BMJ Open Multicentre stepped-wedge cluster randomised controlled trial of an antimicrobial stewardship programme in residential aged care: protocol for the START trial

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ABSTRACT

Introduction Antimicrobial resistance is a growing global health threat, driven by increasing inappropriate use of antimicrobials. High prevalence of unnecessary use of antimicrobials in residential aged care facilities (RACFs) has driven demand for the development and implementation of antimicrobial stewardship (AMS) programmes. The Stepped-wedge Trial to increase antibiotic Appropriateness in Residential aged care facilities and model Transmission of antimicrobial resistance (START) will implement and evaluate the impact of a nurse-led AMS programme on antimicrobial use in 12 RACFs.

Methods and analysis The START trial will implement and evaluate a nurse-led AMS programme via a stepped-wedge cluster randomised controlled design in 12 RACFs over 16 months. The AMS programme will incorporate education, aged care-specific treatment guidelines, documentation forms, and audit and feedback strategies that will target aged care staff, general practitioners, pharmacists, and residents and their families. The intervention will primarily focus on urinary tract infections, lower respiratory tract infections, and skin and soft tissue infections. RACFs will transition from control to intervention phases in random order, two at a time, every 2 months, with a 2-month transition, wash-in period. The primary outcome is the cumulative proportion of residents within each facility prescribed an antibiotic during each month and total days of antibiotic use per 1000 occupied bed days. Secondary outcomes include the number of courses of systemic antimicrobial therapy, antimicrobial appropriateness, antimicrobial resistant organisms, Clostridiodes difficile infection, change in antimicrobial susceptibility profiles, hospitalisations and all-cause mortality. Analyses will be conducted according to the intention-to-treat principle.

Ethics and dissemination Ethics approval has been granted by the Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/591). Research findings will be disseminated through peer-reviewed publications, conferences and summarised reports provided to participating RACFs.

Strengths and limitations of this study

► A multifaceted antimicrobial stewardship (AMS) programme will be implemented across 12 metropolitan and regional residential aged care facilities (RACFs).
► The stepped-wedge randomised controlled design enables the robust evaluation of the intervention while ensuring all residents are eligible to receive its potential benefits.
► Data will be collected monthly for each resident and supplemented with longitudinal biospecimen sampling over 16 months.
► Staff may be employed at more than one trial site and become exposed to the intervention earlier than the scheduled timeframe.
► Substantial engagement with aged care staff and consumers will facilitate delivery of a tailored AMS programme suitable for broader implementation across the RACF network.

Trial registration number NCT03941509.

INTRODUCTION

Antimicrobial resistance has been identified as a global public health emergency, linked to increasing unnecessary use of antimicrobials. Residential aged care is a unique and challenging setting with high infection burden,1 high prevalence of inappropriate antimicrobial use2 and antimicrobial resistance3 in an increasingly frail population with complex care needs.4

The prevalence of antibiotic use over a 12-month period has been reported in up to 45%–79% of residents in the USA (1991–2009),2 Canada (1994–2004),2 UK (2016–2017)6 and in up to 70% of residents in Australian residential aged care facilities.
Up to 70% of antimicrobials are prescribed for infections that do not meet established criteria for appropriateness. High levels of inappropriate prescribing increases the likelihood of colonisation with multidrug-resistant organisms found in up to 50% of residents, with the potential for transmission across healthcare settings without adequate infection control.

Antimicrobial stewardship (AMS) programmes are well-established in hospitals internationally, contributing to reductions in antimicrobial usage and resistance, duration of hospitalisation and drug expenditure. Although there is a need for the integration of AMS programmes in RACFs, few established programmes exist. In 2019, the Australian Government Aged Care Quality and Safety Commission introduced new quality standards requiring all RACFs to incorporate AMS in their care and quality improvement frameworks. Individual RACFs are responsible for the development of their own policies and processes to support appropriate antimicrobial use and infection control. Successful implementation of AMS programmes is particularly challenging in RACFs and is limited by several barriers, including workload, staffing levels and composition, on-site availability of pharmacists and the complexity of diagnosing infections in older people with cognitive impairment. AMS interventions have primarily targeted nursing staff and medical practitioners in RACFs through increased education and promotion of clinical practice guidelines. Nursing staff are consistent members of an RACF workforce and hold an important role in influencing antimicrobial prescribing decisions, including the initial assessment of infection and referral. This provides an opportunity for nurse-led interventions to drive improvements in appropriate antimicrobial use.

Aged care-specific guidance is available to support the development and implementation of AMS in RACFs. Recommendations have included education, guidelines and improving documentation to reduce unnecessary investigations and antimicrobial prescribing for common infections, including urinary tract infections (UTIs), lower respiratory tract infections (LRTIs), and skin and soft tissue infections (SSTIs). Guidelines have primarily targeted aged care staff and incorporated minimum criteria for antibiotic initiation to assist in the initial assessment of signs and symptoms for suspected infections. However, the acceptability, feasibility and effectiveness of these tools in reducing inappropriate antimicrobial prescribing in RACFs remains unclear.

Several systematic reviews have identified multifaceted AMS interventions in RACFs, frequently incorporating education, guidelines, and audit and feedback. To date, six randomised controlled trials (RCTs) have been performed in the USA and/or Canada, the UK and Sweden. Although five studies reported significant reductions in antimicrobial use or inappropriate antimicrobial prescribing, the heterogeneity of intervention components and outcomes limits their comparability to determine successful components of an AMS programme. No RCTs evaluating the effectiveness of a multifaceted AMS programme in Australian RACFs have been published.

The Stepped-wedge Trial to increase antibiotic Appropriateness in Residential aged care facilities and model Transmission of antimicrobial resistance (START) will implement and evaluate the impact of a multifaceted nurse-led AMS programme on antimicrobial use in Australian RACFs.

**METHODS AND ANALYSIS**

**Trial design and setting**

The START trial is a multicentre stepped-wedge cluster RCT (SW-cRCT) that will see the implementation of a nurse-led AMS programme across 12 RACFs in Victoria, Australia. As part of the participatory action cycle for complex interventions, the intervention bundle will be piloted and evaluated for feasibility and acceptability over a 3-month period in two Victorian RACFs. Consumers will review resources targeting residents and families prior to commencement. Qualitative feedback from relevant stakeholders, including aged care staff, residents and their families, at its conclusion will inform tailoring of the intervention prior to the implementation of the SW-cRCT. Aged care staff in this protocol refers to registered nurses (RNs), enrolled nurses (ENs) and personal care attendants (PCAs)/assistants in nursing (AInNs).

The SW-cRCT will be performed over 16 months (figure 1). Each cluster (two RACFs) will transition through three phases at 2-month intervals: control; transition; and intervention. All RACFs will commence the trial in the control phase where usual care will continue to be provided. The transition phase will involve education of staff, residents and family members, and integration of the intervention. The intervention phase will see the implementation of the AMS programme.

The START trial is registered with ClinicalTrials.gov. This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2013 guidelines (online supplementary file 1) and will be conducted in accordance with the
Consolidated Standards of Reporting Trials extension for SW-cRCT. 40

Randomisation and recruitment
Twelve RACFs with a minimum of 50 residents will be selected from a large, private network of RACFs in Victoria, Australia. This includes 10 metropolitan and 2 regional RACFs comprising an average of 100 residents per facility. Facilities will be randomised to different starting times for the intervention phase (see figure 1 for timings of steps) prior to commencement using a computer-generated random sequence performed by an independent statistician. Staff and residents at the RACFs will be blinded to their allocation sequence until they are made aware of their time to transition from the control phase by the study coordinator.

Data will be collected from all residents’ medical and medication records over the length of the trial. This includes permanent residents and residents receiving short-term or respite care admitted to the RACF at any point during the trial. Residents will also be invited to participate in the biospecimen sampling component.

Intervention bundle
The bundled nurse-led AMS programme incorporates education, guidelines, documentation forms, and audit and feedback to support appropriate antimicrobial use in RACFs (table 1). The intervention will target three common infections in RACFs: UTIs, LRTIs and SSTIs.

Education will comprise 1-hour face-to-face presentations with case studies, an equivalent online resource and summary fact sheets. Topics will include inappropriate antimicrobial use, antimicrobial resistance, AMS and strategies to improve appropriate antimicrobial use in RACFs. Face-to-face education will be provided to all aged care staff. A web-based resource with equivalent content will be available for staff unable to attend. General practitioners (GPs) and pharmacists will be provided with the online resource and summary fact sheets specific to their role in AMS. Residents and families will be engaged via monthly meetings and/or discussion forums and provided with fact sheets. Education will be delivered by the study coordinator who is a research pharmacist.

Guidelines for the three targeted infections will include flowcharts of signs and symptoms required to meet minimum criteria for initiation of antibiotics, and recommendations for antimicrobial management. Signs and symptoms will be adapted from aged care-specific guidance from existing guidelines, including minimum criteria for initiation of antibiotics by Loeb et al, 26 McGeers criteria for infection surveillance 10 and the Australian Therapeutic Guidelines. 41 Hard copy and electronic guidelines will be available for all aged care staff, GPs and pharmacists to support consistent decision-making.

Assessment criteria and antimicrobial management plans will be documented by aged care staff and GPs, respectively, on hard copy or equivalent electronic documentation forms in the residents’ medical record to aid the communication of treatment decisions. Antimicrobial management plans will include the indication, dose, frequency, route and duration of therapy. The assessment criteria are primarily targeted towards aged care staff to assist in initial assessment of infections prior to GP referral.

<table>
<thead>
<tr>
<th>Table 1 START intervention bundle components</th>
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<tbody>
<tr>
<td><strong>Component</strong></td>
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<tr>
<td>Education</td>
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<tr>
<td>Audit and feedback</td>
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</table>

*Hard copy forms will be adapted for integration into electronic medical records where necessary.

AMR, antimicrobial resistance; AMS, antimicrobial stewardship; GP, general practitioner; LRTIs, lower respiratory tract infections; SSTIs, skin and soft tissue infections; START, Stepped-wedge Trial to increase antibiotic Appropriateness in Residential aged care facilities and model Transmission of antimicrobial resistance; UTI, urinary tract infections.
and antimicrobial prescribing. The management guidelines are targeted towards both aged care staff and GPs to encourage timely review of antimicrobial prescribing and improve overall knowledge of current antimicrobial recommendations.

Audit and feedback is a common and effective strategy to drive quality improvement and change prescribing behaviour. Prescribing data collected by the research team will be analysed and provided to GPs and aged care staff on a monthly basis. This summarised data will include monthly antimicrobial prescription rates and their appropriateness against the intervention criteria. This feedback will serve to benchmark prescribing at individual RACFs against all participating trial sites to drive continued improvements in appropriate prescribing.

**Trial procedure**

Usual care will be provided to residents during the control phase. Standard care provided by pharmacists, including medication reviews, will continue over the trial. Although a formal AMS programme will not be available for staff during the control phase, a small proportion of staff may be exposed to the intervention at other participating or non-participating RACFs. An assessment of aged care staffing, GPs and pharmacists who provide care at trial sites will be performed prior to trial initiation to identify the proportion of staff crossover.

During the transition phase, the research team will liaise with each RACF to coordinate education and delivery of the intervention bundle over 2 months. Attendance of aged care staff at education sessions will be designated as mandatory by the aged care provider to increase awareness and understanding of intervention procedures. Staff unable to attend will be followed up with additional face-to-face education and/or referred to the online resource.

All aged care staff, GPs and pharmacists will have access to the intervention resources via a password-protected trial website during the transition and intervention phases. Guidelines and documentation forms will be placed in high-visibility areas across nursing stations in RACFs to increase accessibility and encourage uptake. Ongoing education will be provided during the intervention phase at regular intervals, depending on staff turnover and need. The intervention procedure will be incorporated in each facility’s standard operating procedures.

Aged care staff who care for residents with suspected UTIs, LRTIs and/or SSTIs will be directed to perform antimicrobial management plans in each facility’s standard operating procedures.

Qualitative and quantitative feedback will be obtained from management staff at each facility on commencement of the trial, including occupancy, presence of specialist dementia care units, permanent and casual staffing (RN, EN, PCA/AIN, GP and pharmacy) and infectious diseases education and practices.

All data will be entered directly into a secure web-based data entry system. Each resident will be assigned a unique study identity document (ID) to remain unidentifiable outside the facility. Random audits and statistical monitoring of data (5%–10% random sample) will be conducted by the research team throughout the trial to assess the accuracy and completeness of data. As the trial involves standard care and the collection of non-invasive biospecimen collection, adverse events are not anticipated.

Qualitative and quantitative feedback will be obtained from relevant stakeholders, including aged care staff, GPs, pharmacists, and residents and their families, to inform revisions to the intervention bundle following the pilot and trial. Semistructured one-on-one interviews and focus groups,
performed by an external qualitative researcher, and an online questionnaire will be used to explore participants’ awareness, acceptability and impact of the intervention.

### Biospecimen sampling

Residents, or their guardians, who have verbally consented to participate in biospecimen sampling will have nasal, rectal and/or a wound specimen taken monthly over a 12-month period in each RACF. Consent and collection will be performed by trained research nurses. Wound samples will only be obtained in the case of an active infection treated with an antimicrobial. Residents at each facility will be sampled a minimum of 2 months prior and

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**Open access**

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### Table 2 Schedule of enrolment and assessments over the 16-month trial

<table>
<thead>
<tr>
<th>Time point (months)</th>
<th>Study period</th>
<th>Facility</th>
<th>Resident</th>
<th>Resident follow-up (month)</th>
<th>Close-out</th>
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<tbody>
<tr>
<td>Enrolment</td>
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<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16</td>
<td>16 months</td>
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**Interventions**

AMS programme*

Control (usual care)

**Assessments**

**Facility assessment**

Facility characteristics (occupancy and speciality units)

Staffing (nursing, medical and pharmacy)

Infectious disease education and practices

**Baseline resident assessment†**

Demographic and clinical characteristics

Prior antimicrobial use

Prior hospitalisations

Advance care directives

**Monthly resident assessment**

Clinical characteristics

Suspected infections‡

Diagnoses

Investigations§

Microbiology

AMR organisms

Antimicrobial susceptibility

Systemic antimicrobial use

Administration (dose, route and duration)

Indication

Appropriateness¶

Hospitalisation

Transfer to another facility, home or death

Biospecimen collection**

Nasal, rectal and wound specimen

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*Excluding the transition (‘wash-out’) phase.
†Baseline resident characteristics will be performed for all new residents over the 16-month trial.
‡Suspected infections include urinary tract infections, respiratory tract infections, skin and soft tissue infections, and *Clostridioides difficile* infections.
§Investigations include radiology, urinalysis and urine, sputum, nasal/throat, rectal/faecal, wound and blood cultures.
¶Appropriateness is assessed according to minimum signs and symptoms for initiation of antimicrobials as specified in the intervention bundle, and antimicrobial recommendations as per the Australian Therapeutic Guidelines.
**Specific timing to be determined.
AMR, antimicrobial resistant; AMS, antimicrobial stewardship.
post transition. Specimens will be cultured in a microbiology laboratory to identify antimicrobial-resistant organisms. Changes to facility-level susceptibility profiles will be examined over the duration of the trial by the START research team and feedback provided back to RACFs. A detailed procedure manual for biospecimen sampling will be developed and published separately.

Outcome measures

Primary outcomes

Two approaches were selected to provide different perspectives to the assessment of our primary outcome of antibiotic use. These include the cumulative proportion of residents within each facility prescribed an antibiotic at any point during each calendar month of the trial and the rate of total days of systemic antibiotic use per 1000 occupied bed days (OBD). The number of days of therapy per 1000 OBD is a widely used and recommended measure of antibiotic use in residential aged care.7 19 44

All systemic antibiotics will be included according to the second level of the WHO Anatomical Therapeutic Chemical (ATC) classification system for antibacterials (J01).45 Antibiotics will be included irrespective of documented indication, including those outside of the targeted UTIs, LRTIs and SSTIs.

Secondary outcomes

Secondary outcomes include the number of courses of systemic antimicrobial therapy per 1000 OBD, proportion of appropriate antimicrobial use, frequency of carriage of multidrug-resistant organisms, rate of Clostridioides difficile infection, change in facility-level antimicrobial susceptibility profiles, incidence of resident transfers to hospital due to infection and all-cause mortality.

All systemic antimicrobials will be included according to the second level of the WHO ATC classification system for antibacterials (J01).45 Antibiotics will be included irrespective of documented indication, including those outside of the targeted UTIs, LRTI and SSTIs.

Process evaluation

A mixed-methods approach will be undertaken to assess implementation fidelity, sustainability, and procedures and processes associated with the programme implementation. This will be examined through data collected on adherence to components of the intervention bundle, the quality and complexity of delivery of the intervention, and qualitative feedback from aged care staff, GPs, pharmacists, residents and their families. Qualitative feedback will be provided via anonymous online questionnaires, moderated focus groups and/or one-on-one interviews. These qualitative and quantitative methods will be used to measure implementation fidelity by evaluating use and compliance with intervention education, guidelines and documentation forms (eg, completion of education and documentation, and minimum criteria met for prescribing), and resulting changes in antimicrobial use and appropriateness.

Sample size

Sample size calculations were performed in accordance with the approach described by Hemming and Taljaard46 and the use of summative, facility-month level data. Estimated means and SD were obtained from published and unpublished literature examining antimicrobial prescribing in Australian RACFs.1 47 48 This includes unpublished data from a SW-cRCT in 15 RACFs between 2011 and 2015 which identified that approximately 21% of residents received an antibiotic each month (estimated SD of 8%).46 Assuming a between-facility correlation of 0.01, to achieve greater than 80% power at a 5% significance level, 12 RACFs across 6 clusters are required to demonstrate a relative reduction in the proportion of residents receiving an antibiotic of 24% (21%–16% post-intervention). This effect size is consistent with studies of smaller interventions that demonstrated greater than 20% reductions in antimicrobial use.49 50

Although sufficient data is not available to inform a sample size calculation based on the rate of resident-days on antimicrobials, power is expected to be greater as this endpoint as it also incorporates reductions in concurrent antibiotic courses and duration of therapy.

Statistical analysis

Primary outcomes will be analysed using summative facility-month level data as an intention-to-treat analysis. A generalised linear mixed-effects model will be performed to assess whether exposure to the intervention has no impact on antibiotic use (proportion or rate per 1000 OBDs) within each calendar month. This model will include a random effect for RACF, and a categorical, fixed effect for each month to account for secular trends. Model assumptions will be examined to ensure appropriate distributional families and covariance matrices for the random effects are employed. Data from the wash-in, transition period will be excluded from these analyses as we do not consider the data captured within this period to be clearly control or clearly intervention phase data.

Secondary outcomes will be analysed with an analogous approach. The impact of the intervention on primary and secondary outcomes will also be examined for variation by ‘time from implementation’ to identify delayed behaviour change or dissipation in impact over time. Qualitative feedback will be analysed using the Capability, Opportunity, Motivation and Behaviour (COM-B)/Behaviour Change Wheel31 and Acceptability52 frameworks.

Patient and public involvement

The research question was informed by national research priorities to address antimicrobial resistance in RACFs. The trial protocol was designed in collaboration with research partners and their associated consumer representatives. Feedback from relevant stakeholders, including healthcare workers, aged care residents and their families, will inform...
revisions to all components of the intervention bundle following the pilot phase and SW-cRCT. Specific intervention bundle components targeting residents and families will be reviewed by consumer representatives prior to the pilot. A lay summary of findings will be disseminated to aged care staff, residents and their families, and relevant consumer groups at the conclusion of the trial.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the Alfred Hospital Human Research Ethics Committee (HREC) (HREC/18/Alfred/591). Consent to obtain data from residents’ medication charts and records was waived. Verbal informed consent is required from residents, or a person authorised by law to consent on their behalf, for biospecimen sampling. Written informed consent from staff and residents and their families will be sought to participate in focus groups and interviews (online supplemental file 2). Residents will be given a unique study ID and deidentified data will be securely stored on web-based data entry systems.

Research findings from the START trial will be submitted for publication in a peer-reviewed journal and presented at relevant conferences. Participating RACFs will be provided with a report of summarised research findings, including a lay summary for distribution to residents and families.

DISCUSSION

Increasing attention has been directed towards the role of RACFs in the transmission of antimicrobial resistance across the healthcare system. Despite several aged-care specific treatment guidelines and education-centred interventions targeting inappropriate prescribing, minimal studies have performed high quality clinical trials to examine their effectiveness in clinical practice.

The START trial will evaluate the impact of a nurse-led AMS programme on antimicrobial use in RACFs. The stepped-wedge design ensures residents are not excluded from the potential benefits of this intervention while maintaining the robust nature of a RCT. Substantial engagement with key stakeholders over the length of the trial will ensure the development of a tailored programme that may be rapidly translated across a broad network of RACFs nationally.

Staff may be employed at more than one trial site and become exposed to the intervention earlier than the scheduled timeframe. Although it is anticipated that this number will be small, an assessment of staff crossover between trial sites will be performed prior to commencement to better understand this potential risk of bias.

The pilot commenced in August 2019 with the START trial due to commence in late 2020/early 2021. Amendments to the protocol due to increasing infection control precautions during the COVID-19 pandemic may be required and will be subject to approval from the Alfred HREC. This may include considerations to the mode of delivery of education and collection of data by research staff.

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REFERENCES


