

RESEARCH PAPER

Effect of an ongoing pharmacist service to reduce medicine-induced deterioration and adverse reactions in aged-care facilities (nursing homes): a multicentre, randomised controlled trial (the ReMInDAR trial)

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Abstract

Objective: To assess the effectiveness of a pharmacist-led intervention using validated tools to reduce medicine-induced deterioration and adverse reactions.

Design and setting: Multicenter, open-label parallel randomised controlled trial involving 39 Australian aged-care facilities.

Participants: Residents on ≥ 4 medicines or ≥ 1 anticholinergic or sedative medicine.

Intervention: Pharmacist-led intervention using validated tools to detect signs and symptoms of medicine-induced deterioration which occurred every 8 weeks over 12 months.

Comparator: Usual care (Residential Medication Management Review) provided by accredited pharmacists.

Outcomes: Primary outcome was change in Frailty Index at 12 months. Secondary outcomes included changes in cognition, 24-hour movement behaviour by accelerometry, grip strength, weight, adverse events and quality of life.

Results: 248 persons (median age 87 years) completed the study; 120 in the intervention and, 128 in control arms. In total 575 pharmacist sessions were undertaken in the intervention arm. There was no statistically significant difference for change in frailty between groups (mean difference: 0.009, 95% CI: $-0.028, 0.009$, $P = 0.320$). A significant difference for cognition was observed, with a mean difference of 1.36 point change at 12 months (95% CI: 0.01, 2.72, $P = 0.048$). Changes in 24-hour movement behaviour, grip strength, adverse events and quality of life were not significantly different between groups. Point estimates favoured the intervention arm at 12 months for frailty, 24-hour movement behaviour and grip strength.

Conclusions: The use of validated tools by pharmacists to detect signs of medicine-induced deterioration is a model of practice that requires further research, with promising results from this trial, particularly with regards to improved cognition.

Keywords: activity tracker, cognitive function, physical activity, medication safety, health services research, older people

Key Points

- One in five aged care residents experience an adverse event due to their medicines; over half are preventable.
- We assessed the effectiveness of a pharmacist-led intervention using validated tools to reduce medication-related harms.
- Participants in the intervention arm had significantly less deterioration in cognition.

Introduction

Harm from medicines is the most frequent harm in the healthcare system [1–3]. It is also the most preventable [1, 4]. The global costs of medication-related harms exceed \$40 billion annually [5]. Older people are the most frequent users of medicines and experience the most harm, particularly older persons in aged-care. International evidence suggests every month between 5 and 20% of aged-care residents experience an adverse medicine event [6–8]. The majority of these adverse events are serious, life-threatening or fatal, and more than half of this harm is considered preventable [9, 10].

Efforts to improve medicine use in the aged-care setting have predominantly focused on medication review services, educational interventions or deprescribing interventions guided by explicit criteria [11–14]. The majority of evidence shows improvements in medicine use associated with medication reviews, but there is less clear evidence of the impact on clinical outcomes, particularly reductions in adverse medicine events [11–15]. The majority of interventions in aged-care to date have focused on reducing use of potentially inappropriate or harmful medicines, such as those focused on reducing the medication burden, reducing medicines listed on the Beer's criteria or STOPP criteria.

Harms from medicines can occur as a direct result of the pharmacodynamic effects of the medicine or result from the effects of medicines on cognition, activity, strength or appetite [16–19], all of which are factors that contribute to frailty. Improving a clinician's capacity to recognize the early onset of medicine-induced deterioration, such as changes in a person's cognition or activity, may assist in preventing frailty and adverse medicine events [20, 21]. There is significant evidence demonstrating that medicine use is associated with frailty [22–26] and that frail individuals have worse health outcomes than non-frail individuals [22, 23, 27]. Because medicine-induced deterioration is not limited to a single event, an outcome measure that captures multiple domains was required. The Frailty Index [28], which captures physical, medical, psychological and social domains, was considered to encompass the domains affected due to medicine-induced deterioration. This study

aimed to test the effectiveness of an ongoing pharmacist-led service to identify and resolve medicine-induced deterioration and adverse reactions, using frailty as the primary outcome.

Methods

The Reducing Medicine-induced Deterioration and Adverse Reactions (ReMInDAR) trial was a multicenter, open-label, parallel randomised controlled trial involving 39 aged-care facilities with a 12-month follow-up period. The intervention occurred between August 2018 and June 2020 (Supplement 1, Supplementary data are available in *Age and Ageing* online). Approvals were obtained from four ethics committees (Supplement 2, Supplementary data are available in *Age and Ageing* online) [29].

Participants

Residents were eligible if they were taking ≥ 4 medicines or ≥ 1 medicine with anticholinergic or sedative properties. Four or more medicines has been chosen because evidence has demonstrated that gait and cognition may be impaired when a person is taking 5 or more medicines [30]. Residents were excluded if they were frail (≥ 0.40 on the Frailty Index) [27], had moderate or severe dementia (Psychogeriatric Assessment Scales $< 12/21$ [31] or Montreal Cognitive Assessment MoCA $\leq 17/30$) [32] or were receiving palliative or respite care [29]. Our study adopted an 'opt out' approach which meant that residents needed to have the capacity to decline participation if they wish to do so.

Intervention

The intervention was a pharmacist-led service. All pharmacists were trained using a standardised training programme (Supplement 3, Supplementary data are available in *Age and Ageing* online). The pharmacist-led intervention occurred every 8 weeks over 12 months.

The pharmacists reviewed resident care records to identify any new illnesses or conditions present since the last assessment, including any adverse events or any signs

or symptoms noted in the care record that could be indicative of adverse events. The pharmacists also reviewed the medication chart to identify any medication changes. The pharmacist met with the resident and care staff to discuss and identify any concerns that they may have about the residents' health or medications and to assess changes in activity and cognition. The pharmacist assessed the participant's cognition (MoCA test) [32], longitudinal 24-hour movement behaviour using a health-professional grade activity tracker (Activinsights Bands, Activinsights Ltd, Cambridgeshire, UK) and hand grip strength using a dynamometer (Jamar, Illinois, USA). Implementation of the Activinsights, however, was not maintained across the trial due to technical issues unrelated to patient characteristics.

Where medicine-induced deterioration was considered clinically significant, the pharmacists liaised with the participants' doctors to discuss the participants' condition and provide recommendations of actions to take if medication-related problems were indicated.

Comparator

Usual care (Residential Medication Management Review) provided to Australian aged-care residents [33]. Where required as part of usual care during the study period, the RMMR was available for participants in both intervention and comparator groups. Accredited pharmacists are funded to conduct and RMMR every 12–24 months. During the trial period, only nine participants in the usual care arm received the RMMR service; none were conducted by the intervention pharmacist.

Outcome

The primary outcome was change in the Frailty Index [28] from baseline to 12 months. The Frailty Index is the proportion of deficits observed from a set of 39 variables and ranges from 0 to 1 with 0 representing non-frail. The Frailty Index has been validated in an Australian population, where it was shown to have good predictive ability for adverse events of death, falls and hospitalisations [27, 34].

The secondary outcomes were the followings:

- (i) Change in cognition assessed using the MoCA test [32]. The scale ranges from 0 to 30. A 2-point change was shown to be clinically significant in patients with stroke [35]; the population had similar MoCA scores as our participants, and therefore, the change was used as reference in our study.
- (ii) Change in 24-hour movement behaviour assessed using the GENEActiv accelerometer (fitted for 1 week at baseline, 6- and 12-months). The GENEActiv is a research-grade activity tracker that allows high-resolution data collection for up to 1 month [36, 37].
- (iii) Change in grip strength measured using a handheld dynamometer.
- (iv) Change in weight, extracted from the resident serial weight chart.

- (v) Percentage robust, pre-frail and frail measured using the frailty phenotype [38].
- (vi) Rate of adverse medicine events per 100 resident months, extracted from the care record. Adverse events were collected by research assistants based on a selected key word search on the care record. Subsequently, two research pharmacists independently reviewed the events to identify potential medication-related adverse events. A clinical panel comprising two pharmacists and a doctor further reviewed the events and judged them as possible, probable or definite adverse medicine events using an abbreviated Naranjo assessment criteria [39].
- (vii) Change in quality of life using the EQ-5D [40].

All changes were measured as change at 6 and 12 months from baseline values. Research assistants collected data on the study outcome measures for all participants at baseline, 6 and 12 months.

Sample size

The sample size calculation has been reported previously [29]. The total estimated sample size required was 354.

Randomisation

Permuted block randomisation (blocks of four, stratified by gender and facility) was used to randomise residents in a 1:1 ratio. A computer-generated list of resident randomisation codes and unique participant identification numbers was generated electronically by the study statistician for each facility and was provided to the trial project manager. The allocation sequence was concealed from the research assistants enrolling and assessing the participants at baseline. After baseline data collection, the trial project manager assigned the participants either to the intervention or control arm based on the next-randomised allocation.

Blinding

Outcome data at baseline, 6 and 12 months, were collected by research assistants who were blinded to participant allocation. The statistician responsible for the analysis was blinded until the main analyses was complete.

Statistical methods

The analysis followed a pre-specified analysis plan (Supplement 4, Supplementary data are available in *Age and Ageing* online). 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. Since continuous outcomes were changes from baseline, they were assumed to be normally distributed because the sample size was large enough for the Central Limit Theorem to apply [41]. 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 6 and 12 months post-randomisation and statistical significance was assessed at the two-sided 0.05 level. Models were adjusted for the stratification variables (facility and gender). Continuous outcomes were adjusted for baseline values. Poisson or negative-binomial regression models were used for the count outcomes, such as adverse event counts, as appropriate. Multiple imputation for missing data was pre-specified for the primary outcome, while secondary outcomes were complete case analyses.

We undertook *post-hoc* analyses for survivor bias on the statistically significant secondary outcomes due to the imbalance in withdrawal status due to deaths (Supplement 5, Supplementary data are available in *Age and Ageing* online).

Impact of COVID

The final months of the trial were affected by the COVID-19 pandemic which delayed, modified or stopped some pharmacist sessions. Variations to the delivery of the pharmacist intervention were approved by the funder and ethics committee. The variations allowed for remote data review and interview by telehealth where possible when access to sites by 'non-essential' staff was prohibited; from April to June 2020. Pharmacists reviewed medication charts, progress notes and adverse events remotely; however, intervention data including grip strength and MoCA could not be collected remotely. Variations to the data collection for each participant at each pharmacist session and at 12-month data collection were logged to inform trial analysis.

Results

Trial participants were recruited from 39 aged-care facilities both in metropolitan and regional locations across South Australia and Tasmania. After eligibility screening, 282 persons were enrolled, of which 34 withdrew leaving a final sample of 248 (Figure 1). There was an imbalance in the number of withdrawals due to death between the two treatment arms. At the 6 months assessment, there were 15/120 and 9/128 deaths in the intervention and control groups, respectively. However, the imbalance in deaths predominantly occurred in the first 2 months, prior to the first intervention visit, with 5/120 deaths (4%) for intervention arm and 2/128 deaths (2%) for the control group. Our final sample was short of our required sample size of 354 persons, leaving the study under-powered for its primary endpoint. Table 1 presents the cohort characteristics. The median age of participants was 87 years.

Intervention delivery

Overall, 575 individual pharmacist-resident sessions were undertaken; a median of 6 pharmacist sessions per person. Eighty-eight planned pharmacist-resident sessions 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.

In total, 112 (97%) of the 115 people who received the service had at least one medication-related problem or symptom report identified (Table 2). Pharmacists identified 673 medication-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 ranged from 79% in the first session to 64% by the sixth session. Fifty percent of residents had five or more problems or symptoms identified across the study period (range 1–29).

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%. As a proportion of all medicine orders, medicines were stopped on 26% of occasions in the intervention group compared with 22% in the control group, while medicines initiations were 17% in the intervention group compared with 18% in the control group, with all other medicines unchanged at 12 months follow-up ($\chi^2 = 11.3$, $P = 0.0036$).

Primary and secondary outcomes

All participants alive at 12 months completed primary outcome assessments. There was no statistically significant difference for the primary outcome of change in frailty index from baseline between the intervention ($N = 97$, mean change from baseline 0.08, SD 0.076) and the control groups ($N = 111$, mean change 0.089, SD 0.082) at 12 months (mean difference: 0.009, 95% CI: -0.028 , 0.009 ; $P = 0.320$) (Table 3, Figure 2). The analysis was by the original assigned groups. Complete case analyses for secondary outcomes showed a statistically significant difference for cognition, as measured by change in MoCA from baseline, between the intervention ($N = 87$) and the control groups ($N = 107$), with a mean difference of 1.36 point change at 12 months (95% CI: 0.01, 2.72; $P = 0.048$). Mean weight (SD) at 12 months was 75.7 (16.6) kg in the intervention ($N = 96$) and 72.9 (18.4) kg in the control ($N = 108$) arms, a change from baseline measures of 75.6 (16.4) kg in the intervention group and 72.72 (19.2) in the control group. Thus, there was a small mean weight loss in the intervention group and weight gain in the control arms, representing a significant difference at 12 months (mean difference: 1.34 kg, 95% CI: -2.60 , -0.09 ; $P = 0.035$). Changes in 24-hour movement behaviour, grip strength, adverse events and quality of life from baseline were not significantly different between both arms. Point estimates consistently favoured the intervention arm at 12 months for frailty, 24-hour movement behaviour and grip strength. The

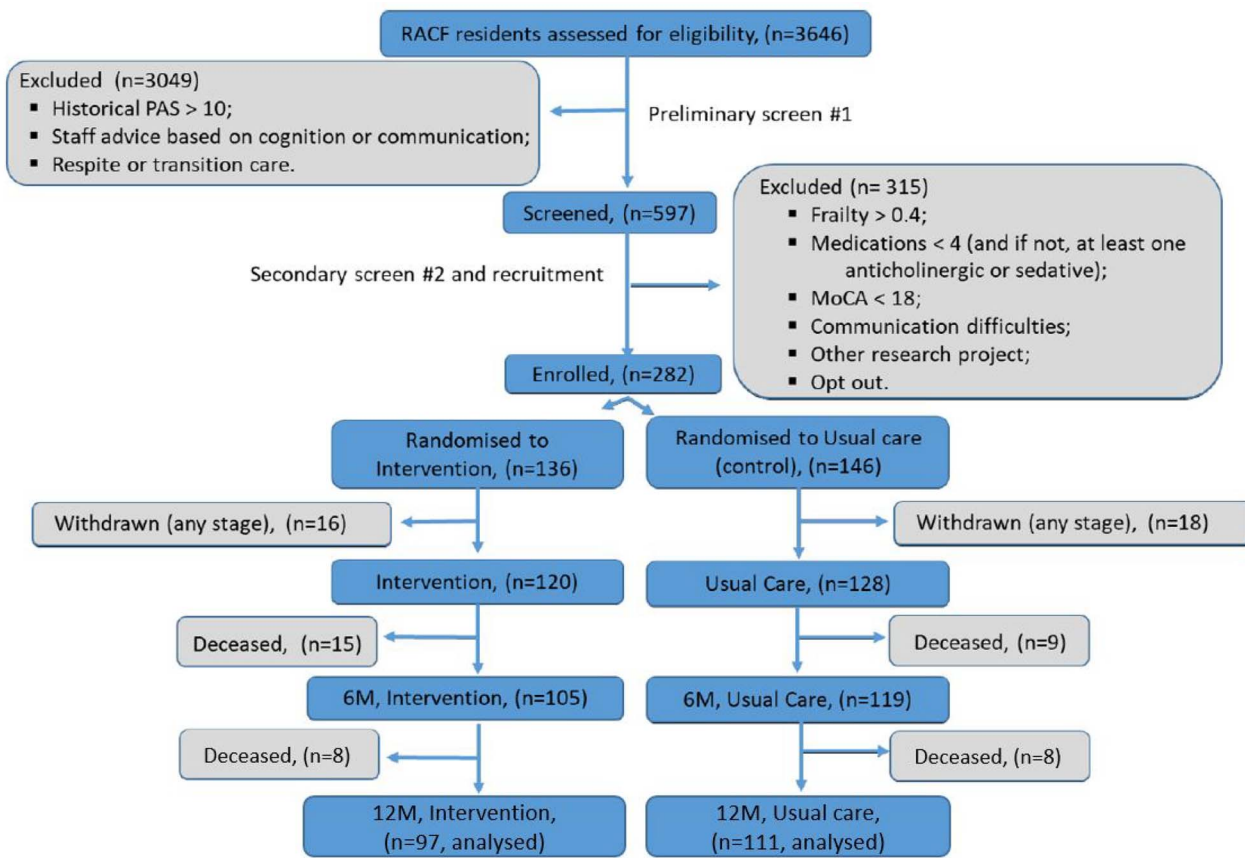


Figure 1. ReMInDAR consort diagram illustrating the numbers and flow of residents in the trial. MoCA: Montreal Cognitive Assessment; PAS: Psychogeriatric Assessment Scales; RACF: Residential Aged Care Facilities.

Table 1. Baseline characteristics by intervention arm

Baseline Descriptor	Intervention arm	Comparison arm
Total number (n) in trial cohort post randomisation (excl. withdrawn)	120	128
Gender = Male, n (%)	41 (34.2%)	39 (30.5%)
Weight*, kg, overall, mean (SD)	75.60 (16.44)	71.72 (19.18)
Male weight*, kg, mean (SD)	83.54 (15.24)	81.03 (17.22)
Female weight*, kg, mean (SD)	71.47 (15.58)	67.65 (18.64)
Height, cm, mean (SD)	164.73 (9.33)	164.85 (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)
Frailty subgroup (Frailty Index ≥ 0.25), n (%)	71 (59.2)	77 (60.2)
Highest Grip Strength, kg, mean (SD)	16.94 (6.9)	17.39 (7.93)
Grip Strength Male, kg, mean (SD)	21.84 (7.11)	24.26 (8.55)
Grip Strength Female, kg, mean (SD)	14.40 (5.25)	14.37 (5.39)
Calculated Montreal Cognitive Assessment (MoCA) score*, (score between 0–1), mean (SD)	0.76 ^a (0.11)	0.741 (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, minutes, mean (SD)	545.00 (80.19)	546.54 (83.09)
GENEActiv—calculated sleep efficiency, %, mean (SD)	76.04 (18.47)	0.78 (15.11)
GENEActiv—average sedentary time per day, minutes, mean (SD)	750.67 (87.15)	743.11 (109.67)
GENEActiv—average light activity time per day, minutes, mean (SD)	97.86 (54.87)	96.12 (51.24)
GENEActiv—moderate intensity activity time per day, minutes, mean (SD)	45.06 (46.08)	50.58 (48.72)
GENEActiv—average moderate-to-vigorous physical activity (MVPA) time per day, minutes, mean (SD)	45.09 (46.14)	50.67 (48.9)
GENEActiv Moderate Vigorous Physical Activity Bout Length, minutes, mean (SD)	2.91 (1.16)	2.90 (1.1)
GENEActiv number of Moderate Vigorous Physical Activity Bouts, mean (SD)	14.3 (11.4)	15.8 (11.2)

*indicates variation between trial arms. ^acorresponds to an MoCA (0–30) score of 23/30 for Intervention arm and 22/30 for control arm.

Table 2. Proportion of persons with a problem or symptom report at each session

Session number	1	2	3	4	5	6
Number of people who received a session	115	109	106	97	91	57
Percent with a problem or symptom report	79%	77%	75%	73%	65%	64%

Table 3. Primary and secondary outcomes at 12 months

Outcome*	Intervention group, Observed Change from baseline, Mean (SD)	<i>n</i>	Control group, Observed Change from baseline, Mean (SD)	<i>n</i>	Modelled Estimate = Intervention – Control (95% CI)	<i>P</i> -value
Primary Outcome						
Frailty Index	0.08 (0.076)	97	0.089 (0.082)	111	−0.009 (−0.028, 0.009)	0.320
Secondary Outcomes						
MoCA (0–30)	−1.89 (4.87)	87	−3.16 (5.88)	107	1.36 (0.01, 2.72)	0.048
Weight, kg	−0.21 (5.57)	96	0.85 (5.22)	108	−1.34 (−2.60, −0.09)	0.035
Grip Strength, kg	0.53 (4.53)	75	−0.15 (4.07)	80	0.47 (−0.71, 1.66)	0.433
EQ-5D	−0.199 (0.339)	107	−0.159 (0.329)	112	−0.023 (−0.110, 0.050)	0.566
Sleep Efficiency%	4.49 (17.86)	29	0.01 (16.05)	36	2.66 (−4.92, 10.24)	0.484
Sleep Time, minutes	−9.66 (59.65)	30	−7.99 (79.38)	40	−1.84 (−32.72, 29.03)	0.905
Sedentary Time, minutes	−7.68 (90.93)	30	−5.04 (85.2)	40	−4.96 (−45.83, 35.91)	0.809
Light Activity, minutes	1.70 (37.14)	30	4.71 (39.78)	40	−4.71 (−22.12, 12.70)	0.590
Moderate Intensity Activity, minutes	5.64 (39.30)	30	−3.9 (35.77)	40	7.06 (−8.23, 22.35)	0.359
Moderate Vigorous Physical Activity, minutes	5.68 (39.39)	30	−3.91 (35.86)	40	7.08 (−8.22, 22.39)	0.358
MVPA bout length, minutes	0.06 (0.88)	30	0.04 (0.76)	40	0.2 (−0.21, 0.61)	0.338
#of MVPA bouts	0.85 (8.29)	29	−0.57 (6.74)	40	0.58 (−2.80, 3.96)	0.731

*Adjusted for baseline value, gender and facility; MVPA: moderate-to-vigorous physical activity.

physical activity point estimates favoured the intervention arm for overall amount of time spent in moderate intensity activity, the length of each bout of time of moderate to vigorous intensity activity, sedentary time and sleep efficiency. Missing data at 12 months due to COVID restrictions prevented the calculation of frailty phenotype.

Overall, 1978 adverse events were recorded, of which 583 were judged as possible, probable or definite adverse medicine events. The majority were for falls or fracture, bleeding or bruising. No significant difference was observed for rate of adverse events between arms (Intervention rate per person per month 0.23 (SD 0.32); comparison rate per person per month 0.2 (SD 0.36) (estimated rate ratio 1.12, 95% CI: 0.78–1.61, $P = 0.55$)).

Sensitivity and post-hoc analyses

We found no evidence of survivor bias in the primary outcome in the sensitivity analysis. In the post-hoc analyses, no difference in baseline values by withdrawal status was found for weight or MoCA (Supplement 5, Table S1, Supplementary data are available in *Age and Ageing* online).

In exploratory subgroup analysis for weight, the direction of the result was variable across the subgroups, thus making it uncertain if the weight result was a clinical effect of the intervention. In subgroup analysis for MoCA, the direction of the result, while not significant, was consistent for both subgroups, suggesting that the result for MoCA is

likely to be an intervention effect (Supplement 5, Table S2, Supplementary data are available in *Age and Ageing* online).

Further *post-hoc* analysis identified that an additional 12% of residents in the intervention arm avoided cognitive decline of two or more points at 12 months, although this did not reach statistical significance (Supplement 5, Table S3, Supplementary data are available in *Age and Ageing* online). This represents a number needed to treat of 8.33; i.e. for every 8.33 residents that pharmacists reviewed every 8 weeks over a year, one would be expected to avoid a clinically relevant cognitive decline.

Discussion

This trial tested a novel intervention, that of ongoing pharmacist assessments using validated tools to identify signs of medicine-induced deterioration affecting cognition and physical activity. The study found no statistically significant difference in the change in frailty index from baseline between intervention and control groups. However, there was a significant difference in the change in cognition scores from baseline, favouring the intervention. In addition, the point estimates for the outcomes of change in frailty, physical activity and grip strength, which are independent objective measures, all favoured the intervention at 12 months. Clinically, the expectation of trajectory in this population is toward a decline in function [42], so a trend toward

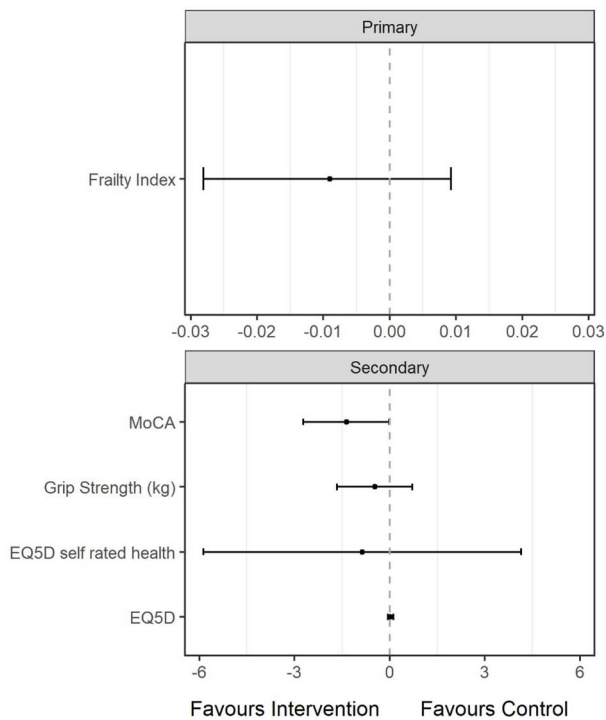


Figure 2. Forest plot for the primary and secondary outcomes, excluding physical activity outcomes. The direction of some outcomes has been changed to favour the intervention on the left.

improved physical activity in the intervention group could be viewed as a favourable outcome.

Our research, due to the intervention design, also documented the proportion of persons who had medication-related problems at each pharmacist session, finding that at least 60% of the cohort had a problem at each 8-week review session. The majority of research to date on medication reviews or pharmaceutical care services has assessed single session services with equivocal results about the effect of the service on clinical outcomes [11–14]. The frequency of new medication-related problems over time in the aged-care population found in our study is potentially biasing outcome assessments for single session pharmacist services in aged-care. Very few studies have tested the effectiveness of multiple session interventions by pharmacists. We found four published papers that had tested an intervention consisting of more than one pharmacist visit in aged-care. One was limited to a review plus a follow-up at 3 weeks [43]; another had a session at 1 and 6 months [44]. Two reported monthly attendance by the pharmacist at the aged-care facility [45, 46], but only one assessed the effectiveness of multiple visits [46]. Of the two studies with monthly pharmacist visits [45, 46], one reported a significant reduction in inappropriate psychoactive medicines use but no difference between groups in fall rates [42]. Another assessed the addition of a geriatric assessment risk guide to pharmacist assessments and found lower rates of potential delirium onset, in newly admitted persons, but not in longer stay residents [46]. Our trial

involved pharmacists using validated tools to detect early signs and symptoms of medicine-induced deterioration and included different outcomes [43–46], and therefore, the findings are not directly comparable.

The strengths of our study include the rigorous trial design, inclusion of 39 facilities and use of validated outcome measures. To our knowledge, changes in 24-hour movement behaviour over time have never been tested in the aged-care setting. All pharmacists received training prior to service implementation and were provided with peer support during service delivery. There were factors that limit the interpretation of our results. We targeted the less frail population within the aged-care setting; thus, our results are not generalizable to all residents. Participants aware of group allocation, which may have led to Hawthorne effect and bias in outcome assessments. We included objective measures such as dynamometer to mitigate some of this bias. Our final sample was short of our required sample size of 354 persons, leaving the study under-powered for its primary endpoint; however, the 95% confidence interval for the primary outcome contained the hypothesised treatment effect of -0.015 . The recruitment shortfall was in part due to the high proportion of frail residents in aged-care in Australia which meant that only 8% of the Australian aged-care population in the facilities recruited were eligible for our intervention. In addition, the COVID pandemic affected the latter part of our trial, with public health restrictions limiting pharmacist access to aged-care facilities. The potential impact of COVID-19 restrictions on the participants will be the subject of further research. Finally, we intended that the pharmacists would have access to continuous physical activity monitoring, which would enable them to monitor the potential sedative effects of medicines, but insufficient internet connectivity in Australian nursing homes resulted in only a small number of participants for which these data were available to the pharmacists.

Conclusions

While we cannot conclude that the intervention was successful, the intervention did show a statistically significant difference in changes in cognition between the intervention and control groups, and point estimates favoured the intervention group for the outcomes of frailty, physical activity and grip strength. In the context of an under-powered study, conducted within the limitations of the COVID-19 pandemic, we consider these results to provide sufficient evidence to recommend further research into pharmacist-led interventions in aged care that focus on proactively identifying clinical signs of medicine-induced deterioration to address the problem of reducing harm from medicines.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Declaration of Conflicts of Interest: Bilton was employed as the ReMInDAR partnership engagement and trial manager to oversee the operations management for the trial. Kang was employed as a research assistant of the ReMInDAR trial.

Registration: Australian and New Zealand Trials Registry ACTRN12618000766213 <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374151&isReview=true>.

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