.43	1.79	0.44	3.15	1.79 (0.44, 3.15)
0.02	0.192	0.133	-2	-1	0.11	1.47	0.12	2.83	1.47 (0.12, 2.83)
0.04	0.192	0.133	-2	-1	-0.09	1.27	-0.08	2.63	1.27 (-0.08, 2.63)
0.02	0.192	0.133	-2	0	-0.30	1.06	-0.29	2.42	1.06 (-0.29, 2.42)
0.04	0.192	0.133	-2	0	-0.60	0.76	-0.59	2.12	0.76 (-0.59, 2.12)
0.02	0.192	0.133	-1	-2	0.67	2.03	0.68	3.39	2.03 (0.68, 3.39)
0.04	0.192	0.133	-1	-2	0.73	2.09	0.74	3.45	2.09 (0.74, 3.45)
0.02	0.192	0.133	-1	-1	0.26	1.62	0.27	2.98	1.62 (0.27, 2.98)
0.04	0.192	0.133	-1	-1	0.21	1.57	0.22	2.93	1.57 (0.22, 2.93)
0.02	0.192	0.133	-1	0	-0.15	1.21	-0.14	2.57	1.21 (-0.14, 2.57)
0.04	0.192	0.133	-1	0	-0.30	1.06	-0.29	2.42	1.06 (-0.29, 2.42)
0.02	0.192	0.133	0	-2	0.82	2.18	0.83	3.54	2.18 (0.83, 3.54)
0.04	0.192	0.133	0	-2	1.03	2.39	1.04	3.75	2.39 (1.04, 3.75)
0.02	0.192	0.133	0	-1	0.41	1.77	0.42	3.13	1.77 (0.42, 3.13)
0.04	0.192	0.133	0	-1	0.52	1.88	0.53	3.24	1.88 (0.53, 3.24)
0.02	0.192	0.133	0	0	0.00	1.36	0.01	2.72	1.36 (0.01, 2.72)
0.04	0.192	0.133	0	0	0.00	1.36	0.01	2.72	1.36 (0.01, 2.72)

Table AppE10. Results for modelled scenarios for survivor causal effect for MoCA

E.2 Imputation of 12 month frailty index measurements after COVID-19 access restrictions

From March 20, 2020, access to residential aged care facilities were restricted due to COVID-19 and pharmacists were unable to implement the intervention. These restrictions may have affected the difference in frailty trajectories between the two groups at the 12 month time point. To estimate the effect of the intervention on the primary outcome if COVID-19 restrictions had not occurred, a sensitivity analysis was conducted, imputing frailty index measurements taken after COVID-19 restrictions.

Measurements of frailty index taken after March 20, 2020 were excluded from the statistical model used for the primary outcome. Imputation of the primary outcome used the following steps:

- The statistical model was run on all patients, excluding those whose frailty index was measured after March 20, 2020;
- The model was used to predict the frailty index for the excluded patients;
- Each imputed dataset added a random error term to the predicted values, assuming a normal distribution with mean 0 and the standard deviation of the model residuals;
- 100 imputed datasets were generated and combined using Rubin's rules.

The point estimates for the primary outcome at 6 and 12 months were larger after excluding or imputing post COVID-19 measurements (Table AppE-11). 95% confidence intervals were narrower after imputation, but still contained zero. However, the point estimate at 12 months after accounting for COVID-19 restrictions (-0.012) is close to the effect size of -0.015 used in the sample size calculation. These results suggest that the treatment effect would have been closer to that expected at the start of the trial if COVID-19 restrictions had not been implemented.

Outcome*	Trial Stage	Intervention, Observed mean	Intervention, Observed variation (SD)	Intervention, Observed number (N)	Control, Observed mean	Control, Observed variation (SD)	Control, Observed number (N)	Intervention-Control (95% CI)	P-value
Frailty Index, all participants	6 Months	0.040	(0.064)	(105)	0.044	(0.062)	(119)	-0.005 (-0.023, 0.013)	0.606
	12 Months	0.080	(0.076)	(97)	0.089	(0.082)	(111)	-0.009 (-0.028, 0.009)	0.320
Frailty Index, excluding post COVID	6 Months	0.040	(0.064)	(105)	0.044	(0.062)	(119)	-0.006 (-0.023, 0.011)	0.510
	12 Months	0.045	(0.065)	(30)	0.062	(0.077)	(32)	-0.012 (-0.039, 0.016)	0.410
Frailty Index, post COVID imputed	6 Months	-			-			-0.006 (-0.023, 0.011)	0.514
	12 Months	-			-			-0.012 (-0.033, 0.009)	0.270

Table App-E-11: Imputation of 12 month frailty index measurements after COVID-19 access restrictions

**Change from baseline, adjusted for baseline, gender and facility.*

Appendix F: Economic analysis Supplementary information

OPD Clinic description	Clinic code	Calculated activity weight[a]	Clinic cost used in analysis[b]	Intervention Arm	Control Arm
Aged Care	20.09	0.0661	$ 339.36	6	1
Allied Health	40.06	0.0349	$ 179.18		
Cardiac technician	40.42	0.0498	$ 255.67	1	
Cardiology	20.22	0.0555	$ 284.94	1	
Dietician	40.23	0.0336	$ 172.50	6	
General Surgery	20.07	0.0482	$ 247.46	6	1
Gynaecology	20.38	0.0534	$ 274.16	1	
Ophthalmology – Allied health	40.15	0.0079	$ 40.56	2	
Ophthalmology/eye procedure	20.17	0.0387	$ 198.69	10	5
Oral & Maxillofacial	20.27	0.05	$ 256.70		3
Orthopaedics	20.29	0.0405	$ 207.93	3	
Plastics	20.46	0.0387	$ 198.69	5	
Pre-admission clinic	40.07	0.0483	$ 247.97	2	
Respiratory	20.19	0.0645	$ 331.14	2	
Wound Care	40.13	0.0322	$ 165.31	1	
Total				46	10

Table AppF-1: Outpatient clinic visits recorded in Tasmanian Hospital data files and allocated codes and costs

[a] *calculated using the "non-admitted_2019-20_nwau_calculator.xls" (available at https://www.ihpa.gov.au/publications/national-efficient-price-determination-2019-20) assuming no funding adjustment factors were applicable for any study participant.*

[b] *calculated by applying the National Efficient Price 2019-2020; which is $5,134 per activity weight*

Allied Health Service	Cost	Description	Source
Audiologist, Hearing check	$143.90	Assessment (Item 600/800)	http://www.hearingservices.gov.au/wps/portal/hso/site/about/legislation/contracts/schedule_fees_2020-21
Dental (general/specialist)	$53.50	D011 Comprehensive Oral Examination, South Australia	Dental Schedule of Fees – ADF Services, Bupa Health Services Pty Ltd. Prices are effective from 1 July 2019.
Dietetics	$102.90	DT01-Dietician –Initial Individual Consultation	Dietitian Schedule of Fees, Bupa Health Services Pty Ltd. Prices are effective from 1 July 2019.
Nurse practitioner (wound care)	$76.00	Nursing 30 mins, Weekday 7am-6pm	https://www.silverchain.org.au/sa/understanding-your-options/costs-and-eligibility/ (last accessed 15/03/21)
Occupational Therapy	$129.22	OT02 Occupational Therapy - Initial Consultation - Home Visit	Occupational Therapy Schedule of Fees, Bupa Health Services Pty Ltd. Prices are effective from 1 July 2019.
Parkinsons Nurse	$76.00	Nursing 30 mins, Weekday 7am-6pm	https://www.silverchain.org.au/sa/understanding-your-options/costs-and-eligibility/ (last accessed 15/03/21)
Physiotherapy	$65.00	T505 Standard Treatment (South Australia)	Physiotherapy Schedule of Fees – ADF Services, Bupa Health Services Pty Ltd. Prices are effective from 12 March 2020
Podiatry	$71.40	F023/024/025 Initial Intermediate /Comprehensive Service (/Diabetes) - Home Based	Podiatry Schedule of Fees, Bupa Health Services Pty Ltd. Prices are effective from 1 July 2019.
Psychology	$112.40	US11 Consultation	Psychology Schedule of Fees – ADF Services, Bupa Health Services Pty Ltd. Prices are effective from 12 March 2020
Remedial massage	$110.00	60 minute initial consult	https://www.claritywellness.com.au/remedial-massage/remedial-massage-prices/ (last accessed 15/03/21)
Social Worker	$80.05	SW05 Initial Consultation – 1st Client	Social Workers Schedule of Fees Effective 1 July 2020, Australian Government Department of Veterans' Affairs
Speech therapy	$148.87	SPT1 Speech Pathology - Initial Consultation	Speech Pathology Schedule of Fees – ADF Services, Bupa Health Services Pty Ltd. Prices are effective from 1 July 2019.

Table AppH-2: Allied health services price sources

Appendix I: Text Alternatives for Complex Figures

I.1 Text alternative for Figure ES-1 and ES-2

I.1.1 Text alternative for Figure ES-1

Figure ES-1 is a flow chart indicating the clinical algorithm proposed for the new ReMInDAR pharmacy service in comparison to the clinical algorithm for the comparator of usual care. Residents in an aged care were allocated to one of two arms. Either the comparator arm of the trial where they continued to receive usual care regardless of any medicine or frailty changes during the year. Or they were allocated to the intervention arm of the trial where they received an additional regular pharmacist service. This additional service is further outlined in the next figure.

I.1.2 Text alternative for Figure ES-2

Figure ES-2 is a decision support flow chart that indicates how a resident is triaged through the clinical management algorithm for the new ReMInDAR pharmacy service. It also indicates the required actions for each decision pathway. It is a cyclical process as resident reviews are conducted on an 8 weekly basis.

Pharmacists review residents' medicine charts to determine if a medicine change has occurred in the previous 8 weeks. They also subsequently interview and assess residents and check their health records to determine if any deterioration is observed (based on changes to their results from 24 movement activity, grip strength, MoCA) or reported through concerns raised by staff or self-reported by residents. If there are no signs of deterioration or concerns raised, or if the concerns are not thought to be related to medicines then they are recorded on the residents care record and staff are advised verbally. However, if the pharmacist identifies that the issue is potentially related to medicines then further action is taken. The risk level is determined for the possible cause of medication induced deterioration and recommendations are made to mitigate the risk. If the risk is low level then the issue is recorded on the residents care record and staff are advised verbally. If the issue is considered high risk, then recommendations are communicated to the GP for consideration. The GP is responsible for implementing any action or change to prescribing. Regardless of risk level the pharmacist will follow up possible causes of medication induced deterioration in a timely fashion, and review of the residents will cycle every 8 weeks.

Return to executive summary

I.2 Text alternative for Figure A-1.

The schematic in Figure A-1 illustrates the relationship between medicines, medicine-induced deterioration, frailty and adverse events. It is well known that medicines can sometimes lead to adverse events, however they also have impacts on daily functions such as:

1) Gait, walking and balance
2) Appetite
3) Cognitive impairment.

Collectively, these medicine-induced impacts on daily functions can be described as 'medicine-induced deterioration'. This deterioration in any daily function can lead to frailty and subsequently to the possibility of an adverse event.

Return to Section A.3.2 Exclusion criteria

I.3. Text alternative for Figures A-2 and A-3.

Text alternative for Figure A-2

Figure A-2 is a flow chart describing the clinical algorithm of the intervention arm of the ReMInDAR pharmacy service in comparison to the comparator trial arm of usual care. Residents in an aged care were allocated to one of two arms. Either the comparator arm of the trial where they continued to receive usual care regardless of any medicine or frailty changes during the year. Or they were allocated to the intervention arm of the trial where they received an additional regular pharmacist service. This additional service is further outlined in the next figure.

Text alternative for Figure A-3

Figure A-3 is a decision support flow chart that indicates how a resident is triaged through the clinical management algorithm for the new ReMInDAR pharmacy service. It also indicates the required actions for each decision pathway. It is a cyclical process as resident reviews are conducted on an 8 weekly basis.

Pharmacists review residents' medicine charts to determine if a medicine change has occurred in the previous 8 weeks. They also subsequently interview and assess residents and check their health records to determine if any deterioration is observed (based on changes to their results from 24 movement activity, grip strength, MoCA) or reported through concerns raised by staff or self-reported by residents. If there are no signs of deterioration or concerns raised, or if the concerns are not thought to be related to medicines then they are

recorded on the residents care record and staff are advised verbally. However, if the pharmacist identifies that the issue is potentially related to medicines then further action is taken. The risk level is determined for the possible cause of medication induced deterioration and recommendations are made to mitigate the risk. If the risk is low level then the issue is recorded on the residents care record and staff are advised verbally. If the issue is considered high risk, then recommendations are communicated to the GP for consideration. The GP is responsible for implementing any action or change to prescribing. Regardless of risk level the pharmacist will follow up possible causes of medication induced deterioration in a timely fashion, and review of the residents will cycle every 8 weeks.

Return to Section A.6 Clinical Claim

I.4. Text alternative for Figure B-1

Figure B-1 is a flow chart describing the recruitment and subsequent steps of trial delivery across the trial timeframe. At each residential aged care facility residents are screened by a research assistant for eligibility and those residents who do not wish to participate are able to opt out. For residents who opt out or who are ineligible, there is no further involvement in the trial.

Eligible residents who chose to participate in the trial are assessed for baseline trial outcomes, and data is also collected from their medicine and health records. Residents are then randomised (1:1) into one of two trial arms, the comparator arm or the intervention pharmacist service for 12 months (which is further described in text below for Figure B-2). The comparator arm continued to receive usual care for 12 months regardless of any medicine or frailty changes during the year. Participants in both arms of the trial are assessed for 6 and 12 month time point outcomes at the respective period of the trial before trial completion.

Return to Section B: Methodology of the ReMInDAR trial - Randomisation

I.5. Text alternative for Figure B-2

Figure B-2 describes the cyclical pharmacist service that is provided, as resident reviews are conducted on an 8 weekly basis. This is a decision support flow chart that indicates how a resident is triaged through the clinical management algorithm for the new ReMInDAR pharmacy service. It also indicates the required actions for each decision pathway.

Pharmacists review residents' medicine charts to determine if a medicine change has occurred in the previous 8 weeks. They also subsequently interview and assess residents and check their health records to determine if any deterioration is observed (based on

changes to their results from 24 movement activity, grip strength, MoCA) or reported through concerns raised by staff or self-reported by residents. If there are no signs of deterioration or concerns raised, or if the concerns are not thought to be related to medicines then they are recorded on the residents care record and staff are advised verbally. However, if the pharmacist identifies that the issue is potentially related to medicines then further action is taken. The risk level is determined for the possible cause of medication induced deterioration and recommendations are made to mitigate the risk. If the risk is low level then the issue is recorded on the residents care record and staff are advised verbally. If the issue is considered high risk, then recommendations are communicated to the GP for consideration. The GP is responsible for implementing any action or change to prescribing. Regardless of risk level the pharmacist will follow up possible causes of medication induced deterioration in a timely fashion, and review of the residents will cycle every 8 weeks.

Return to Section B- Methodology of the ReMInDAR trial – usual care

I.6. Text alternative for Figure B-3

Figure B-3 is a consort flow diagram indicating the numbers and step-wise flow of residents in RACF who were screened, excluded, enrolled, randomised and followed up at each time-point in the trial.

The 39 RACFs that were involved in the trial had 3,646 residents at the commencement of the trial. Overall, 3,049 were excluded in a preliminary desktop based on one or more of the following reasons:

1. having a historical psychogeriatric scale score on the RACF client files of greater than 10 (where a score of 10 or less is considered the threshold for capacity for self-consent);
2. staff advice regarding the residents limitations, cognition or capacity for communication; or
3. being in respite or transition care.

The remaining 597 residents were screened by interview. A further 315 were excluded based on one or more of the following reasons:

1. having a frailty index greater than 0.4;
2. being on less than 4 medications (if one was not a sedative or anti-cholinergic medication);
3. scoring less than 18 in the MoCA administered during screening (corresponding to PAS of >10);
4. having significant communication difficulties;
5. already in a research project that wasn't at a facility-wide level; or
6. resident opted out.

A total of 282 participants were enrolled in the trial and of these 136 were randomised to the intervention arm of the trial and 146 were randomised to the comparison arm. Withdrawals included 16 from the intervention arm and 18 withdrew from the comparison arm. Excluding

those who died left a total of 105 participants for analysis of the primary outcome at 6 months for the intervention arm and 119 for the comparison arm; and 97 participants for analysis of the primary outcome at 12 months for the intervention arm and 111 for the comparison arm.

Return to Section B – Consideration of Deaths

I.7. Text alternative for Figure B-4

Figure B-4 shows a graph comparing the number of deaths for each trial arm for each completed session (or imputed completed session for the control arm based on the pharmacist session dates for their intervention arm counterparts. This is presented numerically in the table below.

Completed session	# of deaths in control	
session 0	2	5
session 1	5	7
session 2	2	2
session 3	2	3
session 4	2	3
session 5	1	2
session 6	2	1

Return to Section B –Cohort Characteristics

I.8. Text alternative for Figure B-5

Figure B-5 is a chart illustrating the proportion of pharmacist case review documentation by recipient throughout the trial. The proportions were from highest to lowest:

1) pharmacist progress notes or patient care record notes (52%),
2) GP communications (27%),
3) resident communications (16%), and
4) RACF nursing staff communications (5%).

Return to Section B – Results - Medication related problems

I.9. Alternative text for figures

Table below shows raw data for chart indicating the number of problems per person identified for each session.

	1	2	3	4	5	6
1	56.8	64.9	66.2	61.2	78.2	64.5
2	25.0	23.4	20.8	19.4	7.3	19.4
3	12.5	10.4	3.9	7.5	7.3	12.9
4 or more	5.7	1.3	9.1	11.9	7.3	3.2

The figure shows a Kaplan Myer analysis of time to the next problem development. We analysed time to develop a new problem after session one and found that 50% had developed a new problem by the next session and 75% had a new problem by the subsequent session, this suggests the time between pharmacist reviews was appropriate at intervals of eight weeks

The final figure is a chart illustrating the proportion and types of medicine related problems that were experienced by residents throughout the trial. The relative proportions of the types of problems from larges to smallest were as follows:

1. Symptom report (83%)
2. Education or information (57%)
3. Toxicity or adverse reaction (51%)
4. Over or under dose (50%)
5. Drug selection (34%)
6. Monitoring (28%)
7. Compliance (20%)

Return to pharmacist recommendations

I.10. Text alternative for Figure B-6a

Figure shows trend lines and statistical variation for each point plotted for the modelled mean change in Frailty Index in intervention and control arms from baseline to 12 month time point. The trend line for the mean change in frailty index is slightly more favourable for the intervention arm, but the differences in the results were not statistically significant. Table below shows the data for this figure:

Outcome*	Trial Stage	Intervention group Mean Change	Intervention group Change variation (SE)	Intervention group number (n)	Control group Mean Change	Control group Change variation (SE)	Control group number (n)	Estimate = Intervention - Control	Estimate = Intervention - Control (95% CI)	P-value
Frailty Index	6 Months	0.040	0.064	105	0.044	0.062	119	-0.005	-0.023, 0.013	0.606
Frailty Index	12 Months	0.080	0.076	97	0.089	0.082	111	-0.009	-0.028, 0.009	0.320

The figure has been overlaid with the imputed effects of the impact of COVID-restrictions calculated from data in table presented below.

Outcome*	Intervention Observed mean	Intervention variation (SE)	Intervention number (n)	Control, Observed mean	Control, variation (SE)	Control number (n)	Intervention -Control variation	Intervention -Control (95% CI)	P-value
Frailty Index, all participants	0.080	(0.076)	97	0.089	(0.082)	111	-0.009	(-0.028, 0.009)	0.320
Frailty Index, excluding post COVID I	0.045	(0.065)	30	0.062	(0.077)	32	-0.012	(-0.039, 0.016)	0.410
Frailty Index, post COVID imputed	-			-			-0.012	(-0.033, 0.009)	0.270

Return to section B

I.11. Text alternative for Figures B-7 and B-8

Text alternative for Figure B7

Figure shows trend lines and statistical variation for each point plotted for the mean observed cognition (MoCA score) in intervention and control arms at the baseline, 6 and 12 month time points. Despite randomisation, this outcome was different at baseline. Both arms declined for coginition, however, there was a statistically significant result with an observed mean difference of 1.36 point change at 12 months, where the intervention arm had the favourable outcome. The estimated change in MoCA that is clinically significant is 2 point change. The change (decline) in MoCA in the control group was over 3 points, a clinically significant decline, while the change in the intervention group less than 2 points.Table below shows the data for this figure:

Outcome	Trial Stage	Intervention group (A) Mean Change	Intervention group (A) Change error (SE)	Intervention group (A) Number (n)	Control Group (B) Mean Change	Control Group (B) Change error (SE)	Control Group (B) number (n)	Estimate A-B	Estimate A-B Variation (95% CI)	P-value
MoCA (0-30) *	6 Months	-0.63	4.07	101	-1.46	3.73	111	0.84	-0.46, 2.13	0.204
	12 Months	-1.89	4.87	87	-3.16	5.88	107	1.36	0.01, 2.72	0.048

Text alternative for Figure B-8

This shows trend lines and statistical variation for each point plotted for the mean observed weight in intervention and control arms at the baseline, 6 and 12 month time points. Despite randomisation, this outcome was different at baseline. The weight of the intervention group remained relatively consistent over time. However, the change in weight over time between the groups was statistically significantly different, with the control arm gaining more weight than the intervention arm (1.34 kg). Table below shows the data for this figure:

Outcome	Trial Stage	Intervention group (A) Mean Change	Intervention group (A) Change error (SE)	Intervention group (A) Number (n)	Control Group (B) Mean Change	Control Group (B) Change error (SE)	Control Group (B) number (n)	Estimate A-B	Estimate A-B Variation (95% CI)	P-value
Weight*	6 Months	-0.13	3.47	99	1.14	4.10	114	-1.31	-2.54, -0.07	0.039
	12 Months	-0.21	5.57	96	0.85	5.22	108	-1.34	-2.60, -0.09	0.035

Return to Section B – Secondary outcomes – adverse events

I.12. Text alternative for Figure B-9

Figure is a pie chart illustrating the proportion and types of adverse events that were experienced by residents throughout the trial. The relative proportions of the 12 types of problems classified from larges to smallest were as follows:

1. Fall or fracture
2. Bleeding or bruising
3. Other
4. Gastroenteritis, vomiting, and nausea
5. Coughing
6. Constipation (new case only)
7. Urticaria

8. Confusion or delirium
9. Indigestion or heat burn
10. Dizziness
11. Faecal incontinence (new case only)
12. Urinary incontinence (new case only)

Return to Section B –

I.13. Alternative Text for Figure APP C-1

The figure shows the layout of the MID assessment report. The table below identifies each item shown in the report, its interpretation and any action that the pharmacist should take:

Item	Interpretation	Action
Patient name	For participant interview	Nil
Room number	For participant interview	Nil
Assessment date	Blank (Pharmacist to fill in)	Record date of assessment
Demographic	For pharmacists' information (DOB, RACF entry date and GP name)	Nil
Availability/ Notes	Blank (Pharmacist to fill in)	Please fill this in if there are certain times or days that are never suitable for an intervention session to allow you to plan any future follow up sessions.
Existing condition list	Blank (Pharmacist to fill in)	Record comorbidities, allergies etc.
Action required from previous session	Blank (Pharmacist to fill in)	• implement and monitor any previous actions.
Current problem list/Potential adverse events	Blank (Pharmacist to fill in)	• List any new conditions/problems affecting the participant since the last visit. • List any adverse events and dates noted in the resident care record
Recent relevant lab results	Important lab results to help pharmacists assess participants' conditions and medicines	Key in any other lab results (and date the test was done) the pharmacists think will be important (e.g. potassium, HbA1c)
Medication	- Medication list collected during any previous review (may be blank). Pharmacist to fill in new medicines - Regular medicines listed first, prn medicines shaded in grey	• Please cross reference with condition to ensure completeness • Record any change in medicines, including medicine name, formulation, route, frequency, start date/cease date, number of prn doses administered
Cognitive assessment scores	- Blank (Pharmacist to fill in) - Subsequent scores are listed in chronological order	• Enter the total score in the next blank row

Item	Interpretation	Action
		• Determine if the change is clinically significant. If yes, could this be due to medicine change or new condition
Weight	Blank (Pharmacist to fill in)- Subsequent weight measurements are listed in chronological order	• Enter the weight (in the resident card record) in the next blank row • Determine if the change is due to changes in appetite (care record or interview), if change could be due to medicine change or new condition
Grip strength	Blank (Pharmacist to fill in)- Subsequent measurements are listed in chronological order	• Undertake assessment at each session. • Enter the values in the next blank row. • Select the best of 3 measurements for data interpretation • Determine if the change is clinically significant. If yes, could this be due to medicine change or new condition
Subjective findings	Blank (Pharmacist to fill in)	• Enter any notes and observations that have not been captured in the above fields • Collate subjective information (e.g. patient interview, progress notes) to help with overall evaluation
Objective findings	Blank (Pharmacist to fill in)	• Collate objective information (e.g. lab report, grip strength) to help with overall evaluation
Overall evaluation	Blank (Pharmacist to fill in)	
Emergency and hospital visit notes	Blank (Pharmacist to fill in)	
Actions	Blank (Pharmacist to fill in)	
Pharmacist session notes	Prepopulated from findings from previous session	NIL

Return to main text

References

1. Parry S, Chow M, Batchelor F, Fary RE. Physical activity and sedentary behaviour in a residential aged care facility. Australasian journal on ageing. 2019;38(1):E12-E8.
2. 6th Community Pharmacy Agreement. Residential medication management review and QUM [Available from: http://6cpa.com.au/medication-management-programs/residential-medication-management-review/.
3. Pharmacy Programs Administrator. Residential Medication Management Review and Quality Use of Medicines. 2019.
4. Al-Jumaili AA, Doucette WR. A Systems Approach to Identify Factors Influencing Adverse Drug Events in Nursing Homes. J Am Geriatr Soc. 2018;66(7):1420-7.
5. Tenhunen ML, Smithers B, Tucker B. Identifying Medication-Related Adverse Drug Events in Nursing Facilities in East Texas. Consult Pharm. 2016;31(8):436-9.
6. Handler SM, Wright RM, Ruby CM, Hanlon JT. Epidemiology of medication-related adverse events in nursing homes. Am J Geriatr Pharmacother. 2006;4(3):264-72.
7. Kapoor A, Field T, Handler S, Fisher K, Saphirak C, Crawford S, et al. Adverse Events in Long-term Care Residents Transitioning From Hospital Back to Nursing Home. JAMA Intern Med. 2019.
8. Gurwitz JH, Field TS, Avorn J, McCormick D, Jain S, Eckler M, et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med. 2000;109(2):87-94.
9. Lim R, Ellett LMK, Widagdo IS, Pratt NL, Roughead EE. Analysis of anticholinergic and sedative medicine effects on physical function, cognitive function, appetite and frailty: a cross-sectional study in Australia. BMJ open. 2019;9(9):e029221.
10. Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice: A review. Eur J Intern Med. 2016;31:3-10.
11. Bennett A, Gnjidic D, Gillett M, Carroll P, Matthews S, Johnell K, et al. Prevalence and impact of fall-risk-increasing drugs, polypharmacy, and drug-drug interactions in robust versus frail hospitalised falls patients: a prospective cohort study. Drugs Aging. 2014;31(3):225-32.
12. Herr M, Robine JM, Pinot J, Arvieu JJ, Ankri J. Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. Pharmacoepidemiol Drug Saf. 2015;24(6):637-46.
13. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Cumming RG, Handelsman DJ, et al. High-risk prescribing and incidence of frailty among older community-dwelling men. Clin Pharmacol Ther. 2012;91(3):521-8.
14. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381(9868):752-62.
15. Widagdo IS, Pratt N, Russell M, Roughead EE. Predictive performance of four frailty measures in an older Australian population. Age Ageing. 2015;44(6):967-72.
16. Jamsen KM, Bell JS, Hilmer SN, Kirkpatrick CM, Ilomaki J, Le Couteur D, et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions Between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. J Am Geriatr Soc. 2016;64(1):89-95.

17. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing. 2016;45(1):115-20.

18. Australian Government Department of Health. Psychogeriatric Assessment Scales (PAS) User Guide 2016 [updated 12 December 2016. Available from: https://agedcare.health.gov.au/aged-care-funding/residential-care-subsidy/basic-subsidy-amount-aged-care-funding-instrument/psychogeriatric-assessment-scales-pas-user-guide.

19. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10):e1-e34.

20. Frankenthal D, Lerman Y, Kalendaryev E, Lerman Y. Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. Journal of the American Geriatrics Society. 2014;62(9):1658-65.

21. Furniss L, Burns A, Craig SK, Scobie S, Cooke J, Faragher B. Effects of a pharmacist's medication review in nursing homes. Randomised controlled trial. Br J Psychiatry. 2000;176:563-7.

22. Lapane KL, Hughes CM, Daiello LA, Cameron KA, Feinberg J. Effect of a pharmacist-led multicomponent intervention focusing on the medication monitoring phase to prevent potential adverse drug events in nursing homes. Journal of the American Geriatrics Society. 2011;59(7):1238-45.

23. Patterson SM, Hughes CM, Crealey G, Cardwell C, Lapane KL. An evaluation of an adapted US model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in Northern Ireland (Fleetwood Northern Ireland study). Journal of the American Geriatrics Society. 2010;58(1):44-53.

24. Potter K, Flicker L, Page A, Etherton-Beer C. Deprescribing in Frail Older People: A Randomised Controlled Trial. PLoS One. 2016;11(3):e0149984.

25. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, et al. Clinical medication review by a pharmacist of elderly people living in care homes--randomised controlled trial. Age and ageing. 2006;35(6):586-91.

26. Crotty M, Whitehead C, Rowett D, Halbert J, Weller D, Finucane P, et al. An outreach intervention to implement evidence based practice in residential care: a randomized controlled trial [ISRCTN67855475]. BMC Health Services Research. 2004;4(1):1-6.

27. García-Gollarte F, Baleriola-Júlvez J, Ferrero-López I, Cuenllas-Díaz Á, Cruz-Jentoft AJ. An educational intervention on drug use in nursing homes improves health outcomes resource utilization and reduces inappropriate drug prescription. Journal of the American Medical Directors Association. 2014;15(12):885-91.

28. Gurwitz JH, Field TS, Rochon P, Judge J, Harrold LR, Bell CM, et al. Effect of computerized provider order entry with clinical decision support on adverse drug events in the long-term care setting. Journal of the American Geriatrics Society. 2008;56(12):2225-33.

29. Kersten H, Molden E, Tolo IK, Skovlund E, Engedal K, Wyller TB. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized

controlled trial. Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences. 2013;68(3):271-8.

30. Roberts MS, Stokes JA, King MA, Lynne TA, Purdie DM, Glasziou PP, et al. Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes. British journal of clinical pharmacology. 2001;51(3):257-65.

31. Rovner BW, Steele CD, Shmuely Y, Folstein MF. A randomized trial of dementia care in nursing homes. Journal of the American Geriatrics Society. 1996;44(1):7-13.

32. Abrahamsen B, Hansen RN, Rossing C. For which patient subgroups are there positive outcomes from a medication review? A systematic review. Pharmacy Practice. 2020;18(4):1-8.

33. Juola AL, Bjorkman MP, Pylkkanen S, Finne-Soveri H, Soini H, Kautiainen H, et al. Nurse Education to Reduce Harmful Medication Use in Assisted Living Facilities: Effects of a Randomized Controlled Trial on Falls and Cognition. Drugs Aging. 2015;32(11):947-55.

34. Pitkälä KH, Juola AL, Kautiainen H, Soini H, Finne-Soveri UH, Bell JS, et al. Education to reduce potentially harmful medication use among residents of assisted living facilities: a randomized controlled trial. J Am Med Dir Assoc. 2014;15(12):892-8.

35. Tappen RM, Newman D, Huckfeldt P, Yang Z, Engstrom G, Wolf DG, et al. Evaluation of nursing facility resident safety during implementation of the interact quality improvement program. Journal of the American Medical Directors Association. 2018;19(10):907-13. e1.

36. Lim R, Bereznicki L, Corlis M, Ellett LMK, Kang AC, Merlin T, et al. Reducing medicine-induced deterioration and adverse reactions (ReMInDAR) trial: study protocol for a randomised controlled trial in residential aged-care facilities assessing frailty as the primary outcome. BMJ open. 2020;10(4):e032851.

37. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

38. National Health and Medical Research Council. National Statement of Ethical Conduct in Human Research 2007 [Available from: https://www.nhmrc.gov.au/guidelines-publications/e72.

39. Yeh Y-C, Liu C-L, Peng L-N, Lin M-H, Chen L-K. Potential benefits of reducing medication-related anticholinergic burden for demented older adults: A prospective cohort study. Geriatrics & Gerontology International. 2013;13(3):694-700.

40. Kersten H, Molden E, Tolo IK, Skovlund E, Engedal K, Wyller TB. Cognitive effects of reducing anticholinergic drug burden in a frail elderly population: a randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2013;68(3):271-8.

41. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc. 2005;53(12):2184-9.

42. Australian Institue of Health and Welfare. Dementia overview 2018 [Available from: https://www.aihw.gov.au/reports-data/health-conditions-disability-deaths/dementia/overview.

43. Zhang X, Dou Q, Zhang W, Wang C, Xie X, Yang Y, et al. Frailty as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis. Journal of the American Medical Directors Association. 2019;20(6):657-63. e4.

44. Colebatch BPharm MClin Pharm KA, Marley MD MBChB J, Doecke C, Miles BSc H, Gilbert BPharm PhD A. Evaluation of a patient event report monitoring system. Pharmacoepidemiology and drug safety. 2000;9(6):491-9.

45. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.

46. Widagdo IS, Pratt N, Russell M, Roughead EE. Construct Validity of Four Frailty Measures in an Older Australian Population: A Rasch Analysis. J Frailty Aging. 2016;5(2):78-81.

47. Chin APMJ, Dekker JM, Feskens EJ, Schouten EG, Kromhout D. How to select a frail elderly population? A comparison of three working definitions. Journal of clinical epidemiology. 1999;52(11):1015-21.

48. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet (London, England). 1999;353(9148):205-6.

49. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. The journals of gerontology Series A, Biological sciences and medical sciences. 2001;56(3):M146-56.

50. Saliba D, Elliott M, Rubenstein LZ, Solomon DH, Young RT, Kamberg CJ, et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. Journal of the American Geriatrics Society. 2001;49(12):1691-9.

51. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489-95.

52. Scarcella P, Liotta G, Marazzi MC, Carbini R, Palombi L. Analysis of survival in a sample of elderly patients from Ragusa, Italy on the basis of a primary care level multidimensional evaluation. Archives of gerontology and geriatrics. 2005;40(2):147-56.

53. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Patterson C. Development of an easy prognostic score for frailty outcomes in the aged. Age and ageing. 2008;37(2):161-6.

54. Guilley E, Ghisletta P, Armi F, Berchtold A, d'Epinay CL, Michel J-P, et al. Dynamics of Frailty and ADL Dependence in a Five-Year Longitudinal Study of Octogenarians. Research on Aging. 2008;30(3):299-317.

55. Kiely DK, Cupples LA, Lipsitz LA. Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. Journal of the American Geriatrics Society. 2009;57(9):1532-9.

56. Armstrong JJ, Stolee P, Hirdes JP, Poss JW. Examining three frailty conceptualizations in their ability to predict negative outcomes for home-care clients. Age and ageing. 2010;39(6):755-8.

57. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SA, et al. Low free testosterone predicts frailty in older men: the health in men study. J Clin Endocrinol Metab. 2010;95(7):3165-72.

58. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of frailty in population-based studies: an overview. BMC geriatrics. 2013;13:64.

59. Ahmed S, de Jager C, Wilcock G. A comparison of screening tools for the assessment of mild cognitive impairment: preliminary findings. Neurocase. 2012;18(4):336-51.

60. Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, Eston RG. Validation of the GENEA Accelerometer. Med Sci Sports Exerc. 2011;43(6):1085-93.

61. Pavey TG, Gomersall SR, Clark BK, Brown WJ. The validity of the GENEActiv wrist-worn accelerometer for measuring adult sedentary time in free living. J Sci Med Sport. 2016;19(5):395-9.

62. Fraysse F, Post D, Eston R, Kasai D, Rowlands AV, Parfitt G. Physical activity intensity cut-points for wrist-worn GENEActiv in older adults. Frontiers in Sports and Active Living. 2020;2.

63. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age and Ageing. 2019;48(1):16-31.

64. Roush JR, Gombold KL, Bay RC. Normative grip strength values in males and females, ages 50 to 89 years old. Internet Journal of Allied Health Sciences and Practice. 2017;16(1):7.

65. Villafane JH, Valdes K, Bertozzi L, Negrini S. Minimal Clinically Important Difference of Grip and Pinch Strength in Women With Thumb Carpometacarpal Osteoarthritis When Compared to Healthy Subjects. Rehabil Nurs. 2014.

66. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001;33(5):337-43.

67. Van Hout B, Janssen M, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health. 2012;15(5):708-15.

68. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. International journal of clinical pharmacy. 2012;34(1):43-52.

69. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. American journal of hospital pharmacy. 1990;47(3):533-43.

70. PCNE D. Classification System 2006: Available from: http://www. pcne. org/sig/drp/documents/drp. PCNE% 20classification% 20V5.1.

71. Cohen J. A coefficient of agreement for nominal scales. Educational and psychological measurement. 1960;20(1):37-46.

72. Friendly M, Meyer D. Discrete data analysis with R: visualization and modeling techniques for categorical and count data: CRC Press; 2015.

73. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E, et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics. 1981;30(2):239-45.

74. Schumock G, Thornton J. Focusing on the preventability of adverse drug reactions. Hospital pharmacy. 1992;27(6):538-.

75. Flinders Centre for Ageing Studies. ALSA: The Australian Longitudinal Study of Ageing 2016 [updated 2016 April 6. Available from: http://www.flinders.edu.au/sabs/fcas/alsa/.

76. Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. Int J Qual Health Care. 2003;15 Suppl 1:i49-59.

77. Theou O, Sluggett JK, Bell JS, Lalic S, Cooper T, Robson L, et al. Frailty, Hospitalization, and Mortality in Residential Aged Care. The Journals of Gerontology: Series A. 2018;73(8):1090-6.

78. Goldstein H, Healy MJ. The graphical presentation of a collection of means. Journal of the Royal Statistical Society: Series A (Statistics in Society). 1995;158(1):175-7.

79. Krishnan K, Rossetti H, Hynan LS, Carter K, Falkowski J, Lacritz L, et al. Changes in Montreal Cognitive Assessment scores over time. Assessment. 2017;24(6):772-7.

80. Wolowacz SE, Briggs A, Belozeroff V, Clarke P, Doward L, Goeree R, et al. Estimating health-state utility for economic models in clinical studies: an ISPOR good research practices task force report. Value in Health. 2016;19(6):704-19.

81. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Archives of general psychiatry. 2002;59(2):131-6.

82. Theou O, Blodgett JM, Godin J, Rockwood K. Association between sedentary time and mortality across levels of frailty. Cmaj. 2017;189(33):E1056-E64.

83. Song J, Lindquist LA, Chang RW, Semanik PA, Ehrlich-Jones LS, Lee J, et al. Sedentary behavior as a risk factor for physical frailty independent of moderate activity: results from the osteoarthritis initiative. American journal of public health. 2015;105(7):1439-45.

84. Mankowski RT, Anton SD, Axtell R, Chen SH, Fielding RA, Glynn NW, et al. Device-measured physical activity as a predictor of disability in mobility-limited older adults. Journal of the American Geriatrics Society. 2017;65(10):2251-6.

85. Jefferis BJ, Parsons TJ, Sartini C, Ash S, Lennon LT, Papacosta O, et al. Objectively measured physical activity, sedentary behaviour and all-cause mortality in older men: does volume of activity matter more than pattern of accumulation? British Journal of Sports Medicine. 2019;53(16):1013-20.

86. Jódar-Sánchez F, Martín JJ, López del Amo MP, García L, Araújo-Santos JM, Epstein D. Cost–Utility Analysis of a Pharmacotherapy Follow-Up for Elderly Nursing Home Residents in Spain. Journal of the American Geriatrics Society. 2014;62(7):1272-80.

87. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, et al. Clinical medication review by a pharmacist of elderly people living in care homes—randomised controlled trial. Age and ageing. 2006;35(6):586-91.

88. Brulhart MI, Wermeille JP. Multidisciplinary medication review: evaluation of a pharmaceutical care model for nursing homes. International journal of clinical pharmacy. 2011;33(3):549-57.

89. Furniss L, Burns A, Craig SKL, Scobie S, Cooke J, Faragher B. Effects of a pharmacist's medication review in nursing homes: Randomised controlled trial. The British Journal of Psychiatry. 2000;176(6):563-7.

90. Roberts MS, Stokes JA, King MA, Lynne TA, Purdie DM, Glasziou PP, et al. Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes. British journal of clinical pharmacology. 2001;51(3):257-65.

91. Chia HS, Ho JAH, Lim BD. Pharmacist review and its impact on Singapore nursing homes. Singapore medical journal. 2015;56(9):493.

92. Christensen D, Trygstad T, Sullivan R, Garmise J, Wegner SE. A pharmacy management intervention for optimizing drug therapy for nursing home patients. The American journal of geriatric pharmacotherapy. 2004;2(4):248-56.

93. HigginsJPT A, Sterne J. Chapter 8: Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions version. 2011;5(0):243-96.

94. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2019;5:354-63.

95. Chiba Y, VanderWeele TJ. A simple method for principal strata effects when the outcome has been truncated due to death. American journal of epidemiology. 2011;173(7):745-51.