Towards simpler medication regimens: understanding and addressing complex medication regimens for older people

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BPharm (Hons)

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Doctor of Philosophy

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Abstract

Background

Older people increasingly use multiple medications in complex medication regimens. Elements of medication regimens that make them complex, such as type of medication formulation, high frequency of administration and additional directions for medication use, increase the burden of medication management for people who manage their own medications. This burden may be exacerbated in people who are frail, have limited dexterity, cognitive impairment or swallowing difficulties. For residents of aged care facilities, this burden of complex medication regimens is usually shared with aged care staff responsible for administering their medication. Currently, as the number of people living in residential aged care facilities (RACFs) is increasing, and residents are older and frailer with more complex care needs, it is increasingly important to optimise medication management to reduce unnecessary burden for both residents and staff.

There is some evidence emerging that medication regimen complexity may be associated with medication non-adherence, adverse drug events, hospitalisation, and mortality. While interventions to simplify medication regimens have been trialled in community and hospital settings, there has been limited research in the RACF setting. It is not known to what extent complex medication regimens are already being addressed in residential aged care.

Aim

The overall aim of this thesis was to evaluate and address the burden of medication regimen complexity on older people and the health systems that serve them. This was undertaken in four parts:

Part A introduces the background and evaluates existing medication-related interventions in RACFs, with a focus on whether these interventions have addressed medication regimen complexity;

Part B investigates the burden of complexity in terms of contribution to adverse drug events from high-risk medications and time taken for medication administration;

Part C begins to address medication regimen complexity through the development, validation and evaluation of a simplification tool; and

Part D comprises the discussion and conclusion.

Methods

In Part A, a systematic review of four databases and the grey literature (January 1995 – July 2018) was undertaken to evaluate medication reconciliation and review in Australian RACFs.

Part B included a population-based cohort study in Hong Kong. People with atrial fibrillation (AF) who were new users of oral anticoagulants (OACs) between 2010 and 2016 were identified from the Hong Kong Hospital Authority's electronic medical records. Oral anticoagulants are a high-risk class of medications for which non-adherence and administration errors linked to regimen complexity could have important adverse outcomes. Cox proportional hazards regression was used to estimate the association between medication regimen complexity, measured using the validated scale Medication Regimen Complexity Index (MRCI), and intracranial, gastrointestinal and other bleeding. Baseline characteristics were balanced using inverse probability of treatment weighting.

Time taken to administer complex medication regimens was investigated through a time-and-motion study in three South Australian RACFs. This study explored the factors that contribute to the time needed to perform different medication administration tasks. A single investigator observed a representative sample of medication administration rounds, including different times of day, units, and staff types. The validated Work Observation Method By Activity Timing (WOMBAT) software was used to record observations.

In Part C, a tool to guide medication regimen simplification in RACFs was developed using nominal group technique. Factors identified and prioritised by the seven-member multidisciplinary expert panel were formulated into an implicit tool. The tool

was validated by testing agreement between two clinical pharmacists applying the tool to a random sample of 50 medication charts.

The validated tool was evaluated in a cluster randomised controlled trial (RCT) of eight RACFs. A cross-sectional analysis of baseline data from this trial was used to explore characteristics of residents with complex medication regimens. Medication regimen complexity was quantified using both number of daily administration times and the MRCI.

Results

The systematic review identified 13 studies, which comprised eight on Residential Medication Management Reviews and five on other comprehensive medication reviews. The studies reported that medication reviews were effective in identifying an average of up to four medication-related problems per review. Between 45 and 84% of recommendations were accepted. There was a lack of clinical and resident-centred outcomes reported, and there was no evidence of simplification as an outcome or of tools being used to simplify medication regimens.

In Part B, people with AF who initiate oral anticoagulants and have the most complex medication regimens had a small but significant increase in risk of experiencing any bleed compared to people with the lowest medication regimen complexity scores (adjusted Hazard Ratio [aHR] 1.46, 95% confidence interval [CI] 1.13-1.87), over a median of 501 days of follow-up. This association was not found to be significant in the first 90 days following OAC initiation.

The main finding of the time-and-motion study was that medication administration took an average of five minutes per resident per round. When analysed by type of residential unit, medication administration for residents in memory support units took an extra minute compared to residents in standard units (5.6 minutes vs 4.7 minutes, respectively). In memory support units, almost half (42%) of tablets/capsules were crushed. There was also a fixed time staff took to prepare for each medication round.

The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE) was developed in Part C. MRS GRACE comprised five ordered open-

ended questions. Based on a review of medication charts, the two clinical pharmacists identified opportunities for simplification for 30/50 and 29/50 residents with moderate agreement at a resident level (Cohen's kappa=0.38, 95% CI 0.12-0.64). This suggested that the tool was suitable for prospective evaluation in the residential aged care setting.

There were 242 residents recruited across eight aged care facilities in South Australia for the cluster RCT evaluating the application of MRS GRACE. In multivariate analysis, frailty was associated with number of daily administration times (Odds Ratio [OR]: 1.13, 95% CI: 1.03-1.24) and MRCI score (OR: 1.26, 95% CI: 1.13-1.41). Dementia severity was inversely associated with both multiple medication administration times (OR: 0.97, 95% CI: 0.94-0.99) and high MRCI score (OR: 0.95, 95% CI: 0.92-0.98).

Conclusion

This thesis identified that medication regimen complexity was not specifically being addressed for people accessing residential aged care, expanded the evidence for clinical and humanistic outcomes of medication regimen complexity, and developed a structured implicit tool to simplify medication regimens. There was existing scope for medication regimen simplification. However, more research is needed into clinical, resident-centred, and economic outcomes of medication regimen complexity. Further studies are needed into the translation of medication regimen simplification interventions in the residential aged care and other settings

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and one submitted publication. The core theme of the thesis is evaluating and addressing the burden of medication regimen complexity on health systems. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences under the supervision of Professor J Simon Bell, Professor Sarah Hilmer, Dr Jenni Ilomäki and Dr Janet Sluggett.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

Declaration

In the case of Chapters Two, Three, Four, Five and Six, my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	% and nature of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
2	Process, impact and outcomes of medication review in Australian residential aged care facilities: A systematic review	Published	55%: concept and design of study, literature search, screening of articles, data extraction and synthesis, preparation of manuscript	**K. Wang:** concept and design of study, screening of articles, data extraction and synthesis, review of manuscript (20%) **JK. Sluggett:** concept and design of study, review of manuscript (5%) **J. Ilomäki:** concept and design of study, review of manuscript (5%) **SN. Hilmer:** concept and design of study, review of manuscript (5%) **M. Corlis:** concept and design of study, review of manuscript (5%) **JS. Bell:** concept and design of study, review of manuscript (5%)	Yes No No No No No

Thesis Chapter	Publication Title	Status	% and nature of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
3	Medication regimen complexity and risk of bleeding in people taking oral anticoagulants: a population-based cohort study in Hong Kong	Submitted	50%: concept and design of study, data analysis and interpretation, preparation of manuscript	**JX. Zhao**: concept and design of study, data analysis and interpretation, review of manuscript (10%) **J. Ilomäki**: concept and design of study, review of manuscript (5%) **JK. Sluggett**: concept and design of study, review of manuscript (5%) **JS. Bell**: concept and design of study, review of manuscript (5%) **BC. Wimmer**: concept and design of study, review of manuscript (5%) **SN. Hilmer**: concept and design of study, review of manuscript (5%) **JE. Blais**: concept and design of study, review of manuscript (5%) **ICK. Wong**: concept and design of study, review of manuscript (5%) **EW. Chan**: concept and design of study, review of manuscript (5%)	No No No No No No No No No

Thesis Chapter	Publication Title	Status	% and nature of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
4	Medication administration in Australian residential aged care: A time-and-motion study	Published	50%: concept and design of study, recruitment, data collection, data analysis and interpretation, preparation of manuscript	**JS. Bell:** concept and design of study, review of manuscript (5%) **J. Ilomäki:** concept and design of study, review of manuscript (5%) **M. Corlis:** concept and design of study, review of manuscript (5%) **ME. Hogan:** concept and design of study, review of manuscript (5%) **T. Caporale:** concept and design of study, review of manuscript (5%) **J. Van Emden:** concept and design of study, review of manuscript (5%) **JI. Westbrook:** concept and design of study, review of manuscript (5%) **SN. Hilmer:** concept and design of study, review of manuscript (5%) **JK. Sluggett:** concept and design of study, recruitment, review of manuscript (10%)	No No No No No No No No No

Thesis Chapter	Publication Title	Status	% and nature of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
5	Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE)	Published	52.5%: concept and design of study, recruitment, data collection, analysis and interpretation, preparation of manuscript	**JK. Sluggett:** concept and design of study, review of manuscript (5%) **J Ilomäki:** concept and design of study, review of manuscript (5%) **SN. Hilmer:** concept and design of study, review of manuscript (5%) **M. Corlis:** concept and design of study, review of manuscript (5%) **LJ. Picton:** data analysis, review of manuscript (2.5%) **L. Dean:** data analysis, review of manuscript (2.5%) **CP. Alderman:** data acquisition, review of manuscript (2.5%) **N. Farinola:** data acquisition, review of manuscript (2.5%) **J Gailer:** data acquisition, review of manuscript (2.5%) **J. Grigson:** data acquisition, review of manuscript (2.5%) **AR. Kellie:** data acquisition, review of manuscript (2.5%) **PJ. Putsey:** data acquisition, review of manuscript (2.5%) **S. Yu:** data acquisition, review of manuscript (2.5%) **JS. Bell:** concept and design of study, review of manuscript (5%)	No No No No No No No No No No No No No No

Thesis Chapter	**Publication Title**	**Status**	**% and nature of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
6	Medication regimen complexity in 8 Australian residential aged care facilities: Impact of age, length of stay, comorbidity, frailty, and dependence in activities of daily living	Published	60%: concept and design of study, data analysis and interpretation, preparation of manuscript	**JS. Bell:** concept and design of study, review of manuscript (5%) **J. Ilomäki:** concept and design of study, review of manuscript (5%) **C. Keen:** data analysis, review of manuscript (5%) **M. Corlis:** concept and design of study, review of manuscript (5%) **ME. Hogan:** concept and design of study, review of manuscript (5%) **J. Van Emden:** concept and design of study, review of manuscript (5%) **SN. Hilmer:** concept and design of study, review of manuscript (5%) **JK. Sluggett:** concept and design of study, review of manuscript (5%)	No No No No No No No No

Declaration

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: Esa Yan Horng Chen

Student signature: **Date:** 23/08/2020

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Simon Bell

Main Supervisor signature: **Date:** 23/08/2020

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My first thanks goes to my supervisors: Professor Simon Bell, Professor Sarah Hilmer, Dr Jenni Ilomaki, and Dr Janet Sluggett. It's not always the case to have supervisors who are also your sponsors, but my supervisors were always generous with encouraging me and putting me in the position to take advantage of opportunities. Thank you so much for your patience and for sharing your knowledge with me. I'm also grateful to Dr Julia Gilmartin-Thomas and Dr Vivienne Mak for their consistent guidance throughout my entire PhD journey on my review panel. A special thank you to Dr Dan Malone, who was the best panel chair I could have asked for and objectively the best panel chair ever.

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Publications and presentations

Publications included in the thesis

1. Chen EYH, Bell JS, Ilomäki J, Corlis M, Hogan ME, Caporale T, Van Emden J, Westbrook JI, Hilmer SN, Sluggett JK. Medication administration in Australian residential aged care: A time-and-motion study. *Journal of Evaluation in Clinical Practice* 2021; 27(1): 103-110.

2. Chen EYH, Bell JS, Ilomäki J, Keen C, Corlis M, Hogan ME, Van Emden J, Hilmer SN, Sluggett JK. Medication Regimen Complexity In 8 Australian Residential Aged Care Facilities: Impact Of Age, Length Of Stay, Comorbidity, Frailty, And Dependence In Activities Of Daily Living. *Clinical Interventions in Aging* 2019; 14: 1783-1795.

3. Chen EYH, Wang KN, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS. Process, impact and outcomes of medication review in Australian residential aged care facilities: A systematic review. *Australasian Journal on Ageing* 2019; 38(S2): 9-25.

4. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Picton LJ, Dean L, Alderman CP, Farinola N, Gailer J, Grigson J, Kellie AR, Putsey PJC, Yu S, Bell JS. Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE). *Clinical Interventions in Aging* 2018; 13: 975-986.

Paper submitted for publication

5. Chen EYH, Zhao JX, Ilomäki J, Sluggett JK, Bell JS, Wimmer BC, Hilmer SN, Blais JE, Wong ICK, Chan EW. Medication regimen complexity and risk of bleeding in people taking oral anticoagulants: a population-based cohort study in Hong Kong.

Publications published during candidature which do not form part of the thesis

1. Sluggett JK, Hopkins RE, Chen EYH, Ilomäki J, Corlis M, Van Emden J, Hogan ME, Caporale T, Ooi CE, Hilmer SN, Bell JS. Impact of Medication Regimen Simplification on Medication Administration Times and Health Outcomes in Residential Aged Care: 12 month follow up of the SIMPLER randomized controlled trial. *Journal of Clinical Medicine* 2020; 9(4): 1053.

2. Sluggett JK, Chen EYH, Ilomäki J, Corlis M, Van Emden J, Hogan ME, Caporale T, Keen C, Hopkins R, Ooi CE, Hilmer SN, Hughes GA, Luu A, Nguyen K, Comans T, Edwards S, Quirke L, Patching A, Bell JS. Reducing the Burden of Complex Medication Regimens: SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) Cluster Randomized Controlled Trial. *Journal of the American Medical Directors Association* 2020; 21(8): 1114-1120.e4.

3. Bell JS, McInerney B, Chen EYH, Bergen PJ, Reynolds L, Sluggett JK. Strategies to simplify complex medication regimens. *Australian Journal of General Practice* 2020; 50(1-2): 43-48.

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5. Hughes GA, Bell JS, Chen EYH, Ooi CE, Caporale T, Hogan ME, Corlis M, Van Emden J, Sluggett JK. Would you like to participate? Factors impacting on participant recruitment for quality use of medicines interventions in residential aged care. *Research in Social and Administrative Pharmacy* 2019; 15(5): e12.

6. Wang KN, Bell JS, Chen EYH, Gilmartin-Thomas JFM, Ilomäki J. Medications and prescribing patterns as factors associated with hospitalizations from long-term care facilities: A systematic review. *Drugs & Aging* 2018; 35(5): 423-457.

7. Sluggett JK, Chen EYH, Ilomäki J, Corlis M, Hilmer SN, Van Emden J, Ooi CE, Nguyen K, Comans T, Hogan ME, Caporale T, Edwards S, Quirke L, Patching A, Bell JS. SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER): study protocol for a cluster randomised controlled trial. *Trials* 2018; 19(1): 37.

8. Chen EYH, Sluggett JK, Bell JS. What Steve Jobs knew about medicines. *Journal of Pharmacy Practice and Research* 2018; 48(5): 401-402.

Conference presentations during candidature

1. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS. Development, validation and application of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE). Oral presentation (symposium speaker), APSA Annual Conference 2019, Melbourne, December 2019.

2. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS, MRS GRACE consensus group. Variation in medication regimen complexity in Australian residential aged care. Poster presentation, Asian Conference for Pharmacoepidemiology, Kyoto, October 2019.

3. Chen EYH, Luu A, Bell JS, Corlis M, Sluggett JK. Top recommendations to make medication regimens SIMPLER in aged care. Oral presentation (presented by Bell JS), Australian Association of Gerontology Conference, Melbourne, November 2018.

4. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS, MRS GRACE consensus group. The Medication Regimen Simplification Guide in Residential Aged CarE (MRS GRACE): helping to make medications simpler. Poster presentation, National Medicines Symposium, Canberra, May 2018.

5. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS, MRS GRACE consensus group. Development and validation of an implicit tool to simplify medication regimens in residential aged care. Poster presentation, Asian Conference for Pharmacoepidemiology, Brisbane, October 2017.

6. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS, MRS GRACE consensus group. The Medication Regimen Simplification Guide in Residential Aged CarE (MRS GRACE): a novel tool to optimise medication regimens for residents of aged care facilities. Oral and poster presentation, Australasian Pharmaceutical Science Association-Australian Society of Clinical and Experimental Pharmacologists and Toxicologists Joint Scientific meeting, Brisbane, December 2017.

7. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS, MRS GRACE consensus group. Development and validation of the Medication Regimen Simplification Guide in Residential Aged CarE (MRS GRACE). Poster presentation, NHMRC National Institute for Dementia Research Australian Dementia Forum, Melbourne, October 2017.

8. Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS, MRS GRACE consensus group. How can medication regimens be simplified for residents of aged care facilities? Oral and poster presentation, Parkville Postgraduate Association's 12th Annual Postgraduate Research Symposium, Melbourne, October 2017.

9. Sluggett JK, Chen EYH. Reducing unnecessary medication complexity in residential aged care. Oral presentation, PSA17, Sydney, July 2017.

10. Chen EYH, Wang KN, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS. Medication review in residential aged care facilities: a systematic review. Oral and poster presentation, Australian Society of Clinical and Experimental Pharmacologists and Toxicologists-Molecular Pharmacology of G Protein-Coupled Receptors Joint Scientific meeting, Melbourne, November 2016.

11. Chen EYH, Wang KN, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS. A systematic review of Australia's medication review program in residential aged care. Oral and poster presentation, NHMRC Cognitive Decline Partnership Centre Annual Meeting, Sydney, November 2016.

12. Chen EYH, Wang KN, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Bell JS. Clinical medication review in Australian residential aged care facilities (RACFs): a systematic review. Oral presentation, Parkville Postgraduate Association's 11th Annual Postgraduate Research Symposium, Melbourne, September 2016.

List of abbreviations

ADE	Adverse drug event
ADL	Activities of daily living
AF	Atrial fibrillation
aHR	Adjusted hazard ratio
AMCI	Antiretroviral Medication Complexity Index
ARC	Antiretroviral Regimen Complexity
CDARS	Clinical Data Analysis and Reporting System
CCI	Charlson Comorbidity Index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DOAC	Direct oral anticoagulant
ED	Emergency department
EMTCI	Epilepsy Medication Treatment Complexity Index
GP	General practitioner
HA	Hong Kong Hospital Authority
HR	Hazard ratio
IQR	Interquartile range
ISMP	Institute of Safe Medication Practices
LTCF	Long-term care facility

MCI	Medication Complexity Index
MRCI	Medication regimen complexity index
MRP	Medication-related problem
MRS GRACE	Medication Regimen Simplification Guide for Residential Aged CarE
OAC	Oral anticoagulant
OTC	Over the counter
OR	Odds ratio
QOL	Quality of life
QUM	Quality Use of Medicines
RACF	Residential aged care facility
RCT	Randomised controlled trial
RMMR	Residential Medication Management Review
SD	Standard deviation
SE	Standard error
SIMPLER	SImplification of Medications Prescribed to Long-tErm care Residents
UMS	Universal Medication Schedule
USA	United States of America
WOMBAT	Work Observation Method By Activity Timing

Aim, objectives, and outline

The overall aim of this thesis was to evaluate and address the burden of medication regimen complexity on older people and the health systems that serve them. This aim was achieved through the following specific objectives:

1. To systematically review Australian literature on comprehensive medication review for residents of residential aged care facilities (RACFs);
2. To investigate the association between medication regimen complexity and safety of oral anticoagulants in people with atrial fibrillation (AF) in a population-based study in Hong Kong;
3. To estimate the time taken to administer medication regimens to residents of RACFs;
4. To develop and validate a medication regimen simplification guide for residents of RACFs; and
5. To investigate the prevalence and correlates of medication regimen complexity in residents of RACFs prior to application of a medication regimen simplification guide.

Part A of the thesis focuses on current interventions that may address medication regimen complexity and medication-related harms. Chapter One includes a background on RACFs and medication use in older people including residents of RACFs. Chapter Two is a systematic review of the Australian literature investigating medication review and reconciliation, which forms the main intervention to identify and resolve medication-related problems in RACFs over the past two decades.

Part B of the thesis focuses on the burden of medication regimen complexity to older people with complex medications regimens and to the health systems they live within. Chapters Three and Four investigate the outcomes of complex medication regimens through a) clinical outcomes of hospitalisation due to bleeding, which is burdensome for older people themselves as well as the wider health system, and b) time spent on medication administration in RACFs, which is burdensome for both RACF staff and residents.

Part C describes the development of a new tool to assist clinicians undertake medication simplification and address the burden of complex medication regimens. Chapter Five introduces the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE). The application of this tool by a clinical pharmacist was evaluated in the Simplification of Medications Prescribed to Long-term care residents (SIMPLER) cluster-randomised controlled trial. Chapter Six investigates the baseline variability in medication regimen complexity of participants in the SIMPLER trial.

Part D of the thesis includes Chapter Seven, a discussion of the main findings of the thesis, strengths, limitations, and future directions. Chapter Eight concludes the thesis.

PART A: EVALUATING CURRENT MEDICATION INTERVENTIONS FOR OLDER PEOPLE

CHAPTER ONE: BACKGROUND

CHAPTER TWO: Process, impact and outcomes of medication review in Australian residential aged care facilities: A systematic review
Chen EYH, Wang KN, Sluggett JK, et al. Process, impact and outcomes of medication review in Australian residential aged care facilities: A systematic review. *Australasian Journal on Ageing.* 2019; 38(S2): 9-25.

PART B: INVESTIGATING THE BURDEN OF MEDICATION REGIMEN COMPLEXITY

CHAPTER THREE: Medication regimen complexity and risk of bleeding in people taking oral anticoagulants: a population-based cohort study in Hong Kong
Chen EYH, Zhao JX, Ilomäki J, et al. Medication regimen complexity and risk of bleeding in people taking oral anticoagulants: a population-based cohort study in Hong Kong.

CHAPTER FOUR: Medication administration in Australian residential aged care: A time-and-motion study
Chen EYH, Bell JS, Ilomäki J, et al. Medication administration in Australian residential aged care: A time-and-motion study. *Journal of Evaluation in Clinical Practice* 2020; online early. DOI: 10.1111/jep.13393.

PART C: ADDRESSING MEDICATION REGIMEN COMPLEXITY: A NOVEL INTERVENTION

CHAPTER FIVE: Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE)
Chen EYH, Sluggett JK, Ilomäki J, et al. Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE). *Clinical Interventions in Aging* 2018; 13: 975-986.

CHAPTER SIX: Medication regimen complexity in 8 Australian residential aged care facilities: impact of age, length of stay, comorbidity, frailty, and dependence in activities of daily living
Chen EYH, Bell JS, Ilomäki J, et al. Medication Regimen Complexity In 8 Australian Residential Aged Care Facilities: Impact Of Age, Length Of Stay, Comorbidity, Frailty, And Dependence In Activities Of Daily Living. *Clinical Interventions in Aging* 2019; 14: 1783-1795.

PART D: DISCUSSION AND CONCLUSION

CHAPTER SEVEN: Discussion

CHAPTER EIGHT: Conclusion

PART A: EVALUATING CURRENT MEDICATION INTERVENTIONS FOR OLDER PEOPLE

1. Chapter One: Background

1.1 Introduction

Older people are using more medications to manage multimorbidity associated with ageing.[1] As more people are getting older, associated demands on health systems are also increasing.[2] In Australia, more people are entering residential aged care, and the point of entry is becoming more acute as government policy encourages and provides support for people to stay in their homes for longer.[3,4] Residents of aged care are a vulnerable population that often rely on aged care staff for medication administration and other care duties.[3] Additionally, the increased number of people with complex care needs needing residential aged care means it is increasingly challenging to provide high quality and safe care for residents.[5] Finding ways to optimise medication management is therefore important.

Medication regimen complexity is of increasing concern as people are supported to stay in their homes for longer and are therefore responsible for managing their increasing medication burden. This includes organising their own medication regimens, which may be prescribed by multiple prescribers in a fragmented care team.[6-8] Medication regimens may then be highly complex if or when people enter residential aged care. Elements of medication regimens including formulations, frequency of administration, and additional directions for medication use, when considered as a whole as ‘medication regimen complexity’ has been associated with medication non-adherence, adverse drug events, hospitalisation and mortality.[9-11]

Medication regimen simplification is a promising intervention because the potential benefits are multifaceted. Simplification, which involves consolidating the number of medication dosing times through administering medication at the same time and optimising the use of medication formulations, may improve clinical outcomes which complex medication regimens have been associated with. Reducing complexity may improve the experience of medication administration for residents by reducing the burden of frequent administration and/or pill burden.[12] For aged care staff

responsible for administering medication, time saved from reduced frequency of administration may be redirected into other care activities that improve the safety and/or quality of care.[5]

The aim of this thesis was to evaluate and address the burden of medication regimen complexity on older people and the health systems that serve them. First, a review of existing medication-related interventions undertaken in Australian residential aged care facilities that may potentially be reducing medication regimen complexity was completed. Then, investigation into the burden of complex medication regimens in terms of clinical outcomes and human resources was undertaken. While the studies were conducted mainly in the Australian residential aged care setting, a population-based study in Hong Kong provided an opportunity to investigate a clinical outcome of medication regimen complexity in older people in a different health system. The research in Hong Kong focused on oral anticoagulants (OACs) because this is a high-risk medication class and non-adherence and administration errors linked to regimen complexity may be associated with serious adverse outcomes. OACs are often but not exclusively used by older people who may have difficulty self-managing their medication regimen due to frailty, limited dexterity or cognitive impairment.[13,14] Finally, a tool to guide medication regimen simplification was developed and validated to address regimen complexity. A cross-sectional analysis explored characteristics of residents with complex medication regimens prior to application of the medication regimen simplification tool.

1.2 Healthcare for a global ageing population

Population ageing is a global trend with wide-ranging implications for individuals and health systems. Overall, people aged 65 years and older comprise the fastest growing age group.[2] In Australia, people aged 65 or older comprised approximately 15% of the population in 2017.[15] Hong Kong reported a similar proportion of 16% in 2017.[16] The oldest group, comprising people aged 80 years and older, is also set to increase.[2] The increasing number of people living longer reflects considerable advances in public health. However, quality of life during these longer life spans, and how we care for the increasing number of older people is now of imminent

importance. This includes a focus on how older people can safely and effectively manage medications to minimise the risk of medication-related harm.

1.2.1 Overall medication burden

Medical conditions, particularly chronic conditions, increase with age, and so too does medication use to treat those medical conditions. Polypharmacy, or the use of multiple medications, is on the rise internationally in line with global ageing trends.[17,18] Older people have a higher risk of medication-related problems than younger people due to changing physiology which can affect the absorption, distribution, metabolism, and excretion of medications.[19] In addition, changing risk-benefit profiles of medications and frequent medication changes increase the burden of medication management. A study of over 350,000 older veterans in the United States of America (USA) aged 65 years and older found a median of four medication changes over a one year period, while the overall number of medications used remained stable.[20] In 12% of participants, there were 10 or more medication changes.[20] Addition of a new medication was the most common type of medication change (occurring in 61% of participants).[20] In contrast, a German study found discontinuation and dosage alterations were the most frequent changes, with 99% of participants experiencing at least one medication change in nine months.[21] The overall number of medications also remained stable.[21] “Treatment complexity and feasibility when making clinical management decisions for older adults with multimorbidity” was identified as a guiding principle for patient-centred care of older adults with multiple chronic conditions by the American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity.[22]

1.2.2 Use of high-risk medications

High-risk medications are medications that have a higher risk of significant medication harm if involved in errors.[23,24] Various lists of high-risk medications have been developed, often based on setting and local use. The National Safety and Quality Health Service Standard requires Australian health services to identify their high-risk medications and develop appropriate protocols to ensure safe use.[25] The Institute of Safe Medication Practices (ISMP) have listed high-alert medications utilised within acute care, community, and long-term care settings.[23,26,27] Common

classes across the various settings include opioids, insulin, and chemotherapeutic agents.[23,24,26,27] However, there is not yet a clear, international consensus on the definition of high-risk medications or list of high-risk medications.[28] Despite the lack of general consensus, the use of high-risk medications is common in older people and may lead to serious adverse outcomes.

For example, in acute care, all antithrombotic medications are considered to be high-risk medications by the ISMP, while only parenteral and OACs are considered as high-risk in long-term care, and only warfarin is listed in community settings.[23,26,27] OACs are indicated for reducing ischaemic stroke risk in people with atrial fibrillation (AF), but may also increase risk of bleeding. In older people, there is some hesitancy in prescribing due to the perceived risk/benefit ratio. A meta-analysis of OAC use in people with and without dementia found a mean prevalence of OAC use of 32% in people living with dementia and 48% in people without dementia.[29] The median age ranged from 73 to 85 years.[29] An audit of 19 RACFs in southeast Queensland found that around 40% of residents who were assessed to have AF, and were indicated OAC use, were not prescribed anticoagulation.[30] These residents also did not have any clinical notes to indicate why OACs had not been prescribed.[30] A retrospective review of 1952 residents of Australian RACFs receiving medication reviews found that only 35% of eligible residents took an anticoagulant, and residents were less likely to receive anticoagulation as they got older.[31] Bleeding risk was identified as a greater influence on anticoagulant prescribing than stroke risk.[31] OACs are high-risk medications but remain guideline-recommended therapy with evidence of efficacy in older people.[32]

The introduction of direct oral anticoagulants (DOACs) has led to an overall increased use of OACs.[33,34] DOACs offer standard dosing, fewer drug interactions, and less intensive laboratory monitoring.[34] While utilisation and public cost of OACs has been steadily increasing, there is room for improvement in OAC prescribing.[35] DOAC uptake has not been equal between populations, with residents of RACFs less likely to receive DOACs.[33] Prescribers may feel more confident with more evidence around the safety profile of OACs and pre-existing risk factors in older people.

1.3 Medication regimen complexity

Medication regimen complexity refers to medication regimen elements in addition to a simple count of the number of medications, or polypharmacy. Polypharmacy is the use of multiple medications, commonly nine or more, or the inappropriate or unnecessary use of medications.[36] Medication regimens comprise other elements in addition to the number of medications. Elements that contribute to the complexity of medication regimens that have been included in various measures of complexity have been administration frequency, route of administration, number of tablets or dosage units per administration, relationship of administration to food, and other additional instructions.[37,38] It is important to consider these elements together as they all contribute to the burden of medication administration and management.[39]

1.3.1 Measuring medication regimen complexity

Multiple approaches to measuring medication regimen complexity are described in the literature. A systematic review of literature published up to May 2012 investigated the different scales and methods.[38] While there were 10 studies that defined complexity using their own algorithms, there were five validated scales used by the majority of studies: Medication Regimen Complexity Index, Medication Complexity Index (MCI), Epilepsy Medication Treatment Complexity Index (EMTCI), Antiretroviral Regimen Complexity (ARC), and Antiretroviral Medication Complexity Index (AMCI).[38] Since the systematic review, new indexes have been created to cater for specific settings in which the existing scales do not perform well.[40] For example, in intensive care units, critically ill hospitalised patients rely completely on the care of medical and care staff who are responsible for their medications.[41,42] In this setting, a patient-oriented index designed assuming chronic medications as the norm was not sensitive enough to be useful.

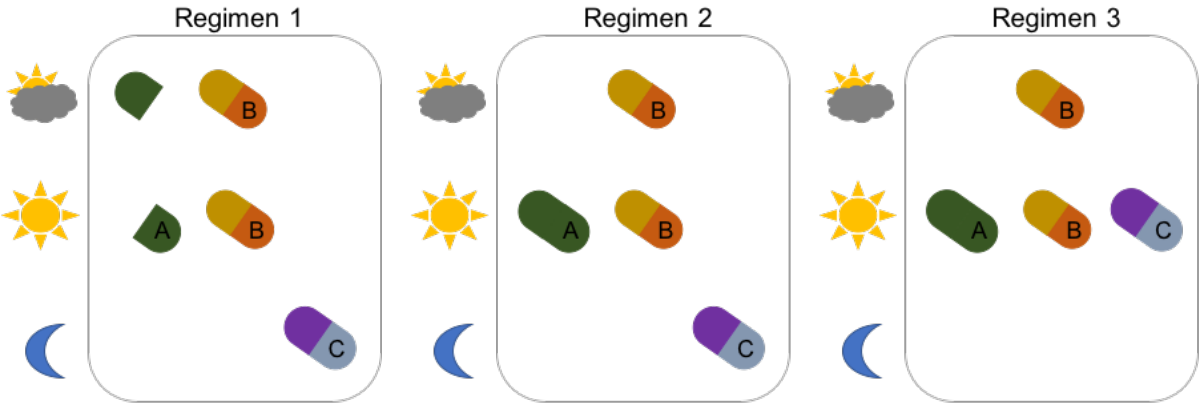
The Medication Regimen Complexity Index (MRCI) has emerged to be the gold-standard and most widely used method of quantifying medication regimen complexity.[11,38] It has been translated and validated in German,[43] Brazilian Portuguese,[44] Spanish,[45] Turkish,[46] and Korean[47] for use internationally.

1.3.2 Use of the Medication Regimen Complexity Index (MRCI)

The MRCI is a validated 65-item scale comprising of three sections. Section A assesses the type and number of different formulations present in the regimen (e.g. tablet, cream, turbuhaler). Section B assesses the frequency of administration for each medication (e.g. once daily, every eight hours). Section C assesses additional directions for medication administration (e.g. to have with food, to break tablets). Scores from each section are added to calculate the MRCI of the medication regimen. The MRCI treats complexity mainly as a dimension related to the medication regimen, largely independent to the patient, although some patient factors such as swallowing difficulties may be included through weighting for need to crush tablets.

The MRCI does not contain a direct count of the number of medications in a regimen. Regimens with the same number of medications may return different MRCI scores based on other complexity factors.[48] The minimum MRCI score is 1.5, which represents an oral tablet with instructions to take one tablet daily when required.[48,49] There is no “maximum” MRCI score as theoretically there is no limit to the number of medications a person can be using.[48]

The MRCI is sensitive enough to discriminate between medication regimens with the same number of medications. This is illustrated in Figure 1, where all regimens have three medications, but different MRCI scores. Regimen 1 receives additional points for the added complexity of having to break tablet A and twice daily administration of tablets A and B. However, MRCI score and medication count still show strong correlation.[48] One limitation of the use of the MRCI is that there is no direct count of the number of overall daily administration times. Section B of the MRCI adds the frequency of each individual medication. That is, Regimens 2 and 3 in Figure 1 have the same MRCI score, despite Regimen 2 having three overall daily administration times, and Regimen 3 having two overall daily administration times. This is particularly relevant in settings such as RACFs, where number of overall daily administration times may determine the number of medication administration rounds needed.



	Regimen 1	Regimen 2	Regimen 3
MRCI section A	1	1	1
MRCI section B	5	4	4
MRCI section C	1	0	0
Total MRCI score	7	5	5

Figure 1: Example medication regimens with the same therapeutic intent

In addition to the original application, the MRCI has been used in two main ways in the literature to quantify regimen complexity: disease-specific and patient-level. Disease-specific use of the MRCI involves counting only those medications used to treat a singular disease. For example, including only antidiabetic medications will produce a diabetes-specific MRCI score.[50,51] This approach has been used to compare complexity of disease-specific regimens and the impact on disease-specific clinical outcomes, such as A1C goals in people with diabetes.[50]

While the MRCI was developed and validated in a cohort of people with chronic obstructive pulmonary disease (COPD), the regimens used in the development and validation included all prescription medications, not only those used to manage COPD.[50] This indicates that a disease-specific application was not the originally intended use of the MRCI. The original MRCI instructions also restrict the MRCI to all regular and pro re nata (PRN, or as needed) prescription medications only.[48] However, people may use complementary and alternative medicines or supplements that have not been prescribed but would contribute to the patient's experience of regimen complexity.[52] To differentiate from the disease-specific uses and original MRCI, the term "patient-level" MRCI score is sometimes used to refer to an MRCI score that includes all the medications a person is using, including prescription and

over-the-counter medications.[52,53] The patient-level MRCI was proposed to be a more practical measure of regimen complexity for patients across different disease states and with comorbid conditions.[53] However, it is still largely a medication-related measure that excludes patient factors, such as health literacy or dexterity, that contribute to the patient perspective on complexity.

Disease-specific and patient-level MRCI are not always correlated. A number of factors contribute to the extent to which they overlap, and the extent to which they can predict clinical outcomes. For example, number of comorbidities and relative severity of conditions may determine the proportion of patient-level MRCI score that disease-specific complexity contributes. Other conditions and medications present in the regimen may impact on clinical outcomes.[50]

1.3.3 Prevalence of complex medication regimens

The prevalence and intensity of complex medication regimens differs among different populations and settings.[51] The use of the MRCI as a validated and gold-standard index has allowed comparison between studies, but what is considered to be a “highly complex” medication regimen has not been well established. MRCI scores can vary relative to individual settings and populations, given different prescribing patterns and guidelines in different countries and risk profiles for medication use in people of various ages.[49,52] As a result, studies using the MRCI have used various cut points established using differing methods, commonly based on sample-specific distributions (Table 1). Few studies have been undertaken in the RACF setting.

Table 1. Summary of studies investigating medication regimen complexity thresholds using the Medication Regimen Complexity Index (MRCI)

Author, year (study type)	Setting (country)	Population	Sample size	Age	Medication assessment (included OTC)	MRCI score	Outcome	MRCI cut point(s)	Determination of cut points
Díez-Manglano et al, 2020[54] (cohort study)	Internal medicine departments in 5 hospitals (Spain)	People with ≥2 chronic, interrelated, progressive diseases whose progression cause disability	223	Mean: 79.8 (SD 8.6)	Not reported (U)	Mean: 32 (SD 15.2)	Mortality	Low: <21 High: ≥21	Lowest MRCI quartile in the study sample
Ruiz Ramos et al, 2020[55] (retrospective observational study)	1 tertiary hospital (Spain)	>65 years and visited emergency department	201	Mean: 77.6 (SD 15.3)	Electronic primary care prescription system (N)	Medians Admission: 21 (IQR 14-30.5) Discharge: 25 (IQR 17.5-33)	Repeat visits to the health care system in those patients who visit emergency departments due to an MRP	>20	Median value
Ayele et al, 2019[56] (cross-sectional study)	1 general hospital (Ethiopia)	>18 years with type 2 diabetes mellitus	275	Mean: 53.7 (SD 9.94)	Hospital medication chart (U)	Range: 2-19	Adherence, glycaemic control	Low: ≤4 Medium: 5–8 High: >8	Adapted from Yeh et al. (2017)

Author, year (study type)	Setting (country)	Population	Sample size	Age	Medication assessment (included OTC)	MRCI score	Outcome	MRCI cut point(s)	Determination of cut points
Morillo-Verdugo et al, 2019[57] (cross-sectional study)	1 tertiary hospital (Spain)	>50 years with HIV taking antiretroviral treatment	223	Median: 53.0 (IQR 52.0-57.0)	Electronic hospital pharmacy dispensing records (U)	Not reported	Polypharmacy	11.25	Receiver operating characteristics curves
Santos et al, 2019[58] (cross-sectional study)	1 general public hospital (Brazil)	All ≥60 years	255	Mean: 75.0 (SD 13.0)	Electronic medical records (U)	Mean: 17.0 (SD 14.5)	ED visit within 30 days of hospitalisation	>16.5	Adapted from Pantuzza et al. (2018)
Pantuzza et al, 2018[59] (cross-sectional study)	2 primary healthcare centres (Brazil)	≥60 years with at least 1 medication	227	Mean: 71.4 (SD 7.5)	Face-to-face interviews (U)	Median: 12 (IQR 3-38)	Standardize the adapted Brazilian version of the MRCI for the population of elderly patients	Low: ≤9.0 Medium: >9 and ≤16.5 High: >16.5	P25 and P75 MRCI percentiles
Colavecchia et al, 2017[60] (retrospective cohort study)	1 hospital (USA)	≥18 years hospitalised for heart failure and discharged to home	1452	Readmitted mean: 68 (SD 15) Not readmitted mean: 68 (SD 15)	Medication discharge list (U)	Readmitted mean: 15 (SD 6.2) Not readmitted mean: 14 (SD 6.8)	30-day hospital readmission	≥15	Adapted from Schoonover et al. (2014)

Author, year (study type)	Setting (country)	Population	Sample size	Age	Medication assessment (included OTC)	MRCI score	Outcome	MRCI cut point(s)	Determination of cut points
Sevilla-Sanchez et al, 2017[61] (cross-sectional study)	1 acute geriatric unit in a referral hospital (Spain)	All with advanced chronic conditions needing palliative care and with limited life expectancy	235	Mean: 86.8 (SD 5.37)	Medical records (U)	Mean: 38.0 (SD 16.54)	Prevalence, causality, severity, and preventability of the ADEs	>38	Sample mean
McDonald et al, 2016[62] (clustered randomised trial)	1 urban home care agency (USA)	All	Intervention: 2550 Control: 5369	Intervention mean: 68.4 (SD 14.1) Control mean: 67.1 (SD 14.4)	Electronic medical records (U)	Not reported	Hospitalisation and ED presentation	≥24.5	Highest quintile of study sample
Yeh et al, 2016[50] (cross-sectional study)	1 healthcare centre (USA)	≥18 years with type 2 diabetes mellitus	368	Mean: 63	Electronic medication list (Y)	Range 2-98.5	A1C goal attainment	Low: ≤20 Moderate: >20 to 40 High: >40	Tertiles in the study sample
Herson et al, 2015[63] (cross-sectional study)	6 RACFs in South Australia (Australia)	≥65 years	383	Mean: 87.5 (SD 6.2)	Extracted from medication records by trained study nurses	Median: 43.5 (range 4-113)	Factors associated with medication regimen complexity	Q1: ≤32.5 Q2: > 32.5–43.5 Q3: >43.5–55.5 Q4: >55.5	Quartiles in the study sample

Author, year (study type)	Setting (country)	Population	Sample size	Age	Medication assessment (included OTC)	MRCI score	Outcome	MRCI cut point(s)	Determination of cut points
Wimmer et al, 2015[64] (cohort study)	1 district in central Stockholm (Sweden)	≥60 years living at home or in a non-home setting	3348	Median: 72 (IQR 66-84)	Clinical examination for home settings and medical records for non-home settings (Y)	Median: 9 (IQR 4-16) Mean: 11.0 (SD 9.6)	Unplanned hospitalisation	14	Receiver operating characteristics curves
Wimmer et al, 2015[65] (cross-sectional study)	1 district in central Stockholm (Sweden)	≥60 years living at home or in a non-home setting	3348	Median: 72 (IQR 66-84)	Clinical examination for home settings and medical records for non-home settings (Y)	Median: 9 (IQR 4-16)	Factors associated with medication regimen complexity	>20	Highest MRCI quintile
Olson et al, 2014[66] (secondary analysis)	15 Medicare-certified home health care agencies (USA)	≥65 years admitted to home care agency after hospital discharge	911	Not reported	Medication records (Y)	Mean: 35.4	Medication-related hospital readmission	33	Receiver operating characteristics curves

Author, year (study type)	Setting (country)	Population	Sample size	Age	Medication assessment (included OTC)	MRCI score	Outcome	MRCI cut point(s)	Determination of cut points
Schoonover et al, 2014[67] (secondary analysis)	Home care agencies (USA)	≥50 years admitted to home care agency after hospital discharge with at least one comorbid condition	Potential for ADE: 181 No potential for ADE: 32	Potential for ADE mean: 70.85 (SE 0.71) No potential for ADE mean: 74.06 (SE 1.94)	Hospital discharge medication lists and home care medication list (U)	Discharge medication list mean: 26.8 (SE 1.50) Home medication list mean: 19.57 (SE 1.49)	Unplanned 30-day hospital readmission	Discharge: ≥22 Home: ≥15	Mean score in discharge and home MRCI in the study samples
Wimmer et al, 2014[68] (prospective cohort study)	1 geriatric evaluation and management unit in a tertiary care hospital (Australia)	All ≥70 years	163	Mean: 85.2 (SD 6.4)	Discharge summaries (Y)	40 (24.5%) had MRCI>35	Hospital discharge destination	>35	Highest quartile of regimen complexity in the study sample

Author, year (study type)	Setting (country)	Population	Sample size	Age	Medication assessment (included OTC)	MRCI score	Outcome	MRCI cut point(s)	Determination of cut points
Willson et al, 2013[69] (case-control study)	4 hospitals (Not reported)	All	Revisit: 92 No revisit: 228	Revisit mean: 50.29 (SD 17.21) No revisit mean: 49.39 (SD 17.46)	Electronic medical records (U)	Revisit admission mean: 27.38 (SD 17.78) No revisit admission mean: 16.21 (SD 14.84)	Hospital readmission for adverse drug events	≥8	Receiver operating characteristics curves

ADE, adverse drug event; ED, emergency department; HIV, human immunodeficiency virus; IQR, interquartile range; MRCI, medication regimen complexity index; MRP, medication-related problem; N, no; OTC, over the counter medication; SD, standard deviation; SE, standard error; U, unknown; USA, United States of America; Y, yes.

1.3.4 Poor health outcomes associated with complex medication regimens

Recent systematic reviews of the literature have investigated clinical outcomes associated with medication regimen complexity in older people, and when measured using measures that include multiple complexity elements (Table 2).[9-11]

Studies investigating clinical outcomes associated with medication regimen complexity were predominantly cross-sectional, case-control and cohort studies. There were no randomised-controlled trials included in the systematic reviews that have investigated whether simplifying complex medication regimens leads to improvements in clinical outcomes.[9-11] No studies have specifically investigated the safety of complex medication regimens in people initiating anticoagulants.

The publication of systematic reviews in 2017, 2018 and 2019 included studies as recently as April 2018. Since the publication of these systematic reviews, additional studies have investigated clinical outcomes related to complexity. These additional studies are summarised below:

- **Adherence**

Manzano-García et al. (2018) was a single-centre observational study in one hospital in Spain that found that global medication regimen complexity was significantly associated with nonadherence to antiretroviral therapy ($p < 0.001$).[70]

- **Re-hospitalisation**

Díez-Manglano et al. (2020) was a cohort study across five hospitals in Spain. People with two or more chronic conditions whose progression cause disability were included. Results found that people in the lowest quartile of MRCI score had significantly less re-hospitalisations in the following year compared to people with higher MRCI scores ($p=0.012$).[54]

- **Adverse drug events (ADEs)**

Curtain et al. (2020), in an Australian study of people aged 65 years or older, found that medication regimen complexity was not significantly different in people with an ADE related hospitalisation compared to people with other medical admissions.[71]

- **Emergency department (ED) presentation**

Ruiz Ramos et al. (2020) studied one hospital in Spain and found that MRCI>20 (the median score of the sample) was associated with repeat emergency department presentation and repeat visits to the health system (hospitals, LTCFs and primary care centres).[55]

Santos et al. (2019), in a cross-sectional study of one hospital in Brazil, found that MRCI>16.5 was associated with ED presentation within 30 days of hospitalisation in multivariate analysis (OR 2.1; 95%CI 1.11-4.02).[58]

- **Mortality**

The cohort study by Díez-Manglano et al. (2020) across five hospitals in Spain also found that people in the lowest MRCI score quartile had a lower risk of mortality over four years compared to people with higher MRCI scores (HR 0.634; 95% CI 0.414–0.970).[54]

Sevilla-Sanchez et al. (2018), a cross-sectional study of people with advanced chronic disease needing palliative care in one acute-geriatric unit in a Spanish hospital, did not find any difference in two year mortality in people with high or low MRCI score (HR 1.21, 95%CI: 0.85 to 1.71).[72]

- **Hospital discharge destination**

Sevilla-Sanchez et al. (2018), a cross-sectional study of people with advanced chronic disease needing palliative care in one acute-geriatric unit in a Spanish hospital, did not find any difference in hospital discharge destination (nursing home, home, intermediate care) between people with high or low complexity.[72]

Trends in medication regimen complexity cannot be generalized across different settings. For example, the relationship between age and medication regimen complexity has been inconsistent between settings. Previous studies in Israeli and Spanish acute hospitals did not find a correlation between medication regimen complexity and age.[73,74] This is in contrast with a Swedish population-based study of community-dwelling older people which showed that people with the most complex medication regimens were older.[65] An Italian population-based study reported that the number of daily medications increases up to 85 years of age, beyond which it may decrease rather than continue to increase.[75]

In the existing literature, there are few studies of medication regimen complexity in residential aged care settings. It has been suggested that residents of RACFs have more complex medication regimens than older people living at home in the community.[65] As older people living permanently in RACFs often do not self-administer their own medication, medication regimen complexity may have different implications in the RACF setting. Therefore, it is important to investigate medication regimen complexity in RACFs separately.

Table 2. Summary of systematic reviews of health outcomes associated with complex medication regimens

Author, year	Search range (# studies)	Study designs (# studies)	Country (# studies)	Population (# studies)	Measures of complexity (# studies)	Association with complexity		
						Positive (# studies)	None (# studies)	Negative (# studies)
Pantuzza et al, 2017[76]	Inception-March 2016 (54)	Cross sectional (37) Prospective cohort (9) Retrospective cohort (8)	USA (25) Brazil (6) Italy (3)	Outpatient (51) Hospital (2) Supported housing facility (1)	MRCI (9) MCI (4) ARCI (3) EMTCI (1) Number of medications (13) Self-perceived complexity scales (2) Differentiated self-report of perceived complexity (4) Dose frequency (5) Other (13)	Non-adherence (29) Adherence (9)	Adherence (16)	

Author, year	Search range (# studies)	Study designs (n)	Country (n)	Population (n)	Measures of complexity (n)	Association with complexity		
						Positive (n)	None (n)	Negative (n)
Wimmer et al, 2017[9]	Inception-June 2016 (16)	Cross sectional (6) Retrospective cohort (2) Prospective cohort (3) Population-based cohort (2) Longitudinal (1) Quasi-experimental (1) Prospective interview and follow-up, retrospective file review (1)	USA (7) Australia (4) Canada (2) Sweden (2) Israel (1)	Home-dwelling (4) Hospital discharge (8) Rehabilitation hospital inpatient (1) Home-dwelling and non-home (2) LTCFs (1) All with at least 80% of participants were aged 60 or over	MRCI (10) MCI (5) Other (1)	Non-adherence (2) Unplanned hospital admission (1) Unplanned hospital re-admission (1) Medication management capacity (1) Family Caregiver Medication Administration Hassles (1) Post-discharge potential adverse drug events (1) All-cause mortality (1) Medication self-administration errors (1)	Adherence (3) ED visit (2) Unplanned hospital re-admission (1) Post-discharge medication modification (1) Change in medication- and health-related problems (1) Staff informant–rated quality of life (1)	Non-adherence (1) Unplanned hospital re-admission from home (1) Hospital discharge to home (1) Knowledge of medication (1) Medication self-administration errors (1)

Author, year	Search range (# studies)	Study designs (n)	Country (n)	Population (n)	Measures of complexity (n)	Association with complexity		
						Positive (n)	None (n)	Negative (n)
Alves-Conceição et al, 2018[11]	January 2004-April 2018 (23)	Cohort (9) Cross sectional (8) Case-control (2) Quasi-experimental (1) Not identified (3)	USA (8) Australia (6) Brazil (2) Israel (2) Sweden (2) Spain (1) Not reported (2)	Hospital (8) Outpatient care facility (5) Home care service (2) Family health unit (1) Adult protective services state agency (1) Church (1) LTCF (1) Multiple (3) Not identified (1)	MRCI (23)	Hospital readmission (6) Non-adherence (4) Hospitalisation (3) Number of hospitalisations (1) Number of days hospitalised (1) COPD assessment test score (1) St George's respiratory questionnaire score (1) Prior year exacerbation of COPD (1) Prior year hospitalisation (1) 6-minute walk test (1) Adverse drug event (2) Hospitalisation for adverse drug event (1) Mortality (1)	Acute care utilisation (1) Medication adherence (1) Post-bronchodilator forced expiratory volume in 1 second (1) Adverse drug event (1) Hospital readmission (1) ED visit (2) Hospital readmission (2) Hospital discharge destination (1)	Medication adherence (2) Quality of life (1)

Author, year	Search range (# studies)	Study designs (n)	Country (n)	Population (n)	Measures of complexity (n)	Association with complexity		
						Positive (n)	None (n)	Negative (n)
Brysch et al, 2018[77]	Inception-March 2017 (11)	Cohort (7) Cross sectional (3) Retrospective analysis (1)	Not reported	Outpatient (11)	MRCI (11)	Non-adherence (1) Unplanned hospital admission from home (1) Hospitalisation (1) Number of hospitalisations (1) Number of hospital days (1) All-cause mortality (1)	Staff informant–rated quality of life (1) Hospital readmission (1) Unplanned hospital admission from non-home settings (1)	Hospital discharge to home (1)
Alves-Conceição et al, 2019[10]	January 2004-April 2018 (12)	Cohort (10) Case-control (2)	USA (5) Australia (3) Sweden (2) Israel (1) Not reported (1)	Hospital (6) LTCF (3) Outpatient care facility (2) Not reported (1)	MRCI (12)	Hospital readmission (3) Non-adherence (2) Hospitalisation (1) Unplanned hospital admission (1) Mortality (1)	Hospital readmission (4) Unplanned hospital re-admission from home (1)	Hospital discharge to home (1)

ARCI, Antiretroviral Regimen Complexity Index; COPD, chronic obstructive pulmonary disease; ED, emergency department; EMTCI, Epilepsy Medication Treatment Complexity Index; LTCF, long-term care facility; MCI, medication complexity index; MRCI, medication regimen complexity index; USA, United States of America.

1.4 Overview of residential aged care services in Australia

Broadly, the Australian approach to aged care service provision includes: community-based home care which provides services to support people living within their own home, and residential care, which is provided in residential aged care facilities (RACFs) with 24-hour supported care for people whose daily tasks and healthcare needs can no longer be met within their own homes.[3,78-80] RACFs may also be known as aged care homes, long-term care facilities, nursing homes, or elderly care homes.[3] Short-term and transition care may also be provided in RACFs to support rehabilitation or recovery.[80] Residential care comprises the majority of government spending in the sector (67% of $18.4 billion in 2017-18).[81]

1.4.1 Characteristics of individuals accessing residential aged care services in Australia

In Australia, the number of people accessing residential aged care is increasing.[4,82] A total of 7% of people aged over 65 accessed permanent or respite residential aged care in 2017-18.[83] In 2018-19, 59% of residents in residential aged care are 85 years or older, two-thirds are women, and one-third were born overseas.[81] The average length of stay was 2.8 years.[84]

People requiring aged care have increasingly complex care needs when entering aged care.[8,85] Of people accessing permanent residential aged care, 64% needed a high level of care due to the types of cognitive and behavioural symptoms experienced.[81] Over half (52%) of residents in Australian residential aged care are living with dementia.[4,86] Compared to residents without dementia, residents living with dementia are more likely to have high care needs for activities of daily living (ADLs), behaviour, and complex health care including taking medications.[86] Polypharmacy is also prevalent in RACFs. Between 36% and 39% of residents experience polypharmacy when defined as nine or more medications.[36,87]

Frailty is also common in Australian RACFs, with prevalence estimated to be up to 85% of residents.[88] Frailty is defined as a ‘progressive age-related decline in physiological systems, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes’.[89] The measurement of

frailty often uses tools that include health measures that indicate higher care needs, such as independent transfer, incontinence and help with dressing.[88,90] The higher care needs of residents is also reflected internationally. A systematic review of the prevalence of frailty in aged care estimated that approximately half of residents experienced frailty.[91] More recently, individual studies from Belgium and Australia have found up to 76-85% of residents could be classified as frail.[88,92] Frailty overlaps considerably with polypharmacy and complex medication regimens to treat multimorbidity.[93]

1.4.2 Medication management in Australian residential aged care

In RACFs, medications are usually managed by a multidisciplinary care team with residents at the centre. The usual prescribers for residents are general practitioners (GPs, synonymous with family physicians), supported by specialist physicians and allied health professionals as required. The care team coordinates to meet the needs of the individual resident. The goal in RACFs is to provide patient-centred care, where residents participate, are involved in their care, and respected as an autonomous individual. 'Patient-centred' care requires good relationships between the residents' and their care teams. The result should be individualised care that meets the resident's unique physical and emotional needs.[94]

Medications are supplied based on GP medication orders (prescriptions) that are dispensed by pharmacists located in community pharmacies separated from the RACF.[3] Medication use and management in Australian RACFs is supported by the 'Guiding Principles for Medication Management in Residential Aged Care Facilities'.[95] These 17 principles assist in the development of local policy and procedures that ensure safe and quality use of medication at a facility level.[3,95] Adherence to these principles, although not directly assessed, can be used as evidence for meeting the Aged Care Quality Standards.

Aged care service providers in Australia must meet minimum quality standards in order to receive government subsidies for residents' care.[96] All providers are assessed against the standards through an accreditation process managed by the Aged Care Quality and Safety Commission.[96] The expectation that "care recipients' medication is managed safely and correctly" was set out in Standard 2: Health and

Personal Care in the 2014 Australian Aged Care Accreditation Standards.[97] This included having a safe medication management system according to legislative, regulatory and professional standards and guidelines.[97] These accreditation standards were succeeded by the Aged Care Quality Standards from July 2019.[96] The current standard states that "risk can be minimised through effective policies and procedures that support safe use of medicines".[98] In the guidance document for aged care providers on the quality standards, consumer preferences with respect to taking medication is specified as an example of the level of detail required in care and services plans.[98]

1.4.3 Medication administration in Australian residential aged care

Most residents in Australian RACFs rely on nurses or medication-endorsed personal care assistants for assistance with administering medications.[3] Staff may also support residents to self-administer medication if residents have been assessed as able to do so; however, this is uncommon.[3,95] All registered nurses are qualified and authorised to administer medications. Enrolled nurses work under the supervision of registered nurses and are authorised to administer medications unless it is noted that they have not completed medication training. In some RACFs, personal care workers or nursing assistants may also administer medication if they have received medication management training.[3,95] This optional vocational training enables personal care workers or nursing assistants to prepare for and provide medication assistance, supporting residents' self-administration, and complete medication documentation.[99] It is delivered by registered training organisations regulated through the Australian Skills Quality Authority.

Regular medications are administered in scheduled medication rounds.[100] Common processes in medication administration rounds are illustrated in Figure 2.

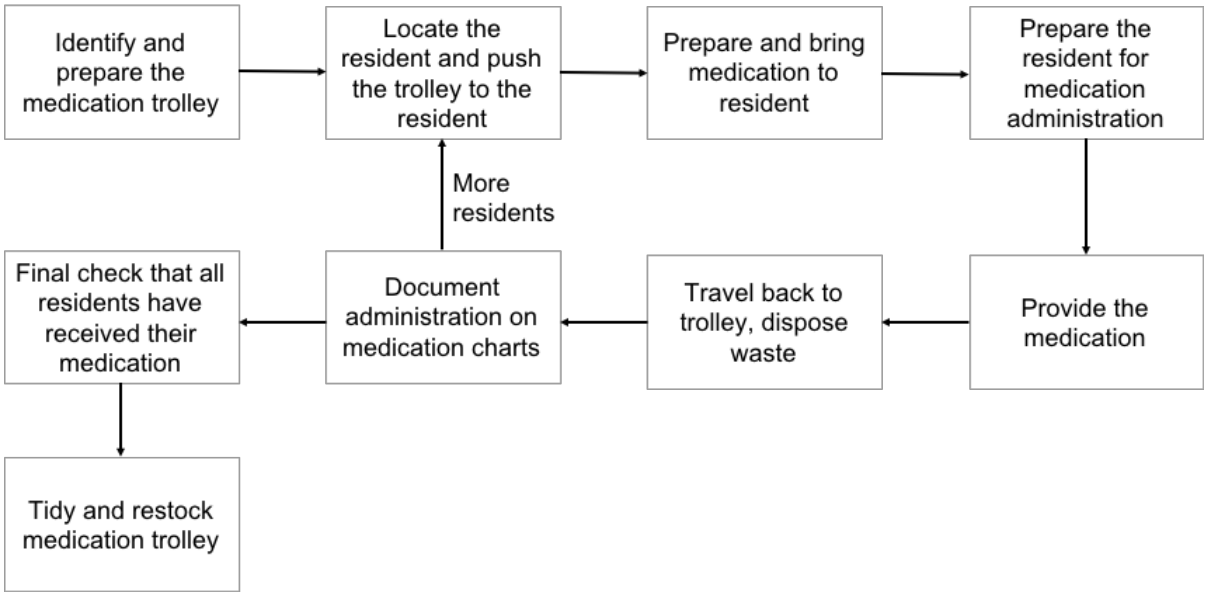


Figure 2: Common processes for a medication administration round in Australian residential aged care facilities (adapted from Qian et al. 2018)[100]

Safe medication management takes time. A significant proportion of staff time is spent on medication administration rounds, which includes complex processes such as modification of dose forms by crushing or cutting tablets, and opening capsules, in approximately one quarter of all oral dose form administration.[101-103] The ability of residential aged care services to provide high-quality care, with resident-centred activities that keep residents mentally and physically active, and which manage dignity, is increasingly challenging.[104] The Australian Nursing and Midwifery Foundation has recommended that an average of 4 hours and 18 minutes of direct care in 24 hours is required to be provided to each resident to ensure safe and quality care.[5] This ranges between 2.5 hours for the residents needing the lowest levels of care and 5 hours for residents needing the highest levels of care.[5] This includes nursing time as well as care time undertaken by allied health professionals such as physiotherapists and social workers.

1.5 Existing medication-related interventions in Australian residential aged care facilities

In Australia, the main pharmacist-led, collaborative medication-related interventions are the Residential Medication Management Review (RMMR) and Quality Use of Medicines (QUM) programs. These programs are government funded and support

pharmacists to participate in these interventions. Pharmacists may also participate in other medication-related interventions, such as Health assessment for people aged 75 years and older, or case conferences with medication components. However, there is no specific remuneration for participation for pharmacists in these programs.[105,106] While there are moves towards embedding pharmacists in RACFs to provide clinical services and on-site medication support, at present, remunerated pharmacist services in RACFs are limited to RMMR and QUM services.[107,108]

1.5.1 Residential Medication Management Reviews (RMMRs)

RMMRs are comprehensive medication reviews that are conducted collaboratively between pharmacists, residents, and their GPs.[109] The main aim of an RMMR is to 'improve the appropriateness of medicines, reduce harm and improve health outcomes, while incorporating the resident's preferences, beliefs, attitudes, and priorities'.[109] RMMRs will be discussed in detail in Chapter Two.

1.5.2 Quality Use of Medicines (QUM)

The QUM program provides funding and a framework for pharmacists to promote QUM at a facility-level.[110] Quality use of medicines is a central tenet of Australia's National Medicines Policy and this program aims to support RACFs to ensure medication use is judicious, appropriate, safe and efficacious.[110] Examples of QUM activities are listed in Box 1. The exact type and frequency of QUM services are agreed upon between the pharmacist (or service provider) and the RACF, with work designed and tailored to meet the needs of the residents and the individual RACF.[111] A recent government-commissioned review of the QUM program found that while the program has successfully been implemented and delivered to RACFs across Australia of all facility sizes and all socio-economic status', the QUM activities delivered did not always have strong evidence supporting their use.[112] This, in conjunction with the flexible nature of the service contract, meant that significant variations were likely in the activities and benefits seen by residents and RACFs. The lack of monitoring for quality and outcomes was identified as a limitation for evaluating the program in meeting the intended objectives and outcomes.[112] Despite this, pharmacists and RACFs provided positive qualitative feedback, reporting that the program was effective and was positively impacting on medication management

practices within RACFs.[112] Guidance on QUM activities have recently been updated to focus on resident-centred care and acknowledge the broad clinical contribution pharmacists can make.[110] Feedback and continuous monitoring for outcomes of QUM services were also included in the delivery process.[110]

Box 1. Examples of Quality Use of Medicines activities (adapted from Pharmaceutical Society of Australia and Pharmacy Programs Administrator)[110,111]

Clinical governance

- Participate in Medication Advisory Committees
- Participate in Drug Use Evaluations
- Advise the healthcare team on medications (e.g. storage, administration, formulation, adverse effects)
- Participate in medication management policy and procedure development
- Assist in the development of nurse-initiated medication lists

Education Activities

- Provide education for nursing staff, residents and carers on medication therapy, disease state management or prescribing trend issues
- Provide medication information to the healthcare team, including the provision of newsletters

Continuous Improvement Activities

- Assist the RACF to meet and maintain accreditation standards and to comply with regulatory requirements
- Conduct medication administration audits and surveys on medication errors, dose form modification, and psychotropic drug use
- Assist with the development of, and report on, quality indicators and other quality measures

Resident focused activities

- Assess competency of residents to self-administer medications
- Opportunistic advice to healthcare team on medication storage requirements, monitoring and standards, including labelling, safe disposal of unwanted and expired medication, and security of medication storage areas

1.5.3 Simplification interventions

While there may be situations in which complex medication regimens are indicated, this is often not the case. Unnecessary medication regimen complexity can be reduced without changing therapeutic intent through medication regimen simplification. Administration times, routes of administration, pill burden and additional directions may be reduced by standardising administration times and routes of administration, the use of long-acting formulations or fixed-dose combinations.[113,114]

Medication regimen complexity was commonly identified by experts as an important factor in polypharmacy review and rationalisation (86% of respondents (n=19) gave a score of “high importance”).[115] However, medication regimen complexity was not included in the international core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy.[116] In practice, the existing RMMR program has not been associated with reductions in MRCI.[117] This is despite previous studies suggesting that recommendations would result in simpler medication regimens. In a review of moderate to high significance medication-related problems identified by RMMRs, 21% (n=21) were untreated indications while 32% (n=32) were toxicity or adverse reaction.[118] Recommendations made by pharmacists from RMMRs were more frequent for ‘cease/withdraw therapy’ (n=145) compared to ‘add drug to therapy’ (n=89).[119] ‘Dose frequency/schedule change’ was also a common recommendation, but it was not specified whether the change was an increase or a decrease.[119]

The recommendation to ‘cease/withdraw therapy’ may be addressed through deprescribing. Deprescribing refers to the ‘stepwise reduction of unnecessary or potentially inappropriate medications after consideration of therapeutic goals, benefits and risks, and medical ethics’.[120] Although deprescribing may decrease the complexity of medication regimens, it only addresses one component of complexity and aims to change the therapeutic intent of the regimen. Simplification aims to address all complexity components of medication regimens to make existing regimens easier to manage.

The novel research presented in this thesis comprises part of the first intervention provided in Australia residential aged care to target unnecessary medication regimen complexity in RACFs.

1.5.4 Tools for optimising medication use

There are many tools available to clinicians when providing interventions to optimise medication use (Table 3). Broadly, tools can be categorised into explicit or implicit tools based on their structure.[121] Explicit tools present recommendations for specific medications and/or situations, with little room for clinical judgement based on context of comorbidities, polypharmacy, or patient preferences. In contrast, implicit tools rely on clinical and clinician judgement about a specific patient or resident.[121] Implicit tools may be more resource intensive, requiring more time and expertise compared to explicit tools.[121] However, implicit tools provide greater flexibility to incorporate each patient's or resident's unique values and goals of care.

At the time of commencing this thesis, there were no explicit or implicit tools available to facilitate medication regimen simplification in RACFs.

Table 3. Examples of tools used to optimise medication use

Tool	Purpose	Structure
American Geriatrics Society Beers Criteria[122]	Identify potentially inappropriate medication use	Explicit list of medications
Deprescribing algorithm[123]	Target medications suitable for deprescribing	Explicit flowchart with implicit judgement
Drug burden index[124]	Measure exposure to anticholinergic and sedative medications	Explicit equation (application of the index requires clinician judgement)
Medication Appropriateness Index[125]	Assess appropriateness of medications in the context of concomitant medications, clinical conditions and settings	Implicit index (application of explicit criteria requires clinician judgement)
Medication Appropriateness Tool for Co-morbid Health conditions in Dementia[126]	Appropriate medication management of co-morbidities for people living with dementia	Explicit list of criteria
STOPP/START[127]	Identify potentially inappropriate medications and potential prescribing omissions	Explicit list of criteria

1.6 Evidence for medication regimen simplification

Medication regimen simplification is an opportunity to improve care. When left to organise their own medication regimens, community-dwelling people rarely identify the simplest method of administration. In a previous study of 464 community-dwelling participants in the USA, only 1% (n=3) were able to organise a simulated 7-medication regimen into three daily administration times, which was the simplest regimen possible while following all of the individual medications' administration instructions.[7] The average number of daily administration times identified was six.[7] In residential aged care settings, it is even less likely that residents would simplify their own regimen. This is because medications are usually supplied in dose administration aids (e.g. sachets, blister packs), most residents do not self-administer their own medications, and may have little knowledge of their medication regimens. However, medication regimens can often be simplified without altering the therapeutic intent of the resident's treatment. This scope for simplification has been established. In patients discharged from a hospital in Germany, 86% of individual medication regimen complexity characteristics were potentially preventable.[128] Almost half of older people living at home in the USA could have their medications simplified.[129]

A range of interventions to reduce complexity have been investigated, targeting medication formulations and health professional practice interventions.

1.6.1 Single-pill combination medications

Fixed-dose single-pill combination medications combine two or more active ingredients in a single dose form. Use of a combination product can simplify medication regimens by reducing pill burden and number of administration times per day, when compared with using the same active ingredients separately.

Multiple studies have investigated the impact of combination versus single-ingredient preparations. A 2007 meta-analysis of nine studies evaluated fixed-dose combination medications for tuberculosis, human immunodeficiency virus (HIV) disease, and diabetes. Overall, fixed-dose combinations decreased risk of medication non-adherence by 26% (pooled relative risk 0.74; 95%CI 0.69-0.80).[130] In

three studies that also included efficacy outcomes, fixed-dose single-pill combinations were at least as efficacious as the free equivalent components, suggesting that this is a safe intervention.[130] These findings were similar to a 2011 meta-analysis of combination therapies for hypertension. Nine of 15 included studies investigated adherence. Adherence and persistence to combination antihypertensive medicines was found to be higher for single-pill combinations compared to using free equivalent components.[131] There was also a saving in annual all-cause and hypertension-related health care costs.[131]

A systematic review of studies published between January 2000 and May 2019 investigated the impact of decreasing pill burden through the use of fixed-dose combinations for all conditions. Out of 67 included studies, 56 (84%) found significantly higher adherence when fixed-dose combinations were used.[132] Seven studies (10%) found no significant difference, and two studies had both positive and negative results regarding adherence.[132] People initiating fixed-dose combination of amlodipine and a statin had a 15% lower risk of ceasing combination therapy when compared to people initiating the free equivalent components.[133] Using a different methodological approach, a group-based trajectory modelling analysis of combination antiretroviral therapy in Brazil suggested that single-pill combinations had a positive impact on adherence compared to multiple tablet regimens.[134]

While single-pill combinations are suitable for people with stable medication regimens, they do not offer flexibility to titrate doses, which is a barrier for this type of simplification. The emergence of 3D printing may in the future offer dynamic, multi-active ingredient tablet manufacturing with doses tailored for individual people to simplify their regiments. While feasibility has been established, there currently remains several technical and regulatory challenges to solve before commercial adoption.[135]

Additionally, these studies all included only the fixed-dose single-pill combination medicines and the free equivalent components in the adherence or persistence. They did not consider the effect on the person’s other medications and their overall medication regimen.

1.6.2 Reducing frequency of administration

Patients generally prefer medication regimens with fewer administration times.[136,137] Some medications may be able to be administered less frequently by increasing the dose of an existing drug while increasing the dose interval (e.g. enalapril can be administered in divided doses or once daily), by using novel formulations of existing medications (e.g. metformin immediate release or extended release), or through substituting a similar drug that allows less frequent dosing (e.g. captopril twice daily to trandolapril once daily).[138,139] Reducing frequency of administration has been of interest mainly as a tool to increase medication adherence, with a considerable body of literature investigating its efficacy.

Systematic reviews and meta-analyses assessing the association between dose frequency and medication adherence measured using electronic monitoring devices have found that overall, once daily dosing was associated with higher mean adherence compared with multiple daily dosing.[37,140]

Other literature reviews have stratified studies by medical conditions. It was possible to reduce dose frequency safely and effectively in regimens for osteoarthritis, diabetes mellitus, angina, depression, Parkinson's disease, COPD, pain syndromes and overactive bladder.[138,141] Improvements were found in health-related quality of life for people with angina, asthma, COPD, Parkinson's Disease and seizure disorders, and no studies reported decreased quality of life.[138] Reduced frequency of dosing was linked to improved adherence in people with asthma, hypertension, diabetes mellitus, depression, epilepsy, respiratory tract infections, and HIV.[138,139,141,142] Cost savings were found with reducing the frequency of daily dosing for diabetic peripheral neuropathic pain, lower respiratory tract infections, immunosuppression following kidney transplantation, ulcerative colitis, hypertension and Parkinson's disease.[138,139]

These studies have a number of limitations. Almost all of the reviews were funded by pharmaceutical companies who may have an interest in demonstrating that new product formulations offering less frequent dosing schedules have advantages over existing products. In two reviews that assessed publication bias, it could not be ruled out.[139,140] The measures of adherence were also heterogenous, which makes

comparisons difficult. Finally, the literature has focused on reducing administration frequency for single therapies, rather than for the overall medication regimen.

1.6.3 Health professional practice interventions

A limited number of interventions targeting health professionals have been trialled to simplify medication regimens, with existing literature pertaining only to hospital and community settings.

Pre-post intervention studies involving pharmacist delivered clinical medication review have shown reductions in medication regimen complexity in hospital settings.[113,143] Another intervention in a hospital setting involved providing a visual medication regimen grid to prompt prescribers to consider medication regimen complexity. The mean doses per day decreased by 2.47 per person in the intervention group, compared to an increase of 3.83 in the control group ($p<0.001$).[144]

A universal medication schedule (UMS) was proposed as a way to simplify regimens by reducing administration times to four standard times daily (morning, noon, evening, bedtime).[145] To support these standard times, the UMS also provided standardised language around those four times to use in medication instructions (e.g. “take one tablet in the morning and one tablet in the evening” instead of “take one tablet twice a day”).[146] People managing their own medications using these standard instructions may be more likely to organise their regimen with fewer daily administration times. Prescriptions with UMS instructions had better adherence compared to prescriptions that did not use UMS instructions.[145]

A cluster RCT investigated the automation of the MRCI calculation with an alert flagging nurses when people with high medication regimen complexity were admitted to a home care agency.[62] These clinical alerts directed nurses to a module prompting evidence-based interventions for regimen simplification. The study found no significant impact on MRCI in intention-to-treat analysis, but the authors note there was low use of the module following the high MRCI alert among nurses in the intervention group. In nurses who used the module, there was a significant reduction in MRCI compared to the control group.[62]

While these interventions have shown that medication regimens can be simplified, the studies did not investigate the sustainability of the interventions or clinical outcomes associated with the simplification. The interventions were also targeted at hospital and community settings.

1.7 Gaps in the literature

Despite being high users of medications and health systems, older people are under-represented in the clinical trials which inform the evidence base for the use of the medications and health systems.[3] An international panel of experts recently identified eight research priorities in geriatric pharmacotherapy and pharmacoepidemiology, including QUM, vulnerable patient groups, polypharmacy and multimorbidity, person-centred practice and research, deprescribing and medication simplification, methodological development, variability in medication use, and national and international comparative research.[147] Both interventional and observational research involving older people is needed to fill the evidence gaps for this increasing and vulnerable population.

In Australia, access to population-wide data with the ability to investigate interventions, including medications, with clinical outcomes is complex, time-consuming and costly. Other countries are already using such data. Hong Kong has an example of a high-quality real-world database that is being used to answer clinical research questions about older people.[148] The Hong Kong Hospital Authority (HA) is the sole provider of government-funded healthcare in Hong Kong, and so has broad coverage of the entire seven million Hong Kong population. HA uses an electronic medical records system named Clinical Data Analysis and Reporting System (CDARS) throughout their entire network of 42 hospitals, 49 specialist outpatient clinics, and 73 general outpatient clinics.[149] CDARS' primary purpose is to provide a retrospective clinical decision support environment via centralised recording and management of patient medical records from all HA provided services, including procedures, prescriptions, imaging, and pathology. It is also used for clinical audit, to aid management decisions, and for research purposes. The accuracy of data are dependent on the clinical staff who input information into the system. Studies published using CDARS have demonstrated high coding accuracy in the outcomes

used to date, including studies investigating questions of relevance to older people such as fracture risk.[148,150,151]

At the time of commencing this thesis there was a need for more literature on the burden and outcomes of complex medication regimens for older people, especially residents of RACFs. There are major challenges imminent with the ability to cope with the increasing number of older people who will need to use residential aged care. Increasing understanding of the current burden will allow adequate planning and may identify areas where care can be delivered more efficiently. Medication regimen simplification may decrease medication burden for residents and staff of RACFs and improve outcomes for residents. This thesis will address current evidence and practice gaps by identifying the burden of medication regimen complexity, evaluating our current medication review system and developing a tool to assist and standardise medication regimen simplification. This evidence is essential to the current and future planning of medication management and quality care for older people.

1.8 Aims and objectives of the thesis

1.8.1 Aim

The overall aim of this thesis was to evaluate and address the burden of medication regimen complexity on older people and the health systems that serve them.

1.8.2 Objectives

The specific objectives of this thesis were:

1. To systematically review Australian literature on comprehensive medication review for residents of RACFs;
2. To investigate the association between medication regimen complexity and the safety of oral anticoagulants in people with AF in a population-based study in Hong Kong;
3. To estimate the time taken to administer medication regimens to residents of RACFs;

4. To develop and validate a medication regimen simplification guide for residents of RACFs; and
5. To investigate the prevalence and correlates of medication regimen complexity in residents of RACFs prior to application of a medication regimen simplification guide.

2. Chapter Two: Process, impact and outcomes of medication review in Australian residential aged care facilities: A systematic review

2.1 Synopsis

This chapter reviews the literature for evidence surrounding an existing major medication intervention in Australian aged care. Medication reconciliation and medication reviews are well-established methods used internationally for identifying and resolving medication-related problems. The Australian Government has funded the provision of comprehensive, multidisciplinary medication review in residential aged care facilities since 1997. Broad uptake of the program has been poor. A recent study of residents who entered permanent residential aged care in Australia between 2012 and 2015, received at least one medication in the previous year and were alive at 90 days post-RACF entry found that 21.5% of residents received an RMMR within 90 days.[152] Until now been no comprehensive evaluation of both peer-reviewed scientific literature and grey literature on the program at the time of this study. It is not known whether pharmacists actively recommend medication regimen simplification when conducting RMMRs, or whether RMMRs are associated with reduced medication regimen complexity.

2.2 Chapter objective

To systematically review Australian literature on medication review for residents of RACFs.

2.3 Publication

This chapter is a reproduction of the following publication:

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REVIEW ARTICLE

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Process, impact and outcomes of medication review in Australian residential aged care facilities: A systematic review

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Abstract

Objective: To systematically review literature reporting processes, impact and outcomes of medication review and reconciliation in Australian residential aged care facilities (RACFs).

Methods: PubMed/MEDLINE, EMBASE, CINAHL, Informit Health and grey literature were searched from 1995 to July 2018. Studies reporting outcomes of a stand-alone medication review or reconciliation interventions in Australian RACFs were included.

Results: Thirteen studies investigated medication review, eight of which studied Residential Medication Management Reviews (RMMRs). Five studies reported that medication reviews identified an average of 2.7-3.9 medication-related problems (MRPs) per resident. One study reported medication reviews had no impact on quality of life, hospitalisation or mortality, but was not powered to assess these. Three studies reported general practitioners' acceptance of pharmacists' recommendations to resolve MRPs, ranging between 45 and 84%.

Conclusions: Medication review may be a useful strategy to identify and prompt resolution of MRPs. However, the impact on clinical and resident-centred outcomes remains unclear.

KEYWORDS

aged care, geriatric medicine, health services, medication review, medication therapy management, pharmacist intervention

1 | INTRODUCTION

Multimorbidity, polypharmacy and age-related psychological decline mean that residents of residential aged care facilities (RACFs) are at high risk of medication-related problems (MRPs). A review of international literature reported that up to 43% of residents use one or more potentially inappropriate medications (PIMs).[1] Over three-quarters of residents in 17 Australian RACFs participating in the INvestigating Services Provided In the Residential care Environment for people with Dementia (INSPIRED) study used anticholinergics, sedatives or PIMs in the previous 100 days.[2] Use of PIMs has been associated with poor health-related quality of life, poor psychological well-being, higher medication costs, hospitalisations and increased risk of mortality.[3-6] Controlled trials of medication review in RACFs in Switzerland, the United States of America (USA) and Northern Ireland have demonstrated that rates of PIM use reduced for residents who received a medication review.[7-9] Conversely, a recent observational study in the United States found higher medication

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review completion rates were associated with improvements in four of 17 medication-related quality indicators but an increase in chronic use of atypical antipsychotic medications among Medicare Part D beneficiaries in RACFs.[10] Medication reconciliation and review have been shown to identify and resolve MRPs in community and hospital settings.[11-14] Available evidence from studies in RACFs is more limited,[12] but suggests the finding may extend to the RACF setting.[15] Pharmacist-led medication reconciliation was identified as the top priority for reducing polypharmacy in Australian RACFs by health professionals and consumers.[16]

Australia has had a national, government-funded collaborative medication review service in RACFs since 1997.[17] This service, known as Residential Medication Management Review (RMMR), is similar to clinical medication review in the UK, comprehensive medication reviews provided under the medication therapy management program in the United States and MedsCheck LTC in Canada.[18-20] Residential Medication Management Reviews are conducted to optimise medication use, improve clinical outcomes and ensure the quality use of medicines (QUM; i.e "judicious, appropriate, safe and effective use of medicines").[21] Medication review programs are increasingly recognised in health policy and quality standards internationally.[18,22-24] However, although studies have reported positive impacts on MRPs and prescribing, results are conflicting for studies that investigated clinical outcomes such as decreased or no change in falls,[9,25] decreased or no change in hospitalisations [8,25-27] and decreased, no change, or increased in mortality.[25-28] Three Australian studies were included in a recent systematic review of randomised controlled trials (RCTs) and observational studies of medication reviews in RACFs but other Australian studies were cross-sectional and, therefore, excluded.[15] It is important to evaluate the evidence from these descriptive studies of "real-world" program outcomes.

The current Australian RMMR program enables residents referred by their general practitioner (GP, or family physician, the primary prescribers in RACFs in Australia) to receive a review from a clinical pharmacist every 2 years or more frequently if clinical circumstances change.[29] A report with recommendations from the RMMR is provided to the GP, who is responsible for implementing the recommendations in consultation with residents, carers and RACF staff.[21] Over 1.15 million RMMRs were subsidised from 2007 to 2016, and the most recent government-funding agreement for national medication management programs allocated $14.2 million to RMMRs.[30,31] Although this is a well-established program, the magnitude of service provision and costs means there is a need to understand the processes, impact and outcomes of the existing and previous iterations of the program in Australia.[32] Recent consultation and reviews continue to consider changes to program structure and eligibility.[33-35] It is also important to understand impact and outcomes for residents in the light of increasing focus on the need for clinical pharmacy services in RACFs.[36] A recent systematic review explored the process and outcomes of the corresponding Australian Home Medicines Review service and reported medication reviews are beneficial for people living in the community.[11] However, no systematic reviews have specifically explored the value of medication review and reconciliation in Australian RACFs.

Policy Impact

Residents of aged care facilities are often exposed to polypharmacy and high-risk medications. This review suggests that the Australian government-funded Residential Medication Management Review (RMMR) program is useful to identify and prompt resolution of medication-related problems.

Practice Impact

This review suggests that RMMRs identify 2.7-3.9 medication-related problems (MRPs) per resident and general practitioners (GPs) accept 45-84% of recommendations to resolve these MRPs. This highlights the value of pharmacists and GPs working together to optimise medication management in this setting.

The objective was to systematically review peer-reviewed and grey literature reporting processes, impacts and outcomes of medication review and reconciliation in Australian RACFs.

2 | METHOD

This review was conducted as per the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Figure 1).[37] The protocol was published prospectively on PROSPERO (CRD42016041773).[38]

2.1 | Search strategy

PubMed, MEDLINE, EMBASE, CINAHL and Informit Health were searched using subject headings and keywords related to medication review, medication reconciliation and RACFs. The search was limited to English language articles with publication dates between January 1995 and July 2018. These publication dates were selected to include research published in the lead-in period to the RMMR program launch in 1997.[21] Conference proceedings, relevant websites, relevant local journals, reference lists and publications of key authors in the field were manually searched to identify relevant full-text articles for inclusion (see Appendix A for full search strategy).

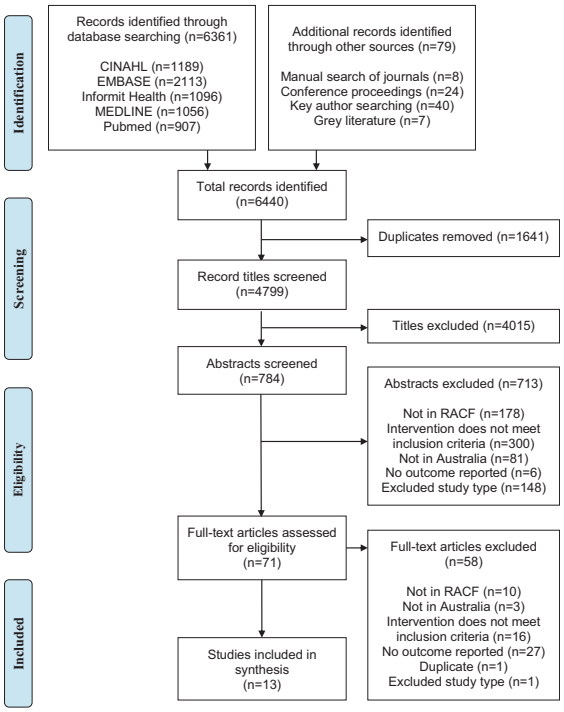

FIGURE 1 Flow chart of the literature search and study selection

2.2 | Study selection and synthesis

Studies reporting any process, impact or outcome of medication review or reconciliation for permanent residents of Australian RACFs were included. RACFs in Australia are synonymous with "nursing homes" or "long-term care facilities" in other countries and provide supported accommodation for people with care needs that can no longer be met in their own homes.[17] Only stand-alone medication review or reconciliation interventions were included. Medication review was defined according to the Pharmaceutical Society of Australia's definition as "evaluation of a resident's complete medication regimen with the aims to optimise clinical outcomes, maximise benefits of medicine use and reduce risks of medicine use".[21] This included but was not limited to evaluation of medication reviews funded through the RMMR program.

Interventions that focused on a specific medication or single class of medications were excluded. However, studies that included a complete medication review but only reported results for a specific medication or class of medication were included. Medication reconciliation was defined according to the World Health Organization as "systematically obtaining, verifying, and documenting a best possible medication history, identifying any discrepancies between this and medication orders written at transitions of care, and resolving these discrepancies in a timely manner".[39] We searched the literature for medication reconciliation interventions completed before medication review or as part of a stand-alone intervention. Literature reviews, editorials, commentaries and case reports were excluded.

After removing duplicate records using EndNote X7.2, EYHC screened titles according to inclusion and exclusion criteria. Abstracts and full texts were screened independently by EYHC and KNW. At both stages, discrepancies were resolved through discussion and referred to a third investigator if consensus could not be reached.

Data were systematically extracted from each article using a pilot tested data extraction form. Process referred to how the program was implemented. For the purpose of the review, impact was operationally defined as an intermediary measure of change brought about by the program. Outcomes were any results that measured the success of the program against its stated aims to optimise medication use (eg, decrease in MRPs or inappropriate prescribing in a resident's therapy) and improve clinical outcomes (eg, quality of life, hospitalisations, mortality).[29,40] Data extraction was completed independently by EYHC and KNW, with discrepancies resolved through discussion.

Studies included in the review categorised MRPs using different systems. To synthesise findings across studies, MRPs identified in each study were mapped to the DOCUMENT (Drug selection, Over or underdose, Compliance, Undertreated, Monitoring, Education, Not classifiable, Toxicity or adverse drug reaction) system.[41] The DOCUMENT system was selected because it has been validated for use with Australian medication review data.[42,43] Results from studies reporting the number of MRPs identified, recommendations made, acceptance and implementation of recommendations were extracted and pooled for analysis. Because of apparent inconsistencies with the use of the terms "acceptance" and "implementation" in the included studies, these terms were not considered to be interchangeable for the purpose of this review.

2.3 | Quality assessment

The corresponding Joanna Briggs Institute Checklist for prevalence studies, cohort studies and RCTs was used to assess the risk of bias for individual studies.[44] Methods used for the identification of outcomes were considered to be valid if based on existing definitions or widely used instruments and applied by trained professionals. Study samples were considered appropriate if the reported sample characteristics were representative of the larger RACF population. When studies did not include a sample size calculation, we calculated power to assess whether the sample size was adequate for assessing the primary outcome. Results of the checklist were reviewed when assessing and critiquing the quality of evidence. Studies were not excluded based on the quality assessment.

3 | RESULTS

Thirteen studies met the inclusion criteria (Table 1). All studies focused on medication review, and no stand-alone medication reconciliation interventions were identified. All studies involved elements of multidisciplinary collaboration but pharmacists were responsible for leading the medication review in 11 studies, geriatricians in one study [45] and a GP in one study.[46] Eight studies included medication reviews conducted under the RMMR program (Table 1).[42,47-53] No additional studies were identified by searching the grey literature.

3.1 | Methodological quality of studies

The assessment of risk of bias is summarised in Appendix B. Nine retrospective studies analysed medication reviews conducted as part of routine clinical care. Four prospective studies analysed medication review interventions.

No studies included an a priori sample size calculation. The resident sample sizes ranged from 48 to 849. Five studies did not report the number of RACFs from which the resident samples were drawn. In the remaining studies where this was reported, the resident samples included between eight and 39 reviews per RACF.

More than one pharmacist or geriatrician delivered the medication review service in nine of the 13 included studies.[42,45,47,49-54] This reflected "real-world" practice and increased generalisability of results.[20] Nine studies used a recognised classification system to categorise MRPs and/or recommendations, which facilitates more reliable comparisons.[47-52,55,56] The lack of parallel comparison groups weakens the quality of evidence. The included studies in this review may also be subject to publication bias, where studies with positive results are more likely to be published.

3.2 | Processes

One study reported the views of GPs and nursing staff regarding medication review.[54] Of those who responded, 90% of nursing staff (n = 9/10) and 60% (n = 9/15) of prescribers found medication review to be beneficial and useful. Some prescribers had negative comments regarding having their prescribing reviewed by pharmacists.[54] No study reported resident perspectives, but six out of 15 prescribers responding to the survey reported their perception that medication reviews improved resident well-being.[54] There were no data in the included studies on resident satisfaction with the RMMR service.

One study conducted a cost analysis of the medication review intervention.[54] From a government perspective, there were overall savings in medication costs ($29.88 per resident reviewed) but an overall increase in pathology expenditure ($2.16 per resident reviewed).[54] The analysis was not a full economic analysis and did not include, for example, the cost of providing the intervention.

One study evaluated PIM use in residents receiving RMMRs before and after a change in the frequency of RMMR eligibility from once a year to once every 2 years and found no significant difference in PIM use.[53]

3.3 | Impact

An average of 2.7-3.9 MRPs was identified per review (n = 5 studies).[42,48-50,54] Among these five studies, three different classification systems were used to categorise the MRPs and one study did not use a recognised classification system.[54]

To investigate the most prevalent MRPs, 4144 MRPs from four studies with a combined resident sample size of 1374 were pooled (Figure 2).[42,48,49,54] The most commonly reported MRPs across the four studies were undertreated conditions (23%, n = 948) (eg, untreated conditions, missing preventative treatments) and drug selection problems (22%, n = 892) (eg, duplication, drug interactions, wrong dose, strength, or form, missing indications, contraindications present). One study reported that the most common undertreatment recommendation was the addition of calcium and cholecalciferol for osteoporosis treatment.[49]

Eight studies reported the types of recommendations identified during medication reviews.[45,48-50,53-55,57] The mean number of review recommendations per resident was between 1.9 and 4.0. Results from seven studies were pooled to examine the most prevalent types of recommendations (n = 1897 residents with 5286 recommendations) (Figure 3).[45,48,49,53-55,57] The most common recommendation made was a change in or new clinical or laboratory monitoring (27% of recommendations, n = 1416). The recommendation to add a medication to the resident's therapy, for example to address undertreated conditions, comprised 6% of recommendations (Figure 3).

Four studies reported the acceptance of recommendations by GPs.[48,50,54,57] Acceptance of recommendations for 1177 residents across three studies was pooled,[48,54,57] in which 45% to 84% recommendations were accepted by GPs. Recommendations related to education or counselling had a higher acceptance rate (98%, n = 186/190) (Figure 4). Recommendations that did not involve changes in therapies had a higher acceptance rate than those that did. The highest acceptance rate involving a change in therapy was to change a dose formulation (82%, n = 106/129), followed by the addition of a new medication to therapy (75%, n = 218/289). The remaining study only reported the three most frequent recommendations in the top 10 anatomic therapeutic chemical pharmacological subgroups.[50]

Three studies reported the implementation of recommendations by GPs,[45,50,55] in which 58%-72% of pharmacist recommendations were implemented. Two of the studies were

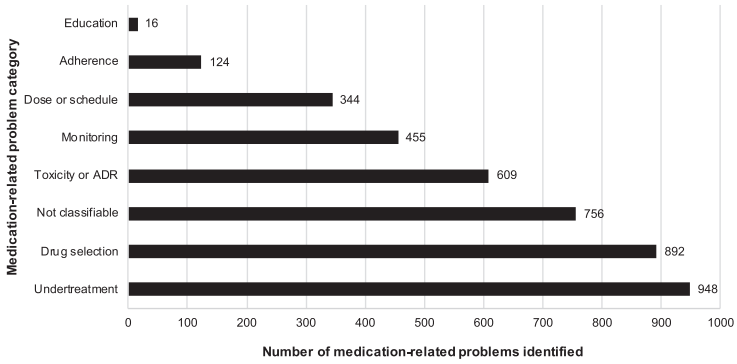

FIGURE 2 Medication-related problems (MRPs) identified by medication reviews in Australian residential aged care facilities

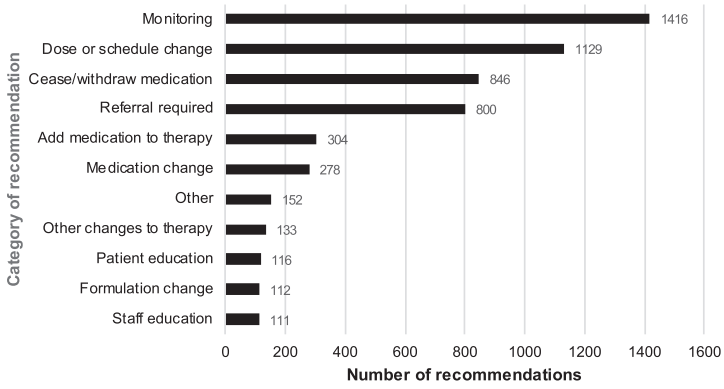

FIGURE 3 Recommendations arising from medication reviews in Australian residential aged care facilities

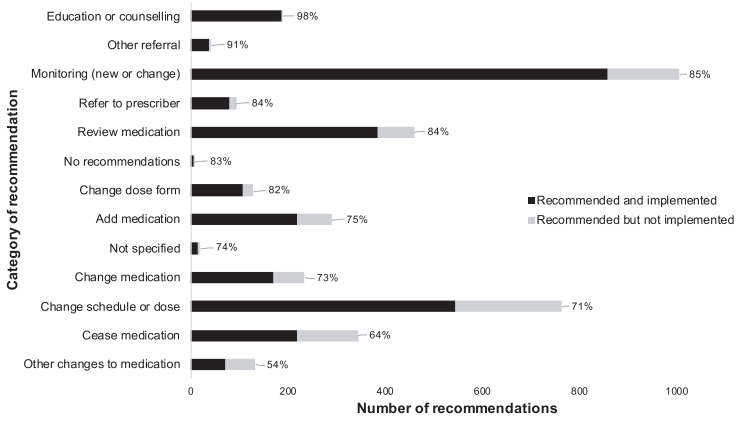

FIGURE 4 Acceptance of recommendations by general practitioners to resolve medication-related problems identified by medication reviews in Australian RACFs. "Other referral" refers to referral to health professionals other than the prescriber, for example podiatrist. "Other changes to medication" are changes to medication other than dose or schedule change, addition, cessation or change in medication, and drug formulation change

conducted retrospectively with access to medication charts and medical records,[50,55] but only one study reported data extraction being cross-checked.[50]

3.4 | Outcomes

One study reported clinical and resident-centred outcomes following medication review as secondary outcomes and was not adequately powered to assess these. Quality of life decreased in both intervention and control groups (a mean decrease of 1.0 (SD ±4.3 and ±4.7, respectively) when assessed using the Quality of Life in Alzheimer's Disease Scale ($P = 0.94$)). In the intervention group, 23/45 residents were hospitalised at least once compared with 24/48 in the control group ($P = 0.99$). After 12 months, 12/45 residents who received the intervention had died, compared to 19/48 residents in the control group (HR: 0.60, 95% CI: 0.30-1.22).[46]

Medication reviews were found to significantly decrease anticholinergic and/or sedative medication burden in two studies.[47,51] Retrospective review of RMMRs found that pharmacist recommendations effectively halved exposure to anticholinergic and sedative medications from one to half of a minimum efficacious dose (ie, the minimum daily dose approved by the United States' Food and Drug Administration [58]) of an anticholinergic or sedative medication per resident, measured using the drug burden index. Overall, 61% of recommendations to reduce anticholinergic or sedative medications were implemented by GPs.[51] Nervous system medications, including paracetamol, were implicated in over one-third (34%, n = 381) of accepted recommendations in three studies that reported by medication class.[45,50,57]

The remaining studies investigated the impacts of comprehensive medication reviews on specific areas of therapy (Table 1). Improvements were found for the appropriateness of prescribing for older people [45,53] and the appropriateness of prescribing of renally cleared medications.[48] There was no impact on the prevalence of use of antithrombotic medications for residents with atrial fibrillation who received a medication review.[52]

4 | DISCUSSION

This systematic review identified a lack of research on clinical and resident-centred outcomes of medication reviews conducted. One study reported that medication reviews had no impact on quality of life, hospitalisation or mortality, but this study was underpowered to detect a significant difference in these outcomes. There was evidence that medication reviews may assist to optimise medication use by decreasing anticholinergic and/or sedative medication burden and inappropriate prescribing. Comprehensive medication reviews were successful in identifying 2.7-3.9 MRPs per resident, with up to 84% of recommendations to resolve MRPs accepted by GPs.

4.1 | RMMR program implications

Residents entering RACFs have more complex care needs, are frailer and experience more polypharmacy than when the RMMR program commenced over 20 years ago. For these reasons, access to medication review services is arguably more important than ever, as is understanding how best to target medication reviews to residents most likely to benefit and determining the clinical impact of the reviews.[17] This systematic review did not identify whether specific residents benefit most from medication review, nor the optimum frequency of medication reviews. It has been estimated that only 38% of residents of Australian RACFs currently receive an RMMR annually.[17] Data do not exist on the proportion of residents at risk of medication misadventure. It was not clear from the seven studies of RMMRs included in this review whether the RMMR service is specifically being targeted to those residents at highest risk of medication-related harm.[42,47-51,53] In Australian RACFs, 35% of residents stay <1 year.[59] Changes to the RMMR funding rules introduced in 2014 meant most residents are eligible for a RMMR every 2 years rather than every year as per the pre-2014 funding rules.[60] The implication has been that many residents now receive only one RMMR. In contrast, comparable programs in the UK, Canada and the United States permit medication reviews to be provided once per year.[10,61,62] Evidence for the optimal frequency for medication review is sparse in both the Australian and international settings. Despite positive comments from prescribers and nursing staff regarding the value of medication review,[54,63] one-third of directors of nursing were able to identify residents who did not receive an RMMR despite having an unmet clinical need.[64] One study compared RMMRs conducted in 2012 and 2015 before and after the funding rule changed and did not find a significant difference in PIM use.[53] An alternative RMMR funding model that incorporates clinical audit procedures and ensures the RMMR service is specifically targeted to residents at high risk of medication-related harm (eg, due to dementia diagnosis or frailty) has been suggested to guide RMMR referral.[60] This may also improve the cost-effectiveness of running a national medication review program, as the prevalence and cost of PIM use are high.[1,5]

This systematic review found that overall 60% of medication review recommendations were accepted for all recommendation classes, except "other changes to medication" (18% acceptance rate). This rate was comparable with international observational studies on medication review (58%-68%).[15] Recommendations for education and monitoring had higher acceptance rates than recommendations to change medication regimens. Higher implementation rates may have been achieved if inter-professional follow-up care were provided. A systematic review of the relationship between GP-pharmacist collaboration and recommendation implementation found medication reviews involving more intensive GP-pharmacist collaboration were more likely to result in regimen changes than reviews without intensive collaboration.[65] This was consistent with findings from a review of international systematic reviews of pharmacist-led medication review in community settings.[14] Inter-professional communication pre- and postmedication review was a central component of medication review models investigated in early Australian and international research.[28,66-68] A post-review discussion between the GP and pharmacist remains part of the program guidelines, and is mandatory unless any changes are considered minor in nature.[21] The current Australian RMMR program does not provide specific funding to incentivise postreview collaboration as in Canada and United

TABLE 1 Summary of included studies

Author (year), study design	Intervention		Population		Results		
	Type	No of participants (No of RACFs)	Mean age (±SD)	Mean number of medications (±SD)	Measure and baseline	Impact	Outcome
Koria et al. (2018),[53] retrospective cohort study	RMMR	112 from 2012 (not reported) 111 from 2015 (not reported)	2012 group: 86.0 (±7.6) 2015 group: 87.4 (±5.9) for 2015	2012 group: 7.7 (±2.9) 2015 group: 7.2 (±2.4)	MAI score, excluding 2 (accuracy of directions and cost-effectiveness) of the 10 criteria. 2012 group: MAI score before review was 26 2015 group: MAI score before review was 27	2012 group: 197 recommendations made that had an impact on MAI. After pharmacist review, MAI score would have been 15.5. 2015 group: 176 recommendations made that had an impact on MAI. After pharmacist review, MAI score would have been 20. Over 50% of recommendations that impacted MAI were to cease a medication	2012 group: After GPs' acceptance of pharmacist recommendations, MAI score was 20. 2015 group: After GPs' acceptance of pharmacist recommendations, MAI score was 22
McLarin et al. (2016),[47] retrospective cross-sectional study	RMMR	814 (not reported)	85.6 (±7.7)	11.4 (±4.9)	ACB (measured using seven scales). 36-67% (depending on scale used) of residents prescribed at least one regular ACM.	Overall number of ACMs prescribed decreased following RMMR and after GP uptake of pharmacist recommendations. 103 recommendations made due to possible anticholinergic adverse events identified by the pharmacist	Significantly lower ACB scores as measured using each of the seven scales. ~30% of recommendations pertaining to ACMs implemented. 114 dosage changes
Nishtala et al. (2016),[52] retrospective cross-sectional study	RMMR	146 (not reported)	88.4 (±7.5)	Not reported	Use of antithrombotic therapies. 115/146 (79%) of residents prescribed antithrombotics. 7% (n = 5) of antiplatelet users were appropriately prescribed. 67 residents were not prescribed antithrombotic therapy according to guidelines	No recommendations made to prescribe antithrombotics for 10 eligible residents for antithrombotic therapy but were not prescribed any antithrombotics. No recommendations made to start antithrombotics for 30 residents eligible (without contraindications) to start guideline-recommended antithrombotics.	N/A

(Continues)

TABLE 1 (Continued)

Author (year), study design	Intervention		Population		Results		
	Type	No of participants (No of RACFs)	Mean age (±SD)	Mean number of medications (±SD)	Measure and baseline	Impact	Outcome
Potter et al. (2016),[46] randomised controlled trial	Medication review conducted by GP	47 intervention 48 control (4)	84 (±6) intervention 84 (±8) control	9.6 (±5.0) intervention 9.5 (±3.6) control	Number of unique regular medicines at 12 months postrandomisation. Intervention: 9.6 regular medications at baseline Control: 9.5 regular medications at baseline	348 deprescribing targets identified for 45 residents.	Withdrawal of identified deprescribing targets achieved in 207 medicines (81%) in 42 people. Mean change in unique regular meds at 12 months in intervention was −1.9 ± 4.1 and in control +0.1 ± 3.5.
Poudel et al. (2015),[45] prospective observational cohort study	Comprehensive geriatric assessment	153 (4)	83.0 (±8.1)	9.6 (±4.2)	Inappropriate prescribing (high-risk medications list created based on 2012 Beers Criteria, McLeod Criteria, the Laroche Criteria, the PRISCUS criteria and the Norwegian General Practice Criteria). ≥1 high-risk medication was prescribed to 58% of residents	Recommendations: Withdrawal of medication 10%, new medication 48%. Cease: due to ADEs (n = 66), no clear indication/medication burden (n = 63), disease cured (n = 16)	17% of high-risk medications creased, altered dose in 3%
Gheewala et al. (2014),[48] retrospective cross-sectional study	RMMR	847 (not reported)	84.9 (±8.8)	11.2 (±4.8)	MRPs (DOCUMENT classification). 2712 MRPs in 98% of residents, mean 3.2 (±1.7) per resident. Inappropriate prescribing of renally cleared medications. 154 residents had CKD. 28 CKD residents were inappropriately prescribed renally cleared medications	3054 recommendations made, mean of 3.6 (±1.9) per resident. Recommendations to monitor renal function were made for 94 (29%) residents with CKD. There were 28 recommendations to resolve MRPs for renally cleared medications in residents with CKD. 2560 (84%) recommendations implemented, mean 3.0 (±1.9) per resident.	93% (n = 87) recommendations to monitor renal function were accepted by GPs 71% (n-20) recommendations to change treatment for residents inappropriately prescribed renally cleared medications were accepted by GPs

(Continues)

TABLE 1 (Continued)

	Intervention		Population		Results		
Author (year), study design	**Type**	**No of participants (No of RACFs)**	**Mean age (±SD)**	**Mean number of medications (±SD)**	**Measure and baseline**	**Impact**	**Outcome**
Kaur et al. (2012),[49] retrospective cross-sectional study	RMMR	296 (6)	82.0 (±11.1)	11.3 (±4.8)	MRPs (Strand et al. 1990 definition)[84]. 802 MRPs total 2.7 (range 0-12) per review	741 recommendations made. 37 recommendations implemented (49% of known outcomes, n = 75).	N/A
Khalil et al. (2011),[55] retrospective cross-sectional study	Medication review by pharmacist as part of routine clinical care	48 (1)	86.0 (±not reported)	9.0 (±not reported)	MRPs (PNCE V5.01, 2006 classification). Number of MRPs not reported.	196 recommendations made, mean 4 (range 1-7) per resident. ~70% of recommendations implemented.	N/A
Nishtala et al. (2011),[50] retrospective cross-sectional study	RMMR	500 (62)	84.0 (±9.0)	7.4 (±3.5)	MRPs (Bergen District Nursing Home study classification). 1433 MRPs identified in 96% of residents (mean of 3.0 per resident).	Number of recommendations not reported. 73% recommendations accepted. 58% recommendations implemented	N/A
Nishtala et al. (2009),[51] retrospective cross-sectional study	RMMR	500 (62)	84.0 (±9.0)	7.4 (±3.5)	DBI, a measure of exposure to medications with anticholinergic and sedative properties. Mean DBI before review: 0.59 (SD ± 0.60)	Mean DBI after pharmacist recommendations would have been 0.47 (SD ± 0.53), a 20% decrease (n = 0.12) from baseline.	Mean DBI after GP uptake of recommendations was 0.52 (SD ± 0.58).
Stafford et al. (2009),[42] retrospective cross-sectional study	RMMR	96 (not reported)	83.9 (±9.3)	9.7 (±3.8)	MRPs (DOCUMENT classification). Mean of 3.9 (±2.0) MRPs identified per resident.	Number of recommendations not reported. Acceptance of recommendations not reported.	N/A
Smith et al. (2002),[57] prospective observational cohort study	Medication review by pharmacists	202 (14)	86.4 (±not reported)	3.9 (±2.8)	MRPs (no formal definition). Number of MRPs not reported.	409 recommendations made, frequently cease therapy (n = 160), then change to dose regimen (n = 79), and biochemical tests (n = 56). 141 changes were made in 69 (51% of 135 residents whose medications were discussed with GP) residents.	N/A

(Continues)

TABLE 1 (Continued)

Author (year), study design	Intervention		Population		Results		
	Type	No of participants (No of RACFs)	Mean age (±SD)	Mean number of medications (±SD)	Measure and baseline	Impact	Outcome
Elliott and Thomson (1999),[54] prospective observational cohort study	Medication review by pharmacists	128 (4)	82 (±8.9)	7.4 (±3.4)	MRPs (actual or potential problems, no formal definition). 254 MRPs identified at baseline.	247 recommendations made. 149 (60%) recommendations implemented.	N/A

Abbreviations: ACB: anticholinergic burden; ACM: anticholinergic medication; ADEs: adverse drug events; CKD: chronic kidney disease; DBI: drug burden index; GP: general practitioner; MAI: medication appropriateness index; MRP: medication-related problem; RACF: residential aged care facility; SD: standard deviation.

States,[19] or remuneration for case conferencing as suggested by a previous evaluation of the RMMR program.[60] Lack of opportunity for collaboration in resident follow-up has been identified as a barrier to clinical decision-making and deprescribing in the RACF setting.[60,69] There is increasing focus on integrating clinical pharmacists within RACFs which would support inter-professional communication.[36]

4.2 | Clinical implications

One of the included studies reported clinical outcomes of medication review as secondary outcomes and was not adequately powered to assess these.[46] Small sample size was also identified as a factor that limited interpretation of the findings from the three Australian studies included in the recent international systematic review of medication reconciliation and review in RACFs.[12] Earlier Australian studies have reported medication review improved pain and mobility but were not associated with changes in morbidity or survival, although measuring improvements in these outcome measures is difficult.[26,28] It is also inherently difficult to compare outcomes among residents who did and did not receive RMMRs, given that residents who were unwell, had more complex medication regimens or were at higher risk of medication-related harm may be more likely to receive RMMRs. Although the RMMR program has existed for over 20 years, there is a lack of Australian research into clinical and resident-centred outcomes in the RACF setting.

Undertreatment was the most common MRP identified in this systematic review, although only one study described the specific health conditions that were undertreated. This is counter-intuitive because medication review is often advocated as a method to decrease polypharmacy.[70,71] In the present review, 16% (n = 846/5286) of all recommendations were to cease a medication. Planned and supervised medication cessation, known as deprescribing, is an area of increasing interest in RACFs. Deprescribing may include the conscious decision to withhold guideline-recommended therapies in accordance with the residents' goals of care. For this reason, apparent undertreatment may actually reflect an intentional prescribing decision informed by discussions with the resident and their family members. In a survey of residents in South Australia, 41% of residents wanted to decrease their number of regular medications and 79% of residents indicated a willingness to have medications deprescribed if recommended by their doctor.[72] Lack of information on goals of care in RMMR referrals has been identified as a barrier for deprescribing.[69] No studies investigated to what extent residents' goals of care were considered in medication review recommendations, so it is unknown to what extent the MRPs identified by pharmacists reflected intentional and unintentional undertreatment. Another factor contributing to this finding may be that people with dementia are less likely

to be prescribed guideline-recommended medications for chronic conditions.[73] Clinicians may perceive the benefits and risks of medicines are different among older people with and without dementia. More than half of all residents in Australian RACFs are living with dementia.[73]

The most common recommendation related to the need for additional tests or monitoring (27% of recommendations, n = 1416/5286). This finding was consistent with common recommendations in international studies of similar interventions.[8,25,74] Although close monitoring is often necessary in older people due to physiological changes that occur with ageing, there may also be inconsistent understanding of the role and value of routine laboratory monitoring in this setting.[57,75] For example, intensive management of type 2 diabetes is no longer recommended for residents of RACFs. Care should instead be individualised to maximise the residents' quality of life.[76] While monitoring may detect and prevent adverse drug events (ADEs), in some cases the rate of detection may not justify invasive testing.[77,78] Where laboratory tests have occurred, results may not have been well documented or communicated to allied health professionals involved in the resident's care. Over half of all residents included in an Australian study did not have serum creatinine values recorded in clinical notes, despite 61% of residents receiving one or more renally cleared medications.[48] Careful consideration of what monitoring is necessary may avoid the cost, time and burden to residents in the RACF setting.[79]

4.3 | Strengths and limitations

A strength of this review was the inclusion of a range of prospective and retrospective studies including medication reviews delivered as part of research studies and as part of routine clinical care. This allowed a comprehensive and robust evaluation of all aspects of the medication review intervention.

A limitation of this review was that studies that included medication reviews as part of complex multifactorial interventions were excluded. This included medication reviews conducted in conjunction with multidisciplinary case conferences.[26,28] Other complementary interventions include QUM activities that are independently subsidised by the Australian government. The QUM program is a complementary service whereby pharmacists work with local stakeholders to deliver interventions at a facility level to improve medication management.[17] Interventions specifically addressing particular classes of medications were also excluded by our criteria. The processes for assessing single medication classes may be similar to a complete medication review and may be relevant in reducing MRPs and risk of ADEs.

The use of different MRP classification systems limited comparison between studies included in this review. For example, we were unable to separate medication dose increases from decreases, while the implications may be quite different. Similar categories from three different classification systems were re-classified into the DOCUMENT system to facilitate comparisons between studies.[41] However, there were inherent limitations with this approach because each classification system differs in terms of definitions, structure and approach. These factors can influence the apparent number of MRPs identified.[80] The terminology of MRPs identified, recommendations made, acceptance and implementation of recommendations were not consistently applied to differentiate between the four categories, despite having different clinical implications. Therefore, our pooled analyses may not be a true reflection of MRPs. Additionally, the sensitivity and specificity of MRPs identified could not be evaluated.

To investigate the uptake of recommendations, the included studies used the terms "acceptance" and/or "implementation," but no study provided definitions. In our pooled analysis of "acceptance" and "implementation," we used the author terms and did not consider the terms interchangeable. Therefore, our results for "acceptance" and "implementation" are not directly comparable. In general, the difference between acceptance and implementation may be that the resident did not accept the recommendation, in which case the GP would agree with the recommendation but not change the therapy due to resident preference. The difference between "recommendation" and "acceptance" may also be due to a difference in information available to the pharmacist and the GP. The GP may accept the recommendation in principle but not implement the recommendation due to having access to clinical information that was not available to or considered by the pharmacist at the time of medication review.

4.4 | Future directions

While the high rate of acceptance of recommendations found in this systematic review may translate to resident benefit, there was minimal published evidence to support this. Hospitalisations, pain, cognitive function or resident-reported outcomes were only reported in one study, which was not powered to assess these outcomes. Evidence from international studies with similar interventions is mixed. While one US study found that medication review reduced hospitalisations,[81] a RCT in the UK showed a reduction in the number of falls, but no impact on GP visits, hospitalisations or mortality.[25] Further longitudinal studies with parallel comparison groups are needed to investigate these and other resident-reported outcomes. Given the small sample sizes of existing studies, the increasing availability of "big data" for recipients of aged care services could play a role in understanding the impacts and outcomes of medication reviews on a wider population

level.[82] The need for a core outcome set for medication review intervention studies, including standard measurement instruments, has been suggested.[83] This evidence would inform targeting of medication reviews and may allow medication review data to be used at policy level to manage medication-related risk.

5 | CONCLUSIONS

Collaborative medication reviews are a useful strategy to identify and resolve MRPs in RACFs and may improve the optimal use of medicines. However, there were no adequately powered data on the impact of medication review on clinical and resident-centred outcomes. It was unclear what proportion of residents at high risk of MRPs receive a medication review. There were no studies that focused on stand-alone medication reconciliation. Future studies of medication interventions in RACFs which assess clinical and resident-centred outcomes are needed.

CONFLICT OF INTEREST

This work is supported by the NHMRC Partnership Centre: Dealing with Cognitive and Related Functional Decline in Older People known as the Cognitive Decline Partnership Centre (CDPC) (grant number GNT9100000). KNW is supported by an Australian Government Research Training Scholarship. JKS is a pharmacist accredited to provide medication reviews to residents of aged care homes. JI and JKS were supported by an NHMRC Early Career Fellowship. MC is employed by an organisation that provides residential aged care services. JSB is funded through an NHMRC Dementia Leadership Fellowship. No other authors have any conflicts of interests to declare.

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APPENDIX A
Search strategy

MEDLINE VIA OVID

1 exp Aged/
2 Homes for the aged/
3 exp Nursing Homes/
4 Long-term care/
5 Assisted Living Facilities/
6 residential aged care facilit*.mp.
7 Aged care hom*.mp.
8 care home$1.mp.
9 (long-term adj2 facilit$3).mp.
10 Nursing home$1.mp.
11 (Residential$1 adj2 facilit$3).mp.
12 ((Residential$1 or home$1 or house$1) adj2 (old or elderly or aged or geriatric$1)).mp.
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14 exp Medication errors/
15 exp Utilization Review/
16 Medication Therapy Management/
17 Pharmacists/
18 medicat* use$.mp.
19 medica* reconciliation.mp.
20 (medicat* review$ OR medicine* review$).mp.
21 (medica* adj3 management).mp.
22 pharmaci*.mp.
23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 exp Australia/
25 Australia*.mp.
26 (New South Wales or NSW or Victoria or VIC or South Australia or SA or Western Australia or WA or Northern Territory or NT or Queensland or QLD or Tasmania or TAS or Australian Capital Territory or ACT).mp.
27 (Sydney or Melbourne or Adelaide or Hobart or Brisbane or Perth or Darwin or Canberra).mp.
28 24 or 25 or 26 or 27
29 13 and 23 and 28
30 RMMR*.mp.
31 Residential medication management review*.mp.
32 30 or 31
33 29 or 32
34 limit 33 to (yr="1995 -Current" and english)
35 limit 34 to (addresses or autobiography or biography or comment or dictionary or directory or editorial or festschrift or letter or portraits)
36 34 not 35

PUBMED

(((((((((Homes for the aged) OR Nursing homes) OR Long-term care) OR Residential aged care facilit*) OR Aged care hom*)) AND (((((((Medication reconciliation) OR Utilization review) OR Medication therapy management) OR Medication review) OR Medicine review) OR Medicines review) OR Medication management) OR Pharmacist)) AND Australia[Affiliation])) OR ((((RMMR) OR RMMRs) OR Residential medication management review*) OR Residential medication management review)

Publication date from 1995/01/01 to 2018/07/31.

EMBASE VIA OVID

1 exp Aged/
2 exp Very elderly/
3 exp Frail elderly/
4 exp Nursing home/
5 exp Home for the aged/
6 Residential care/
7 Residential aged care facilit*.mp.
8 Aged care hom*.mp.
9 (long-term adj2 facilit$3).mp.
10 Nursing home$1.mp.
11 ((Residential$1 or home$1 or house$1) adj2 (old or elderly or aged or geriatric$1)).mp.
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 exp Medication therapy management/
14 exp "Drug use"/
15 exp Inappropriate prescribing/
16 Pharmacist/
17 Medicat* use$.mp.
18 Medica* reconciliation.mp.
19 Medicat* review$.mp.
20 (medicat* adj3 management).mp.
21 Pharmaci*.mp.
22 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 exp Australia/
24 Australia*.mp.
25 (New South Wales or NSW or Victoria or VIC or South Australia or SA or Western Australia or WA or Northern Territory or NT or Queensland or QLD or Tasmania or TAS or Australian Capital Territory or ACT).mp.
26 (Sydney or Melbourne or Adelaide or Hobart or Brisbane or Perth or Darwin or Canberra).mp.
27 23 or 24 or 25 or 26
28 12 and 22 and 27
29 RMMR*.mp.
30 Residential medication management review*.mp.
31 29 or 30
32 28 or 31
33 limit 32 to (yr="1995 -Current" and english)

CINAHL

S1 (MH "Aged+")
S2 (MH "Nursing Homes+")
S3 (MH "Nursing Home Patients")
S4 (MH "Long Term Care")
S5 Residential Aged Care Facilit*
S6 Aged Care Hom*
S7 Long-term N2 Facilit*
S8 "Nursing Hom*"
S9 ((Residential# or home# or house#) N2 (old or elderly or aged or geriatric#))
S10 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S11 (MH "Medication Reconciliation")
S12 (MH "Record Review")
S13 (MH "Medication History")
S14 (MH "Medication Compliance")
S15 (MH "Medication Errors+")
S16 (MH "Drug Utilization")
S17 (MH "Utilization Review+")
S18 (MH "Pharmacists")
S19 Medicat* Use*
S20 Medica* Reconciliation
S21 Medicat* Review*
S22 Medicine* Review*
S23 Medicat* N3 Management
S24 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 or S23
S25 AF Australia
S26 S10 AND S24 AND S25
S27 RMMR*
S28 Residential medication management review*
S29 S27 OR S28
S30 S26 OR S29
S31 Limit S30 to Publication Year: 1995-2018
S32 Narrow S31 by Language: English
S33 Narrow S32 by SubjectAge: -aged, 80 and over, and—middle aged: 45-64 years

INFORMIT HEALTH COLLECTION

(SUBJECT:Aged OR (SUBJECT:"Older people") OR (SUBJECT:"Old age homes") OR (SUBJECT:"Long-term care") OR (SUBJECT:Nursing ! SUBJECT:hom*) OR (ID:residential ID:aged ID:care ID:facility) OR (Aged % care % hom*) OR (Residential ! aged ! care ! facility*)) AND (SUBJECT:Drugs OR (Medicat* % management) OR (Medica* %2 reconciliation) OR (Medicat* % review*) OR (Medicine* % review*) OR (Pharmacis*)) limit to date 1995-2018.

APPENDIX B
Assessment of risk of bias

TABLE 1B JBI Critical Appraisal Checklist for prevalence studies

Author (year), retrospective cross-sectional study	Sample frame appropriate to address the target population	Study participants sampled in an appropriate way	Adequate sample size	Study subjects and setting described in detail	Data analysis conducted with sufficient coverage of the identified sample	Valid methods used for identification of the condition	Condition measured in a standard, reliable way for all participants	Appropriate statistical analysis	Response rate adequate or low response rate managed appropriately
McLarin et al. (2016)	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	N/A
Nishtala et al. (2016)	Unclear	Yes	Unclear	No	Yes	Yes	Yes	Yes	N/A
Gheewala et al. (2014)	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	N/A
Kaur et al. (2012)	Unclear	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes
Nishtala et al. (2011)	Unclear	Unclear	Yes	No	Unclear	Yes	Yes	Yes	N/A
Khalil et al. (2011)	No	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes
Stafford et al. (2009)	Yes	No	Yes	Yes	Unclear	Yes	Yes	Yes	N/A
Nishtala et al. (2009)	Yes	Yes	Yes	No	Unclear	Yes	Unclear	Yes	N/A

TABLE 2B JBI Critical Appraisal Checklist for cohort studies

Author (year), prospective observational cohort study	Similar groups recruited from the same population	Similar measurement of exposure of groups for assignment	Valid and reliable exposure measures	Confounders identified	Adjustment to deal with confounders	Groups free of outcome at moment of exposure	Valid and reliable outcome measures	Reported sufficient follow-up time	Follow-up complete or explored for loss to follow-up	Follow-up adjustment for incomplete follow-up	Statistical analysis appropriate
Koria et al. (2018)	N/A[a]	N/A[a]	Yes	Unclear	No	Unclear	Yes	Unclear	N/A	N/A	Yes
Poudel et al. (2015)	N/A[a]	N/A[a]	Yes	No	No	Unclear	Yes	Unclear	Yes	N/A	Yes
Smith et al. (2002)	N/A[a]	N/A[a]	Yes	Unclear	No	Unclear	Unclear	Yes	N/A	N/A	Yes
Elliott and Thomson (1999)	N/A[a]	N/A[a]	Yes	No	No	Unclear	Unclear	Yes	Yes	N/A	Yes

[a]Single group.

TABLE 3B JBI Critical Appraisal Checklist for randomised controlled trials

Author (year)	True randomisation used to assign participants	Concealed allocation	Treatment groups similar at baseline	Participants blinded to assignment	Those delivering treatment blinded to assignment	Outcome assessors blinded to assignment	Treatment groups treated equally excepting intervention	Follow-up complete or explored for loss to follow-up	Participants analysed in the same random groups	Same outcome measurement for groups	Reliable outcome measurement	Appropriate statistical analysis	Appropriate trial design or any design deviations explained
Potter et al. (2016)	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

2.4 Updated literature review

An updated search of Pubmed, MEDLINE, EMBASE, CINAHL and Informit Health from January 2018 to May 2020 was conducted to identify recent literature published since the publication of the systematic review. There were 2147 records identified. After removing duplicates and screening titles, abstracts, and full-text articles, there were an additional four studies that met the inclusion criteria (Table). All four studies involved the RMMR program. The additional studies contributed to the range of processes, impact and outcomes results.

Two studies investigated process elements of RMMRs.[153,154] In both studies, pharmacists expressed their belief that medication reviews improved medication management for residents. A qualitative study used semi-structured interviews to explore pharmacist perspectives on RMMRs for residents with advanced dementia.[153] Trust and interdependence were seen as essential elements for effective collaboration on medication reviews but were limited by the reality that these elements need time to build.[153] Factors identified as barriers to high-quality medication reviews were remuneration for case conferencing, inadequate frequency, and lack of accountability for follow-up.[153] Remuneration was also seen as a barrier among respondents of a questionnaire of pharmacists in Western Australia.[154] This was supported by the finding that the average time to complete an RMMR was approximately 2 hours.[154]

Two studies reported impact of RMMRs on medication regimen complexity and appropriate use of QT-prolonging medications.[117,155] Both studies were retrospective cross-sectional analyses, which were common among previously included studies. Neither study found that RMMRs resulted in improvements to their outcomes. There was a trend towards statistical significance that suggested that GPs were implementing recommendations that led to reduced medication regimen complexity.[117] There were few recommendations found in regard to QT-prolonging medications, and GP acceptance was not reported.[155] Pouranayatihosseinabad et al. reported that 74% of recommendations were accepted by GPs, which was consistent with those included in the published study.[117]

The additional studies added to the findings by increasing understanding of process and impact of RMMRs. However, there remains a lack of clinical and resident-centred outcomes.

Table 1. Studies on Residential Medication Management Reviews reporting processes, impact and/or outcomes, published August 2018-May 2020

Author (year), study design	Intervention	Population		Results		
	No of participants (No of RACFs)	Mean age (±SD)	Mean number of medications (±SD)	Process	Impact	Outcome
Pouranayatihos seinabad et al. (2018), retrospective cross-sectional analysis	285 (not reported)	85.5 (±7.7)	8.8 (±3.3)	N/A	Medication regimen complexity index (MRCI) score baseline median: 25.5 (IQR 19.0-32.5) Post RMMR median MRCI score: 25.0 (IQR 19.0-33.5) 764 recommendations made; 29% (n=222) increased MRCI score; 30% (n=229) decreased MRCI score	Post GP uptake median MRCI score: 25.0 (IQR 19.0-33.0) 74.5% (n=569) of recommendations accepted by GPs
Disalvo et al. (2019), semi-structured interviews	15 (N/A)	N/A	N/A	Pharmacist perspectives on barriers and facilitators to RMMR's potential for improving medication use. RMMR program structures were seen as restrictive for collaborative practice, with a lack of accountability.	N/A	N/A

Author (year), study design	Intervention	Population		Results		
	No of participants (No of RACFs)	Mean age (±SD)	Mean number of medications (±SD)	Process	Impact	Outcome
Christensen et al. (2019), retrospective cross-sectional analysis	400 (not reported)	79 (±13)	12 (±4)	N/A	Mean number of medications with known risk of QT prolongation at baseline: 0.2 (±0.5) Mean risk of QT prolongation (RISQ-PATH score) at baseline: 9.5 (±4) Risk of QT prolongation was identified in 9% (n=6) of residents taking a medication with a known risk of QT prolongation (n=66). The recommendations made were dose reduction (n=2), assess/monitor/review (n=2) and no recommendation (n=2).	N/A

Author (year), study design	Intervention	Population		Results		
	No of participants (No of RACFs)	Mean age (±SD)	Mean number of medications (±SD)	Process	Impact	Outcome
Czarniak et al. (2020), questionnaire	30 (not reported)	N/A	N/A	Extent and characteristics of RMMR services provided in Western Australia. 57% (n=17) of respondents performed 1-50 RMMRs in the previous 12 months. Average of 127 minutes spent per RMMR. 93% (n=28) of respondents felt RMMRs results in improved resident outcomes.	N/A	N/A

GP, general practitioner; IQR, interquartile range; MRCI, Medication Regimen Complexity Index; N/A, not applicable; RACFs, residential aged care facilities; RMMR, Residential Medication Management Reviews; SD, standard deviation.

PART B: INVESTIGATING THE BURDEN OF MEDICATION REGIMEN COMPLEXITY

3. Chapter Three: Medication regimen complexity and risk of bleeding in people taking oral anticoagulants: A population-based cohort study in Hong Kong

3.1 Synopsis

This chapter investigates whether overall medication regimen complexity in people using OACs is associated with the risk of bleeding. This study was undertaken at the Centre for Safe Medication Practice and Research (CSMPR), University of Hong Kong, as part of an Endeavour Cheung Kong Fellowship. CSMPR have access to a unique population-based database, which presented an excellent opportunity to investigate clinical outcomes associated with medication regimen complexity. Atrial fibrillation (AF) is a condition associated with older age managed using OACs, which are high-risk medications. A study identified in the systematic review described in Chapter Two reported that medication regimen complexity was a potential reason that OACs were not being recommended to eligible residents after a medication review.[156] Prescribers may choose not to prescribe OACs to people who they perceive are at high risk of bleeding. Barriers to OAC prescribing includes perceived increased risk of bleeding in older people, or a reluctance to add medications for older people with cognitive and/or functional impairment or other comorbidities which may lead to polypharmacy and complex medication regimens.[31,157,158] However, there was no evidence from my research to suggest medication regimen complexity was associated with the risk of bleeding. Additionally, this was the first study to investigate the complexity of medication regimens in people with atrial fibrillation. This study contributes to our understanding of the impacts of medication regimen complexity on the safety of OACs.

3.2 Chapter objective

To investigate the association between medication regimen complexity and safety of oral anticoagulants in people with AF in a population-based study in Hong Kong.

3.3 Submitted paper

At the time that this thesis was submitted, this paper was submitted to the journal *JAMA Internal Medicine*.

Medication regimen complexity and risk of bleeding in people who initiate oral anticoagulants for atrial fibrillation: a population-based study

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Abstract

Importance

Oral anticoagulants (OACs) are high-risk medications due to risk of bleeding. Clinicians do not routinely consider the overall complexity of a patient's medication regimen when assessing bleeding risk when deciding whether or not to initiate an OAC.

Objective

This study assessed the association between overall medication regimen complexity and bleeding in people with atrial fibrillation (AF) initiating oral anticoagulants.

Design

Population-based cohort study using the Hong Kong Clinical Database and Reporting System between 2010-2016. Follow-up until December 31, 2017.

Setting

Public-sector primary, secondary and tertiary care provided by the Hong Kong Hospital Authority, Hong Kong.

Participants

All inpatients and outpatients diagnosed with AF and initiated on OACs (warfarin, dabigatran, rivaroxaban, apixaban) within the study period. Baseline characteristics were balanced using inverse probability of treatment weighting.

Exposure

The 65-item validated Medication Regimen Complexity Index (MRCI) was computed for each person and categorized into quartiles Q1 <=14, Q2 >14.0-22.0, Q3 >22.0-32.5 and Q4 >32.5, with higher scores indicating greater medication regimen complexity.

Main outcomes and measures

First bleed (intracranial haemorrhage, gastrointestinal bleeding or other bleeding) resulting in hospitalisation. People were censored at discontinuation of the index OAC, death or end of the follow-up period, whichever occurred first. Cox regression was used to estimate associations between MRCI and bleeding during all follow-up, and at 30-, 60- and 90- days post-initiation.

Results

There were 19 292 new users of OACs with AF (n=9092 warfarin and n=10,200 direct oral anticoagulants [DOACs]). The mean (standard deviation) age at initiation was 73.9 (11.0) years. People were followed for a median (interquartile range) of 501 (119-1040) days. People with more complex medication regimens had increased risk of bleeding (Q3: adjusted hazard ratio (aHR) 1.32, 95%CI 1.06-1.65; and Q4: aHR 1.46, 95%CI 1.13-1.87, compared to Q1). No significant association between MRCI and bleeding risk was observed during the initial 30-, 60- or 90-days of treatment. In subgroup analysis, the highest quartile of regimen complexity was associated with an increased risk of bleeding among both warfarin and DOAC users.

Conclusion and relevance

Among people with AF who initiate an OAC, having a more complex medication regimen is associated with higher bleeding risk over periods longer than 90 days. Medication regimen complexity may be a risk factor to consider when assessing bleeding risk.

Keywords

Medication regimen complexity; anticoagulant; atrial fibrillation; bleeding; adverse drug event; warfarin

Introduction

Oral anticoagulants, such as warfarin and direct oral anticoagulants (DOACs), are indicated to reduce ischaemic stroke risk in older people with atrial fibrillation (AF). Oral anticoagulants (OAC)s are high-risk medications due to an increased risk of serious adverse drug events (ADEs) such as intracranial, gastrointestinal, and other bleeding, particularly in older people. In the United States (US), bleeding requiring hospitalization was highest in people initiating warfarin (4.66 per 100 person-years) compared to DOACs (between 2.35 and 4.57 per 100-person-years).[1] A recent population-based cohort study of OAC users demonstrated incidence of major bleeding increased with age, from 3.5% per year in people 65-74 years to 6.1% in people 75-89 years and 10.5% in people 90 years and over.[2] Prescription claims data suggest that OAC use is increasing in people aged 65 years and older, including in vulnerable population such as those with dementia in Australia and in the United Kingdom (UK).[3,4]

As an age-related condition, people with AF are increasingly treated with complex regimens to manage comorbidities.[5-7] Number of medications, multiple daily doses, different formulations and specific dosing instructions (e.g. split tablets, take with food) are all factors that contribute to medication regimen complexity.[8] Regimen complexity may affect an individual's ability to correctly self-manage and administer medications.[9] While the use of multiple medications (polypharmacy) is strongly correlated with medication regimen complexity, other aspects of complexity such as specific dosing instructions have shown independent association with outcomes such as adherence.[10,11] Complex medication regimens have been associated with medication non-adherence in older people.[5,12] In intensive-care units, medication regimen complexity has been correlated with longer lengths of stay and higher number of drug interactions.[13] There is growing evidence that medication regimen complexity is an independent predictor of clinical outcomes such as hospitalisation.[12,14]

Warfarin is complex to administer due to variable dosing, multiple tablet strengths, need for international normalized ratio monitoring, and drug-drug and drug-food interactions.[15,16] In contrast, DOACs have standard dosing regimens and require less intensive monitoring. However, both OACs contribute to overall medication regimen

complexity.[13] A physician's perception of patients' ability to adhere with their treatment regimen can be a barrier to prescribing of OACs.[17] Despite this, no previous studies have characterized medication regimen complexity in people with AF.[18]

The association between overall medication regimen complexity and bleeding risk among people initiating OACs has not been investigated. This is an important clinical question because decisions to initiate OACs, including balancing of stroke and bleeding risk, are made within the context of people with AF, who are generally older and use multiple medications.[19] In the US, over half of people 75 years and older with AF use five or more medications.[20] People with AF admitted to an Australian hospital used a mean (±standard deviation (SD)) of 11.3±4 medications.[21] In an Italian hospital, a cross-sectional study of older people admitted to an acute geriatric unit showed that people with AF had significantly more comorbidities (Charlson Comorbidity Index score of 3 vs. 2, $P < 0.001$) and used a higher number of medications (4 vs. 3, $p<0.001$) compared to people without AF.[22] Current risk assessment scores used to inform prescribing do not consider medication regimen factors.[23,24] The objective of this study was to evaluate the association between overall medication regimen complexity and bleeding risk in people with AF who initiate OACs.

Methods

Study design and data source

A population-based cohort study was undertaken using electronic medical records from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the sole comprehensive public-funded population-wide healthcare provider to Hong Kong's population of over seven million people.[25] Electronic medical records, including demographics, date of hospital admission and discharge, diagnoses, procedures, laboratory tests, and medication prescription records, are centralized in the Hospital Authority system and regularly audited. The records cover all patient consultations with the Hospital Authority,

including inpatient, discharge and outpatient clinic visits. All medications that are prescribed at any consultation are captured. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM were used for identifying diagnoses and cause of death respectively in CDARS. Deidentified data were extracted. CDARS has demonstrated high coding accuracy, with positive predictive values over 90% for diagnosis records for AF, intracranial haemorrhage, gastrointestinal bleeding, and ischaemic stroke.[26,27] CDARS has been extensively used to study the outcome of oral anticoagulant use.[28,29] This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468) and registered with the Monash University Human Research Ethics Committee. Informed consent was not required for the use of de-identified data in the absence of patient contact.

Population

People aged 18 years or older with a diagnosis of AF (ICD-9-CM code 427.3) between 1 January 2010 and 31 December 2016 were included. Individuals with a diagnosis of valvular disease, hyperthyroidism and those who underwent valve replacement at or prior to their AF diagnosis were excluded using the ICD-9-CM codes listed in Supplementary Table 1.

The index date was defined as the first day of a prescription of an OAC (warfarin, dabigatran, rivaroxaban, apixaban) following the first recorded AF diagnosis. Warfarin and dabigatran were captured from 2010, rivaroxaban from 2012 and apixaban from 2013. Medication names were used to identify OACs from electronic prescription records. To select new users of OAC, people with any prescription of an OAC within 180 days before index date were excluded.

Exposure

Medication regimen complexity was quantified using the validated 65-item Medication Regimen Complexity Index (MRCI). This is the most widely used measure of overall regimen complexity.[8,30] The MRCI assigns weights for each medication in the regimen across three domains of formulation, dose frequency, and special instructions.[8] The points were then summed for the total MRCI score. Fields

extracted from CDARS used to calculate MRCI included prescription start and end date, medication name, route, medication strength, dosage, medication frequency, and unit of measurement of the medication (e.g. millilitres). The MRCI score on the index date was calculated for each person. Prescriptions were included if the person's index date fell in the duration on and between the prescription start and end dates. Vaccines were excluded. Information on special administration instructions were deduced from CDARS records where possible, such as splitting tablets (e.g. 0.5 tablet) or having with food. There are no widely accepted cut-offs for MRCI scores considered to be "high" or "low".[31,32] The population was divided into quartiles based on MRCI scores (quantiles 1-4 (Q1-4), with 1 being the lowest and 4 being the highest MRCI scores). This approach to categorization of MRCI has been used in previous studies.[33-37]

Primary and secondary outcomes

The primary outcome was defined as the first episode following index date of any of: intracranial haemorrhage (ICH), gastrointestinal bleeding (GIB), other bleeding requiring hospitalisation. Other bleeding was defined as including hemopericardium, hemoptysis and haemorrhage from the kidney, throat, or vagina, epistaxis, hemarthrosis, hematuria and metrorrhagia (Supplementary Table 1). We examined outcomes occurring in the first 30-, 60-, and 90-days, and through the entire follow-up period, with follow-up occurring from the index date until the first occurrence of any outcome of interest, end of study period (31 December 2017), death, switching to another oral anticoagulant, or discontinuation of the index oral anticoagulant. Discontinuation of therapy was defined as a gap greater than 10 days between the end of one prescription and the start of the next prescription. The mean gap for OAC prescriptions was five days. To capture most of the continuous users, we doubled this period and kept it short enough to get a reliable estimate for the 30-day follow-up. Secondary outcomes were the first episodes of ICH and GIB, and all-cause mortality.

Statistical analysis

Baseline characteristics were expressed as means (standard deviation [SD]) for continuous variables and as frequencies (percentages) for categorical variables.

Incidence rates were calculated by dividing the number of events over follow up time. Cumulative incidence of any bleed over time and all-cause mortality were depicted using Kaplan-Meier curves.

To account for confounding and indication bias between exposure groups, inverse probability of treatment weighted approach was applied. Propensity scores were estimated using logistic regression based on age (continuous), sex, oral anticoagulant, index year, medical history of myocardial infarction, congestive heart failure, hypertension, diabetes, cancer, chronic obstructive pulmonary disease (COPD), ischaemic stroke/transient ischaemic attack/systemic embolism, vascular disease, renal disease, or prior bleed; recent use (<90 days prior to index date) of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta blocker, amiodarone, dronedarone, aspirin, clopidogrel, non-steroidal anti-inflammatory drugs (NSAIDs), histamine type-2-receptor antagonist, calcium channel blocker, statins, selective serotonin re-uptake inhibitor (SSRI)/selective noradrenaline re-uptake inhibitor (SNRI), oral corticosteroids and spironolactone; and CHADS2-VASc and HAS-BLED score (continuous). In Hong Kong, most aspirin and NSAIDs use is recorded in CDARS. The covariates identified by ICD-9-CM and identification of medications are listed in supplementary material. Balance between baseline characteristics in exposure groups was assessed using standardized mean differences, with differences <0.2 considered balanced.

Cox proportional hazard regression was used to estimate cause specific hazard ratios (HR) and their confidence intervals (CI). Characteristics with a standardised mean difference >0.1 after adjustment were also included in the Cox regression model to further adjust the model. Subgroup analyses were conducted to investigate the effect of MRCI within age groups (<80 and 80 years or older) and type of OAC (warfarin and DOACs). Analyses were conducted in R v 3.6.3 (Comprehensive R Archive Network) with RStudio v 1.2.5042.

Results

Baseline characteristics

Of 71,630 people with AF identified, there were 19,292 new users of an OAC with a mean (SD) age at initiation of 73.9 (11.0) years (Figure 1). The median follow-up was 501 (IQR 119-1040) days. MRCI scores ranged from 1.5-129.5; while the mean (SD) MRCI score was 24.82 (14.62). Quartile cut-offs were identified as MRCI scores ≤14 (26.2%), >14.0-22.0 (25.3%), >22.0-32.5 (24.1%), and >32.5 (24.4%) (Table 1). People with the most complex medication regimens had more comorbidities. The mean (SD) number of medications prescribed increased with increasing complexity quartile, from 4.7 (1.6) in Q1, 7.6 (1.6) in Q2, 10.2 (1.9) in Q3, and 15.0 (3.7) in the highest complexity Q4.

Bleeding outcomes

There were 2494 people who had a bleeding event during the follow up period. The highest medication complexity quantile (Q4) had the most people experiencing any bleed (n=717, 15.2%) (Table 2). Rate of all-cause mortality was also highest in the highest quantile (Q4). Quantile 2 had the highest number of ICHs (n=140, 3.0%), while Q4 had the highest number of GIBs (n=318, 6.7%). The crude incidence rate of bleeding was highest in the first 30 days after OAC initiation for all levels of medication regimen complexity. Unweighted Kaplan-Meier curves are provided in Supplementary Figure 1.

People with the higher complexity scores had higher risk of bleeding outcomes compared with people with the lowest complexity scores (aHR 1.33, 95%CI 1.06-1.66 for Q3 and aHR 1.45, 95%CI 1.13-1.87 for Q4), after balancing baseline characteristics (Table 3). For the initiation periods of 30-, 60- and 90-days following OAC prescription, MRCI did not have a significant impact on the bleeding risk. When analysed by type of bleed, MRCI was not associated with higher risk of ICHs (aHR 1.05, 95%CI 0.55-1.99 for Q2; aHR 1.29, 95%CI 0.68-2.42 for Q3; aHR 1.09, 95%CI 0.54-2.17 for Q4). People with higher complexity scores had a higher risk for GIB (aHR 1.51, 95%CI 1.13-2.01 for Q3; aHR 1.76 95%CI 1.27-2.45 for Q4).

Subgroup analyses

In subgroup analyses by age, MRCI was significantly associated with an increased risk of bleeding for people aged under 80 years across all higher complexity quantiles (Q2-4) (Figure 2). Results for people aged 80 years or older were not significant. In analyses between OACs, high MRCI score (Q4) was associated with increased risk of bleeding in people initiated on warfarin and in people initiated on DOACs (HR 1.50, 95%CI 1.06-2.12 and HR 1.43, 95%CI 1.02-1.99, respectively).

Discussion

To our knowledge, this was the first study to characterise medication regimen complexity in people with AF. The main finding was that medication regimen complexity is an independent predictor of bleeding in people who initiate OACs. This has important clinical implications. Firstly, increasing rates of multimorbidity in people with AF mean that people who initiate OACs have increasingly complex medication regimens.[38] Medication regimen complexity may increasingly need to be considered when making treatment decisions. Second, widely used bleeding risk assessment tools such as HAS-BLED do not consider the overall complexity of a person's medication regimen.[23]

Our results are the first to demonstrate an association between overall medication regimen complexity and bleeding risk. This result is concordant with preliminary findings that suggested MRCI was associated with 12-month medication-related hospitalization in people with heart failure and AF.[39] However, the study did not find a significant association between MRCI and all-cause hospitalization.[39] Our findings are also consistent with secondary analyses of the landmark randomised trials that demonstrate polypharmacy is associated with increased bleeding risk. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and Apixaban for Reduction in Stroke and Other Thromboembolic

Events in Atrial Fibrillation (ARISTOTLE) study showed polypharmacy was associated with an increased risk of bleeding.[40,41] Polypharmacy (defined as ≥5 medications) was prevalent in two-thirds of the ROCKET AF cohort. Both warfarin and rivaroxaban were associated with increased risk of major bleeding in the presence of polypharmacy.[40] In ARISTOTLE, the risk of major bleeding increased with increasing number of concomitant medications (6-8 medications: HR 1.24, 95%CI 1.04-1.49; 9 or more: HR 1.72, 95%CI 1.41-2.10).[41] Polypharmacy was associated with increased GIB but not ICH.[41] A US study of people 75 years or older found that use of five or more medications was associated with an increased risk of major bleeding (HR 1.16, 95%CI 1.12-1.20).[20]

In our study, the incidence of bleeding was highest in the initiation period, consistent with previous studies that found that higher risk of bleeding within this period.[42-44] However, in adjusted analysis, MRCI score was not associated with bleeding within 90-days following OAC initiation. This could be because the additional risk associated with regimen complexity is small relative to the risk of bleeding due to other factors, such as prior bleeding, during this initial period. The increased risk of ADEs due to interactions or medication errors that arise from managing complex medication management may be more likely to materialize over a longer period of time.[45,46] Limited literacy, cognitive decline and multimorbidity were independent predictors of dosing errors over nine years.[46] Additionally, we estimated MRCI on the index date. Medication regimens may have changed throughout the follow up period. However, the decision to initiate an OAC is made on the index date and so assessing complexity at this time is consistent with how knowledge of bleeding risk would be used by clinicians in routine clinical practice.[49] A cohort study of people with AF found that over half had new comorbidities diagnosed during the follow-up.[38] Subsequent initiation or discontinuation of medications throughout the follow-up period, including those which would impact bleeding risk such as aspirin, were not considered in our analyses.

Our findings are consistent with existing literature investigating complexity as measured by dosing frequency, which is included as a domain in the MRCI.[50,51] A comparison of persistence and discontinuation between once-daily rivaroxaban and twice-daily dabigatran showed people using rivaroxaban were 11% less likely to

become non-persistent (have large gaps between prescription refills) and 29% less likely to discontinue therapy.[52] A Turkish study compared people receiving once-daily and twice-daily DOACs, and did not find a difference in bleeds, despite finding lower adherence in people in the twice-daily dosing group.[53] A proposed mechanism was the smaller pharmacokinetic risk of medication dose errors (missing a dose or taking an extra dose) for DOACs with twice-daily regimens compared to once-daily regimens.[53] However, the presence of three or more additional medical conditions was an independent risk factor for bleeding.[53] Our study calculated the MRCI based on the patients' complete medication regimen rather than the complexity of only the OACs. A once-daily DOAC may have been taken as part of an overall medication regimen that had more than one administration time. This is in contrast to studies which have investigated outcomes related to complexity of only medications for specific conditions. Complexity of medication regimens to treat single indications have been found to represent less than 20% to an overall MRCI score.[54] Hence, overall MRCI may be a more important indicator of clinical outcomes.

An intervention to reduce medication regimen complexity such as simplification may not reduce the risk of bleeding but may support an individual to self-manage their medications at home when an additional medication is added. A range of interventions have been trialled and developed to identify and reduce unnecessary medication regimen complexity among recipients of community-based home care services and residential aged care.[51,57] Whether medication regimen complexity is a modifiable risk factor for bleeding requires further investigation.

Strengths and limitations

This study used large real-world population-based data and investigated validated clinical outcomes.[25,44] A strength of this study was the large sample size. We used a validated scale to calculate MRCI, so results are comparable to other studies internationally that have used MRCI to quantify complexity despite MRCI distributions varying depending on populations.[14,32,35,36,48,55]

Our calculation of MRCI was conservative. Only prescriptions current on the index date were included, however, prescription durations for many chronic medications were long and so would likely have been captured. Similar to other studies using

electronic medical records, complementary and alternative medications and any non-prescribed over-the-counter medications were not captured in CDARS and so were not included. Furthermore, electronic medical records cannot measure adherence to OACs. Non-adherence to OACs has been associated with lower risk of bleeding.[56] Additional patient-specific administration instructions, such as crushing tablets to aid swallowing difficulties, may have been counselled but not recorded. These factors may have contributed to an underestimation of complexity. There may be residual confounding factors despite a rigorous approach to balance known and measured factors. Finally, the relationship between MRCI and bleeding may not be causal.

Conclusion

Higher medication regimen complexity is associated with increased bleeding risk over treatment periods longer than 90 days among people with AF. Medication regimen complexity may be a bleeding risk factor to consider when initiating an OAC.

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Conflicts of interest and financial disclosures

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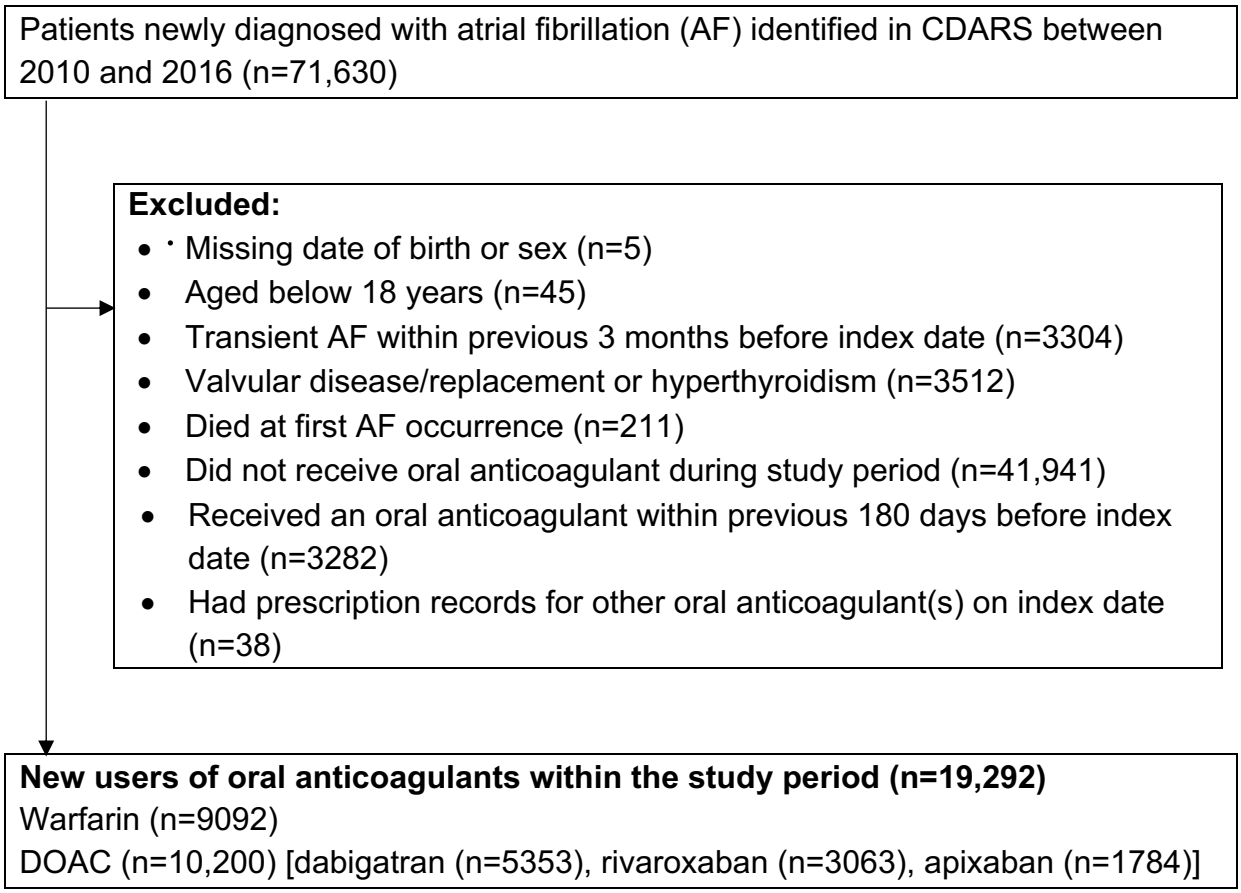


Figure 1. Study flowchart of participant selection

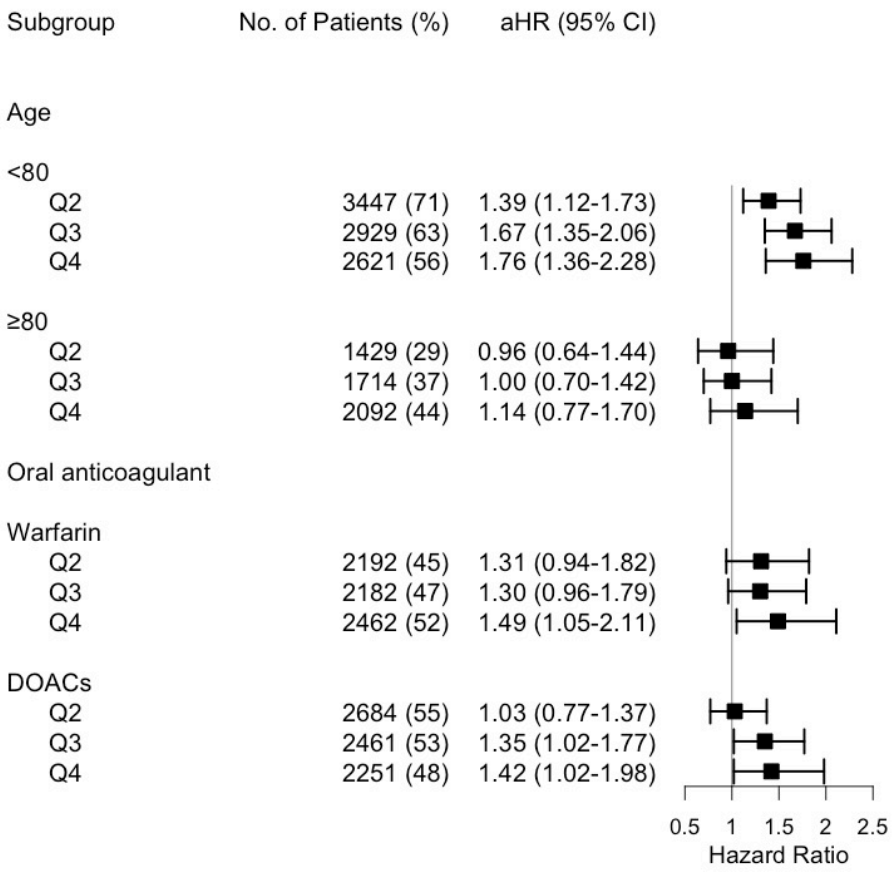


Figure 2. Forest plot of subgroup analysis for full follow-up. aHR, adjusted hazard ratio, adjusted for Charlson Comorbidity Index score, prior bleeding, and recent use of amiodarone, dronedarone, or clopidogrel.

Table 1. Baseline characteristics, mean (SD) unless specified

MRCI quartile	Q1 (n=5060)	Q2 (n=4876)	Q3 (n=4643)	Q4 (n=4713)	SMD*	Adj SMD*
Definition (MRCI)	0-14.0	>14.0-22.0	>22.0-32.5	>32.5		
Follow up, days	764 (719)	734 (685)	653 (646)	548 (582)		
Age, years	70.4 (11.6)	73.2 (10.8)	75.2 (10.3)	77.1 (10.0)	0.6200	-0.0239
Female, n (%)	2182 (43)	2335 (48)	2352 (51)	2430 (52)	0.1692	0.0440
Oral anticoagulant, n (%)						
Warfarin	2256 (44.6)	2192 (45.0)	2182 (47.0)	2462 (52.2)	0.1536	-0.0432
Dabigatran	1508 (29.8)	1478 (30.3)	1304 (28.1)	1063 (22.6)	-0.1738	-0.0100
Rivaroxaban	897 (17.7)	776 (15.9)	712 (15.3)	678 (14.4)	-0.0916	0.0284
Apixaban	399 (7.9)	430 (8.8)	445 (9.6)	510 (10.8)	0.1013	0.0617
Baseline medical conditions, n (%)						
Congestive heart failure	682 (13.5)	1072 (22.0)	1336 (28.8)	1956 (41.5)	0.6534	-0.0471
Hypertension	1868 (36.9)	2460 (50.5)	2620 (56.4)	3115 (66.1)	0.5978	0.0448
Diabetes mellitus	467 (9.2)	984 (20.2)	1539 (33.1)	2196 (46.6)	0.7049	-0.0390
Prior ischemic stroke or TIA or systemic embolism	1188 (23.5)	1486 (30.5)	1552 (33.4)	1547 (32.8)	0.2178	-0.0231
Vascular disease	446 (8.8)	875 (17.9)	1249 (26.9)	1809 (38.4)	0.7275	-0.0381
Myocardial infarction	94 (1.9)	225 (4.6)	434 (9.4)	722 (15.3)	0.5118	0.0529
COPD	119 (2.4)	195 (4.0)	314 (6.8)	1089 (23.1)	0.7552	0.0190

Renal disease	118 (2.3)	295 (6.1)	439 (9.5)	886 (18.8)	0.5841	-0.0907
Cancer	304 (6.0)	373 (7.7)	340 (7.3)	461 (9.8)	0.1478	0.0398
Prior bleed	576 (11.4)	733 (15.0)	834 (18.0)	1215 (25.8)	0.3823	-0.1048
Medications prescribed in the 90 days prior to index date, n (%)						
ACEI/ARB	1520 (30.0)	2340 (48.0)	2637 (56.8)	3008 (63.8)	0.6984	0.0318
Beta blocker	2623 (51.8)	3130 (64.2)	3103 (66.8)	2937 (62.3)	0.3100	-0.0381
Calcium channel blocker	2251 (44.5)	2834 (58.1)	2886 (62.2)	3360 (71.3)	0.5559	-0.0269
Amiodarone	324 (6.4)	502 (10.3)	688 (14.8)	957 (20.3)	0.4190	-0.1765
Dronedarone	68 (1.3)	40 (0.8)	33 (0.7)	25 (0.5)	-0.0886	-0.1113
Aspirin	3274 (64.7)	3699 (75.9)	3664 (78.9)	3880 (82.3)	0.4144	0.0583
Clopidogrel	250 (4.9)	373 (7.6)	455 (9.8)	614 (13.0)	0.2862	-0.1282
Dipyridamole	29 (0.6)	59 (1.2)	101 (2.2)	135 (2.9)	0.1774	0.0462
NSAID	216 (4.2)	297 (6.1)	363 (7.8)	497 (10.5)	0.2441	-0.0282
H2RA	2491 (49.2)	2795 (57.3)	2746 (59.1)	2818 (59.8)	0.2138	-0.0351
Proton pump inhibitor	875 (17.3)	1212 (24.9)	1531 (33.0)	2169 (46.0)	0.6427	-0.0845
Statin	1808 (35.7)	2514 (51.6)	2765 (59.6)	2831 (60.1)	0.4967	-0.0421
SSRI/SNRI	50 (1.0)	107 (2.2)	178 (3.8)	267 (5.7)	0.2675	0.0404
Oral corticosteroid	82 (1.6)	162 (3.3)	319 (6.9)	1066 (22.6)	0.7838	0.0546
Spironolactone	63 (1.3)	117 (2.4)	137 (3.0)	239 (5.1)	0.2281	0.0249
Risk scores						
CHADS2	1.46 (1.25)	2.02 (1.38)	2.38 (1.45)	2.76 (1.46)		
CHAD2S2-VASc	2.67 (1.59)	3.46 (1.75)	3.99 (1.80)	4.54 (1.82)	1.0726	-0.0354
HAS-BLED	2.16 (1.14)	2.65 (1.20)	2.90 (1.20)	3.26 (1.22)	0.9291	-0.0578

Charlson Comorbidity Index	0.81 (1.07)	1.28 (1.38)	1.65 (1.49)	2.47 (1.93)		

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CHADS2, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism (doubled); CHA2DS2-VASc, congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, age 65–74 years, prior stroke/transient ischemic attack/systemic embolism (doubled), vascular disease, and sex category (female); HAS-BLED, hypertension, abnormal liver or kidney function, stroke history, bleeding history, labile international normalized ratio [not included], elderly [age >65 years], drug, and alcohol use; H2RA, histamine type-2-receptor antagonist; MRCI, medication regimen complexity index; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardised mean difference; SNRIs, selective noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack.

*maximum standardised pairwise difference, crude and adjusted using inverse probability of treatment weighting with no truncation

Table 2. Incidence of bleeding events

MRCI quartile	**Q1**		**Q2**		**Q3**		**Q4**	
	Events	**Incidence/ 100 py**	**Events**	**Incidence/ 100 py**	**Events**	**Incidence/ 100 py**	**Events**	**Incidence/ 100 py**
All follow up – range (1-2,927 days), mean 685.8 days								
All bleeding	520	4.7	612	6.2	645	7.8	717	10.1
Intracranial bleed	95	0.8	140	1.3	139	1.5	128	1.6
GI bleed	183	1.6	225	2.2	266	3.0	317	4.2
Other bleeding	254	2.2	287	2.8	297	3.4	318	4.2
Mortality	265	2.4	398	4.1	476	5.7	915	12.9
Incidence of bleeding – 30 day follow up								
All bleeding	75	19.0	92	24.6	113	32.0	139	39.7
Intracranial bleed	12	3.0	30	8.0	34	9.5	36	10.2
GI bleed	25	6.3	32	8.5	37	10.4	50	14.1
Other bleeding	36	9.1	27	7.2	44	12.3	45	12.7
Mortality	17	0.2	23	0.2	45	0.5	147	2.1
Incidence of bleeding – 60 day follow up								
All bleeding	109	14.3	128	17.8	164	24.2	191	28.9
Intracranial bleed	14	1.8	34	4.7	43	6.3	43	6.4
GI bleed	38	4.9	46	6.3	56	8.2	72	10.7
Other bleeding	36	9.1	27	7.2	44	12.3	45	12.7
Mortality	26	0.2	47	0.5	74	0.9	238	3.4

Incidence of bleeding – 90 day follow up								
All bleeding	130	11.7	155	14.8	201	20.5	235	24.7
Intracranial bleed	16	1.4	41	3.9	50	5.0	46	4.7
GI bleed	45	4.0	51	4.8	71	7.1	89	9.2
Other bleeding	67	6.0	61	5.7	84	8.4	90	9.3
Mortality	36	0.3	62	0.6	104	1.3	293	4.1

Table 3. Association between MRCI quarter and bleeding over various follow up periods

	Unadjusted HR (95%CI)	**Adjusted HR (95%CI)**
30-day follow up		
Q1	1	1
Q2	0.89 (0.38-2.05)	1.00 (0.48-2.09)
Q3	1.08 (0.48-2.45)	1.25 (0.61-2.54)
Q4	1.06 (0.46-2.44)	1.15 (0.54-2.45)
60-day follow up		
Q1	1	1
Q2	0.88 (0.46-1.68)	0.99 (0.55-1.78)
Q3	1.13 (0.61-2.12)	1.28 (0.73-2.26)
Q4	1.17 (0.60-2.31)	1.27 (0.68-2.39)
90-day follow up		
Q1	1	1
Q2	0.89 (0.51-1.56)	0.98 (0.59-1.65)
Q3	1.16 (0.67-2.00)	1.30 (0.79-2.14)
Q4	1.28 (0.71-2.32)	1.37 (0.78-2.40)
All follow up		
Q1	1	1
Q2	1.14 (0.90-1.45)	1.17 (0.93-1.49)
Q3	1.27 (1.01-1.60)	1.33 (1.06-1.66)
Q4	1.43 (1.10-1.85)	1.45 (1.13-1.87)
MRCI: medication regimen complexity index. *adjusted for Charlson Comorbidity Index score, prior bleeding, and recent use of amiodarone, dronedarone, or clopidogrel		

Supplemental Table 1. International Classification of Diseases codes, Ninth Revision, Clinical Modification (ICD-9-CM) codes used in the study

ICD-9-CM codes	Descriptions
Atrial fibrillation	
427.3	Atrial fibrillation and flutter
Transient atrial fibrillation	
Cardiac surgery (procedure codes)	
00.5	Other cardiovascular procedures
35	Operations on valves and septa of heart
36	Operations on vessels of heart
37	Other operations on heart and pericardium
Pericarditis	
391	Rheumatic fever with heart involvement
393	Chronic rheumatic pericarditis
420	Acute pericarditis
423.2	Constrictive pericarditis
036.41	Meningococcal pericarditis
074.21	Coxsackie pericarditis
093.81	Syphilitic pericarditis
098.83	Gonococcal pericarditis
Myocarditis	
130.3	Myocarditis due to toxoplasmosis
391.2	Acute rheumatic myocarditis
398.0	Rheumatic myocarditis
422	Acute myocarditis
429.0	Myocarditis, unspecified
032.82	Diphtheritic myocarditis
036.43	Meningococcal myocarditis
074.23	Coxsackie myocarditis
093.82	Syphilitic myocarditis
Pulmonary embolism	
415.1	Pulmonary embolism and infarction
Valvular heart diseases/replacement or hyperthyroidism	
242	Thyrotoxicosis with or without goitre
394.0	Mitral stenosis

Valvular heart surgery (procedure codes)	
35.20	Open and other replacement of unspecified heart valve
35.22	Open and other replacement of aortic valve
35.24	Open and other replacement of mitral valve
35.26	Open and other replacement of pulmonary valve
35.28	Open and other replacement of tricuspid valve
Intracranial haemorrhage	
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other and unspecified intracranial haemorrhage
Gastrointestinal bleeding	
531.0	Acute gastric ulcer with hemorrhage
531.2	Acute gastric ulcer with hemorrhage and perforation, without mention of obstruction
531.4	Chronic or unspecified gastric ulcer with hemorrhage
531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
532.0	Acute duodenal ulcer with hemorrhage
532.2	Acute duodenal ulcer with hemorrhage and perforation
532.4	Chronic or unspecified duodenal ulcer with hemorrhage
532.6	Chronic or unspecified duodenal ulcer with hemorrhage and perforation
533.0	Acute peptic ulcer of unspecified site with hemorrhage
533.2	Acute peptic ulcer of unspecified site with hemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
533.6	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
534.0	Acute gastrojejunal ulcer with hemorrhage
534.2	Acute gastrojejunal ulcer with hemorrhage and perforation, without mention of obstruction
534.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
534.6	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation
535.01	Acute gastritis, with hemorrhage
535.11	Atrophic gastritis, with hemorrhage
535.21	Gastric mucosal hypertrophy, with hemorrhage
535.31	Alcoholic gastritis, with hemorrhage
535.41	Other specified gastritis, with hemorrhage

535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage
535.61	Duodenitis, with hemorrhage
535.71	Eosinophilic gastritis, with hemorrhage
562.02	Diverticulosis of small intestine with hemorrhage
562.03	Diverticulitis of small intestine with haemorrhage
562.12	Diverticulosis of colon with haemorrhage
562.13	Diverticulitis of colon with haemorrhage
569.3	Hemorrhage of rectum and anus
569.85	Angiodysplasia of intestine with haemorrhage
569.86	Dieulafoy lesion (hemorrhagic) of intestine
578.0	Hematemesis
578.1	Melena
578.9	Hemorrhage of gastrointestinal tract, unspecified
Other bleeding	
423.0	Hemopericardium
459.0	Haemorrhage NOS
593.81	Vascular disorders of kidney
599.7	Haematuria
623.8	Other specified noninflammatory disorders of vagina
626.2	Excessive menstruation
626.6	Metrorrhagia
719.1	Hemarthrosis
784.7	Epistaxis
784.8	Haemorrhage from throat
786.3	Haemoptysis
Charlson comorbidity index	
Myocardial infarction	
410	Acute myocardial infarction
412	Old myocardial infarction
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure
404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified

404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428	Heart failure
Peripheral vascular disease	
441	Aortic aneurysm and dissection
443.9	Peripheral vascular disease, unspecified
785.4	Gangrene
V43.4	Blood vessel replaced by other means
Cerebrovascular disease	
430-438	Cerebrovascular disease
Chronic obstructive pulmonary disease	
490-496	Chronic Obstructive Pulmonary Disease and Allied Conditions
500	Coal workers' pneumoconiosis
501	Asbestosis
502	Pneumoconiosis due to other silica or silicates
503	Pneumoconiosis due to other inorganic dust
504	Pneumonopathy due to inhalation of other dust
505	Pneumoconiosis, unspecified
506.4	Respiratory conditions due to chemical fumes and vapors
Dementia	
290	Dementias
Paralysis	
342	Hemiplegia and hemiparesis
344.1	Paraplegia

Diabetes without chronic complication	
250	Diabetes mellitus
250.0	Diabetes mellitus without mention of complication
250.1	Diabetes with ketoacidosis
250.2	Diabetes with hyperosmolarity
250.3	Diabetes with other coma
250.7	Diabetes with peripheral circulatory disorders
Diabetes with chronic complication	
250.4	Diabetes with renal manifestations
250.5	Diabetes with ophthalmic manifestations
250.6	Diabetes with neurological manifestations
Chronic renal failure	
582	Chronic glomerulonephritis
583.0	Nephritis and nephropathy, not specified as acute or chronic, with lesion of proliferative glomerulonephritis
583.1	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
583.2	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
583.4	Nephritis and nephropathy, not specified as acute or chronic, with lesion of rapidly progressive glomerulonephritis
583.6	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal cortical necrosis
583.7	Nephritis and nephropathy, not specified as acute or chronic, with lesion of renal medullary necrosis
585	Chronic kidney disease
586	Renal failure, unspecified
588	Disorders resulting from impaired renal function
Mild liver disease (Various cirrhodites)	
571.2	Alcoholic cirrhosis of liver
571.4	Chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
Moderate-severe liver disease	
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without bleeding
456.2	Esophageal varices in diseases classified elsewhere

572.2	Hepatic encephalopathy
572.3	Portal hypertension
572.4	Hepatorenal syndrome
572.8	Other sequelae of chronic liver disease
Ulcers	
531	Gastric ulcer
532	Duodenal ulcer
533	Peptic ulcer site unspecified
534	Gastrojejunal ulcer
Rheumatoid arthritis and other inflammatory polyarthropathies	
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.4	Polymyositis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.81	Rheumatoid lung
725	Polymyalgia rheumatica
Acquired Immune Deficiency Syndrome	
042	Human immunodeficiency virus [HIV] disease
Malignancy	
140-149	Malignant neoplasm of lip, oral cavity, and pharynx
150-159	Malignant neoplasm of digestive organs and peritoneum
160-165	Malignant neoplasm of respiratory and intrathoracic organs
170-172, 174-176	Malignant neoplasm of bone, connective tissue, and breast
179-189	Malignant neoplasm of genitourinary organs
190-195	Malignant neoplasm of other sites
200-208	Malignant neoplasm of lymphatic and hematopoietic tissue
Metastatic solid tumour	
196	Secondary and unspecified malignant neoplasm of lymph nodes
197	Secondary malignant neoplasm of respiratory and digestive systems
198	Secondary malignant neoplasm of other specified sites
199	Malignant neoplasm without specification of site

HASBLED score	
Bleeding – same as intracranial haemorrhage, gastrointestinal bleeding and other bleeding	
Hypertension	
401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
437.2	Hypertensive encephalopathy
Renal disease	
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
580	Acute glomerulonephritis
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis and nephropathy not specified as acute or chronic
584	Acute kidney failure
585	Chronic kidney disease
586	Renal failure unspecified
590.0	Chronic pyelonephritis
753.1	Cystic kidney disease
Liver disease	
570	Acute and subacute necrosis of liver
571	Chronic liver disease and cirrhosis
573	Other disorders of liver
790.4	Nonspecific elevation of levels of transaminase or lactic acid dehydrogenase [LDH]
Ischaemic stroke	
433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction

433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434	Occlusion of cerebral arteries
436	Acute, but ill-defined, cerebrovascular disease
437.0	Cerebral atherosclerosis
437.1	Other generalized ischemic cerebrovascular disease
Systemic embolism	
444	Arterial embolism and thrombosis
445	Atheroembolism
Transient ischaemic attack	
435	Transient cerebral ischemia
Alcohol use	
291	Alcohol-induced mental disorders
303	Alcohol dependence syndrome
305.0	Nondependent alcohol abuse
357.5	Alcoholic polyneuropathy
425.5	Alcoholic cardiomyopathy
535.3	Alcoholic gastritis
571.0	Alcoholic fatty liver
571.1	Acute alcoholic hepatitis
571.2	Alcoholic cirrhosis of liver
571.3	Alcoholic liver damage, unspecified
790.3	Excessive blood level of alcohol
977.3	Poisoning by alcohol deterrents
980	Toxic effect of alcohol
V11.3	Personal history of alcoholism
CHADS2 / CHA2DS2-VASc	
Congestive heart failure – same as in Charlson Comorbidity Index	
Hypertension, ischaemic stroke, systemic embolism, transient ischaemic attack – same as in HASBLED score	
Vascular disease	
410-414	Ischemic heart disease
443.8	Other specified peripheral vascular diseases

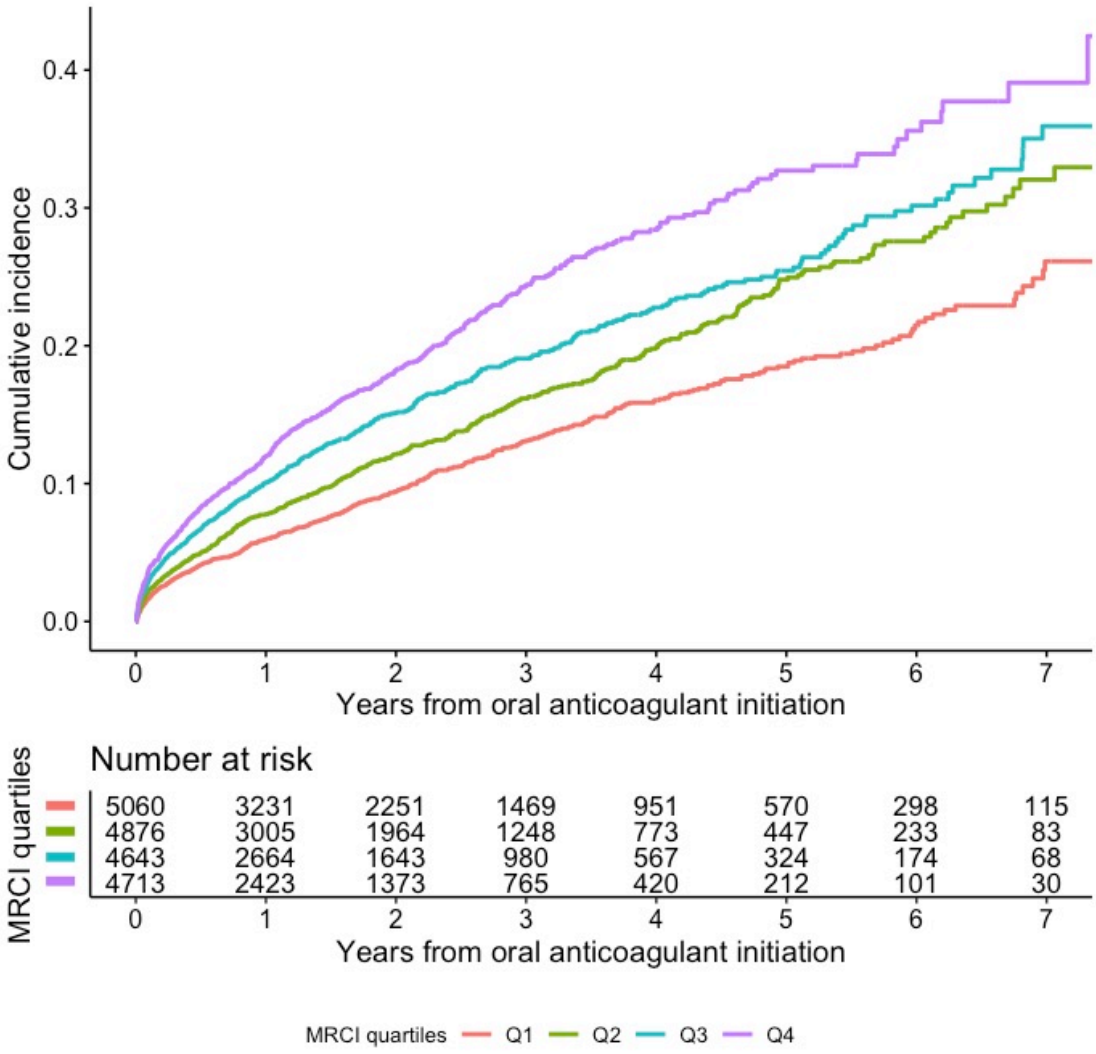
443.9	Peripheral vascular disease, unspecified
Diabetes	
250	Diabetes mellitus

Supplemental Table 2. Drugs used in the study

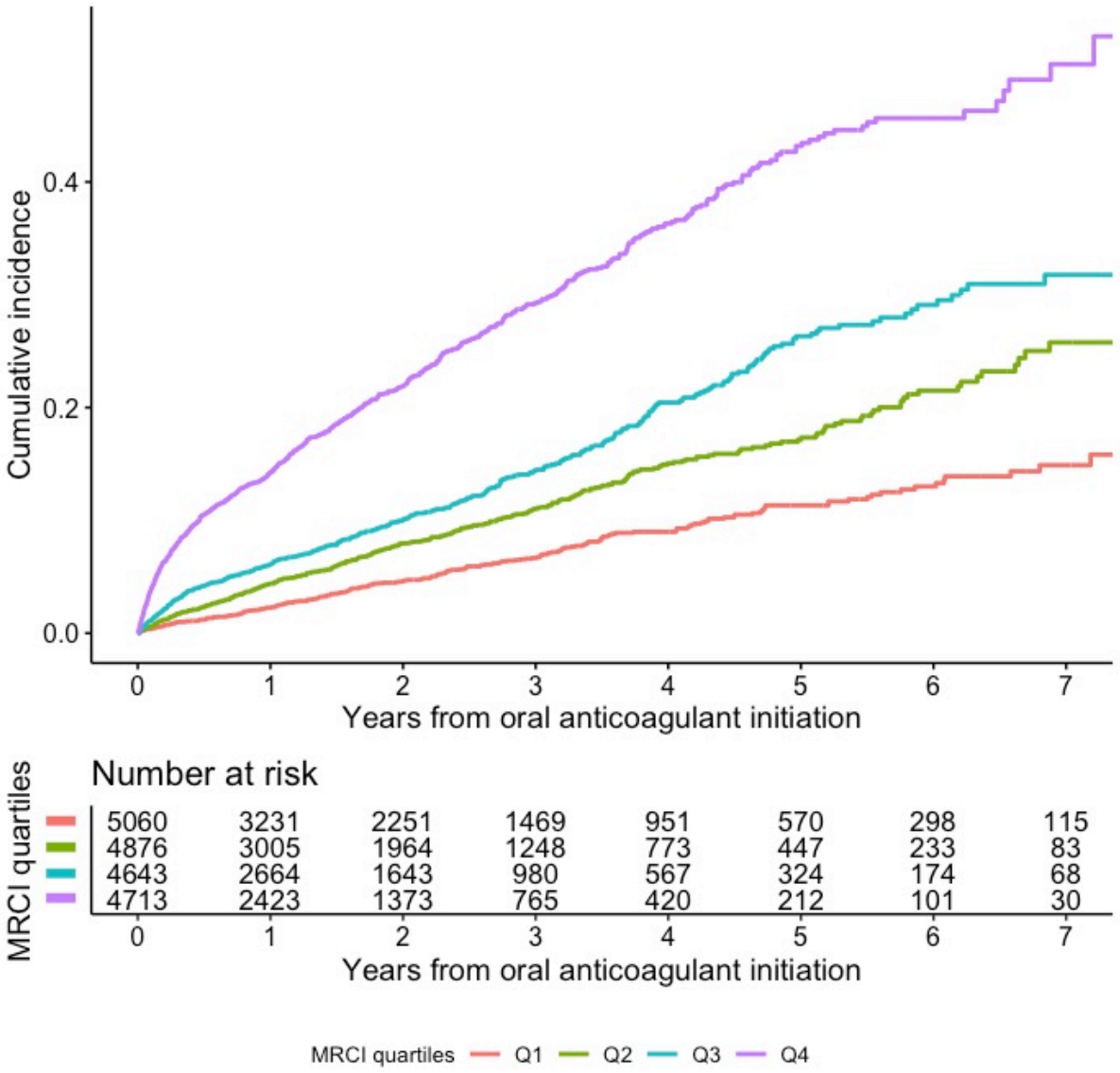
Drug class or drug	Drug name(s)
Angiotensin-converting enzyme inhibitors/Angiotensin II Receptor Blockers	Captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril, azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Beta blockers	Acebutolol, atenolol, bisoprolol, carvedilol, celiprolol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, sotalol
Calcium channel blockers	Amlodipine, diltiazem, felodipine, lacidipine, lercanidipine, nifedipine, nimodipine, verapamil
Amiodarone	Amiodarone
Dronedarone	Dronedarone
Aspirin	Aspirin
Clopidogrel	Clopidogrel
Dipyridamole	Dipyridamole
Nonsteroidal anti-inflammatory drugs	Diclofenac, ibuprofen, indomethacin, mefenamic acid, naproxen, piroxicam, sulindac, celecoxib, etoricoxib, meloxicam
Histamine type-2-receptor antagonists	Cimetidine, famotidine, ranitidine
Proton pump inhibitors	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
Statins	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin
Selective serotonin reuptake inhibitors/Selective noradrenaline reuptake inhibitor	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine
Oral corticosteroid	Prednisolone, hydrocortisone, fludrocortisone, methylprednisolone
Spironolactone	Spironolactone

Supplemental Figure 1. Unweighted Kaplan-Meier curves

a) Kaplan-Meier curve of first bleeding event



b) Kaplan-Meier curve of all-cause mortality



4. Chapter Four: Medication administration in residential aged care: A time-and-motion study

4.1 Synopsis

This chapter quantifies the burden of complex medication regimens in terms of time of medication administration. In RACFs, medication administration is usually undertaken by registered nurses, enrolled nurses, or care staff.[3,95] The time and resources required for medication administration can be considered to be another type of burden of complex medication regimens, both for staff and residents. Understanding the time taken to administer medications is important because if it is possible to reduce medication regimen complexity it may be possible to direct nursing time to other direct care activities. Ability to comply with medication administration within a prescribed time frame (e.g. eight-hourly intervals for medications used three times daily) decreases as the frequency of daily doses increases.[37]

4.2 Chapter objective

To estimate the time taken to administer medication regimens to residents of RACFs.

4.3 Publication

This chapter is a reproduction of the following publication:

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Medication administration in Australian residential aged care: A time-and-motion study

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Abstract

Rationale/aim: Medication administration is a complex and time-consuming task in residential aged care facilities (RACFs). Understanding the time associated with each administration step may help identify opportunities to optimize medication management in RACFs. This study aimed to investigate the time taken to administer medications to residents, including those with complex care needs such as cognitive impairment and swallowing difficulties.

Method: A time-and-motion study was conducted in three South Australian RACFs. A representative sample of 57 scheduled medication administration rounds in 14 units were observed by a single investigator. The rounds were sampled to include different times of day, memory support units for residents living with dementia and standard units, and medication administration by registered and enrolled nurses. Medications were administered from pre-prepared medication strip packaging. The validated Work Observation Method By Activity Timing (WOMBAT) software was used to record observations.

Results: Thirty nurses were observed. The average time spent on scheduled medication administration rounds was 5.2 h/unit of average 22 residents/day. The breakfast medication round had the longest duration (1.92 h/unit). Resident preparation, medication preparation and provision, documentation, transit, communication, and cleaning took an average of 5 minutes per resident per round. Medication preparation and provision comprised 60% of overall medication round time and took significantly longer in memory support than in standard units (66 vs 49 seconds per resident per round for preparation, 79 vs 58 for provision; $P < .001$ for both). Almost half (42%) of tablets/capsules were crushed in memory support units. The time taken for medication administration was not significantly different among registered and enrolled nurses.

Conclusions: Nurses took an average of 5 minutes to administer medications per resident per medication round. Medication administration in memory support units took

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an additional minute per resident per round, with almost half of tablets and capsules needing to be crushed.

KEYWORDS
aged, long-term care facilities, medication administration, medication safety, time and motion study

1 | INTRODUCTION

People entering residential aged care are increasingly frail, have a high prevalence of cognitive impairment and often have complex care needs.[1-3] Residents often have medication regimens comprising multiple administration times, formulations, and administration instructions.[4,5] Medication administration is a complex and time-consuming task in residential aged care facilities (RACFs). Residents take a median of 13 regular and as-needed medications.[3,5] Around a third to almost half of medications are administered two or more times a day.[3,5] Addressing the complexity of medication management in residential aged care is a research priority in Australia and internationally.[6,7] Most residents rely on nurses or care workers for assistance with medication administration and other instrumental activities of daily living. Medication administration can be challenging for residents living with dementia and for residents with dysphagia.[8] Over half of residents in aged care have swallowing difficulties which may necessitate modification of medications prior to administration or giving medications one by one.[8] Medication preparation and administration are therefore important aspects of safe and high-quality care in RACFs.[6]

Regimens that are complex and time-consuming to administer may be associated with a higher risk of administration errors.[9] In Australia, medications are administered by registered nurses (RNs), enrolled nurses (ENs), and care workers with medication credentials according to standardized processes. Medication administration errors, in which the medication administered differs from the medication ordered (such as wrong dose, given at the wrong time), are a source of harm.[9] Administration errors were implicated in 6 out of 13 medication-related deaths in Australian residential aged care investigated by the coroner from 2000 to 2013.[10] In the United Kingdom (UK) Care Homes' Use of Medicines study, staff administration errors were observed for 22% of residents.[9] Medication administration is generally considered as "must do" work when staff are short on time. For this reason, medication administration may be completed under time-pressure which may increase the risk of errors.[11,12]

Medication rounds represent a large portion of nursing time. Australian and Canadian studies have reported medication administration accounts for 27% to 38% of shift time for staff employed to undertake this activity.[13-15] Identifying efficiencies may help relieve time-pressure.[16] Identifying possibilities to shift time to focus on high-risk parts of the medication round or to other resident care activities, while maintaining safe medication administration, is likely to be valuable. Previous studies have used trained observers to record the amount of time spent on various tasks in RACFs.[13,14,17,18] Few have undertaken in-depth observations of medication administration rounds. One previous study observed 12 morning medication rounds in two units of a single Australian RACF which averaged 3 hours for 35 residents. Almost one-third of that time was spent on medication preparation.[13] Further research is required to understand the generalizability of these findings and to identify areas for support to facilitate both efficient and safe medication practices. The present study aimed to investigate the time taken to administer medications to residents, including those with complex care needs such as cognitive impairment or dysphagia.

2 | METHODS

A "time and motion" study design was conducted according to relevant criteria of the Suggested Time And Motion Procedures (STAMP).[17,19,20] Independent continuous observation of workflow and methods was used. This method was consistent with previous time and motion studies of health care workers in hospitals and RACFs.[21-25] Ethics approval was granted from the Monash University Human Research Ethics Committee (project number 11054) and the study was reviewed by the participating aged care provider organization's ethical review panel.

2.1 | Study setting

In Australia, residential aged care is provided in private and public-sector RACFs. The RACFs provide supported accommodation for predominantly older people who have care needs that can no longer be supported in their own homes.[1] Residents are supported to self-administer medications if assessed as able to do so, but most require assistance from nurses and care workers.[1] Although variation in medication administration practices exists, medications are administered in accordance with national guidelines and State-based regulations.[26] Briefly, medications are prescribed by general practitioners, dispensed and packed into dose administration aids by offsite community pharmacies, and delivered to the RACF. Immediately prior to administration, medications are removed from dose administration aids or original packaging and checked against the medication administration chart. Medications may need to be altered to facilitate administration (eg, crushed). Medication administration is documented on medication administration charts and nurses and care workers monitor for and document any adverse events.[27] Tasks may not always be performed linearly and may often overlap.[27]

2.2 | Study context

This study was conducted over 10 weekdays and 2 weekend days in July and August 2018. Three metropolitan private, not-for-profit RACFs operated by the same South Australian aged care provider organizations participated. Medications were supplied to these RACFs in pre-packed medication strip packaging.[28] Paper-based medication administration charts were used for documentation. In the participating RACFs, regular medication rounds were completed by one EN or RN. Other medication rounds for controlled medications (eg, opioids) were completed by two nurses, one of whom needed to be a RN. The three participating RACFs had six scheduled regular administration rounds each day.

2.3 | Participant selection and enrolment

Prior to the observation periods, the residential services manager at each RACF provided information about the study to all nursing staff involved in medication administration. Two investigators and the residential services manager sampled the medication administration rounds for observation. The rounds were purposively sampled to include different times of day, memory support units for residents living with dementia and other units, and medication administration by RNs and ENs. Nurses responsible for the identified medication rounds were then approached individually and invited to participate. Nurses who consented to participate provided informed written consent and completed a demographic questionnaire which captured information about their role (ie, RN or EN), years of experience working in aged care, years of experience nursing, and years of experience in their current position.

There were 11 breakfast administration rounds (8:00 AM), 11 noon, 7 afternoon (2:00 PM), 11 pre-dinner (4:00 PM), 8 dinner (5:00 PM) and 9 bedtime (8:00 PM) rounds observed during the study period. Administration outside of scheduled regular administration rounds (eg, pro-re-nata [PRN] medications) were not observed. Residents who self-administered medication were not included in the observation of the medication administration round.

2.4 | Observations

Observations were undertaken by a single investigator (E.Y.C). Medication administration in the participating RACFs comprised a series of discrete activities including preparing the medication trolley, resident and medication; providing the medication; documentation; transit; communication; cleaning up; miscellaneous care and other activities. The definition and classification of each discrete activity was adapted from a previous time-and-motion study in Australian RACFs in consultation with a research nurse experienced in medication administration (Appendix S1).[13] Time taken to complete discrete activities involved in medication preparation and administration were recorded using a tablet computer running the Work Observation Method By Activity Timing (WOMBAT) software (Appendix S2). WOMBAT software was specifically developed for time-and-motion studies and captures time and duration information in addition to activity classifications. The WOMBAT software has been validated in time-and-motion studies of healthcare workers' activities conducted in a variety of hospital settings.[29-33] A pilot observation period was undertaken prior to the study period to familiarize the observer with the RACF layout and discrete activity definitions in the WOMBAT software. The duration of the entire round was also recorded. The medication administration round started when the nurse either started preparing the medication trolley (if needed and as indicated by the nurse) or when the nurse began transit out of the medication room. The medication administration round ended when the trolley was returned to the medication room and the nurse indicated the round had finished, or when the nurse returned to the medication room without the trolley (in cases where the trolley remained in the medication room for the duration of the round) and the nurse indicated that the round had finished.

2.5 | Data analysis

The mean (±SD) length of time to complete an overall medication round was determined. The mean time needed for staff to undertake each activity, the frequency of each activity, and proportion of time spent on each activity in the administration round were also calculated. Analyses were stratified by the time of day of the administration round, activity category, type of RACF unit (memory support unit or not), nursing qualification, route of medication administration and method of preparation. Comparisons between continuous variables that were not normally distributed were made using the Mann-Whitney *U*-test. Comparisons between multiple groups were made using a one-way analysis of variance test. A statistically significant difference was defined as $P < =.05$. Data were analysed using R version 3.5.0 (Comprehensive R Archive Network) with RStudio version 1.1.453.

3 | RESULTS

3.1 | Sample

Out of 32 nurses invited, 30 nurses provided consent to participate. The sample comprised of 24 ENs and 6 RNs. Seventeen nurses were observed for two or more medication rounds. Participants had a mean of 14.4 years (±12.6) of experience working in aged care, 11.2 years (±10.9) of nursing experience, and 9.6 years (±10.3) of experience in their current position.

3.2 | Overall duration of the administration round

A total of 51.91 hours of medication administration across 57 medication administration rounds in 14 RACF units were observed. The average time taken for the six scheduled rounds was 5.2 hours each day per facility. Approximately half of this was spent on breakfast, noon and afternoon rounds. These rounds were typically completed during a

single day shift. The duration of each scheduled medication administration round varied. The breakfast medication round was the longest, with an average of 1.92 (±0.53) hours spent administering medications to a median of 22 residents (ie, 7.8 minutes for each resident) (Table 1).

3.3 | Time spent on discrete activities

The average time for round preparation, which included any initial arranging, stocking and cleaning of the trolley directly before medication administration, was 61 seconds (±49) per round. Medication preparation and provision took similar amounts of time and collectively comprised 60% of the time spent on the medication round. Among the three RACFs included in the study, significant differences were found in medication preparation, medication provision, documents, communication, and cleaning up (Table C1, Appendix S3).

The average time spent on resident preparation, medication preparation, medication provision, documentation, transit, communication, and cleaning up was 5 minutes per resident per round. Medication preparation took an average of 53 seconds (±44) per resident per round (Table 2). Medication provision took an average of 63 seconds (±50) per resident per round and was the single longest activity, with the exception of miscellaneous care and "other."

TABLE 1 Total time taken to complete scheduled medication administration rounds

	Mean number of observations per round	Mean (SD) in hours	Range in hours
Breakfast	129	1.92 (0.53)	1.05-2.71
Noon	37	0.48 (0.17)	0.09-0.70
Afternoon	25	0.30 (0.12)	0.11-0.44
Pre-dinner	51	0.70 (0.38)	0.11-1.33
Dinner	48	0.58 (0.50)	0.09-1.43
Bedtime	91	1.22 (0.54)	0.56-2.38

Communication during a medication round, which included all communication for the nurse being observed, comprised 7.4% of the total observed time and most frequently involved care workers (20%), telephone calls (18%), RNs (15%), and residents (13%). Residents' family comprised 3% of communication, and the "other" 31% was a mixture of communication with the observer, physicians, and other allied health professionals (eg, pharmacists).

3.4 | Staff role

RNs were responsible for 10 of the observed medication rounds; half of these were on weekends. There were no significant differences between RNs and ENs in terms of the average time spent per resident on resident preparation, medication preparation, medication provision, documentation, transit, communication, and cleaning up (mean 4.95 vs 4.99 minutes, respectively) (Table C2, Appendix S3).

3.5 | Memory support units

The average time spent on resident preparation, medication preparation, medication provision, documentation, transit, communication, and cleaning up was 5.6 minutes per resident per round in memory support units and 4.7 minutes per resident in other units. The proportion of total time spent on the round activities in each unit was consistent across units, but medication preparation, medication provision, documentation and transit took significantly longer in memory support units (Table 2) than other units.

3.6 | Route of administration

Tablets and capsules were the most commonly administered form of medication within the medication round (Table 3). These dose forms

TABLE 2 Time taken to complete parts of the medication round per resident per medication administration round

	Overall		Stratified by unit type				
			Memory support units		Other units		*P*
	Count of observations (n = 3777) n (%)	Mean (SD) in seconds	Count of observations (n = 885) n (%)	Mean (SD) in seconds	Count of observations (n = 2892) n (%)	Mean (SD) in seconds	
Resident preparation	41 (1.1)	36.7 (25.6)	18 (2.0)	42.5 (27.9)	23 (0.8)	32.2 (23.3)	0.351
Medication preparation	1024 (26.7)	53.2 (44.1)	232 (25.7)	66.4 (52.5)	792 (27.0)	49.4 (40.5)	<.001
Medication provision	886 (23.1)	63.0 (50.1)	205 (22.7)	78.5 (66.5)	681 (23.2)	58.3 (42.9)	<.001
Documentation	414 (10.8)	40.4 (51.5)	113 (12.5)	31.4 (27.9)	301 (10.3)	43.8 (57.6)	0.026
Transit	679 (17.7)	33.1 (25.7)	139 (15.4)	36.2 (23.4)	540 (18.4)	32.4 (26.2)	0.003
Communication	294 (7.7)	47.1 (52.3)	68 (7.5)	48.4 (54.0)	226 (7.7)	46.7 (51.9)	0.447
Cleaning up	253 (6.6)	24.3 (23.9)	66 (7.3)	33.1 (30.3)	187 (6.4)	21.2 (20.3)	<.001
Miscellaneous care	171 (4.5)	73.5 (165.1)	41 (4.6)	109.7 (304.8)	130 (4.4)	62.1 (81.1)	0.351
Other	15 (0.4)	82.7 (48.0)	3 (0.3)	85.3 (30.0)	12 (0.4)	82.1 (52.6)	1

Notes: *P* values compare memory support units and standard units.

TABLE 3 Time taken to prepare and provide different formulations of medications per formulation per medication administration round

	Medication preparation		Medication provision	
	Count of observations (n = 1026) n (%)	Mean time (SD) in seconds	Count of observations (n = 886) n (%)	Mean time (SD) in seconds
Tablets/capsules	644 (62.8)	65.1 (47.7)	577 (65.1)	67.6 (47.7)
Patch	10 (1.0)	61.3 (60.5)	10 (1.1)	72.9 (81.9)
Injection	30 (2.9)	52.0 (47.8)	39 (4.4)	60.4 (28.5)
Topical	26 (2.5)	27.2 (18.8)	27 (3.1)	82.9 (46.8)
Liquid	90 (8.8)	31.7 (18.7)	93 (10.5)	56.7 (79.7)
Respiratory	70 (6.8)	28.8 (22.7)	56 (6.3)	43.6 (22.7)
Eye/ENT	69 (6.7)	24.9 (22.9)	82 (9.3)	42.7 (25.4)
Powders	85 (8.3)	38.5 (25.4)	NA	NA
Other	2 (0.2)	21.5 (2.1)	2 (0.2)	122.0 (66.5)

TABLE 4 Time taken to (A) prepare and (B) provide tablets in different ways per resident per medication administration round

	(A) Time taken to prepare numbers of tablets in different ways per resident per medication administration round			
	Not crushed		Crushed	
	Count of observations (n = 500)	Mean (SD) in seconds	Count of observations (n = 144)	Mean (SD) in seconds
1–5	371	49.8 (38.2)	114	77.8 (41.6)
6-10	92	91.4 (55.5)	24	136.2 (54.1)
11+	14	97.8 (50.5)	1	162.0
Missing	23	47.3 (30.2)	5	54.2 (40.18)

	(B) time taken to provide numbers of tablets in different ways per resident per medication administration round					
	Whole and together		One by one		Crushed	
	Count of observations (n = 280)	Mean (SD) in seconds	Count of observations (n = 158)	Mean (SD) in seconds	Count of observations (n = 139)	Mean (SD) in seconds
1–5	237	52.1 (41.3)	105	81.4 (46.3)	101	62.7 (31.3)
6–10	34	68.1 (57.5)	43	106.6 (47.8)	20	85.7 (42.2)
11+	4	58.8 (19.4)	8	156.8 (76.5)	2	27.5 (12.0)
Missing	5	91.8 (109.5)	2	41.5 (30.4)	16	68.1 (48.8)

took less time to administer compared to other formulations but took the longest to prepare overall (Table 4A). Topical medications (ie, creams or ointments) took the longest to provide at a mean of 83 seconds per administration, followed by patches at a mean of 73 seconds per administration.

3.7 | Method of preparation and administration

There were 644 observations of tablets/capsules being prepared, and 577 observations of tablet/capsules being provided (Table 3). The difference was due to medications being prepared but not provided, such as when the resident could not be found, was toileting or bathing, or refused medication. In these cases, the medications would often be put aside to attempt provision later.

Overall, 22% of tablets/capsule observations (n = 144/644) required crushing. This proportion was higher in memory support units (42%, n = 68/144) compared with standard units (15%, n = 76/500). Crushed tablets/capsules took longer to prepare and administer compared with whole tablets/capsules (Tables 4A,B) when 10 or less tablets were given at once.

Tablets/capsules that were provided one by one took the longest to provide (mean of 91.61 ± 51.75 seconds), compared with crushed tablets (mean of 66.12 ± 36.05 seconds) or when the nurse provided the resident with their medications whole (ie, without any dose alterations) and together at the same time (ie, not one by one) (mean of 54.84 ± 45.39 seconds).

4 | DISCUSSION

The main finding of this time-motion study involving 57 rounds across 14 RACF units was that medication administration activities took an average of 5 minutes per resident per round. The overall average time

spent on medication administration during the 6 scheduled rounds was 5.2 hours per day for a unit of average 22 residents. This was consistent with previously published estimates that medication administration consumes approximately one-third of shift time for staff.[13-15] Medication administration in memory support units took an additional minute per resident per round, with almost half of tablets and capsules needing to be crushed prior to administration in this setting. The time taken for medication administration was not significantly different among RNs and ENs.

Medication administration to residents living with dementia in memory support units took 1 minute longer than the time taken for residents in other units. The average time of 5 minutes per resident per round was longer than the 3.3 minutes reported by Qian et al in a previous Australian study of medication administration that did not include memory support units,[13] and comparable to the 4.8 minutes reported by McDerby et al. who included residents living with advanced dementia.[16] A Canadian study found that medication administration for residents living with moderate to advanced dementia in memory support units took 3.5 (±1.1) minutes per resident per round compared to 3.1 (±1.1) minutes for residents with or without cognitive impairment in standard units, and 4.2 (±1.0) minutes for residents in behavioural care units.[14] Over half the residents of RACFs are living with dementia,[34] many of whom do not live in memory support units. Our findings have implications for appropriate scheduling of staff and care tasks throughout the day for residents with complex care needs, and government funding for these activities. More time is needed to deliver care to residents living with dementia, who have complex care needs, compared to residents without dementia.[2,14]

A factor that may contribute to this extra time is preparing and administering dose modifications. Crushing was required for almost half of observed tablet/capsule administrations in memory support units. Overall many residents had swallowing difficulties and 22% of tablets and capsules were crushed. It was encouraging that 60% of total medication administration round time was spent on medication preparation and provision, where there is high potential for error.[35] Inappropriate medication modification (eg, cutting or crushing tablets) has been reported for 17% to 32% of medications in previous Australian RACF studies.[16,36,37] In these previous studies, non-oral formulations were more likely to be involved in medication administration errors. Compared with tablets or capsules in pre-packed administration aids, liquids were four times more likely to be administered incorrectly; topical, transdermal and injectable medications were 20 times more likely to be administered incorrectly; and inhalers were more than 30 times more likely to be administered incorrectly.[38] A recent Australian pilot study suggested that integrating a pharmacist in RACFs may reduce inappropriate dose modification and the corresponding risk of medication-related harm.[16] Our study did not observe and document administration errors in RACFs. Further research is needed to understand the time needed to ensure dose modification is undertaken in a safe and efficient manner.

Although resident and medication factors are major determinants of the time needed to safely administer medications, other activities also consume a large proportion of time. There may be scope to improve efficiency in activities such as communication, documentation, and transit, allowing time to be shifted to elsewhere within the medication round to improve safety, or to other resident care activities. A pilot study focused on improving operational efficiency in medication administration, including optimizing medication storage, clarifying the labelling on resident medications and frequent removal of ceased or expired medication reduced time spent administering medications from 4.8 (±1.1) to 3.2 minutes (±1.7) in the intervention group ($P < .05$).[16] A cluster RCT investigating the impact of a structured intervention to simplify medication regimens on resident health outcomes and the efficiency of medication administration in RACFs is currently underway in eight RACFs in South Australia.[39] Additionally, the use of electronic medication systems has been suggested to improve efficiency and safety of medication administration by improving workflow and facilitate access to updated resident information.[40] It is unclear from previous studies in RACFs and hospitals if electronic medication systems lead to significant differences in time spent on medication administration or care tasks, but have suggested that prescribing error rates may be reduced.[31,40,41]

While there is potential that reducing the amount of time spent on medication rounds may reduce opportunities to detect and deliver other "ad hoc" care, the relatively low proportion of time spent on other care activities during the medication administration round suggests that the impact on other resident care would be small. Miscellaneous care and "other" activities, which included ad hoc resident care or assistance that may have otherwise been missed, comprised nearly 3.5 of the 52 hours observed during medication rounds. Involving other care staff in these activities outside of the medication administration round where possible may enable nursing time to be spent on other care activities and decrease distraction and medication administration errors.[27]

4.1 | Strengths and limitations

A strength of this study is the higher number and type of units observed and mix of staff compared to any previous Australian study.[13] The study involved observing more than 1000 separate occasions of medication preparation. The large sample size provided an opportunity to measure average time taken for activities involved in medication administration for a range of different times and resident care needs. Observations were undertaken over a wide range of hours (07:00 AM to 10:00 PM) and a mix of weekdays and weekends. Direct continuous observation, although labour-intensive, allowed close observation and therefore accurate measurement of discrete activities undertaken within the medication administration round.[17] However, having an observer shadow nursing staff during medication administration may have been disruptive to the normal work routine of participants.

Limitations include that the three RACFs were operated by the same aged care provider organization, which may limit generalizability to other aged care providers. It was a limitation that the study involved a single observer. Use of multiple observers may have improved the reliability of

time measurements. However, using multiple observers may have introduced possible inconsistences between observers in how time was measured. The study did not investigate the impact of interruptions nor the clinical appropriateness of dose form alterations. Like previous studies, this study did not analyse clinical outcome data or investigate staff perception of acute time pressure. The study did not investigate the time necessary to safely administer medications nor the time taken to communicate with residents appropriately. Further research is required to investigate the relationship between time and safe medication administration and quality care.

5 | CONCLUSION

Nurses took on average 5 minutes to administer medications to residents with complex care needs at each medication round. Nurses took an additional 1 minute per resident per round to administer medications to residents living with dementia. Altering medication prior to administration by crushing also increased the time needed for medication administration. Overall, medication preparation and provision took approximately equal time and together comprised 60% of the medication round. Further research is needed to understand the adequate time needed for safe medication administration, but it may be possible to make parts of the medication administration round more efficient.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Appendix A: Activity classifications

Table B1: Nurses' activities in morning medication rounds, adapted from Qian et al. *J Nurs Manag*, 2016.

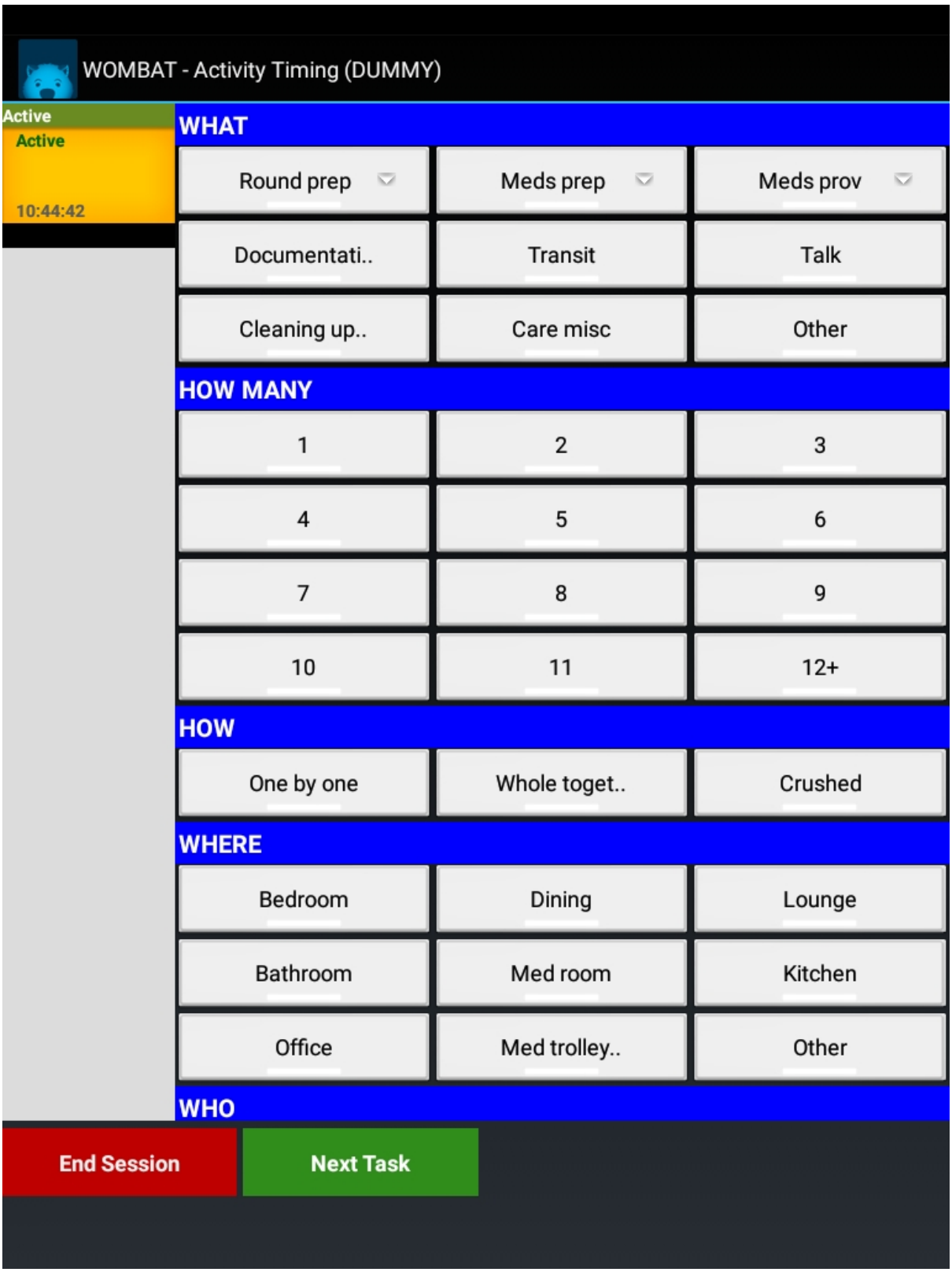
Category	Activity	Activity description
Preparation for administration or round	Medications and consumables	• Prepare a medication trolley (e.g. get spoons, cups, medication administration records, refrigerated medication, rubbish bag or general waste, pureed fruit/custard/etc for crushed medications)
	Resident	• Locate a resident or check if a resident is ready for medications • Prepare a resident for medication administration (e.g. help a resident to sit up and lay back down) • Prepare a cup of water/juice (non-thickened fluids) • Prepare thickened fluids or custard, or similar, in which to mix medications or to give after medication administration • Bring prepared medications and other supplies (e.g. tissue, spoon) to a resident
Preparation of medication	Tablets or capsules	• Prepare packed tablets or capsule (e.g. check the medication, open the plastic sachet, transfer into a cup) • The number of tablets or capsules administered to each resident at each administration time was also noted alongside "Preparation of tablets or capsules" and "Provision of tablets or capsules".
	Powders, granules or effervescent tablets	• Prepare powder medications (e.g. locate on trolley, check the medication, open the package, put the powder into a drinking cup, add water, stir)
	Liquid	• Prepare liquid medications (e.g. locate on trolley, check the medication, pouring the liquid medication into a small plastic cup) • Prepare resource (e.g. a drink to supply nutrition, get from refrigerator)

	Cream, gel, ointment or lotion	• Prepare topical medications (e.g. lotions, creams, paints; e.g. locate on trolley, including checking with administration records, checking expiry date)
	Eye or ear drop, gel or ointment, nasal spray or drops	• Prepare eye drops/ointment, ear drops, nasal sprays/drops (e.g. check the expiration date, get from refrigerator)
	Patch	• Prepare patches (e.g. writing the date on the patch)
	Miscellaneous respiratory	• Prepare metered dose inhalers with spacers (e.g. get the spacer, attach the inhaler to the spacer) • Prepare nebulizer (e.g. check the expiration date, put nebulizer into the nebulizer equipment) • Prepare oxygen concentrator
	Other	• Prepare injections (e.g. wipe the insulin bottle cap with an alcohol swab, open the package of the syringe, measure the insulin) • Check injections prior to administration (Registered nurses only)
Provision of medication	Tablets or capsules	• Provide tablets where resident able to take by themselves with nurse waiting • Provide medication in meals and feeding • Provide and help take tablets
	Powders, granules or effervescent tablets	• Provide powder/granule medications
	Liquid	• Provide liquid medications • Provide nutrition drink • Return to resident and check drink is finished
	Cream, gel, ointment or lotion	• Provide topical medications (including taking cap off and putting it back on)

	Eye or ear drop, gel or ointment, nasal spray or drops	• Provide eye drops/ointment • Provide ear drops • Provide nasal sprays or drops
	Patch	• Provide patches
	Miscellaneous respiratory	• Provide puffers/inhalers • Provide nebulizer
	Other	• Provide a rectal medication • Provide a pessary or vaginal cream • Provide medications via PEG feed • Provide injections
Cleaning up	Cleaning up	• Travel back to medication trolley • Dispose clinical or general wastes or put medications (e.g. eye drops) back into trolley or refrigerator • Bring/collect spoons and cups to/from wash-up room. • Plug in medication trolley to electric socket • Alcohol hand wash • Water hand wash • Put on/take off gloves

Communication	Verbal communication ("talk")	• Verbal communication with a resident, including redirecting residents who may be wandering • Verbal communication with another nurse • Verbal communication with other internal staff (i.e. physiotherapist, kitchen staff) • Verbal communication with an external health professional (e.g. a doctor) • Verbal communication with a visitor • Receive/answer/make a phone call • Answer call bells • Contact a registered nurse to administer pro re nata (as needed) or controlled medication, or to check insulin or other injections
Documentation	Documentation	• Use medication administration record, including Nicki pump and controlled analgesic patch records, signing off administration or refusals (ongoing documentation throughout the shift) • Use paper notes or handover sheet • Use controlled drugs register
Transit	Transit	• Push a medication trolley • Walk/stand in corridor, dining room, etc. • Prepare a controlled medication (i.e. retrieve from safe)
Other	Other	• Other activities not included above (e.g. interaction with the observer)

Appendix B: Screenshot of WOMBAT layout




76% 10:47 am
WOMBAT - Activity Timing (DUMMY)
Active
Active
10:44:42
Cleaning up..
Care misc
Other
HOW MANY
1
2
3
4
5
6
7
8
9
10
11
12+
HOW
One by one
Whole toget..
Crushed
WHERE
Bedroom
Dining
Lounge
Bathroom
Med room
Kitchen
Office
Med trolley..
Other
WHO
Resident
Care staff
RN
Phone
Family
Other
End Session
Next Task

Appendix C: Supplementary tables

Table C1: time taken to complete parts of the medication round by RACF per resident per medication administration round

	RACF #1 (n=15.63 hours)		**RACF #2** (n=18.46 hours)		**RACF #3** (n=17.82 hours)		**P**
	Number of observations (N=981)	Mean time (SD) in seconds	Number of observations (n=1487)	Mean time (SD) in seconds	Number of observations (n=1309)	Mean time (SD) in seconds	
Resident preparation	16	41.3 (31.7)	16	27.1 (20.8)	9	45.7 (16.3)	0.950
Medication preparation	312	59.9 (52.4)	374	49.8 (41.1)	338	50.9 (37.9)	0.010
Medication provision	222	70.0 (50.1)	342	61.6 (47.2)	322	59.6 (52.6)	0.023
Documentation	81	63.0 (70.6)	204	31.3 (44.0)	129	40.6 (43.9)	0.014
Transit	197	32.9 (30.6)	263	33.8 (23.7)	219	32.5 (23.0)	0.863
Communication	61	67.3 (72.5)	94	38 (33.7)	139	44.4 (50.2)	0.021
Cleaning up	34	22.1 (18.1)	122	19.2 (18.7)	97	31.5 (29.2)	0.002
Miscellaneous care	55	85.0 (105.2)	65	56.3 (66.4)	51	83.0 (272.9)	0.930
Other	3	80.3 (30.3)	7	82.6 (55.7)	5	84.4 (54.4)	0.912
RACF: residential aged care facility; SD: standard deviation. P values compare the 3 residential aged care facilities							

Table C2: time taken to complete parts of the medication round by different nurse classification per resident per medication administration round

	Registered nurse (n=7.64 hours)		**Enrolled nurse** (n=44.27 hours)		P
	Number of observations (n=540) n (%)	Mean time (SD) in seconds	Number of observations (n=3296) n (%)	Mean time (SD) in seconds	
Round preparation	7 (1.3)	49.3 (44.7)	56 (1.7)	62.5 (49.5)	0.289
Resident preparation	12 (2.2)	28.8 (23.5)	29 (0.9)	40.0 (26.1)	0.125
Medication preparation	148 (27.4)	59.4 (47.2)	874 (26.5)	52.2 (43.5)	0.074
Medication provision	126 (23.3)	63.8 (44.6)	758 (23.0)	62.9 (51.0)	0.636
Documentation	66 (12.2)	41.9 (67.4)	348 (10.6)	40.1 (48.1)	0.900
Transit	105 (19.4)	39.0 (37.6)	574 (17.4)	32.1 (22.7)	0.381
Communication	35 (6.5)	41.8 (32.4)	259 (7.9)	47.8 (54.5)	0.933
Cleaning up	19 (3.5)	22.2 (14.6)	234 (7.1)	24.5 (24.5)	0.753
Miscellaneous care	21 (3.9)	50.0 (68.5)	150 (4.6)	76.8 (174.3)	0.332
Other	1 (0.2)	172.0 (NA)	14 (0.4)	76.4 (42.7)	0.132
SD: standard deviation; P values compare registered nurses and enrolled nurses.					

PART C: ADDRESSING MEDICATION REGIMEN COMPLEXITY: A NOVEL INTERVENTION

5. Chapter Five: Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE)

5.1 Synopsis

This chapter describes the development and validation of a tool to identify opportunities for medication regimen simplification. While regimen simplification may be addressed during existing medication review, Chapter Two did not identify evidence to suggest this is currently common practice. a study of a sample of RMMRs performed between 2011 and 2012 did not identify that RMMRs reduced medication regimen complexity.[117] This could be because pharmacists or GPs do not prioritise medication regimen simplification, or because recommendations to start medications to address undertreatment (a common MRP identified by medication reviews) cancelled out any simplification. The medication charts used in this Chapter were from residents that were eligible for RMMRs, however, the date of the last RMMR was not recorded in this study. It is possible that some or all of the medication charts had already received been reviewed as part of an RMMR service, which may have already addressed some medication regimen complexity. This suggests that a previous RMMR may not have impacted the number of residents for whom simplification might be possible in our sample.

There was also no evidence that tools that were available to support medication regimen simplification. This was a practice gap that we addressed by developing this novel tool to assist medication regimen simplification. This tool was subsequently evaluated in the SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) cluster-randomised controlled trial.[114,159] The prevalence and factors associated with having a complex medication regimen among participants in the SIMPLER study is presented in Chapter Six.

5.2 Chapter objective

To develop and validate a medication regimen simplification guide for residents of RACFs.

5.3 Publication

This chapter is a reproduction of the following publication:

Chen EYH, Sluggett JK, Ilomäki J, Hilmer SN, Corlis M, Picton LJ, et al. Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE). *Clinical Interventions in Aging* 2018; 13: 975-986.

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ORIGINAL RESEARCH

Development and validation of the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE)

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Background: Residents of aged care facilities use increasingly complex medication regimens. Reducing unnecessary medication regimen complexity (eg, by consolidating the number of administration times or using alternative formulations) may benefit residents and staff.

Objective: To develop and validate an implicit tool to facilitate medication regimen simplification in aged care facilities.

Method: A purposively selected multidisciplinary expert panel used modified nominal group technique to identify and prioritize factors important in determining whether a medication regimen can be simplified. The five prioritized factors were formulated as questions, pilot-tested using non-identifiable medication charts and refined by panel members. The final tool was validated by two clinical pharmacists who independently applied the tool to a random sample of 50 residents of aged care facilities to identify opportunities for medication regimen simplification. Inter-rater agreement was calculated using Cohen's kappa.

Results: The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE) was developed as an implicit tool comprising of five questions about 1) the resident; 2) regulatory and safety requirements; 3) drug interactions; 4) formulation; and 5) facility and follow-up considerations. Using MRS GRACE, two pharmacists independently simplified medication regimens for 29/50 and 30/50 residents (Cohen's kappa=0.38, 95% CI 0.12–0.64), respectively. Simplification was possible for all residents with five or more administration times. Changing an administration time comprised 75% of the two pharmacists' recommendations.

Conclusions: Using MRS GRACE, two clinical pharmacists independently simplified over half of residents' medication regimens with fair agreement. MRS GRACE is a promising new tool to guide medication regimen simplification in aged care.

Keywords: medication therapy management, long-term care, geriatrics, drug administration, medication regimen complexity

Introduction

Older people are using increasingly complex medication regimens. The number of people aged 65 years and older who use five or more medications in the USA tripled from 13% to 39% between 1988 and 2010.[1] Residents of aged care facilities, also known as "nursing homes," "long-term care facilities," or "residential aged care facilities,"[2] use an average of four to 17 regular medications.[3] Increasing regimen complexity accompanies increasing polypharmacy, which has been attributed to changing resident mix, better adherence to disease-specific clinical practice guidelines and reluctance to discontinue medications initiated by other prescribers.[4]

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Medication regimen complexity is a function of the number of medications, number of medication administration times, multiple or complicated dose formulations, and special instructions for medication administration (eg, to crush tablets, take with food or a specific fluid).[5] Initiatives to reduce the number of medications through "deprescribing" have attracted widespread attention.[6,7] Simplification without altering therapeutic intent of medication regimens is possible through addressing the other factors that contribute to unnecessary complexity, and is of increasing interest.[8–10] Medication regimen simplification has been identified as a priority area for geriatric pharmacotherapy by a panel of international experts.[11] The Victorian Government Department of Health and Human Services has introduced a new quality indicator for "more than four administration times" for aged care services in Victoria, Australia.[12] Recent Australian recommendations for the prevention of injury-related deaths in residential aged care services contain two recommendations (27 and 37) that support the need for medication regimen simplification. Recommendation 37 also recommends the development of standardized procedures to achieve medication simplification.[13]

Although only a small number of residents may self-administer their medications,[2] there are multiple reasons to implement structured and comprehensive approaches to reduce medication regimen complexity in aged care facilities. Complexity is an independent risk factor for hospitalization from aged care facilities and discharge to aged care facilities.[14,15] High complexity is associated with direct costs through time and workload to administer medications, and indirect costs through poorer resident health outcomes.[16,17] Furthermore, unnecessarily complex medication regimens are burdensome and may lead to difficulty adhering to prescribed administration times, increased risk of potentially inappropriate medication use, increased risk of medication administration error, and decreased resident satisfaction.[18,19] Reducing the number of medication administration times has been found to improve health-related quality of life in people with a variety of medical conditions.[20] Despite this, there remains no structured method to guide medication regimen simplification in aged care facilities. The aim of this study was to develop and validate a judgment-based (ie, implicit) tool[21] to facilitate medication regimen simplification in aged care facilities.

Method

Study design

This study was completed in two phases. Phase 1 focused on development of a regimen simplification tool. The developed tool was then validated in phase 2. Qualitative elements of this study in the development phase were reported according to the consolidated criteria for reporting qualitative studies where possible.[22] This study was approved by the Monash University Human Research Ethics Committee (project number 0731). For the validation in phase 2, individual resident consent to review their medication charts was waived by the Monash University Human Research Ethics Committee due to the non-identifiable nature of the copies of the medication charts used.

Phase 1: development of the medication regimen simplification tool

A modified nominal group technique (NGT) was used to develop the medication regimen simplification tool. NGT is a structured process to explore a research question, clarify ideas, and gain consensus among experts.[4,23,24] An expert panel was convened in October 2016. The panel was purposefully selected to comprise health professionals with practical experience in aged care and consumer representation. Potential panelists were identified through their clinical leadership roles and with the assistance of an organization that provides aged care services. Potential panelists were approached by email with a short statement of the purpose of the meeting. The panel was held at an aged care facility and moderated by two pharmacist researchers with experience using NGT (JSB and JS).

Following introductions, the facilitators introduced the concept of medication regimen complexity and the aim of the session. The focus was specifically identified as simplifying the existing regimen, rather than discontinuing medications. The panel was divided into two multidisciplinary pairs and one group of three. This approach was chosen to encourage collaboration and sharing of perspectives. Firstly, each pair and group of three generated and presented an exhaustive list of factors to consider when deciding whether a medication regimen could be simplified. Secondly, these factors were grouped into themes through moderated discussion with the full panel. Thirdly, each multidisciplinary pair or group of three was assigned a theme by facilitators, and separately tasked with formulating question or statement prompts that could be incorporated into an implicit tool. The panel discussed all the questions and statements for duplication, feasibility, and priority, and the final key questions for the tool were determined. Discussion points were transcribed during the session.

Each multidisciplinary pair and group of three applied the draft simplification tool to identify opportunities for simplification for a sample medication regimen listed on a

non-identifiable medication chart of a resident of an aged care facility. The panel performed an initial face validity check and discussed the ordering of the prompts and saturation of factors important to consider for regimen simplification. The tool was refined by investigators, taking care to capture all ideas generated at the meeting. The five prioritized factors were formulated as questions and circulated to the full expert panel for endorsement.

Phase 2: validation of the medication regimen simplification tool

The validity of the developed tool was established by comparing the proportion of residents in a sample whose regular medications could be simplified (eg, any change to the administration time, route of administration, or use of combination or extended release preparations) when the tool was applied by two people independently.

Sample selection

A stratified random sample of 50 residents from a census sample of 439 residents from 10 Australian aged care facilities were used to validate the developed tool. Non-identifiable medication administration charts were collected as part of an earlier unrelated study undertaken by the research team. The random sample in the present validation study was selected from medication charts for residents with two or more medication administration times (n=432) because there was no scope to reduce the number of administration times for residents with one administration time.

Clinical and medication data

The medication charts had standard dose administration times of pre-breakfast, breakfast, mid-morning, lunch, mid-afternoon, tea, evening, and settling. The name, strength, dose, dose form, route, administration time, and start date were recorded for each medication. Resident age (in years), allergies, medical diagnoses, and any notes pertaining to medication administration were also recorded.

Application of the medication regimen simplification tool

Two clinical pharmacists (A and B) were introduced to the concept of medication regimen simplification and the developed tool. The two clinical pharmacists independently applied the developed tool to the non-identifiable medication charts. The clinical pharmacists had three and ten years' experience performing medication reviews for residents of aged care facilities, respectively. A working relationship between the clinical pharmacists did not exist prior to this study. When applying the simplification tool, the pharmacists were instructed to assume each resident's medication regimen had already been reviewed for clinical appropriateness. The pharmacists also assumed that the resident and facility would be willing and able to accommodate any recommendation. The pharmacists manually noted details of any recommended changes (medication name, form, route, dose, administration time, and any required monitoring or follow up), and reasons for not being able to simplify a medication regimen (if applicable).

Statistical analysis

Primary outcome measure

The agreement between two users of the developed tool when applied to a sample of residents whose regular medications could be simplified was established using inter-rater reliability analysis using Cohen's kappa. A dichotomous variable of "able to simplify the medication regimen" and "not able to simplify the medication regimen" was used. The inter-rater reliability was considered slight if between 0.0 and 0.2, fair if between 0.21 and 0.4, moderate if between 0.41 and 0.6, substantial if between 0.61 and 0.8, and almost perfect if between 0.81 and 1.0.[25,26] To assist interpretation of kappa, the maximum attainable kappa was also calculated.[27] Average proportions of agreement for positive and negative responses, and raw percentage agreement were also reported to support interpretation.[25] Microsoft Excel (2013) (Microsoft Corporation, Redmond, WA, USA) and SAS v9.4 (SAS Institute, Cary, NC, USA) were used for data analysis.

Secondary outcome measures

A secondary analysis was conducted for simplification that included a decrease in administration times. The inter-rater agreement for ability to decrease the number of regular administration times per day was calculated separately. All recommendations for and barriers to simplification were analyzed descriptively.

Sample size calculation for validation phase

To detect with 80% power a Cohen's kappa value of 0.8 against a null hypothesis value of 0.4,[25] the minimum required sample size was estimated to be 42 residents.[27] A probability of simplification of 0.5 was assumed, based on a previous proportion of older people with medication regimens that could be simplified.[28] A random number generator was used to select the final sample of 50 residents.[29] The final sample contained the same proportion of residents with each number of dose administration times as the census sample.

Results

Phase 1: development of the simplification tool

Eleven people were approached to participate in the expert panel meeting. Two people declined an invitation to participate due to travel. Two people who agreed to participate did not attend the meeting. Seven people attended the expert panel meeting (five male and two female members). Panel members had experience in prescribing, reviewing, administering or receiving medications in aged care (a general medical practitioner [GP, or family physician], a clinical pharmacologist, a geriatrician, two medication review pharmacists, a nurse practitioner, and a consumer advocate).

During the five-hour meeting, the expert panel generated 52 ideas in small groups. Investigators grouped these ideas into three broad themes: 1) environment/system (eg, multiple prescribers, continuity of care, a single "gate keeper" for the overall regimen); 2) resident/carer (eg, variation in symptoms with time, patient preference and understanding of medications); and 3) medication/regimen (eg, size and presentation of solid oral dose forms, medication absorption profile). A series of question or statement prompts were generated by further small group work. When applied to a medication chart, the panel were able to use the prompts to simplify the medication regimen. The prompts and the initial tool were assessed to have good content and face validity, respectively, after application to a sample medication chart from an aged care facility. The initial prompts were condensed into five questions for the final tool: the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE) and an accompanying explanatory statement (Box 1; see Figure S1 for full explanatory statement).

Phase 2: validation of the simplification tool

Of the 50 residents included in the validation phase, the mean age (±SD) was 82.3±9.8 years and 76% were female (n=38).

Box 1 Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE)

Consideration can be given to administering all medications at the same time each day unless the following apply:

1. Is there a resident related factor that precludes simplification?
2. Is there a regulatory or safety imperative that precludes simplification?
3. Is simplification likely to result in any clinically significant drug–drug, drug–food, or drug–time interactions?
4. Is there no alternative formulation available that can support less complex dosing?
5. Is simplification likely to result in any unintended consequences for the resident or facility?

Residents took a mean (±SD) of 9.9±4.2 regular medications. In total, residents in the validation sample took 491 regular medications. The most frequent number of regular administration times per day was four (34%, n=17), while 14% (n=7) of residents had two administration times per day, 26% (n=13) had three, 16% (n=8) had five, and 10% (n=5) had six or more (Figure 1).

Each pharmacist identified opportunities and made recommendations for simplification for 30/50 and 29/50 residents' medication regimens (Figure 1A). There were 22 residents who both pharmacists agreed could have simplified medication regimens, and 13 residents' medication regimens that both pharmacists agreed could not be simplified. Simplification recommendations were made for all residents with five or more administration times (Figure 1A). Three quarters of simplification recommendations were to move an administration time without changing the dose administered (Table 1). The raw agreement between pharmacists was 70%. The proportions of positive and negative agreement were 75% and 63%, respectively. The pharmacists had fair agreement regarding simplification of medication regimens (Cohen's kappa=0.38±0.13, 95% CI 0.12–0.64). The maximum obtainable kappa statistic was 0.96.

Each pharmacist decreased the number of regular administration times for 23/50 residents, of which 18 were for the same residents (Figure 1B). Both pharmacists eliminated one administration time for 21 residents, and two administration times for two residents (not the same residents). Neither pharmacist was able to recommend simplification for residents with two administration times. The pharmacists had moderate agreement regarding decreasing administration times only (Cohen's kappa=0.48±0.12, 95% CI 0.24–0.72).

When classified by the anatomical therapeutic chemical (ATC) main group, nervous system medications were the most frequently implicated in recommendations (ATC group N) (Figure 2). Paracetamol was the most frequently implicated drug in this class (n=10/60 and 8/46 recommendations). Twelve percent of nervous system medications could be simplified (n=19/144 and 17/144). Cardiovascular medications (ATC group C, eg, atorvastatin, furosemide) had the highest level of disagreement, with pharmacists A and B recommending simplification for 19% and 9% of cardiovascular medications (n=16/85 and 8/85 medications), respectively.

All barriers to simplification noted during the validation were possible barriers identified during the development phase. Barriers related to medication, resident, and facility factors. Medication factors included frequent dosing of medications for Parkinson's disease, and time-specific administration of medications due to behavior or

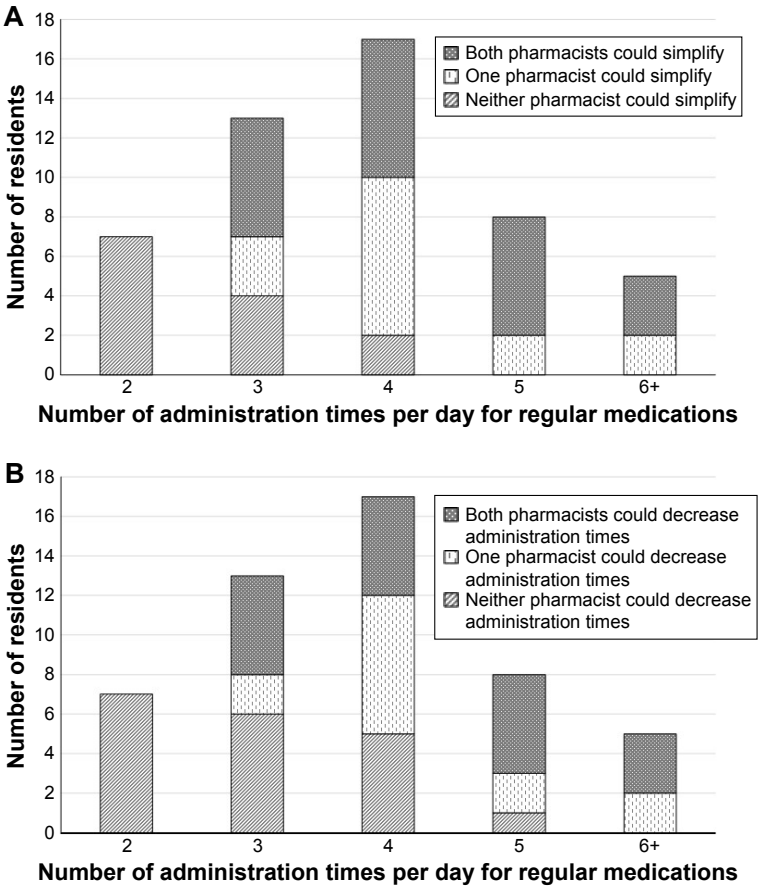

Figure 1 Agreement and ability to (**A**) simplify and (**B**) decrease regular administration times for residents in the validation sample, stratified by number of administration times per day for regular medications.

symptomatic management. Examples of resident related factors were swallowing difficulty, and existing anxiety about taking multiple tablets. Facility related barriers included special administration procedures surrounding controlled analgesic medications and warfarin.

Discussion

To our knowledge, MRS GRACE is the first tool to assist clinicians to identify opportunities to simplify medication regimens in aged care facilities. Taking medications is a burden for both staff and residents in aged care facilities,

Table 1 Frequency of each type of recommendation to simplify medication charts

Type of recommendation to simplify	Pharmacist A n=60 (%)	Pharmacist B n=46 (%)	Example
Change of an administration time with no change in dose at each administration time	47 (78.3)	34 (73.9)	Atorvastatin 20 mg 1 evening to 1 tea
Change of an administration time with a change in dose at an administration time (same total daily dose)	13 (21.7)	12 (26.1)	Spironolactone 25 mg 1 breakfast and 1 mid-afternoon to 2 breakfast
Change in strength of formulation given (same total daily dose)	0 (0)	3 (6.5)	Sertraline 50 mg 1 breakfast and 1 evening to 100 mg 1 breakfast
Change of formulation	7 (11.7)	4 (8.7)	Paracetamol 500 mg IR 2 breakfast, 2 lunch, 2 tea and 2 evening to paracetamol 665 mg MR 2 breakfast, 2 mid-afternoon and 2 evening
Total unique recommendations	60	46	

Note: Recommendations could have been counted in more than one category if applicable.
Abbreviations: IR, immediate release; MR, modified release.

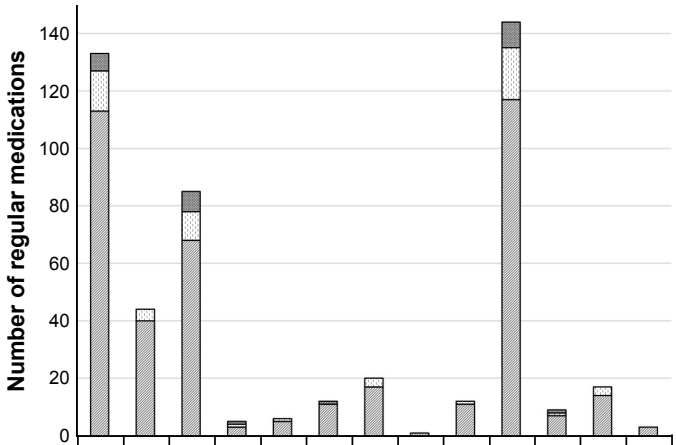

Figure 2 Agreement and ability to simplify regular medications in medication regimens of residents in the validation sample, categorized by Anatomic Therapeutic Chemical (ATC) main group classification.
Abbreviations: A, alimentary tract and metabolism; B, blood and blood forming organs; C, cardiovascular system; D, dermatologicals; G, genito-urinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones and insulins; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; R, respiratory system; S, sensory organs; V, various.

with many residents resisting medications. Reducing the number of times a day that the stress of taking medications occurs has benefits for both staff and residents. Furthermore, the residents can benefit from the opportunity costs that arise from freeing up nursing time from unnecessarily frequent medication administration. This tool provides a standardized approach to regimen simplification which may counteract the variability that may already be present in clinical pharmacist and other medication reviews for consistent results.

The scope for simplification of medication regimens in aged care facilities is substantial, despite pharmacists regularly performing similar clinical work and undergoing accreditation to perform full medication reviews. The medication charts used in the present study were from aged care facilities where clinical pharmacists conduct Australian Government funded residential medication management reviews (RMMRs).[2] Therefore, it would appear that further simplification is possible even among recipients of medication review. MRS GRACE may serve as a prompt and reminder for pharmacists or physicians when conducting medication management reviews.

A wide range of stakeholders were consulted in the development of MRS GRACE. At the beginning of the development phase, our panel of experts generated a comprehensive list of distinct factors. Although a number of concepts were subsequently considered peripheral to regimen simplification, concepts judged important to optimizing medication regimens were incorporated into the explanatory statement where relevant. Examples included ensuring the accuracy of medication records, recognizing that residents may have multiple prescribers with different treatment priorities and the need to ensure continuity across transitions of care. The expert panel recognized that regimen simplification is distinct from "medication reconciliation" and "deprescribing",[30] although successful simplification is dependent on first obtaining an accurate medication list and ensuring all medications are clinically indicated. The incorporation of all relevant aspects identified contributed to face validity of the developed tool.

MRS GRACE was purposefully developed as a judgement-based, or implicit, tool.[21] Implicit tools, such as the Medication Appropriateness Index (MAI), avoid making

recommendations for specific medications or situations.[31] Clinicians are thereby able to use it in different aged care settings and across different countries because the tool prompts evaluation of each individual facility's protocols and processes. The implicit format was considered the most appropriate for older people living in aged care facilities, due to its flexibility and the lack of evidence to inform prescribing in this setting.[32,33] This also means there is no single ideal "solution" as to how a medication regimen may be simplified. MRS GRACE includes in the explanatory statement some further guidance should clinical knowledge be limited (eg, consult a pharmacist for full range of formulations). Therefore, although agreement calculated by Cohen's kappa was fair, the higher raw agreement demonstrates that the tool is effective in aiding pharmacists to simplify medication regimens. The similar proportion of positive and negative agreements also indicates a lack of bias during interpretation and application of the tool.

While highly mobile, implicit tools rely on the user having good pharmacological knowledge and familiarity with different product formulations. For example, to effectively consider question 4 "Is there an alternative formulation that can support less complex dosing?", clinicians must combine knowledge of available formulations with knowledge of each resident's ability to use alternative formulations (eg, due to swallowing difficulties that require medications to be crushed). While MRS GRACE was validated by two pharmacists, it was piloted during the expert panel meeting by a range of different health professionals. The expert panel perceived that application of MRS GRACE could be undertaken by any health professional group with the knowledge required to apply the implicit tool in their context.

The expert panel identified and the validation study subsequently confirmed that medication regimen complexity may be unavoidable for various reasons. This may be due to the medication itself. "Time critical" medications, such as short-acting insulins or medications for Parkinson's disease, may cause harm or reduced efficacy if administration is early or delayed.[34] Other reasons relate to the resident. Some residents may prefer to spread their medications over multiple administration times rather than take all medications at the same time each day. The expert panel recognized that, "Is there a resident related factor that precludes simplification?", was considered an important first prompt to elucidate whether residents desire a simplified medication regimen. However, a specific list of medications or reasons that preclude simplification is not included in the tool as there may be cases where barriers can be addressed at the discretion of the clinician. This also increases the generalizability of MRS GRACE, as medications or reasons that preclude simplification may also be country-specific.

MRS GRACE prompts users to evaluate barriers to simplification through the wording "clinically significant" in question 3. In the validation phase, this was a source of disagreement. For example, one pharmacist considered that the falls risk associated with administering mirtazapine at dinner outweighed the potential benefit of administering mirtazapine with residents' other dinner medications, and therefore did not suggest changing bedtime administration times. The "clinically significant" judgement was also a source of simplification recommendations through correcting common medicine misconceptions. A recurring example in the validation was moving the administration time of atorvastatin. The misconception was that statins should be taken at night to increase drug efficacy. However, while short-acting statins are slightly but significantly more effective if taken at night, long-acting statins (eg, atorvastatin) are effective at any time.[35]

Limitations

In developing the tool, a limitation was that we were unable to consult with residents directly to ascertain resident related factors prioritized as important to residents taking medication regimens. We instead engaged a resident advocate to contribute to the development of MRS GRACE. However, the resident perspective would also be considered when deciding whether to implement the identified opportunities for simplification, a step that may often be outside the scope of MRS GRACE.

In the validation phase, agreement was measured between two pharmacists despite the tool not being specifically targeted for pharmacist use. Clinical information about the resident that may impact on decision making was not available and pharmacists A and B were unable to speak with residents, caregivers or facility staff. Therefore, it was not possible to fully consider the resident perspective or facility resources section of the simplification tool (questions 1 and 2, respectively), or clarify any unintended consequences that the simplified medication regimen may have (question 5). This may have decreased agreement as disagreement between the pharmacists in the validation phase may be resolved in practice by consulting the prescriber or care manager in the aged care facility.

There was also no scope to assess the clinical appropriateness of the simplified regimen, or if a prescriber would have accepted and implemented the simplification

recommendations generated as a result of using the tool. While the safety of the regimen is the ideal measure, it is very difficult to quantify. We used inter-rater reliability as an adequate surrogate marker, assuming that the pharmacists applied the tool as intended, to simplify medication regimens without sacrificing safety.

Future directions

Simplification could be undertaken as a stand-alone activity, or as part of comprehensive medication review programs and geriatric assessments undertaken by physicians and pharmacists in aged care facilities. However, further research is needed to explore possible differences and similarities in application of the tool by different health professionals. It may also be appropriate to use MRS GRACE following medication reconciliation on admission to aged care facilities, or after returning from hospital. The panel suggested that a single "simplification champion" could act as a "gate keeper" to take responsibility for coordinating regimen simplification in aged care facilities at these times. Research to understand uptake of simplification recommendations, and impact of medication simplification on outcomes for residents and aged care providers, is currently underway in an ongoing randomized controlled trial (SImplification of Medications Prescribed to Long-tErm care Residents [SIMPLER]).[36]

Conclusion

By applying MRS GRACE, two clinical pharmacists independently simplified two-thirds of residents' medication regimens with fair agreement. MRS GRACE is a validated tool that may be adopted by clinicians and aged care providers as a standardized approach to simplification and may reduce the burden of medication administration for aged care providers.

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Disclosure

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Supplementary material

Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE): Explanatory statement and specific instructions
The purpose of this validated tool is to identify opportunities to reduce unnecessary complexity in medication regimens. Simpler medication regimens may increase residents' satisfaction and are easier for carers to administer. Consider undertaking a full medication reconciliation and review before applying this simplification tool to ensure all current medications are listed and appropriate. Identification of a "simplification champion" responsible for the medication regimen may assist in implementing the simplest regimen. These processes may also help to inform simplification. Please note: the term "simpler medication regimens" refers to regimens that have fewer administration times, decreased pill burden and/or fewer routes of administration. Consideration can be given to administering medications at the same time each day unless the following apply:
Question 1: Is there a resident related factor that precludes simplification?
Definition Resident related factors include individual needs and preferences, and cannot be generalized. Resident needs refers to factors related to cognitive and functional status. Resident preferences refers to lifestyle or comfort factors of taking a medication regimen. **Instructions** Clinicians should engage in an open and respectful discussion to elucidate the resident's needs and preferences. Consultation with the resident, the resident's family and other health professionals may also be of assistance in determining whether needs and preferences can be accommodated to allow simplification. Medical conditions, such as dementia, may influence the approach to simplification. **Examples** Simplification may not be appropriate if the resident: • prefers to have more frequent administration times if it means less tablets at each administration time • has difficulty swallowing whole oral formulations or requires medications to be crushed, precluding some modified-release formulations • had a previous adverse drug event that would limit simplification options (for example, a previous reaction to once daily atenolol may restrict options for simplification of twice daily metoprolol) • wishes but cannot be supported to self-administer medications in a simplified regimen.
Question 2: Is there a regulatory or safety imperative that precludes simplification?
Definition A regulatory imperative refers to aspects of medication ordering, storage, and administration that must comply with laws and regulations. A safety imperative refers to any aspect of medication ordering, storage, and administration that occurs in order to reduce risk of medication misadventure. These are generally facility level factors. **Instructions** Medication administration is often determined by legislative requirements. Individual facilities may have policies dictating medication administration times, equipment and/or personnel. Refer to relevant local authorities for clarification. **Examples** Simplification may not be feasible if the facility cannot accommodate: • administering opioid analgesics or other controlled medications in the same medication round as other medications due to legal requirements • having qualified staff available to administer medications via a variety of routes and to administer medications that may not be able to be packed in a dose administration aid in the same medication round (for example, to apply topical medication).

Figure S1 (*Continued*)

Question 3: Is simplification likely to result in any clinically significant drug–drug, drug–food, or drug–time interactions?

Definition

Drug–drug interactions occur when co-administration of two or more medications results in changes to the pharmacological effect of any of the medications.

Drug–food interactions occur when administration of a medication with or without food results in changes to the pharmacological effect of the medication or results in clinically significant side effects.

Drug–time interactions occur when there is a clinically significant change in medication efficacy related to changing the time of day the medication is administered. Drug–time interactions may also occur due to certain side effects of a medication that would limit normal daily activities.

Instructions

Not all drug interactions will preclude simplification. Clinical judgement should be exercised to determine if the interaction can be accommodated. Prescribers and facility managers may need to be consulted to determine feasibility.

Examples

There may be ways to accommodate simplification despite "medication myths":

- increased laboratory monitoring in the initial period (for example, when changing administration of thyroxine from before breakfast to with breakfast).

Simplification may not be appropriate where:

- there are two medications that must have separated dose administration times due to pharmacokinetic interaction (for example, bisphosphonates and calcium and/or iron supplements)
- the resident experiences significant nausea if the medication is not given with food
- there are lifestyle limiting diurnal or nocturnal side effects (for example, giving a sedative medication in the morning)
- a condition has effects that must be managed with medication at specific times (for example, Parkinson's disease or behavioral disturbance related to specific daily activities).

Question 4: Is there no alternative formulation available that can support less complex dosing?

Definition

Medications can be available in a variety of dosage formulations and can be administered via different routes.

Instructions

Simpler medication regimens generally have as few different routes of administration as possible. However, administering the same dosage form multiple times a day may be easier than administering different dosage forms at the same time of day. Consult references or pharmacists for a full range of products that are available.

Examples

Simplification may not be possible if there are no:

- long-acting or controlled-released formulations
- combination products
- alternate dosing regimens (for example, monthly instead of daily vitamin D).

Question 5: Is simplification likely to result in any unintended consequences?

Definition

Changing any part of a medication regimen may have consequences for the resident or facility staff that may not be immediately clear. Medication regimens that appear simpler on the medication chart do not necessarily translate to medication regimens that are simpler to administer in practice.

Instructions

Consider all persons who will be involved in the simplified medication regimen and what will be required to ensure the new regimen is successfully implemented and received. Consult prescriber or facility manager for guidance. Special attention may need to be given to people with dementia as it may be more difficult to assess changes and identify adverse outcomes among people with dementia.

Examples

Simplification may not be desirable if it would result in a need to:

- perform additional invasive monitoring (for example, more frequent blood tests)
- increase time spent on administration (for example, changing from a daily oral medication to a weekly patch may require more nursing time to apply and monitor patch adhesion)
- increase the level of qualification needed for staff administering the medication regimen (for example, changing formulation may preclude administration from a dose administration aid)
- increase the overall cost of the medication regimen if alternative medications or formulations are more expensive for the resident or facility.

Figure S1 The Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE): explanatory statement and specific instructions.

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6. Chapter Six: Medication regimen complexity in 8 Australian residential aged care facilities: impact of age, length of stay, comorbidity, frailty, and dependence in activities of daily living

6.1 Synopsis

This chapter characterises the baseline prevalence and factors associated with complex medication regimens among residents who participated in the SIMPLER study conducted in eight RACFs in South Australia. This information helps to demonstrate and quantify how complex medication regimens interact with other factors to contribute to and multiply medication burden. Findings may also assist in the identification of residents who would benefit most from a simplification intervention, providing an opportunity for prioritisation of these residents for review and simplification.

6.2 Chapter objective

To investigate the prevalence and correlates of medication regimen complexity in residents of RACFs.

6.3 Publication

This chapter is a reproduction of the following publication:

Chen EYH, Bell JS, Ilomäki J, et al. Medication Regimen Complexity In 8 Australian Residential Aged Care Facilities: Impact Of Age, Length Of Stay, Comorbidity, Frailty, And Dependence In Activities Of Daily Living. *Clinical Interventions in Ageing* 2019; 14: 1783-1795.

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ORIGINAL RESEARCH

Medication Regimen Complexity In 8 Australian Residential Aged Care Facilities: Impact Of Age, Length Of Stay, Comorbidity, Frailty, And Dependence In Activities Of Daily Living

This article was published in the following Dove Press journal:
Clinical Interventions in Aging

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Objective: To explore variation in medication regimen complexity in residential aged care facilities (RACFs) according to resident age, length of stay, comorbidity, dementia severity, frailty, and dependence in activities of daily living (ADLs), and compare number of daily administration times and Medication Regimen Complexity Index (MRCI) as measures of regimen complexity.

Methods: This study was a cross-sectional analysis of baseline data from the SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) cluster-randomized controlled trial. The SIMPLER study recruited 242 residents with at least one medication charted for regular administration from 8 RACFs in South Australia. Comorbidity was assessed using the Charlson Comorbidity Index (CCI). Dementia severity was assessed using the Dementia Severity Rating Scale. Frailty was assessed using the FRAIL-NH scale. Dependence in ADLs was assessed using the Katz ADL scale.

Results: The median age of participants was 87 years (interquartile range 81–92). Over one-third of participants (n=86, 36%) had 5 or more daily medication administration times. The number of daily administration times and MRCI scores were positively correlated with resident length of stay (r_s=0.19; 0.27), FRAIL-NH score (r_s=0.23; 0.34) and dependence in ADLs (r_s=−0.21; −0.33) (all p<0.01). MRCI was weakly negatively correlated with CCI score (r_s=−0.16; p=0.013). Neither number of daily administration times nor MRCI score were correlated with age or dementia severity. In multivariate analysis, frailty was associated with number of daily administration times (OR: 1.13, 95% CI: 1.03–1.24) and MRCI score (OR: 1.26, 95% CI: 1.13–1.41). Dementia severity was inversely associated with both multiple medication administration times (OR: 0.97, 95% CI: 0.94–0.99) and high MRCI score (OR: 0.95, 95% CI: 0.92–0.98).

Conclusion: Residents with longer lengths of stay, more dependent in ADLs and most frail had the most complex medication regimens and, therefore, may benefit from targeted strategies to reduce medication regimen complexity.

Keywords: Aged, nursing homes, medication regimen complexity, frailty index, activities of daily living, multimorbidity, long-term care facilities

Plain Language Summary

This study analyzed data collected from 242 residents from 8 residential aged care facilities (RACFs) in South Australia. We were interested in the characteristics of residents with differing levels of medication regimen complexity. The complexity of a medication regimen

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depends on the number of medications, the form of medications, how often the medications need to be taken, and additional directions for how to take the medications. We measured medication regimen complexity in two different ways: counting the overall number of times medications were given each day and using a previously published scale (the Medication Regimen Complexity Index). The measures gave similar results when the complexity of medication use was examined among residents of varying age, length of stay in the RACF, health conditions, cognitive impairment, frailty and need for help in day-to-day activities. By both measures, residents with longer lengths of stay, were dependent in activities of daily living and had advanced frailty were more likely to have the most complex medication regimens and may benefit the most from targeted strategies to reduce medication regimen complexity.

Introduction

With more older people now receiving community-based aged care, residents admitted to RACFs are increasingly older, frailer and have more complex care needs.[1] A review of international literature reported that up to 74% of residents of long-term care facilities use 9 or more regular medications.[2] However, there are other factors apart from the number of medications that contribute to a resident's medication burden. Medication regimen complexity is also a contributing factor. Medication regimen complexity includes the number of doses of medications, the medication schedule (i.e. what times the medications are administered), medication formulation (e.g. tablet, patch, inhaler), preparation requirements (e.g. need to crush, mix with thickened fluids or inhaler priming), and special instructions for administration (e.g. take on an empty stomach).[3]

Complex medication regimens are challenging for residents and RACF staff to administer and, therefore, may increase risk of medication administration errors such as administration of the wrong medication, to the wrong resident, or at the wrong time.[4–6] Medication administration errors in RACFs have been reported to occur during 7.1% to 24.6% of observed administration events.[7–9] Higher medication regimen complexity has been associated with a higher likelihood of medication discrepancies in ambulatory care patients.[10] Emerging evidence also suggests that complex medication regimens may be associated with medication non-adherence, adverse drug events, hospitalization, hospital readmission, and mortality among RACF residents and in community settings.[11–13] Simplifying complex medication regimens may help to improve these outcomes for residents. In RACFs, simplification is important from an organizational level to minimize risk of harm from medication errors for residents who often cannot manage their own medications. Complex medication regimens have been associated with an increased risk of hospitalization from RACFs.[11] Simplification may also benefit staff who administer medication, who may experience frustration over frequent medication administration.[4]

Complexity of medication regimens has been measured using a variety of methods in older people.[14] The Medication Regimen Complexity Index (MRCI) is the most common method and has been used internationally to characterize complex medication regimens in RACFs.[14–17] In practice, the MRCI has some limitations. The first is that the MRCI score can be time-consuming to calculate. Automatic methods of calculation have been developed but are not widely accessible.[18,19] The second is that the MRCI does not specifically account for the overall number of daily administration times. The number of daily administration times reflects the frequency of medication administration organized over 24 hrs.[20] A United States' (US) study showed community-dwelling older people demonstrate large variability in the number of times they would administer medications each day when presented with the same seven medications.[20] Fewer studies have investigated number of daily administration times as a measure of complexity.[21] Reducing the number of daily administration times may improve resident quality of life, satisfaction and convenience, and free up nursing time to focus on other aspects of clinical care.[13,22–24] Number of daily administration times is an easier measure of complexity to calculate in clinical practice than MRCI.

Increasing awareness of the potential for medication-related harm in RACFs has highlighted the need to identify residents with high medication burden who will benefit most from medication management interventions. It is important to understand the prevalence and correlates of complex medication regimens to better target potential interventions, including to those who are frail, dependent in activities of daily living (ADLs) or are living with dementia. Previous studies in community and hospital settings have found scope to simplify medication regimens measured using number of daily administration times.[21,25,26] However, medication regimen complexity in RACFs has not been explored using number of daily administration times. The objective of this study was to explore variation in medication regimen complexity in RACFs according to resident age, length of stay, comorbidity, dementia severity, frailty, and dependence in ADLs, and compare number of daily administration times and MRCI as measures of regimen complexity.

Methods

Study Design And Setting

This study was a cross-sectional analysis of baseline data collected from the SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) study (Australian New Zealand Clinical Trials Registry Trial ID ACTRN12617001060336).[27] The SIMPLER study is an ongoing cluster-randomized controlled trial conducted in eight metropolitan and rural RACFs in South Australia. In Australia, RACFs are synonymous with "nursing homes" or "long-term care facilities" and provide 24-hour supported accommodation for predominantly older people whose care needs can no longer be supported at home.[1] The SIMPLER study was approved by the Monash University Human Research Ethics Committee and conducted in accordance with the World Medical Association Declaration of Helsinki. The full SIMPLER study design and methodology have been described previously.[27]

Participants

Study participants were recruited between April and October 2017. All eligible residents were invited to participate by trained research nurses who were employed as part of the study. Residents were eligible if they took at least one regular medication and were able to complete structured assessments in English. Residents who were estimated to have less than 3 months to live or deemed medically unstable (e.g. experiencing delirium) based on the judgement of senior RACF nursing staff were excluded. Residents could also be excluded at the discretion of the nursing staff or primary physician. Residents provided written informed consent to participate. Where the resident was unable to provide informed written consent, consent to participate was sought from the resident's guardian, next-of-kin, or significant other.[27]

Data Source/Measurements

Four trained research nurses collected baseline demographic and clinical data using a web-based standard data collection form. Cognitive impairment was assessed using the Dementia Severity Rating Scale (DSRS). This scale consists of 12 cognitive and functional domains and was completed with input from a staff informant.[28,29] The DSRS is suitable to assess impairments in residents with and without a documented dementia diagnosis.[29] The DSRS is not a diagnosis tool for dementia and was used to capture the many residents who may have some level of cognitive impairment without a documented dementia diagnosis. ADLs were assessed using the 6-item Katz ADL scale.[30] The DSRS and Katz ADL scales were completed with input from a staff-informant who had known the resident for at least 2 weeks. Frailty was assessed using the 7-item Fatigue, Resistance, Ambulation, Incontinence or illness, Loss of weight, Nutritional status, and Help with dressing in nursing homes (FRAIL-NH) scale.[31,32] The FRAIL-NH was constructed from four items from the Katz ADL scale, two items from the Mini Nutritional Assessment Short Form, and one item from the Quality of Life in Alzheimer's Disease Scale.[33] A score between 6 and 14 was considered indicative of advanced frailty.[33] Clinical diagnoses were extracted from each participant's medical record of "active" conditions. A Charlson Comorbidity Index (CCI) score was calculated for each participant using the version updated and validated by Quan et al (2011).[34] We did not weight for age because correlations with age were investigated separately. Where severity of certain diagnoses was not recorded (e.g. the severity of "liver disease" was not recorded), the diagnoses were assumed to be mild. The DSRS, Katz-ADL, FRAIL-NH, and CCI are all validated scales that have been previously used in studies in the RACF setting, allowing comparison with existing literature.[28–34] Length of stay was calculated from the time of first admission to an RACF within the aged care provider organization to the date of baseline data collection.

Medication Assessment

Prescription and non-prescription medication data were extracted by hand directly from hard copies of each resident's medication administration chart and recorded in a Microsoft Access (2017) database.[18] Data extracted included medication name, strength, dose, formulation, frequency of administration, time of administration, and special instructions for administration. Medications were classified using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system.[35] If a participant was taking two different formulations of the same medication it was counted as two medications. Regular medications were defined as those that were charted for administration on a regular basis with a frequency of administration of at least once weekly.

Outcome

Medication regimen complexity was assessed using two methods: number of daily administration times and the MRCI.

Number Of Daily Administration Times

The overall number of daily administration times was operationally defined as the total number of charted medication administration times over a 24 hrs period for regular mediations.[27] This was calculated by counting the number of unique times of administration over a 24 hrs period extracted from the medication chart (e.g. 08:00, 17:00). All prescription and non-prescription medications (e.g. multivitamins, complementary and alternative medication) present on their medication administration chart ("charted") for administration daily or more frequently were included, regardless of the dose formulation. The application of once-daily patches (e.g. glyceryl trinitrate patches) was considered to be an administration time while the removal was not. The following were excluded when calculating the number of daily administration times: pro re nata (PRN, or as required) and short-term medications, nutritional drinks, and regular medications administered less than daily (e.g. 6 monthly injections, once weekly tablets, patches applied every third day).

Medication Regimen Complexity Index (MRCI)

The MRCI is a 65-item validated tool and the most widely used measure of medication regimen complexity.[3,14] There are three sections that comprise the MRCI score: section A refers to formulation of the medication, section B refers to frequency of administration, and section C refers to additional or special instructions for administration. MRCI scores are cumulative for each medication in the regimen, including PRN medication. As such, there is no maximum MRCI score. Higher scores indicate more complex medication regimens. MRCI scores were calculated using SAS statistical software using the data extracted from the resident's medication administration chart. The algorithm used was based on the original MRCI[3] with the following updates for new formulations: wafers and oral-disintegrating tablets were given the same value as sublingual sprays/tablets. Soft-mist inhalers, a new formulation introduced since the development of the MRCI, were given the same value as metered-dose inhalers, the closest equivalent dose form. There was no information available to assess "take/use as directed" and "tapering/increasing dose" in section C.

It is possible to have medication regimens with the same MRCI score, but a different number of daily administration times. The prescribed frequency of a medication (section B) does not necessarily reflect the overall number of daily administration times. For example, a resident taking two once-daily medications (e.g. candesartan 16mg once daily and atorvastatin 40mg once daily) may take both together in a single daily administration time. Alternatively, the resident may separate the doses to two daily administration times by taking candesartan in the morning and atorvastatin in the evening. In this example, the single and separated administration times of two once-daily medications are considered equally complex by the MRCI's Section B. However, two daily administration times are more complex than one daily administration time.

Statistical Analysis

Demographic data were summarized using medians and interquartile ranges (IQRs). Age, length of stay in the RACF, DSRS score, FRAIL-NH, Katz-ADL score, MRCI score, and number of daily administration times were analyzed as continuous variables. Associations were presented as scatter plots. We reversed the Katz-ADL scale score for presentation in scatterplots by giving points for dependence (rather than independence) in order to assist with interpretation alongside the other scales. Correlations were evaluated using the Spearman correlation coefficient. Univariate and multivariate logistic regression models were performed to calculate odds ratios (OR) and 95% confidence intervals (CIs) to examine associations between the above continuous variables and multiple administration times (model 1) and high MRCI score (model 2). The outcome of multiple administration times was defined as five or more daily administration times. High MRCI scores were classified as scores in the upper quartile (>55.5). In our multivariate model, we included only FRAIL-NH and not Katz-ADL as the two scales assess frailty and disability, respectively, but have a number of items in common. Analyses were conducted in SAS v 9.4 (SAS Institute, Inc., Cary, NC) and R v 3.5.0 (Comprehensive R Archive Network) with RStudio v 1.1.453. Results were considered significant if $p<0.05$.

Results

There were 242 permanent residents recruited from 8 RACFs in South Australia (Figure 1). The median age of participants was 87 years and the age distribution was left-skewed. The sample was representative of the resident population within the wider organization (n=703), in which the median age was 87 years (IQR 81–92), there were 523 females (74%) and 356 residents were living with dementia (50.6%). The recruited sample of residents was also similar to the wider aged care population in Australia with respect to age (62% vs 59% aged 85 years

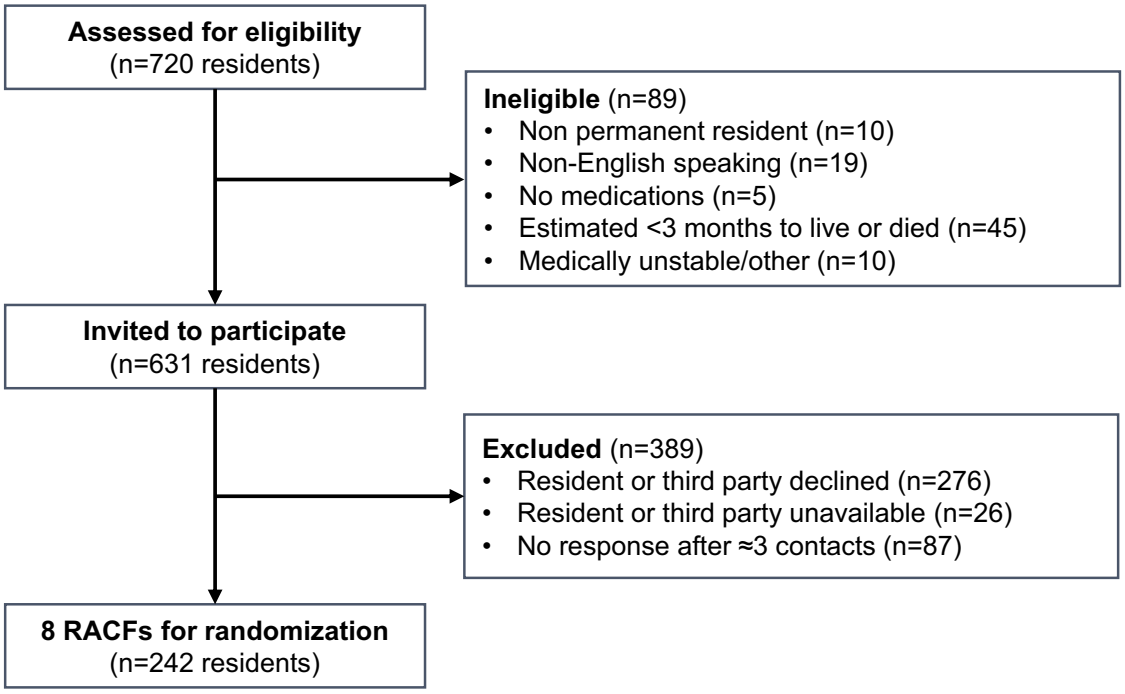

Figure 1 Study recruitment flow diagram.
Abbreviation: RACFs, residential aged care facilities.

or older), sex (74% vs 67% female), and length of stay (2.54 years vs 2.92 years).[36] The sample was also comparable to previous studies in RACFs in Australia with respect to age and length of stay.[11,37–39]

Participants took a median of nine regular medications (IQR 6–12). Over half (n=128, 53%) were taking nine or more regular medications. Number of regular medications was significantly correlated with length of stay (r_s=0.13, p=0.04) and DSRS score (r_s=−0.23, p<0.001). Correlations between scores of all correlates tested are reported in the supplementary material. In total, residents were charted 3287 medications, which included 2235 regular medications and 1094 PRN medications. The most prevalent therapeutic subgroups were for analgesics (n=231 residents) and drugs for constipation (n=201 residents). Tablets or capsules were the most common dosage form (n=1699, 75% of regular medications) charted. Formulations with the highest proportion of residents in the "high" complexity group were nebulizers (n=19/28, 68%), aerolizers (n=8/12, 67%), and pre-filled injections (n=11/17, 65%). Two-thirds (n=1440, 63%) of regular medications were charted for once-daily administration.

Over one-third of participants (n=86, 36%) had five or more administration times per day. The median MRCI score was 42. The frequency of medication administration contributed most to the overall MRCI score (Table 1 and Figure 2). Total MRCI score was positively correlated with number of daily administration times (r_s=0.47, p<0.001) (Figure 2). Section B of the MRCI had a stronger correlation with number of daily administration times (r_s=0.56) than section A (r_s=0.33) and section C (r_s=0.27) (all p<0.001).

Both number of daily administration times and MRCI score were positively correlated with length of stay in RACF (r_s=0.185, p=0.004 and r_s=0.265, p<0.001, respectively), FRAIL-NH score (r_s=0.231 and r_s=0.335, respectively, both p<0.001) and dependence in ADLs (r_s=0.211 and r_s=0.327, respectively, both p<0.001). The MRCI score was weakly negatively correlated with CCI score (r_s=−0.160, p=0.013) (Figures 3 and 4). There were no significant correlations between number of daily administration times and age (r_s=0.01, p=0.91) or DSRS score (r_s=0.00, p=0.95); or MRCI and age (r_s=0.02, p=0.74) or DSRS score (r_s=−0.02, p=0.79).

Table 1 Baseline Characteristics Of SIMPLER Participants

Characteristic Median (Interquartile Range) Unless Specified	Total n=242
Age in years	87 (81–92)
Female; n (%)	179 (74%)
Rural; n (%)	48 (20%)
Length of stay in the residential aged care facility (RACF) in years	2.5 (1.0–4.7)
Charlson Comorbidity Index (CCI) score[a]	2 (2–3)
Documented dementia diagnosis; n (%)	131 (54%)
Dementia Severity Rating Scale (DSRS) score[b,c]	21 (11.8–38.3)
Frailty in Nursing Homes (FRAIL-NH) score[b,d]	7 (3–10)
Katz Index of Independence in Activities of Daily Living (Katz-ADL)[b,e,f]	1 (1–3)
Number of charted medications	13 (9–17)
Regular Pro re nata (PRN)	9 (6–12) 4 (2–7)
Most prevalent medications charted (ATC code); n (% of residents)	
Paracetamol (N02BE01) Docusate with sennosides (A06AB56) Macrogol (A06AD15) Colecalciferol (A11CC05) Furosemide (C03CA01)	224 (93%) 145 (60%) 103 (43%) 85 (35%) 76 (31%)
Number of medication administration times per day	4 (3–5)
Medication Regimen Complexity Index (MRCI) score	42 (28.5–55.5)
Section A score (formulation) Section B score (frequency) Section C score (special instructions for administration)	9 (5–13) 19.8 (14–26) 11 (7–17)

Notes: [a]Possible range: 0–24, 0=none of the Charlson comorbidities. [b]Missing for n=2. [c]Possible range: 0–54 (mild impairment, 0–18; moderate impairment, 19–36; severe impairment, 37–54). [d]Possible range: 0–14 (non-frail, 0–1; frail, 2–5; most frail, 6–14). [e]Possible range: 0–6 (dependence in all domains, 0; independence in all domains, 6). [f]When reversed to score for dependence: 5 (3–5).
Abbreviation: ATC, Anatomical Therapeutic Chemical.

In univariate logistic regression, length of stay was associated with both multiple medication administration times (OR: 1.10; 95% CI: 1.01–1.20) and high MRCI score (OR: 1.13; 95% CI: 1.03–1.24) (Table 2). In the multivariate logistic regression model, FRAIL-NH score was associated with multiple medication administration times (OR: 1.13; 95% CI: 1.03–1.24) and high MRCI score (OR: 1.26; 95% CI: 1.13–1.41). The DSRS score was inversely associated with both multiple medication administration times (OR: 0.97; 95% CI: 0.94–0.99) and high MRCI score (OR: 0.95; 95% CI: 0.92–0.98).

Discussion

The main findings were that residents who were frailer and dependent in ADLs were more likely to have complex medication regimens when measured using number of daily administration times and MRCI score. To our knowledge, this was also the first study to establish the strong correlation between number of administration times and MRCI in RACFs. Effectively identifying residents with complex medication regimens is important to better target medication management interventions, such as medication regimen simplification, to particularly vulnerable residents. MRCI is likely to be time-consuming for clinicians to calculate in routine clinical practice unless incorporated into an electronic medication management system. In contrast, a count of daily administration times is easier for RACF nurses and other health professionals to measure and screen for medication regimen complexity.

Medication regimen complexity was positively correlated with frailty and dependence in ADLs. This was consistent with a previous study in Australian RACFs in which MRCI was associated with dependence in ADLs.[40] Increasing frailty and dependence in ADLs may coincide with underlying changes in medical conditions which prompt prescribing of additional medications. Increasing frailty and dependence in ADLs may also necessitate changes to routes of administration (for example, crushed medications and mixing with thickened fluid to aid swallowing). Physicians and pharmacists may not proactively simplify medication regimens for frail residents and residents requiring assistance with ADLs for a number of reasons. Physicians and pharmacists may overestimate the capability and availability of RACF clinical staff to assess and simplify medication regimens. Similarly, there may be a perception that because residents are supported to take medications there is less need for simplification than in other settings.[41] It is also possible that physicians and pharmacists do not fully recognize the complexity of a resident's medication regimen because they are not typically involved in medication administration. In a previous study, provision of a visualization of a patient's medication regimen for 1 week to the patient's treating physician was able to reduce medication regimen complexity by a mean of 2.47 (standard deviation, SD 1.55) doses per day in a hospital setting.[26]

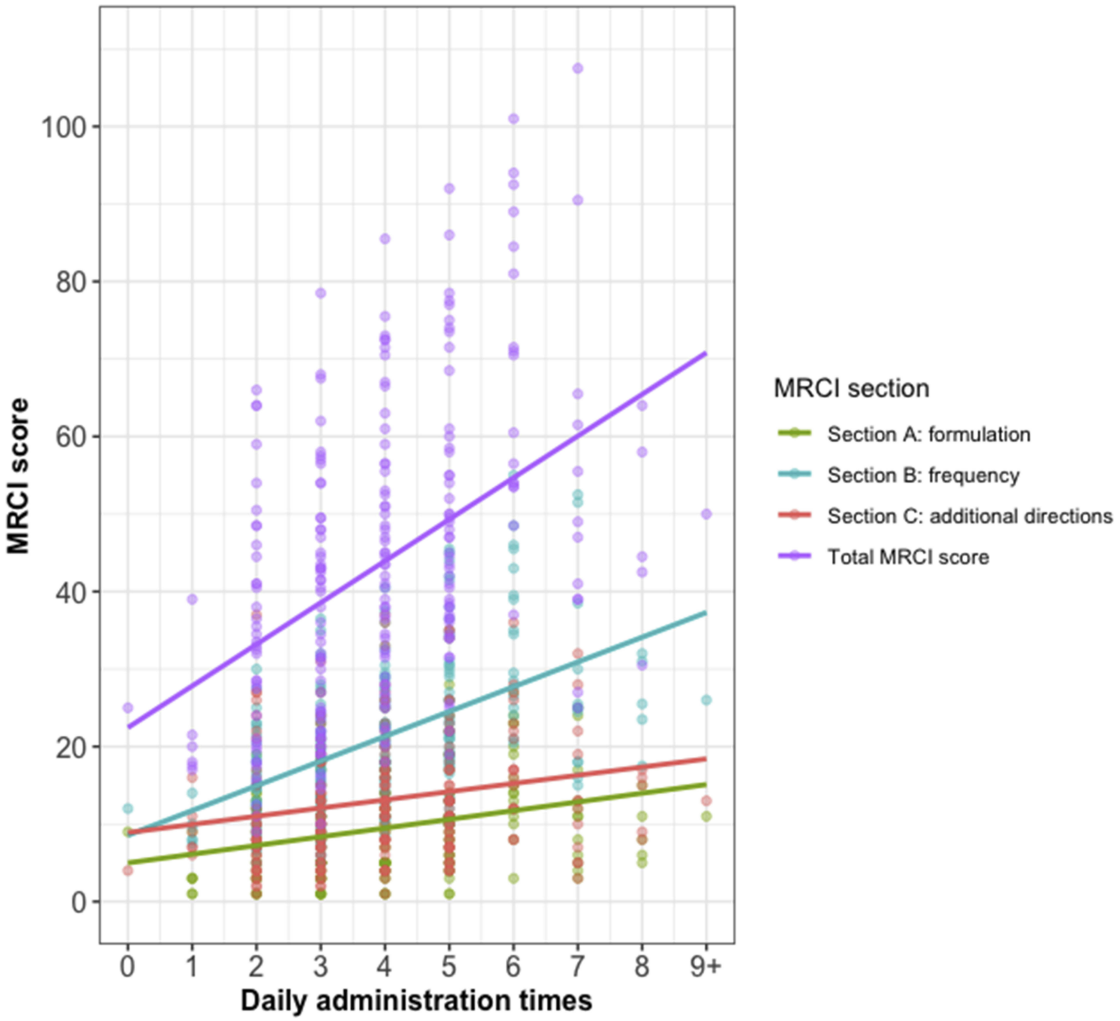

Figure 2 Scatter plot of Medication Regimen Complexity Index (MRCI) score versus daily administration times with linear regression lines.

Medication regimen complexity was positively correlated with length of stay. Over time, medications may be added and not ceased from the medication chart. Residents of RACFs may have multiple prescribers who are reluctant to discontinue medications prescribed by others.[42] A previous German study reported that the number of PRN medications increased with length of stay.[43] The Ageing@NH study of newly admitted residents to Belgian RACFs found an increase in the proportion of residents with extreme polypharmacy (the concomitant use of >10 medications) and residents using PRN medications over 2 years.[44] Additionally, residents of Australian RACFs can be referred for government-funded collaborative medication reviews every 2 years unless more frequent reviews can be justified on the basis of clinical need.[45] In these collaborative medication reviews, clinical pharmacists undertake a systematic, comprehensive medication review and evaluate medication management and make recommendations, such as ceasing medication or changing formulations, to the resident's primary physician for implementation.[46] It has been estimated that 38% of all RACFs residents will receive a collaborative medication review annually.[1] This means that residents with longer RACF stays may have up to 2 years between comprehensive medication reviews and may not have had a recent comprehensive medication review in which medication regimen complexity could have been addressed.

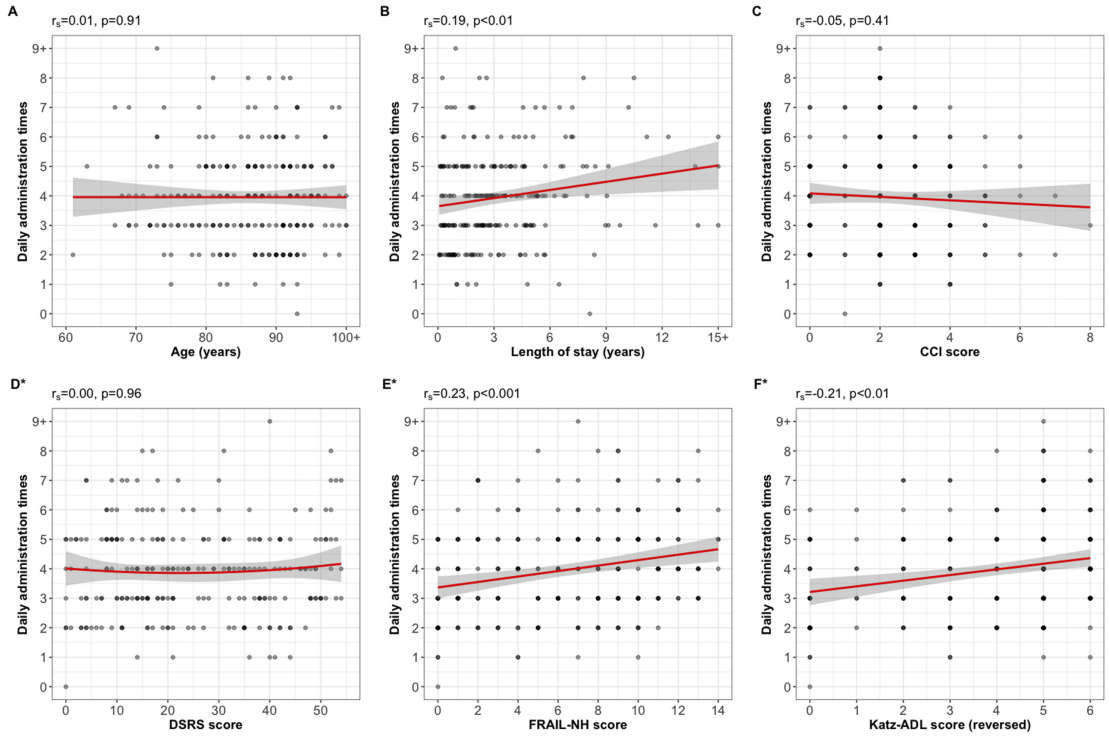

Figure 3 Plots of correlation of daily administration times with (**A**) age, (**B**) length of stay, (**C**) Charlson Comorbidity Index (CCI) score, (**D**) Dementia Severity Rating Scale (DSRS) score, (**E**) Frailty in Nursing Homes (FRAIL-NH) score, and (**F**) Katz Index of Independence in Activities of Daily Living (Katz-ADL) score, reversed to score for dependence. Solid lines: linear regression line; shaded areas: 95% confidence intervals. *Missing for n=2.

Our study found an inverse association between medication regimen complexity and dementia severity in multivariate analysis. Previous studies have reported residents with cognitive impairment are less likely to have complex medication regimens,[40,47,48] and are less likely to experience polypharmacy, or the concomitant use of multiple medications (commonly >8).[2,49] Recently, there has been focus in Australia on implementing a palliative approach to medication prescribing for residents with advanced dementia, and deprescribing for all older adults experiencing inappropriate polypharmacy.[50,51] Deprescribing refers to reducing medications after consideration of therapeutic goals, benefits and risks, and medical ethics.[52] Physicians may increasingly recognize the value of deprescribing medications for which the benefits no longer outweigh risks, especially in people with dementia and those who may have a shorter life expectancy.[40,44,53] This finding may also be a reflection of documented undertreatment in people living with dementia, particularly in pain management.[44,54]

Medication regimen complexity was correlated with comorbidity when complexity was measured using MRCI but not daily administration times. This was unexpected because prescribing according to disease-based clinical practice guidelines has been described as a key contributor to polypharmacy and medication regimen complexity for people with multimorbidity.[42] Our study found a median CCI score of 2, which was consistent with a previously published study in Australian RACFs.[17] Residents with multimorbidity may have been more likely to have been referred for medication reviews, and may have a clinical need to receive medication reviews at more frequent intervals. This closer monitoring may help to decrease medication regimen complexity, although a retrospective study of comprehensive medication reviews for residents of RACFs did not find any significant impact on MRCI.[37] Where pharmacists were given education and encouraged to simplify medication regimen, clinical medication reviews were found to reduce medication regimen complexity for older people in hospitals.[55] We measured comorbidity using CCI, which does not measure total comorbidity. Previous studies have suggested that chronic pulmonary disease, diabetes, and congestive heart failure are particularly associated with higher MRCI score,

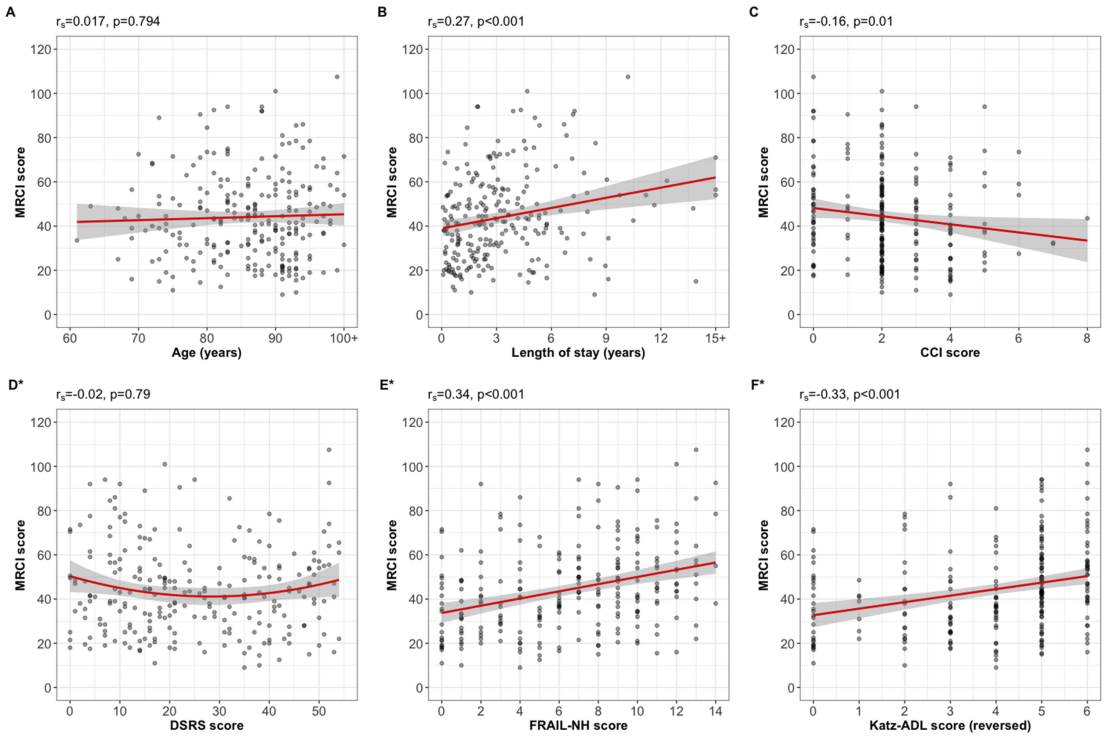

Figure 4 Plots of correlation of Medication Regimen Complexity Index (MRCI) score with (**A**) age, (**B**) length of stay, (**C**) Charlson Comorbidity Index (CCI) score, (**D**) Dementia Severity Rating Scale (DSRS) score, (**E**) Frailty in Nursing Homes (FRAIL-NH) score, and (**F**) Katz Index of Independence in Activities of Daily Living (Katz-ADL) score, reversed to score for dependence. Solid lines: linear regression line; shaded areas: 95% confidence intervals. *Missing for n=2.

while cognitive impairment is associated with lower MRCI scores.[40,56] The CCI also does not include some medical conditions associated with medications that have frequent administration that may increase medication regimen complexity, such as Parkinson's Disease and chronic pain syndromes.[22] However, it should be noted that complexity of medications for single conditions has not been found to be representative of overall complexity of the whole medication regimen, which often has medications to treat multiple conditions.[57] Additionally, PRN medications are included when calculating MRCI score, whereas they were not included in a count of daily administration times. It is possible that PRN medications for symptom management may be more prevalent in residents with more medication conditions. Interventions to reduce complexity should be targeted to residents with conditions associated with higher MRCI but involve a full regimen review.

A previous validation study in Australian RACFs found that all residents with five or more administration times could have their medication regimens simplified.[58] Medication simplification refers to:

> The process of consolidating reducing medication complexity through strategies such as administering medications at the same time, standardizing routes of administration, using long-acting formulations in preference to shorter-acting agents, and switching from multiple single-ingredient preparations to a combination formulation where possible.[27]

A study of discharge prescriptions in Germany found that 18% of multidose medications could be simplified to once-daily dosing.[25] Regimen simplification may be valuable to complement other medication management interventions including medication reconciliation, review, and deprescribing. Our finding that over one-third of residents had five or more administration times suggests there is significant opportunity to reduce the number of administration times. Medication regimen simplification using structured tools[58] on or soon after admission to RACFs may be a useful strategy to reduce the number of administration times. Observation of 23 medication rounds across two Australian RACFs found that between 3.5 and 4.8 mins (SD 0.6–1.1) were spent on medication administration per

Table 2 Univariate And Multivariate Logistic Regression Analysis

	Multiple Medication Administration Times		High MRCI Score	
	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Gender male	0.65 (0.34–1.20)	0.71 (0.36–1.36)	0.50 (0.22–1.03)	0.59 (0.25–1.28)
Age (years)	1.01 (0.98–1.05)	1.00 (0.97–1.04)	1.02 (0.98–1.06)	1.01 (0.97–1.06)
Length of RACF stay (years)	1.10 (1.01–1.20)	1.09 (0.99–1.20)	1.13 (1.03–1.24)	1.10 (1.00–1.22)
CCI	0.98 (0.82–1.16)	1.03 (0.86–1.23)	0.91 (0.75–1.11)	0.97 (0.78–1.18)
DSRS	0.99 (0.98–1.01)	0.97 (0.94–0.99)	0.99 (0.98–1.01)	0.95 (0.92–0.98)
FRAIL-NH	1.06 (0.99–1.14)	1.13 (1.03–1.24)	1.13 (1.04–1.22)	1.26 (1.13–1.41)
Katz-ADL	0.90 (0.77–1.03)	–	0.81 (0.67–0.96)	–

Note: [a]Multivariate model did not include Katz-ADL due to collinearity with FRAIL-NH score.
Abbreviations: ADL, activities of daily living; CCI, Charlson Comorbidity Index; CI, confidence interval; DSRS, Dementia Severity Rating Scale; MRCI, Medication Regimen Complexity Index; OR, odds ratio; RACF, residential aged care facility.

resident per round.[59] Reducing administration times would enable RACF staff to shift time spent administering medications to provision of other care activities, although further studies are required to determine how much time could be redirected towards other care activities as a result of simplifying medication regimens.

Strengths And Limitations

A strength of our study was that we extracted medication information directly from medication administration charts and so were able to accurately assess MRCI and administration times with high internal consistency, including all charted prescription and non-prescription medications. Although clinical diagnoses were extracted directly from medical records, we may have underestimated overall comorbidity using the CCI score because we only collected information about current diagnoses and because the CCI was developed to predict mortality and does not account for all diagnoses and their severity. However, the CCI has become widely used as a general measure of multimorbidity in the RACF setting.

An important strength of our study was the inclusion of a sample of residents that was representative of the wider resident population of the aged care provider organization in terms of age, sex and dementia diagnosis.[60] However, we were not able to determine whether the sample was representative in terms of health status and medication use. The complexity of medication regimens in this study was higher than among residents who received medication reviews in Australia in 2011–12 (median MRCI score of 25.5); however, this may also be partly explained by an increase in polypharmacy over time.[37] This study's median MRCI was also high when compared to studies in RACFs in Brazil and Portugal, although the participants were also younger and had lower rates of polypharmacy.[15,16] These international studies did not include non-prescription medications. This may reflect the trend for Australian RACFs to cater to residents who have complex care needs or are most frail.[42] Finally, only associations were investigated in this study; conclusions about causation cannot be made.

Conclusion

Residents of RACFs who were dependent in ADLs, had advanced frailty, and with longer lengths of stay were more likely to have the most complex medication regimens and, therefore, may benefit from targeted strategies to reduce medication regimen complexity. A count of daily administration times could be used to identify residents with these characteristics who may benefit from interventions to reduce medication regimen complexity.

Data Sharing Statement

Final data set access will be limited to study investigators. Other study-related documents, study protocol and model consent form have been previously published and can be accessed at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=372482.

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PART D: DISCUSSION AND CONCLUSION

7. Chapter Seven: Discussion

7.1 Main findings

The overall aim of this thesis was to evaluate and address the burden of medication regimen complexity on older people and the health systems that serve them.

In Chapter Two, a systematic review of medication reconciliation and review in Australian RACFs found that although existing medication reviews were successful in identifying and resolving medication-related problems among recipients, there was no evidence to suggest medication reviews reduce medication regimen complexity. There was also no evidence of any tools or algorithms having been developed or evaluated in Australia that could be used collaboratively by clinicians to simplify medication regimens.

The potential clinical outcomes and burdens of complex medication regimens were investigated in Chapters Three and Four. In Chapter Three, a population-based cohort study in Hong Kong showed that older people with AF who received an OAC commonly had complex medication regimens. Higher medication regimen complexity was not associated with a higher risk of intracranial, gastrointestinal, or other bleeding for people with AF in community settings in the first 90 days of initiating oral anticoagulants. Over the longer full follow up period (median of 501 days), there was a small but significant increased risk of bleeding. This adds to the body of literature on independent risk factors for bleeding in people who receive OACs. This knowledge is important for assessing treatment benefits and risks. Chapter Four quantified the burden of complex medication regimens in terms of the time taken for nurses to administer medications in Australian RACFs. A total of 57 medication rounds were observed across different times of day, unit types, and staff responsible for medication administration. In an average unit of 22 residents, the overall time spent on medication administration rounds was 5.2 hours. Crushing or cutting tablets, which adds to complexity, occurred in 22% of tablet and capsule administrations observed, and this increased the time needed for medication preparation and administration.

To address the gap in medication regimen simplification identified in Chapter Two, Chapter Five described the development and validation of a novel tool to help clinicians simplify medication regimens. A seven-member expert panel reached consensus on five implicit criteria to comprise the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE). These criteria were successfully applied to a sample of 50 medication regimens by two independent clinical pharmacists to validate the tool. There was moderate agreement between the pharmacists, who found that 29/50 and 30/50 of the regimens could be simplified. MRS GRACE was subsequently evaluated in the SIMPLER cluster RCT.[114] Chapter Six uses the baseline data collected from the SIMPLER study participants to investigate the factors associated with medication regimen complexity in residents of aged care facilities. Simplification is a service that may be delivered within or in a similar way to existing medication review programs in RACFs, although Chapter Two and subsequent research from Tasmania suggests that this is not currently occurring.[117] Findings from the SIMPLER study suggest that medication regimen simplification may relieve the burden of complex medication regimens by reducing the number of daily medication administration times. The tool was recently adapted and piloted among recipients of community home care services.[160] Simplification was possible for 56% (n=14) of participants. Half of the participants had simplification recommendations implemented at follow up.[160] Further translation and implementation of the tool is expected with clinical articles describing the tool recently published in Australian Journal of Pharmacy and accepted for publication in Australian Journal of General Practice.[161,162]

7.1.1 Measuring medication regimen complexity

The research in this thesis used various measures of medication regimen complexity appropriate to the aims and methods of the individual studies. Chapter Three, a population-based study using electronic medical records for 19,292 older people, used the MRCI algorithm. Chapter Four, an observational study interested in time taken for medication administration rounds, considered dose alterations and other methods of administration.[163] Chapters Five and Six were set in RACFs where staff are responsible for most medication administration. Chapter Five used number of

daily administration times, while Chapter Six used both number of daily administration times and the MRCI.[164,165]

Although MRCI has become a gold-standard measure of medication regimen complexity, it does have limitations in the RACF setting.[38] The MRCI was validated in a cohort of community-based people with COPD who managed their own medications.[48] When determining the MRCI score, PRN medications are given half the weight of the corresponding frequency when given regularly on the basis that symptoms would prompt administration. The process of PRN medication administration in RACFs is not so straightforward, as nurses and care workers are usually responsible for deciding and administering PRNs.[3] Additionally, many residents with cognitive decline may not communicate symptoms verbally, potentially making it easier for nurses and care staff to miss cues that PRN medications are needed.[166] In RACFs, a majority of residents (94%) have one or more PRN medications charted.[167]

The MRCI assigns more weight to administration frequencies less than daily. For example, once daily has a score of 1, while once weekly is considered to be more complex and has a score of 2.[48] This may be because people managing their own medications may lose track of medications administered less than daily; that is, it is less complex to remember to take something every day than it is to remember to take something once a week. However, in an RACF setting where medications are prescribed on a medication chart and trained staff are responsible for administration, once weekly may be viewed as a simpler option. Conversely, medications with irregular and less frequent dosing intervals such as transdermal opioids are frequently implicated in medication incidents, which are a leading source of complaint (33%) to the Aged Care Quality and Safety Commission in Australia.[85,168]

In an RACF setting, the overall number of daily administration times determines medication administration rounds for aged care staff, rather than the frequency of individual medications. Chapter Four demonstrated that each medication round involves a proportion of ‘fixed time’ irrespective of the number of medications administered during that round (e.g. preparation of the medication trolley). However, individual medications are the basis of frequency of administration scoring in the MRCI. Therefore, overall number of administration times was addressed in the

simplification tool developed for use in RACFs in Chapter Five. Overall number of daily administration times was used as the primary endpoint in the SIMPLER study in recognition that addressing this aspect of complexity had the most opportunity to benefit for both residents and staff.[159] For residents, consolidating administration times may decrease disruption to leisure or social activities and allow redirected time from medication administration to be spent on other resident-centred care activities, such as non-pharmacological interventions that support residents' independence and dignity.[169] For staff, time saved from streamlined medication administration rounds may mean less time pressure for safe medication administration practices. Number of daily administration times is also a more convenient measure to calculate in everyday practice. Chapter Six investigated the correlation between MRCI score and overall number of daily administration times to validate the use of daily administration times as a measure of overall medication regimen complexity in RACFs.[165] The results showed that MRCI and number of administration times were moderately correlated, despite dose frequency of individual medications within the regimen (section B of the MRCI) being responsible for the highest proportion of the total MRCI scores.[165] This finding suggests that a count of overall daily administration times is a simple and meaningful indicator of medication regimen complexity in the residential aged care setting.

Medication regimen complexity was not included in the international core outcome set for clinical trials of medication review in multi-morbid older patients with polypharmacy.[116] This may be because medication regimen complexity defined using the MRCI is difficult to benchmark. The thesis established that range of MRCI scores was varied across countries and settings. There are no established levels of 'low' or 'high' complexity, or widely used thresholds that are associated with clinical outcomes. Additionally, since resident preference is important, some people may prefer not to have their medication regimens simplified. Medication regimen complexity is benchmarked across all 180 public-sector residential aged care facilities in Victoria, Australia using the indicator 'more than 4 medication administration times'. Addressing medication regimen complexity has also been identified as a priority in recent international consensus principles for medication management in frail older people.[170] Lack of knowledge of medication regimen simplification as a stand-alone concept could also have influenced the participants

who were interviewed about what they would expect from a medication review and who participated in the Delphi questionnaire survey. When considering important factors about medication regimens that you do not have to use personally, complexity may not be prioritised.

Although the development of the core outcome set specified that feasibility issues were not considered in selecting the set, it is worth noting that calculating the MRCI score requires relatively more data and can be time-consuming to calculate. While software exists to automate the calculation of MRCI, their use is not widespread.[171] This is one reason why number of daily medication administration times may be a more practical indicator of complexity for inclusion in a core outcome set than MRCI.

7.1.2 Current burden of medication regimen complexity

This thesis further characterised the prevalence of complex medication regimens in older people and found it impacts various groups differently. Results presented in Chapters Five and Six from two different Australian RACF populations consistently reported that approximately one third of residents in Australian RACFs had five or more administration times.[164,165] Residents who were more dependent in ADLs and more frail were more likely to have complex medication regimens in the study presented in Chapter Six.[165] Additionally, the prevalence of medication regimen complexity in older people with AF in an international setting was established in Chapter Three.

There was no association between dementia severity and medication regimen complexity in Chapter Six.[165] This is consistent with existing literature on the inverse relationship between dementia and medication regimen complexity.[63] People living with dementia who reside in RACFs have also been found to be less likely to experience polypharmacy.[87] The lack of association between regimen complexity and dementia severity may be because physicians proactively deprescribe medications for people living with dementia.[172] Physicians may also be less likely to initiate new medications for people with dementia, particularly those with advanced dementia or swallowing difficulties.[173] However, the time-motion study conducted in Chapter Four found that medication administration for residents living in memory support units took an average of one extra minute per resident per round.[163] If

people living with dementia do not have more complex medication regimens, this increased time may be attributable to increased needs in other care domains such as needing to crush medication and staff-resident communication. 'Miscellaneous care' had a higher average time for residents in memory support units (109.7 seconds compared to 62.1 seconds, p=0.351). Increased care needs may also indirectly increase the time needed for all activities, which is difficult to measure and account for separately. The longer length of time needed to administer medications to residents with dementia has aged care policy and resourcing implications. This is because people are now admitted to residential aged care later and with more complex multimorbidity including dementia than when the current funding models for residential aged were developed.[8,85]

Chapter Six also identified that residents who were more dependent in ADLs and more frail had more complex medication regimens.[165] These residents may need more care time aside from medication administration. This may be due to people who are frail having high rates of comorbid cardiovascular, endocrine, and respiratory conditions.[174-177] These conditions have been associated with more complex medication regimens among residents of aged care facilities.[63] Care time outside of medication administration rounds was not investigated in Chapter Four. Resident information such as Katz-ADL score or frailty score was also not collected, as the study focused on medication administration only. However, it is likely that if increased care time is needed for residents more dependent in ADLs and more frail, it could be partly attributed to them having complex medication regimens with more daily administration times, formulations and/or extra administration needs such as having to give tablets one at a time or crushing them.

Decreased pill burden and decreased frequency of administration are generally preferred by consumers.[132,136,137] A cross-sectional study of RACF residents living with dementia identified that polypharmacy (defined as five or more medications) was associated with lower self-reported health-related QOL.[178] However, a similar study in Australian RACFs did not find a link between staff-informant QOL and overall medication regimen complexity when measured using the MRCI.[179] This may be because the weighting of items in the MRCI do not reflect the impact they have on medication-taking experience for consumers. Since the MRCI originated for a

community-dwelling COPD cohort, it reflects the consumer experience better than the experience of someone administering medication to another person. However, the MRCI was developed by researchers and validated by an expert panel comprised of an adherence expert, pharmacy practice academic, research nurse, clinical pharmacist, and a home medication review consultant.[48] Patients, patient advocates, or nurses responsible for administering medications were not included. There may, as a result, be some gap in the weighting for what consumers find burdensome in every day use. For example, when investigating perceived medication burden among community-dwelling patients across six community pharmacies in England, while overall MRCI score showed a probable but non-significant association, dosing frequency was the only variable that significantly increased burden.[39] This may suggest that Part B (frequency) is underweighted.

In the SIMPLER study, medication regimen complexity was measured primarily through number of daily administration times.[114] There were no significant differences in staff-informant QOL between the residents who did and did not receive the simplification intervention, or before and after receiving the intervention.[114] This suggests that while simplification did not improve QOL by that measure, there was also no negative impact. It may also be that existing and validated QOL measures do not focus on medication-taking experience. The improvement in experience that simplification offers may not be large enough to be measured by the QOL scales. The use of a humanistic scale that specifically considers medication-related burden may be a more effective impact measure.[180] Additionally, it has been previously suggested that it takes a 10-point increase in the MRCI score to be clinically relevant.[181] It was not clear whether this clinical significance refers to QOL or other outcomes.

Simplification through decreasing the number of daily administration times may help to increase the efficiency of nursing time spent on medication administration rounds. However, Chapter Four did not investigate the minimum time required to safely administer medications. Dosing frequency often contributes the most to overall complexity. Chapter Four demonstrated that the medication administration round includes time spent per resident as well as time spent on the administration round itself (e.g. preparation of the medication trolley and travel). Consolidating daily

administration times may release time from the medication round that could be redirected to improving medication administration safety or resident-centred care. Medication regimen simplification was a concept that was identified as an important area for study by both aged care providers and researchers to improve staff and resident experience.[182]

7.1.3 Medication reviews to address medication regimen complexity

In a recent pilot study in Canberra, Australia, comprehensive medication review was identified as one of the most frequently performed activities of an embedded aged care pharmacist.[108] The systematic review conducted in Chapter Two identified one paper that included medication regimen complexity as an outcome of medication reviews.[117] It found that although 30% of pharmacists' recommendations reduced MRCI, RMMRs did not significantly reduce average MRCI scores, either after recommendations or after GP uptake of recommendations.[117] Simplification may be a lower priority in medication reviews, which have typically focused on medication-related problems such as drug interactions, dose optimisation, and monitoring, despite having practical benefits for residents and staff.[183]

There may be value in incorporating a measure of regimen complexity into the medication review process. However, the MRCI can be time-consuming to calculate. It contains 65-items across three sections that are summed to obtain the total score.[48] While the MRCI can and has been automated,[171] many clinicians and aged care nursing staff do not have easy access to these programs. Similar barriers have been encountered when Drug Burden Index has been proposed as a tool to guide medication review.[184,185] Where it has been automated and integrated into existing systems, MRCI at hospital admission has been suggested to predict complexity of care needed and so could be a tool used to assist resource allocation.[186] It is also possible that a lack of tools available to support simplification was a barrier.

In the SIMPLER RCT, MRS GRACE was applied as a stand-alone intervention delivered by a pharmacist in the SIMPLER cluster-RCT. The intervention reduced the mean number of daily administration times without any significant changes in harms.[114] The reduction in administration times was sustained over 12 months of follow-up.[187] This could be replicated in practice by having simplification as a stand-

alone intervention, conducted as one of a number of activities of an on-site residential aged care pharmacist, or potentially through telehealth. MRS GRACE could also be applied in as part of a multidisciplinary service conducted by pharmacists in collaboration with other health professionals such as nurses or nurse practitioners. This would complement existing medication review services (Figure 3). The accompanying explanatory statement for MRS GRACE prompts medication reconciliation and review before applying the tool to situate the simplification process into the established suite of activities.[164] Integration of automated MRCI calculation and the MRS GRACE into medication review software may help to prompt simplification. A similar electronic clinical decision support tool with automated alerts and care management information has been successful in home care patients.[62] Alternately, a count of overall number of administration times may also be used as a quick indicator of medication regimen complexity. This has the benefit of also being the domain of medication regimen complexity that consumers report as most burdensome.

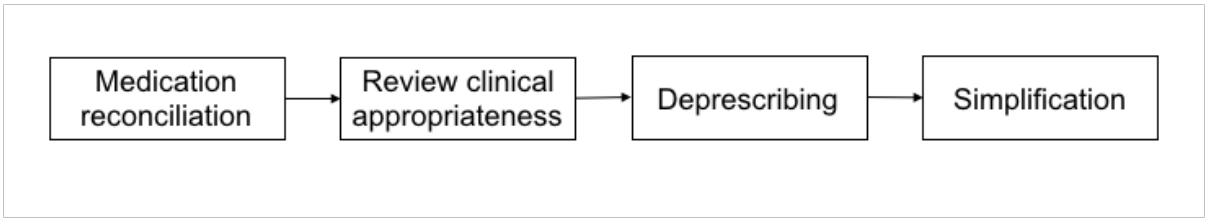

Figure 3: Flow of medication review services incorporating simplification

In Chapter Two, undertreatment was the most common MRP identified during RMMRs.[183] The systematic review also identified a study that investigated the impact of RMMRs on anticoagulant use in residents with atrial fibrillation.[156] The retrospective review of 146 residents used validated risk assessment scores and identified risk factors such as dementia, previous fall, renal failure and concomitant bleeding risk medication, to determine the appropriateness of anticoagulant prescribing. The results suggested that according to guidelines, anticoagulants were underutilised in residents of Australian RACFs.[156] This was consistent with literature on underuse of anticoagulants, although the studies either did not consider, or did not report consideration of residents' goals of care or whether the GP had discussed the benefits and risks with residents.[31,156,188] Overall, RMMRs did not result in

recommendations to start antithrombotic medication for any of the residents in whom it appeared to be indicated and did not have any contraindications for therapy.[156] The authors cited a lack of good quality clinical trial evidence for the use of antithrombotic medication in older people, medication regimen complexity, multimorbidity, and limited life expectancy as possible reasons for underutilisation and the lack of recommendations to initiate guideline-recommended therapy.[156] While this study investigated RMMR reports completed before the subsidisation and widespread use of DOACs in Australia,[156] a more recent study using RMMR data has also found underuse of anticoagulants.[31] That study suggested that physicians considered bleeding risk as the most important factor when prescribing anticoagulants, rather than stroke risk.[31] These safety concerns in older people, compounded by caution regarding medication regimen complexity and multimorbidity, may be unnecessarily leading to undertreatment. Results from Chapter Three suggest there is no association between bleeding risk and medication regimen complexity in people initiating oral anticoagulants, including in people aged 80 years or older. These results should be interpreted with caution in the RACF setting as this was a population-based study that may not be representative of a residential aged care population with increased frailty. However, the results may help prescribers and pharmacists performing comprehensive medication reviews avoid undertreatment by providing more evidence to consider when weighing the risks and benefits of anticoagulants for individual residents with complex medication regimens.

7.1.4 Medication regimen complexity is a multidisciplinary problem that needs an interdisciplinary intervention

The systematic review in Chapter Two found that increased collaboration between health professionals involved in resident care resulted in increased uptake of recommendations.[183] The RMMR program funded by the Australian Government is a collaborative, multidisciplinary process.[109] A pilot study identified that communication was an important role and benefit of an “aged care pharmacist” employed permanently and co-located in RACFs.[108] Almost 80% of the pharmacist’s activities were initiated at the request of the residents or their care team. Pharmaceutical opinion was the most frequently requested activity, in part due to the convenience of having the pharmacist on-site.[108] While communication occurs as part of most

activities, stand-alone communication accounted for 6.8% of total activity time.[108] Importantly, multidisciplinary stakeholder consultation was a key element of the development of MRS GRACE and its subsequent evaluation in the SIMPLER study.[159,164] This was particularly important because application of MRS GRACE was trialled as a part of a one-off intervention by a clinical pharmacist who was external to the aged care provider organisation and not necessarily known to the residents' usual nurses and GPs.[114]

Interdisciplinary care for older people is especially important because multiple chronic conditions may mean they receive care from multiple specialist physicians.[8] One-third of residents living in RACFs received specialist attendance; however, this represents reduced access compared to people using home support (74%), home care (65%), and those who did not use aged care services (58%).[189] Medications are commonly prescribed according to clinical practice guidelines, which are designed for individual medical conditions and rarely consider the impact of multimorbidity on treatment options and outcomes.[8,190] Adherence to multiple individual guidelines may lead to polypharmacy and more complex medication regimens.[8] Interdisciplinary care, where different disciplines work together rather than separately to consider the whole of the resident's needs, may help to improve medication management.[191]

Chapter Six found that Charlson's Comorbidity Index (CCI) did not correlate with number of daily administration times, and was significantly and negatively correlated with MRCI. Medication regimen complexity has been shown to be associated with certain medication conditions such as COPD, congestive heart failure, and diabetes, which may not reflect the same weighting as they receive in the CCI.[63] Some medical conditions may require treatment with medications that require frequent dosing due to pharmacodynamic and pharmacokinetic limitations (for example, Parkinson's disease, pain medication, or lubricant eye drops), or more complex routes of administration (for example, insulin for people with diabetes or inhalers for people with COPD).[48,138] There is also evidence that the efficacy of some drugs may be affected by the time of administration, however, more investigation is needed into the clinical value of time-specific administration in people with multimorbidity and complex medication regimens.[192]

A lack of interdisciplinary collaboration with nurses who administer medications to residents may also lead to increased medication regimen complexity if medications are not added to existing medication administration rounds. Additional medications may be added to existing medication administration rounds, which would not increase the number of daily administration times, but would increase the MRCI score. The results from Chapter Five suggest that there are many cases where number of daily administration times could be simplified and while the length of stay of the medication charts used was not collected, it is unlikely they all did not have regimen changes since admission. A lack of discussion with nursing staff who administer medications may arise from prescribers and pharmacists who pre-pack dose administration aids not being co-located on site. It may also be that some additional medications present unavoidable complexity, such as sedatives.

Recognising the importance of involving the entire care team, MRS GRACE was developed using a process that included collaboration with stakeholders from a range of backgrounds including those who would be involved in the RMMR process, to ensure the tool was multidisciplinary in nature.[164] While the tool was validated by clinical pharmacists, MRS GRACE was designed as an implicit tool to help clinicians simplify medication regimens that can be used by any health professional with knowledge of residents' preferences, pharmacological properties of medications, and the availability of different medication products and formulations. MRS GRACE does not discriminate medications or medical conditions.[164] Additionally, to encourage collaboration between members of the health care team, referral points are included in the accompanying explanatory document.[164]

7.1.5 The challenge of getting comprehensive data to inform care and enhance clinical outcomes

In a field where data are increasingly available, the use of pharmacoepidemiological approaches to investigate medication safety and health outcomes in real world scenarios has been invaluable for older people who are typically underrepresented in clinical trials. However, in Australia, the aged care setting remains "data rich but information poor".[193] Many aged care providers will collect information such as medication use and quality indicators, but these data from residents of RACFs in Australia are not currently routinely linked in population-based databases. This limits

the ability to investigate clinical outcomes of RMMRs and other interventions in RACFs with high quality, longitudinal data. For example, in Chapter Two, there was a clear gap in the literature on the clinical outcomes of comprehensive medication reviews. This is despite RMMRs being an Australian Government-funded service for over 20 years.[183] In contrast, Chapter Three presented the use of a population-based database to investigate the impact of medication use on clinical outcomes. Unfortunately, the population-based database did not easily distinguish people living in RACFs. Population-based databases do not usually include information for interventions such as RMMRs. The Registry of Older South Australians, launched in 2018, links data from health and aged care sectors and may present a unique opportunity to explore clinical outcomes of RMMRs for residents of RACFs.[194]

Chapter Two also found a gap in evidence for resident-centred outcomes. The experience of residents is arguably the most important outcome of any intervention. An important area for future development may be inclusion of resident and patient reported outcomes into large databases. Administrative data are primarily collected and coded for reimbursement purposes rather than evaluating resident experience. Adding subjective, resident or patient reported outcomes, such as a QoL or goal attainment scale, as part of routinely collected reimbursement data may help to centre the resident or patient in their care.[195] New aged care quality standards introduced in 2019 were developed using a consumer-centred approach.[78] The experience of residents was assessed by the Aged Care Quality and Safety Commission using a 10 question survey developed in consultation with residents to identify their priorities.[78,196] Responses were generally positive.[78] The areas of inquiry in this experience survey included feeling safe, enjoying the food, having someone to talk to, being treated with respect, and having healthcare needs met. These domains are often not addressed by studies of medication interventions in RACFs, which tend to use endpoints such a change to medications, hospitalisation or mortality.[183,197] Such outcomes are objective, generally easily measured and routinely collected in practice. In Chapter Two, the outcome investigated by most studies was the identification and resolution of medication-related problems. Safety is important while residents are receiving direct care; however, this must be delivered and handled in a way that also improves residents' experience and quality of life.

7.2 Strengths and limitations

Strengths and limitations of specific research studies have been discussed previously in Chapters Two to Six. This section will discuss the strengths and limitations of this thesis overall.

7.2.1 Strengths

This thesis used diverse methodology to investigate the aim and objectives, including methods that are not commonly used in RACF settings.

Chapter Two used a systematic review of both scientific and grey literature to evaluate comprehensive medication reviews in Australian RACFs. There was a lack of longitudinal studies and RCTs identified in the review. RCTs are considered the best quality evidence for determining the efficacy of health service interventions. Additionally, there was only one study out of 14 that was an RCT that included clinical or resident-centred outcomes. This thesis addressed some of these gaps. Chapter Three was a population-based cohort study using variable-rich data and validated outcomes. It involved an international sample of 19,292 older people to investigate a clinical outcome over time. Chapter Four used an observational time-and-motion study, a method commonly used in hospital settings. This involved collecting primary data in the residential aged care setting using a purpose-built data collection template in WOMBAT software. MRS GRACE was developed using nominal group technique and then validated by two independent clinical pharmacists. Nominal group technique combines qualitative and quantitative methodologies and is an increasingly popular method for generating group consensus.[198] MRS GRACE was also developed as an implicit rather than explicit tool that requires clinician judgement and expertise to apply. Part of this clinician judgement and expertise is assessing the residents' preferences. Chapter Six presented cross-sectional analyses of baseline data collected from a cluster RCT to investigate resident characteristics associated with complex medication regimens.

This thesis included research that was informed by, and included, a number of stakeholders in aged care. Consumers, carers, and aged care providers were part of the conception of medication regimen simplification as a possible useful service. A

multidisciplinary team was involved for all studies included in this thesis. This collaboration increases the relevance and likelihood of translation of the research to real-world scenarios that involve multidisciplinary teams. The value of this approach is evident through the anecdotal early interest in the MRS GRACE tool among researchers of different backgrounds and among aged care provider organisations in Australia and internationally.

7.2.2 Limitations

Organisational culture may be an important factor determining quality of care.[199] It is unclear how generalisable the findings in this thesis are across different aged care provider organisations. Although the research reported in Chapters Four and Six included multiple RACF sites, the RACFs were part of a single aged care provider organisation that invested in research and development, including in relation to improving medication management.

There could have been bias due to the selection of RACFs from the same provider, which has standard procedures and largely share the same pharmacy group providing medications. A recent report on residential care quality indicators from the Royal Commission into Aged Care Quality and Safety found differences in quality indicators between government-run, not-for-profit, and for-profit run RACFs.[200] Not-for-profit run RACFs had the highest number of emergency department presentations or hospitalisation for medication-related events per 100 residents per facility. It is unclear whether this reflected quality of care. The analyses relied on hospital coding and the overall rate of events coded as medication-related were low. The comparison was not adjusted for risk and may also reflect baseline differences in resident profile. Differences may also arise due to location given that in several states such as Victoria, government-run RACFs are predominately located in rural and regional areas whereas larger profit RACF are predominately located in metropolitan areas.

This thesis did not include person-level factors that influence complexity in the definition of medication regimen complexity. Characteristics such as socioeconomic status, health literacy, cultural and environmental factors may modulate an individual's ability to manage their medication regimen.[201] Research conducted in the

United States has suggested that people with lower health literacy dose their medications on more frequent occasions than people with higher health literacy when presented with the same set of dosing instructions.[202] These are all important considerations when assessing the appropriateness of medication changes.[53] The MRCI, which has become the gold standard measure of regimen complexity, does not include person-level factors.[38,48] A new algorithm for determining the complexity of medication regimens is being developed to include factors such as drug dosage form, product characteristics and packaging, dosage schemes, additional instructions, patient characteristics (sociodemographic characteristics, health-related conditions, experiences, attitudes towards disease/therapy), and process characteristics.[201] The ability to use this algorithm in the future will, however, be limited by data availability, as these parameters may not be routinely collected and/or included in large, population-based databases.

7.3 Implications for policy and clinical practice

The research presented in this thesis has had real and important implications for policy and clinical practice. Chapters Two, Four, Five, and Six were undertaken in the long-term aged care setting, which is and will continue to undergo changes in response to the changing needs of residents who are increasingly frail on admission. The research is also important in terms of the recommendations that will arise from the current Royal Commission into Aged Care Quality and Safety in Australia that was established in 2018.[203] Findings from this thesis have already been presented to the Royal Commission and have been cited in the Commissioner's Interim Report sub-titled *Neglect*.[85,193] All research publications contributing to this thesis also have clinical implications that are translatable to existing practice.

The Royal Commission terms of reference included the quality of aged care services, how best to deliver aged care services, and how to ensure that aged care services are person-centred.[203] Pharmacists were consulted in the Commission hearings and their evidence contributed to the Commission's interim report.[85] The systematic review in Chapter Two was included in evidence given by Dr Janet Sluggett on "Access to aged care and clinical care" to the Commission.[204] MRS GRACE and the SIMPLER study in Chapters Five and Six were included in the

NHMRC Cognitive Decline Partnership Centre's submission.[205] The Commission's final report is expected to be released in November 2020.[203]

It was announced in November 2019 that medication safety was to become the next National Health Priority Area.[206] Residential aged care was a setting identified as an important focus within this new Priority Area.[107] Research from Chapters Two, Five and Six were referenced in the Pharmaceutical Society of Australia's 'Medicines Safety: Aged Care' report, which was launched in the Australian Federal Parliament in February 2020.[107] The identification of this new national health priority area may mean increased funding and coordination in projects that translate and/or improve medication-related interventions for older people. Already, from April 2020, RMMR funding was increased to include remuneration for pharmacists to participate in up to two follow-up services with residents within nine months of the initial comprehensive review.[207] These follow-up services are remunerated at a rate of $56.33 for the first and $28.16 for the second follow-up service.[207] Research presented in Chapter Two discussed the lack of remunerated follow-up as a barrier to interprofessional collaboration and clinical decision-making.[183]

The third World Health Organization's Global Patient Safety Challenge – *Medication without harm* was launched in 2017.[24] Australia's response to the Challenge identified three flagship areas: polypharmacy, reducing harm from high-risk medications, including OACs, and improving medication safety at transitions of care. Chapter Three studied the safety of OACs in older people with complex medication regimens, who often also experience polypharmacy. Additionally, the data used included inpatient and outpatients and assessed safety of OACs in an initiation period up to 90 days, which potentially has implications for OAC safety during transitions of care.

A new quality indicator 'Percentage of residents with more than four regular administration times' was introduced in a pilot program of the existing quality indicator program in Victorian public RACFs.[208] This indicator is now being collected on quarterly on a voluntary basis across all public-sector RACFs in Victoria. A tool such as MRS GRACE (Chapter Five) can be used to address this quality indicator and improve resident and staff experience of medication taking. Main findings from the SIMPLER study have shown that the application of MRS GRACE by a clinical

pharmacist working with a multidisciplinary care team was successful in reducing the number of administration times.[114] Furthermore, there was a sustained reduction in number of administration times up to 12 months after study enrolment.[187] An ongoing trial is investigating the integration of on-site pharmacists in residential aged care.[197] Simplification could be a good value activity for pharmacists integrated into the residential aged care team.

Medication regimen simplification is within the scope of practice for pharmacists and GPs but may require some education to introduce the concept. Research from this thesis has contributed to a clinical manuscript for The Australian Journal of General Practice, a practical article aimed at GPs. Patterns of high prescribing to older adults are measurable as trends at a physician level, so addressing simplification resources to physicians is important.[209] Implementing simplification in the curriculum for pharmacy students is also showing promising results, with students being able to organise complex medications into simplified UMS dosing times.[210] Teaching simplification as a concept during undergraduate training may help students improve people's medication-taking experience through simplification in practice.

7.4 Future directions

Findings from this thesis have already been used for further research. MRS GRACE has been extended to community-dwelling older people through a pilot and feasibility study in which simplification activities were provided to older people receiving community-based care packages.[211] The simplification intervention was valued by stakeholders and some participants reported being "happy" with their simplified medication regimen.[160] There is large scope of impact in community-based home care as older people receive visits from nurses and care workers and the timing of the travel and/or visits may be made more efficient. Being able to self-manage a medication regimen is often a determinant of being able to continue to live independently at home. If a person needs support to administer their medications, consolidating dose administration times to coincide with a nurse or family member visit may allow people to remain living at home.

In this thesis, medication regimen complexity was measured at one point in time. A 12-month follow-up of the SIMPLER study demonstrated that a once-off

simplification intervention achieved sustainable decreases in daily administration times.[187] Longitudinal studies investigating trends in medication regimen complexity over time would further characterise the burden and may also be useful in prioritising interventions for older people. The use of more advanced statistical methods, such as accounting for a time-varying exposure in Chapter Three, may also increase the precision of estimates of the impact of complexity on clinical outcomes.

The MRCI treats complexity mainly as a dimension related to the medication regimen, largely independent to the patient, although some patient factors such as swallowing difficulties may be included through weighting for need to crush tablets. The adaptation of a 'patient-level' MRCI more accurately reflect medication regimen complexity in real world settings. However, 'patient-level' MRCI is still largely a medication-related measure. The Medication-Related Burden Quality of Life (MRB-QoL) scale V.1 has been developed to address the impact that medications may have on psychological, social, physical and financial well-being of individuals.[180] The MRB-QoL is a comprehensive tool that contains subscales in five domains: routine and regimen complexity, psychological burden, functional and role limitation, therapeutic relationship and social burden. Initial testing has found that it has good construct validity and internal consistency.[180] Further validation of this indicator to consider the patient-perspective on complexity, including patient factors such as health literacy or dexterity, would be important to understand how patients relate to complex medication regimens.

In Chapter Two, there were no studies that investigated to what extent residents' goals of care were considered in medication review. Future studies that include retrospective review of comprehensive medication review recommendations should investigate whether recommendations were made considering the resident's goals of care. For example, 'undertreatment' was a frequent recommendation but medications may be deprescribed intentionally while an indication is still present because the resident and their prescriber has assessed that the benefits no longer outweigh the risks (perhaps due to the length of treatment needed for evidence-based benefit). It was not reported if 'undertreatment' recommendations were made with goals of care in mind. Recommendation reports could be analysed for acknowledgement of goals of care.

Since the publication of this paper, there have been updates to the RMMR program that will require evaluation in future research. RMMRs can now be referred by specialists in pain medicine, specialist physicians, specialist psychiatrists and specialists in palliative medicine, in addition to GPs.[207] This could encourage interdisciplinary care. The lack of remuneration for follow-up care as a barrier for high-quality medication reviews has also been addressed by new funding for dedicated remuneration for up to two follow-up consultations within nine months after the initial comprehensive medication review was added to the RMMR program. These follow-up services are remunerated at a rate of $56.33 for the first and $28.16 for the second follow-up service.[207] However, remuneration for the initial RMMR, which can be a time-consuming process, involving travel, coordinating time to communicate with the resident, and writing a report of the recommendations, remains stable ($111.09 in 2019, when this paper was published, and $112.65 in 2020 at the time of thesis submission). Elliott et al. (1999) found that the time needed is highly variable (between 20 and 180 minutes per review), with more time needed for residents with complex medication regimens who are becoming increasingly prevalent in RACFs.[212] The opportunity for follow-up could increase the recommendation and implementation of activities that may be perceived as lower priority such as simplification.

Pharmacists are trained in the therapeutic and pharmacological properties of medications and are therefore well placed to apply MRS GRACE. However, the tool may be suitable for application by other health professional groups such as geriatricians, nurse-practitioners or registered nurses. A future direction is exploring models of collaboration between pharmacists and these other health professionals for the purpose of simplifying medication regimens. Ideally, MRS GRACE would be used at least with the involvement of residents to consider resident-related factors, which includes their individual preferences. Including nursing staff involved in the medication administration may also be valuable in understanding regulatory and safety imperatives or unintended consequences.

This thesis did not include any economic evaluation of the burden of medication regimen complexity. This is potentially an important area for further evaluation if the intervention is to be scaled-up and funded. A broad-ranging analysis including the

cost of the intervention and potential cost savings involved with decreased time and burden would provide good evidence for large scale implementation.

Findings from Chapter Three on the time taken to administer medications could be used in an economic analysis. However, it would be best to use the time necessary for safe medication administration and to communicate with residents appropriately. To study the time necessary to safely administer medications, future studies should include an assessment of medication errors, and/or an observer to also assess medication administration and communication with residents against pre-determined criteria for safe administration (for example, correct use of eye drops or inhalers). Additionally, extra time may be taken by residents refusing medication was a reason for some missing medication provision. However, the data collected in Chapter Three for when medications were prepared but not provided in the medication administration round are not complete with respect to reasons for each occasion. The reasons were noted separately to the WOMBAT tool. Anecdotally, there were few cases of nurses 'struggling' to administer medications. The time taken up by refusals and the relationship between complex medication regimens and refusals is an area for future research.

Improving health data infrastructure in Australia will increase the ability to investigate clinical outcomes in older people, which would allow robust evaluation of medication safety and medication-related interventions. The Registry of Older South Australians and introduction of electronic medical and medication record systems by aged care providers represent a great opportunity to address clinical questions for residents of RACFs.[194] These developments in Australia mirror the advances in the availability of administrative and electronic medical record data internationally. Additionally, the adoption of MyHealthRecord, an online summary of health information controlled by individuals, by the wider community may also represent rich sources of information that can be used to investigate gaps identified by this thesis.[213] MyHealthRecord especially will deliver more data than ever before into the hands of consumers and their health care team. This increased visibility may have unforeseen impacts on the way medications are managed and may impact medication regimen complexity if medication lists are being centralised and reviewed regularly through the electronic record.

8. Chapter Eight: Conclusion

Findings from this thesis have improved the understanding of the burden of medication regimen complexity for older people, including residents of RACFs, and created a novel tool to help address this burden. There is good evidence that collaborative medication reviews in Australian RACFs are successful in identifying and resolving medication-related problems, but there is currently no evidence that RMMRs reduce medication regimen complexity or optimise prescribing of anticoagulants. Good quality population-based data were used to find that having a complex medication regimen should not necessarily be a barrier to prescribing anticoagulants for older people with AF in community settings. However, use should be monitored carefully as regimen complexity is associated with increased bleeding risk over treatment periods longer than 90 days. In RACFs, medication administration with complex elements, such as dose modification, took longer for each resident in each medication round. Each medication round had preparation time in addition to resident administration. Consolidating administration times may allow medication round time to be more effectively used for other resident-centred care activities. To assist with medication regimen simplification, a new tool was developed and evaluated in a cluster RCT. MRS GRACE was developed with clinical and consumer input and validated by pharmacists. Analyses of the baseline data collected in the RCT showed overall number of administration times is an alternate measure of complexity that may be useful for RACFs and older people. Findings from this thesis have contributed to policy evaluations which can inform the expansion of clinical activities of health professionals such as pharmacists to include medication regimen simplification.

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APPENDICES

Appendix 1

The Medication Regimen Complexity Index (MRCI)

This appendix contains a reproduction of the Medication Regimen Complexity Index (MRCI) from George et al., *Ann Pharmacother*, 2004, including updates described in Chapter Six.

Instructions

1. MRCI applies only to prescribed medications. All entries are to be made only on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made on clinical judgement.
2. There are three sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marevan 5mg, 3mg and 1mg mdu), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. Ventolin MDI 1-2 puffs, 2-3 times daily will get weightings for ‘metered dose inhalers’, ‘variable dose’ and ‘twice daily’; but not for ‘multiple units at one time’).
5. In certain cases the dosing frequency needs to be calculated (e.g. Ranitidine 1mane and 1nocte is 1twice daily).
6. It is possible that with certain ‘use as directed’ instructions, the regimen will not get a score under dosing frequency (e.g. Prednisolone 5mg mdu).
7. If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. Ventolin MDI 2 puffs bd and prn, will get scores for ‘metered dose inhalers’, ‘multiple units at one time’, ‘twice daily’ as well as ‘prn’).
8. Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. Ventolin MDI or Ventolin nebuliser twice daily will get scores for both ‘metered dose inhalers’ and ‘nebuliser’ under dosage forms, but needs to be scored two times for ‘twice daily prn’).
9. In cases where there is no matching option, choose the closest option (e.g. six time daily could be considered as ‘q4h’).

Part A

Sum the weighting corresponding to each dosage form present in the regimen.

Dosage Forms		Weighting
Oral	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
	Wafers/oral-disintegrating tablets	2
Topical	Creams/Gels/Ointments/Lotions	2
	Dressings	3
	Paints/Solutions	2
	Pastes	2
	Patches	2
	Sprays	1
	Shampoos	2
Ear, eye & nose	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
Inhalation	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Soft mist inhalers	4
	Other DPIs	3
Others	Dialysate	5
	Enemas	2
	Prefilled injection	3
	Injection – ampoules/vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

Part B

Multiply the number of medications in the regimen corresponding to the dosing frequency in each category by the assigned weighting. In cases where there is no exact option, choose the closest option.

Dosing frequency	**Weighting**	**Weighting x no. of medications**
Once daily	1	
Once daily prn	0.5	
Twice daily	2	
Twice daily prn	1	
Three times daily	3	
Three times daily prn	1.5	
Four times daily	4	
Four times daily prn	2	
q 12h	2.5	
q 12h prn	1.5	
q 8h	3.5	
q 8h prn	2	
q 6h	4.5	
q 6h prn	2.5	
q 4h	6.5	
q 4h prn	3.5	
q 2h	12.5	
q 2h prn	6.5	
prn/sos	0.5	
On alternate days or less frequently	2	
Oxygen prn	1	
Oxygen <15hrs	2	
Oxygen >15hrs	3	
Total for Section B		

Part C

Multiply each corresponding additional direction present in the regimen by the assigned weighting

Additional directions	**Weighting**	**Weighting x no. of medications**
Break or crush tablet	1	
Dissolve tablet/powder	1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)	1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)	1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)	1	
Relation to food (e.g. pc, ac, with food)	1	
Take with specific fluid	1	
Take/use as directed	2	
Tapering/increasing dose	2	
Alternating dose (e.g. one mane & two nocte, one/two on alternate days)	2	
Total for Section C		

Appendix 2

Chapter Three: Ethics approval

This appendix contains the ethics approval letters for the cohort study presented in Chapter Three from the following committees:

- The University of Hong Kong/Hospital Authority Hong Kong West Cluster
- Monash University

香港大學
University of Hong Kong

醫院管理局
HOSPITAL AUTHORITY

香港大學及醫管局港島西醫院聯網研究倫理委員會

Institutional Review Board of the University of Hong Kong/
Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB)

Address: Rm 901, 9/F, Administration Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong Tel 2255 3923 2255 4086

Dr. Esther Chan

Pharmacology and Pharmacy

The University of Hong Kong

27-Nov-18

Dear Dr. Chan,

IRB Reference Number: **UW 13-468**

The HKU/HA HKW IRB is authorized by a joint agreement of the University of Hong Kong and Hospital Authority Hong Kong West Cluster to review and monitor clinical research. It serves to ensure that research complies with the Declaration of Helsinki and acts in accordance to ICH GCP guidelines, local regulations and Hospital Authority and the University policies.

In accordance with our standard operating procedures, we have duly performed ethics and scientific review of your application/submission. We hereby write to inform you that your application/ submission has been approved, on the above date, by an expedited process with details shown below.

Protocol title	:	Pharmacoepidemiology and pharmacoeconomics of anticoagulant and antiplatelet therapy for cardiovascular disease in Hong Kong
Study site(s)	:	Queen Mary Hospital
IRB reviewer	:	Dr. S L Lui, Deputy Chairman of the HKU/HA HKW IRB
Document(s) approved	:	01. Protocol Amendment Application Form dated 15 November 2018 (Addition of Co-Investigator - Ms. Esa Yan Horng CHEN)
	:	02. Study Protocol; Version V10 dated November 14, 2018
Document(s) reviewed	:	03. Short CV of Co-Investigator; signed and dated 20/11/18
Regular Progress Report(s) Required	:	Every 12 months from the date of initial approval and during the period of the study

You, being the principal investigator of the study at your study site, are reminded to comply with our requirements and to maintain communication with us during the period of the study by undertaking the principal investigator's responsibilities including (but not limited to):

- if the study is an industry-sponsored clinical study, submitting to us a copy of the fully executed indemnity agreement satisfying the Hospital Authority's requirement prior to commencement of the study (if it has not been submitted yet);
- observing and complying with all applicable requirements under our standard operating procedure ("HKU/HA HKW IRB SOP"), the Declaration of Helsinki and the ICH GCP (if applicable)
- submitting regular progress report(s) at the required intervals (as specified above) in accordance with the requirements in the IRB SOP;
- not implementing any amendment/change to any approved study document/material without our written approval, except where necessary to eliminate any immediate hazard to the subjects or if an amendment/change is only of an administrative or logistical nature;
- notifying us of any new information that may adversely affect the rights, safety or well-being of the subjects or the proper conduct of the study;
- reporting any deviation from the study protocol or compliance incident that has occurred during the study and may adversely affect the rights, safety or well-being of any subject in accordance with the requirements in the IRB SOP;
- submitting safety reports on all SAEs observed at your study site or SUSARs reported from outside your study site in accordance with the requirements in the IRB SOP; and
- submitting a final report in accordance with the requirements in the IRB SOP upon completion or termination of the study at your study site.

In addition to the above, you are also reminded to observe and comply with other applicable regulatory and management requirements including (but not limited to):

- if required by Hong Kong laws or regulations, obtaining a certificate for clinical trial through the Hong Kong Department of Health and complying with the associated requirements; and
- obtaining the necessary consent from the management of your institution/department in accordance with the requirements of your institution/department; and
- obtaining prior approval before commencing the study from the appropriate head(s) of the study site (e.g. Head / COS / Nurse Manager / Department Manager etc) with regards to the use of facilities and subject recruitment logistics/arrangement. It is advisable to print IRB's Reference Number on all recruitment materials for potential and actual study participants.
- **comply with the new reporting requirement of study results with effect from June 2015 as stated in the World Health Organization (WHO) Statement on Public Disclosure of Clinical Trial Results for any phases of clinical trials on: (1) the main findings within 12 months, or at most within 24 month, of study completion, and (2) the key outcomes within 12 months of study completion. These results must be posted in a free-to-access, public available, searchable clinical trial registry. The full text of the WHO Statement is available in http://www.who.int/ictrp/results/reporting/en/\.**

Yours sincerely,

Mr. Chris Yip
HKU/HA HKW IRB Secretary

MONASH University

Monash University Human Research Ethics Committee

Confirmation of Registration

Project Number: 17798
Project Title: Pharmacoepidemiology and pharmacoeconomics of anticoagulant and antiplatelet therapy for cardiovascular disease in Hong Kong
Chief Investigator: Dr Jenni Ilomaki
Registration Date: 31/01/2019
Expiry Date: 31/01/2024

Terms:

1. Registration is valid whilst you hold a position at Monash University, and approval at the primary HREC is current.
2. This notification does not constitute HREC approval. It is the responsibility of the Chief Investigator to ensure that approval from the primary HREC continues for the duration of the research.
3. End of project: You should notify MUHREC at the conclusion of the project or if the project is discontinued before the expected date of completion.
4. Retention and storage of data: The Chief Investigator is responsible for the storage and retention of the original data pertaining to this project in accordance with the *Australian Code for the Responsible Conduct of Research*.

Kind Regards

Professor Nip Thomson

Chair, MUHREC

CC: Professor Simon Bell, Dr Janet Sluggett, Ms Esa Chen

Appendix 3

Chapter Four: Ethics approval

This appendix contains the ethics approval letters for the time-and-motion study presented in Chapter Four.

MONASH University

Monash University Human Research Ethics Committee

Approval Certificate

This is to certify that the project below was considered by the Monash University Human Research Ethics Committee. The Committee was satisfied that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted approval.

Project Number: 11054
Project Title: A time-and-motion study of medication administration by nurses and care workers in residential aged care homes
Chief Investigator: Dr Janet Sluggett
Expiry Date: 30/01/2023

Terms of approval - failure to comply with the terms below is in breach of your approval and the *Australian Code for the Responsible Conduct of Research*.

1. The Chief Investigator is responsible for ensuring that permission letters are obtained, if relevant, before any data collection can occur at the specified organisation.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash letterhead and the Monash University complaints clause must include your project number.
6. Amendments to approved projects including changes to personnel must not commence without written approval from MHUREC.
7. Annual Report - continued approval of this project is dependent on the submission of an Annual Report.
8. Final Report - should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected completion date.
9. Monitoring - project may be subject to an audit or any other form of monitoring by MUHREC at any time.
10. Retention and storage of data - The Chief Investigator is responsible for the storage and retention of the original data pertaining to the project for a minimum period of five years.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

CC: Assoc Professor Simon Bell, Dr Jenni Ilomaki, Ms Esa Chen, Prof Sarah Hilmer, Ms Tessa Caporale, Ms Michelle Hogan, Ms Megan Corlis

List of approved documents:

Document Type	File Name	Date	Version
Questionnaires / Surveys	Questionnaire_170919	19/09/2017	170919
Consent Form	Consent form_180115	15/01/2018	180115
Explanatory Statement	Participant information_180116	16/01/2018	180116
Supporting Documentation	FRA_180105_Risk-Management-Research placements_SA	16/01/2018	180116

Appendix 4

Chapter Four: Participant information and consent form.

This appendix contains the following documents for the time-and-motion study presented in Chapter Four:

- Participant information sheet
- Participant consent form
- Participant demographic questionnaire

MONASH University

COGNITIVE DECLINE PARTNERSHIP CENTRE

INFORMATION SHEET FOR RESEARCH PARTICIPANTS

A TIME-AND-MOTION STUDY OF MEDICATION ADMINISTRATION IN RESIDENTIAL AGED CARE HOMES

Project number: 11054

Dr Janet Sluggett (Chief investigator)
Centre for Medicine Use and Safety
Monash University
Phone: 03 9903 9533
Email: janet.sluggett@monash.edu

Ms Michelle Hogan (Helping Hand contact)
Project Officer, Research and Development
Helping Hand Aged Care
Phone: 08 8224 7871
Email : mehogan@helpinghand.org.au

You may be invited to participate in a research project involving the observation of medication administration processes in residential aged care homes.

What does the research involve?
The primary purpose of this research project is to measure the average time it takes to administer medications in residential aged care homes.

There is currently little information about how long it takes to administer medications in aged care homes. Improving our understanding of the medication administration process will allow health care professionals and aged care providers to identify opportunities to optimise medication administration. The results of this study will be used as part of the assessment of the impact of the Simplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) study that aimed to simplify medication regimens by reducing the number of times that medications need to be given each day.

Participation in this project will involve a one-time collection of basic information about yourself, and being observed carrying out your normal duties during the medication administration round. The investigator will be using a tablet computer device to record the time observed to complete specific tasks relating to medication administration (e.g. crushing tablets, measuring liquids). You may occasionally be asked by the investigator to clarify details of a task, to verbally state which task you are performing, or to specify the dementia status of a resident.

It is anticipated that it will take 5-10 minutes of your time to fill out the consent form and the questionnaire in order to participate.

Why may you be chosen for this research?
You are receiving this information because you are involved in administering medications in Helping Hand Aged Care homes. You may be approached by a study investigator before commencing a medication administration round and asked if you would like to participate. The medication administration rounds chosen will been chosen to accommodate the investigators' availability. The purpose of this study is to measure the average time taken to administer medications, not to assess individual performance.

What are my rights?
Your participation is completely voluntary and you have the right to withdraw at any time. Whether or not you choose to participate will not have any consequence.

What are the possible risks?
Participating in this project does not pose any foreseeable risk for you. It is not anticipated that completing a questionnaire or being observed carrying out your normal role will cause you any harm or distress. You have the right to withdraw from further participation at any stage or to decline to answer specific questions without consequence.

What are the possible benefits?
There are no costs associated with participating in this project, nor will you be paid. You may not directly benefit from participating in this project. However, information obtained in this project may benefit others in the future by improving the way medications are used in residential aged care homes.

How will confidentiality, data access and security be arranged?
Your personal information will be kept strictly confidential and no identifiable data will be reported. Data recorded on the tablet computer will not be linked to individuals or contain identifiable details. All project data will be securely stored at the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University or on a secure website hosting platform for five years. A report of the study may be submitted for publication, but you will not be identifiable in such a report or in any published results. You may request a copy of this report by contacting the chief investigator.

Funding and conflicts of interest
This project is supported by the National Health and Medication Research Council (NHMRC) Cognitive Decline Partnership Centre (CDPC). The CDPC receives support from the NHMRC and Funding Partners including Helping Hand Aged Care, HammondCare, Brightwater Care Group and Alzheimer's Australia. Three of the study investigator team (Ms Megan Corlis, Ms Tessa Caporale, and Ms Michelle Hogan) are employees of Helping Hand, but do not work directly with employees who will be approached regarding participation in this research, nor will they be involved in obtaining consent from employees to participate in this study.

Approval for this project has been granted by the Monash University Human Research Ethics Committee and the Helping Hand ethical review panel. This research will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research.

If you have any ethical concerns about this project or questions about the rights of participants please contact:

Executive Officer, Monash University Human Research Ethics Committee (MUHREC)
Room 111, Building 3e, Research Office
Monash University VIC 3800
Tel: (03) 9905 2052 Fax: (03) 9905 3831
E-mail: muhrec@monash.edu

Thank you,

Dr Janet Sluggett (Chief investigator)

MONASH University

COGNITIVE DECLINE PARTNERSHIP CENTRE

CONSENT FORM FOR RESEARCH PARTICIPANTS

A TIME-AND-MOTION STUDY OF MEDICATION ADMINISTRATION IN RESIDENTIAL AGED CARE FACILITIES

Project number: 11054

Chief investigator: Dr Janet Sluggett
Centre for Medicine Use and Safety, Monash University
381 Royal Parade
PARKVILLE VIC 3052
Email: janet.sluggett@monash.edu

I have been invited to participate in the research project stated above, involving the observation medication administration processes in residential aged care homes.

I agree to the following:	Yes	No
I have read and understood the participant information	☐	☐
I understand that participating in this project involves providing basic demographic information	☐	☐
I understand that participating in this project involves being observed during my normal work shift carrying out my normal duties	☐	☐
I understand that I can refuse to answer any questions and can withdraw consent to participate at any time without consequence	☐	☐
I understand that my personal information will be kept confidential and that the data collected will not be linked to me individually	☐	☐
I consent to participate in this project	☐	☐

Participant name (please print) _____

Participant Signature _____ Date _____

MONASH University

COGNITIVE DECLINE PARTNERSHIP CENTRE

DEMOGRAPHIC QUESTIONNAIRE FOR RESEARCH PARTICIPANTS

A TIME-AND-MOTION STUDY OF MEDICATION ADMINISTRATION IN RESIDENTIAL AGED CARE FACILITIES

Project number: 11054

AGE	
SEX	
CURRENT ROLE	
AVERAGE NUMBER OF HOURS WORKED PER FORTNIGHT	
HIGHEST EDUCATIONAL QUALIFICATION	
YEARS OF EXPERIENCE IN AGED CARE	
YEARS OF EXPERIENCE ADMINISTERING MEDICATION	
YEARS OF EXPERIENCE IN CURRENT ROLE	

Appendix 5

Chapter Five: Ethics approval

This appendix contains the ethics approval letters for the nominal group technique presented in Chapter Five.

MONASH University

Monash University Human Research Ethics Committee

Approval Certificate

This is to certify that the project below was considered by the Monash University Human Research Ethics Committee. The Committee was satisfied that the proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research* and has granted approval.

Project Number:	0731
Project Title:	Development and validation of a medication regimen simplification guide
Chief Investigator:	Dr Janet Sluggett
Expiry Date:	03/10/2021

Terms of approval - failure to comply with the terms below is in breach of your approval and the *Australian Code for the Responsible Conduct of Research*.

1. The Chief Investigator is responsible for ensuring that permission letters are obtained, if relevant, before any data can occur at the specified organisation.
2. Approval is only valid whilst your hold a position at Monash University.
3. It is responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash letterhead and the Monash University complaints clause must include your project number.
6. Amendments to approved projects including changes to personnel must not commence without written approval from MHUREC.
7. Annual Report - continued approval of this project is dependent on the submission of an Annual Report.
8. Final Report - should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected completion date.
9. Monitoring - project may be subject to an audit or any other form of monitoring by MUHREC at any time.
10. Retention and storage of data - The Chief Investigator is responsible fo the storage and retention of the original data pertaining to the project for a minimum period of five years.

Thank you for your assistance.

Professor Nip Thomson

Chair, MUHREC

Appendix 6

Chapter Five: Participant information and consent form

This appendix contains the following documents for the nominal group technique presented in Chapter Five:

- Participant information sheet
- Participant consent form

MONASH University

COGNITIVE DECLINE PARTNERSHIP CENTRE

INFORMATION SHEET FOR RESEARCH PARTICIPANTS

DEVELOPMENT AND VALIDATION OF A MEDICATION REGIMEN SIMPLIFICATION GUIDE

You have been invited to participate in a research project as a member of an expert panel to advise on the development of a novel guide for simplifying medication regimens.

Purpose of this research project

The primary purpose of this research project is to develop and pilot test a structured process to simply medication administration for residents of aged care facilities.

Your rights

Whether or not you choose to participate will not have any adverse consequence. Your participation is completely voluntary and you have the right to withdraw at any time. Your personal information will be kept strictly confidential. All project data will be securely stored at the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University for five years. A report of the study may be submitted for publication, but you will not be identified in such a report or in any published results unless you give consent to be named in the acknowledgements section. You may request a copy of this report by contacting the chief investigator.

Description of project

Participation in this project will involve being a part of an expert panel to develop, pilot test, and perform an initial face-validity check of a draft of the guide for medication regimen simplification. There are currently no routinely implemented structured approaches specifically designed to simplify medication regimens in residential aged care facilities. The development of a systematic and structured approach will allow health care professionals to identify opportunities to simplify medication regimens during routine care. The guide will be used in the intervention arm of a cluster randomised controlled trial investigating the impact of a structured process to simply medication administration for residents of aged care facilities

It is anticipated that the expert panel will meet once for approximately four hours at Helping Hand Aged Care offices in North Adelaide. Your identity will be known by other members of the expert panel, but the panel discussion will not be audio or video recorded, and no identifiable data will be collected.

Your safety

Participating in this project does not pose any foreseeable risk for you. It is not anticipated that completing an interview or participating in a focus group will cause you any distress. You have

the right to withdraw from further participation at any stage or to decline to answer specific questions without consequence.

Possible benefits

You may not directly benefit from participating in this project. However, information obtained in this project may benefit others in the future by improving the way medications are used in residential aged care settings.

This research will be conducted according to the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research.

This project has been approved by the Monash University Human Research Ethics Committee (project number 0731).

Funding and conflicts of interest

This project is supported by the NHMRC's Cognitive Decline Partnership Centre. Dr Sluggett, the chief investigator, is a pharmacist accredited to provide medication reviews to residents of aged care facilities. She does not have a direct financial interest in this research.

If you have any ethical concerns about this project or questions about the rights of participants please contact:

Executive Officer
Monash University Human Research Ethics Committee (MUHREC)
Room 111, Building 3e
Research Office
Monash University VIC 3800
Tel: (03) 9905 2052
Fax: (03) 9905 3831
E-mail: muhrec@monash.edu

If you have any questions about the project you can contact the chief investigator:

Dr Janet Sluggett
Centre for Medicine Use and Safety
Monash University
381 Royal Parade
PARKVILLE VIC 3052
Email: janet.sluggett@monash.edu

MONASH University

COGNITIVE DECLINE PARTNERSHIP CENTRE

CONSENT FORM FOR RESEARCH PARTICIPANTS

DEVELOPMENT AND VALIDATION OF A MEDICATION REGIMEN SIMPLIFICATION GUIDE

Chief investigator: Dr Janet Sluggett
Centre for Medicine Use and Safety
Monash University
381 Royal Parade
PARKVILLE VIC 3052
Email: janet.sluggett@monash.edu

I have been invited to participate in the research project stated above, involving the convening of an expert panel to develop a novel guide for simplifying medication regimens.

I have read and understood the participant information and I hereby consent to participate in this project.

I consent to the following:	Yes	No
Participating in an expert panel to develop, pilot test, and performing an initial face-validity check of a guide for medication regimen simplification	☐	☐
Having my name included in an acknowledgements section of any reports produced and/or published as a result of this study	☐	☐

Participant name (please print) _____

Participant Signature _____ Date _____