PROJECT PROTOCOL

Evaluating the impact of a new model of care designed to improve evidence-based management of community-acquired pneumonia.

Short title: IMPROVing Evidence-based treatment Gaps and outcomes in community Acquired Pneumonia (IMPROVE-GAP).

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Statement of compliance
This document is a protocol for a research project.
This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval and the NHMRC Statement on Ethical Conduct in Human Research.
This protocol reflects the recommendations from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement
Trial sponsor: The HCF Research Foundation
Intended Trial Registry: www.clinicaltrials.gov
BACKGROUND AND RATIONALE

Each year community acquired pneumonia (CAP) causes 61,000 hospital admissions (2006/7 data) and incurs costs of more than AUD300 million in Australia. At our institution, there are over 1000 admissions under General Internal Medicine (GIM) Units with per year with a diagnosis of CAP (2014/15 data). These patients have an average hospital length of stay (LOS) of 5 days and incur average clinical costs of AUD6,724 per admission (2012/13 data). Prolonged LOS not only has significant implications for organizational costs but is also strongly associated with adverse patient outcomes including loss of function due to de-conditioning and higher incidence of hospital-acquired adverse events such as hospital-acquired infections, intravascular-device associated complications and antibiotic-related side effects. Reducing LOS therefore benefits both the patient and the health system. General Internal Medical (GIM) services manage the largest proportion of CAP patients at Western Health, with 47% of CAP admissions managed by GIM in 2012/13 (average age 75 with proportions with at least 1, 2 or 3 active co-morbidities 70%, 43% and 27% respectively). With population ageing, the elderly and highly multi-morbid population treated by GIM units will constitute the bulk of Australia’s future health service burden for CAP.

A number of interventions for improving clinical outcomes in CAP are now supported by recently accrued level 1 evidence. Following a Cochrane review in 2011 that suggested adjunct corticosteroids accelerate time to clinical stability, a number of large well designed studies published in high profile journals have since demonstrated favorable outcomes. Most notable are two landmark large randomized controlled trials (RCT); a study of the effect of corticosteroid on reducing treatment failure in severe CAP published in JAMA, and a study published in the Lancet in 2015 that demonstrated faster clinical recovery and shorter LOS (by 1 day) without an increase in complications associated with CAP (ie, acute respiratory distress syndrome, empyema, respiratory failure with intubation, persistence of pneumonia, and mortality associated with community-acquired pneumonia). There was a slightly higher risk of hyperglycaemia associated with steroid use in this population, though this can be effectively treated with insulin and no long-term effects of hyperglycaemia were observed. No other adverse events were shown to be an increased risk in patients receiving corticosteroids for the treatment of CAP. Subsequent meta-analyses (2000 patients from 14 RCTs) confirmed these findings, as well as demonstrating a statistically significant reduction in severe complications (need for vasopressors or mechanical ventilation) for CAP in patients routinely prescribed corticosteroids. Routine adjunctive corticosteroid is now widely supported though as yet not
consistently deployed.\textsuperscript{11,12} The most widely cited international guidelines for the treatment of CAP are those of the Infectious Diseases Society of America, published in 2007, which are based on evidence that has been superseded by these more recent studies. Current evidence clearly demonstrates that benefits outweigh risks in appropriately selected patients.

Early mobilization safely and effectively reduces LOS when applied appropriately\textsuperscript{14} as does early switch to oral antibiotics guided by a set of well-defined basic clinical and laboratory criteria.\textsuperscript{15} Recently, a RCT incorporating both measures demonstrated a LOS reduction of 2 days compared to standard care.\textsuperscript{16} A meta-analysis of nutritional support in malnourished medical inpatients (a patient cohort that includes those admitted with CAP) showed that systematic screening for risk of malnutrition and targeted nutritional therapy intervention reduces non-elective readmission rates.\textsuperscript{17}

No existing study has assessed bundling all four established interventions (corticosteroid, early switch to oral antibiotics, early mobilization and systematic screening for malnutrition with targeted nutritional therapy). However, adherence to consensus guidelines for CAP is notoriously poor\textsuperscript{18} suggesting the major challenge will be in bridging the “evidence-practice gap” and particularly changing clinician behavior. Generalist clinicians are becoming increasingly overwhelmed by a plethora of guidelines for multiple illnesses that may co-exist in the same patient. Currently at Western Health, 43% of CAP patients receive corticosteroids, 63% physiotherapy (median time to initiation 2 days) and 65% a guideline-compliant antibiotic. No parenteral antibiotic stopping rules are in place (median 3 days). There is a current compliance rate of 72% for malnutrition risk screening in inpatients across the health service. We believe therefore, that in order to address this gap between evidence and practice, an alternative service model is necessary to ensure best practice specifically for this leading contributor to health service burden.

We propose evaluating a stand-alone over-arching “syndrome-based” clinical service for CAP analogous to those already applied in other areas (e.g. “stroke-services” credited with substantial improvements in outcomes from acute cerebrovascular disease).\textsuperscript{19} Our proposed “CAP Service” would have core responsibility for ensuring comprehensive and rigorous current evidence-based best practice by application of a standardized set of management algorithms incorporating interventions supported by Level 1 evidence.

Service evaluation will take the form of a stepped-wedge study design, a type of cluster RCT that is particularly well-suited to implementation and health services research.\textsuperscript{20}
Importantly, we have already successfully implemented this design in health services research at Western Health.\textsuperscript{21} The primary research question is to quantify the impact of a dedicated CAP Service delivering consistent and standardized evidence-based care on length of stay, health service costs, 30- and 90-day readmission rates, and mortality.

**AIMS**

To evaluate the efficacy and cost-effectiveness of an evidence-based optimized care delivery model (the CAP Service) on:
- Raw unadjusted length of acute hospital stay;
- Total individual per-separation clinical costing (currently performed routinely by Western Health’s dedicated clinical costing unit using the Power Performance Manager™ software platform);
- 30- and 90-day readmission rates and;
- Mortality.

**METHODS**

*Study overview, design and setting*

This evaluation will quantify the impact of the optimized model of care that will be rolled out throughout the organization in a controlled, phased manner that is consistent with a stepped-wedge cluster randomized design.\textsuperscript{20,24} It will be conducted at two hospital campuses (Footscray Hospital and Sunshine Hospital) of a single health service (Western Health, Melbourne).

In stepped wedge cluster designs, outcomes are compared between intervention and non-intervention clusters using now well-developed statistical techniques to control for sources of internal bias and confounding.\textsuperscript{25} This has significant logistic, financial and ethical advantages over conventional cluster- and individual-RCT approaches.\textsuperscript{20,21,23,24} Importantly, members of our team (Investigators ES, MS and TH) have world-leading expertise in the design and analysis of studies undertaken in this way and these have led to high profile publication.\textsuperscript{24}

By study conclusion, all clusters are receiving the intervention, meaning it has effectively already been implemented across the whole service and can then be
continued indefinitely if it proves effective. This approach allows a seamless transition to local implementation and has been estimated to reduce the “time to clinical translation” by as much as 17 years when compared with conventional approaches.\footnote{26}

Western Health has 4 GIM units at each campus (Footscray and Sunshine) meaning a total of 8 units that would constitute the 8 separate clusters used in the stepped-wedge design. After a 10-week period of baseline data collection (during which all 8 units receive conventional care), the CAP Service intervention would be rolled out throughout the 8 GIM units, with two units each assigned (by pre-determined randomization schedule) to commence the intervention at either 11, 21, 31 or 41 weeks. All 8 GIM units would therefore receive the intervention for the final 10 weeks of the study (see Figure 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Stepped-wedge roll out of CAP Service by Medical Unit}
\end{figure}

\textbf{Eligibility criteria}

\textit{Inclusion criteria}
All adult patients (aged \(\geq 18\)) admitted to Western Health GIM units will be eligible to participate. Only participants who meet a standardised CAP case definition\footnote{27} will be enrolled. The conventional case-definition as used in recent studies of CAP\textsuperscript{11,28} is as follows:

1) New infiltrate on chest X-ray and:
2) The presence of at least one of the following acute respiratory signs and symptoms:
   a. Cough

\begin{table}
\centering
\begin{tabular}{cccccccc}
\hline
\textbf{Time block} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
\hline
\textbf{Medical Unit} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
\hline
1 & Usual care & Usual care & Usual care & Usual care & Usual care & Usual care & Usual care & Usual care \\
2 & Usual care & Usual care & Usual care & Usual care & Intervention & Intervention & Intervention & Intervention \\
3 & Usual care & Usual care & Usual care & Usual care & Intervention & Intervention & Intervention & Intervention \\
4 & Usual care & Usual care & Usual care & Usual care & Intervention & Intervention & Intervention & Intervention \\
5 & Usual care & Usual care & Usual care & Usual care & Intervention & Intervention & Intervention & Intervention \\
\hline
\end{tabular}
\caption{Stepped-wedge roll out of CAP Service by Medical Unit}
\end{table}
b. Sputum production
c. Dyspnoea
d. Core body temperature ≥38.0°C
e. Auscultatory findings of abnormal breathing sounds or rales
f. Leucocyte count > 10,000/μl or <4000/μl.

Importantly, because all of these features will have been documented either in the patient’s medical record or in the hospital results system during routine admission procedures, eligibility will be able to be determined in real-time on the morning following admission, without any need to intrude on the patient themselves.

Exclusion criteria
Subjects for whom a decision is made to implement palliative care on admission will be excluded. Those who have already been recruited to and enrolled in another research trial will also be excluded. Otherwise, there will be no exclusion criteria for main study participation. This will ensure that all patients with CAP have data collected so that a comprehensive and representative assessment of health service performance can be made in both control and intervention arms. However, for those in the intervention arm, the interventional algorithm (see Figure 2) will make it clear that some patients may not receive some of the specified interventions. Patients with specific contraindications to corticosteroid therapy or early mobilization will not receive them (see interventions section and treatment algorithm, below). In addition, the algorithm specifies that in patients for whom a decision has been made to palliate later in their admission, that none of the interventions are likely to be beneficial and that ongoing treatment should be at the discretion of the treating medical unit. This approach ensures the CAP Service intervention is generalizable to the entire CAP hospital population. Additionally, this strategy facilitates direct transition to health service implementation following completion of the research trial.
Interventions

The intervention is the optimized evidence-based care model (the CAP Service) a multidisciplinary physiotherapist-led team (with medical and dietetics input) that will conduct daily rounds of all patients assigned the intervention. For the duration of the research trial, it is planned that the service will operate 7-days per week.

The CAP Service will apply a set of protocols (using a custom-designed decision support algorithm) to ensure rigorous application of interventions each with proven efficacy as outlined below.
**Intervention 1**

Routine prescription of 50mg daily of prednisolone within 36-hours of presentation to ED, for 7 days (following checklist exclusion of those with contraindications as follows)\textsuperscript{11,12}:

- active intravenous drug use;
- acute burn injury, gastrointestinal bleeding in the past 3 months;
- known adrenal insufficiency;
- pregnancy or breastfeeding;
- a condition requiring >0.5mg/kg prednisolone per day and
- severe immunosuppression defined as one of the following: infection with human immunodeficiency virus and a CD4 cell count below 350 cells per μL, immunosuppressive therapy after solid organ transplantation, neutropenia below 500 cells per μL or neutrophils of 500–1000 cells per μL during ongoing chemotherapy with an expected decrease to values below 500 cells per μL, cystic fibrosis, or active tuberculosis.\textsuperscript{11}

Known diabetics will be monitored for hyperglycaemia (see monitoring and adverse events below) and appropriate management implemented at the discretion of the treating team in accordance with WH procedures and practices already routinely applied.

Any variation from the above dose and duration, such as use of tapered dosage, and time from admission until first dose will also be recorded. Alternative medical reasons given for non-prescription of corticosteroid, or reduced duration of administration, will be noted.

**Intervention 2**

Guideline-consistent antibiotic prescription and constrained parenteral antibiotic duration (using pre-defined “stopping rules”).\textsuperscript{15,16}

Current antibiotic prescribing practice on the GIM unit is according to an in-house guideline that is in turn based on the Australian Antibiotic guidelines.\textsuperscript{29} Patients are stratified as having either “mild”, “moderate” or “severe” disease according to standardised pneumonia severity criteria. We use the CORB score which we have found to be the scoring system that is both simplest to use, and has the highest predictive value for poor outcomes.\textsuperscript{8} Based on this score most inpatients receive either intravenous penicillin and doxycycline, or roxithromycin (for those with mild or
moderate disease), or ceftriaxone and azithromycin (for those with severe disease). This guideline would continue to be applied to determine initial antibiotic therapy in both the usual and best-practice groups.

Patients will be switched from IV to oral therapy according to the following criteria for clinical improvement assessed on a daily basis by the CAP Service team using a standardized check-list\textsuperscript{16}:

- ability to maintain oral intake;
- stable vital signs (temperature $\leq$ 37.8 degrees Celsius; respiratory rate $\leq$ 24 breaths/min; systolic BP $\geq$ 90 mm Hg without vasopressor support for at least 8 hours); and
- absence of septic metastases/major exacerbated co-morbidities (e.g. heart failure, chronic obstructive pulmonary disease).

Any reason for alternative antibiotic selection (such as allergy or advice from an Infectious Diseases Consultant) will be noted. Protocol compliance will be measured by adherence to IV antibiotic stopping rules, where the switch to oral therapy is made within 24-hours of the patient meeting the above criteria for clinical improvement.

**Intervention 3**

Physiotherapy-led early (<24h) and progressive mobilization, following checklist exclusion of those with contraindications as follows (formulated from literature and WH vital signs protocols):\textsuperscript{30}

- Systolic blood pressure $>180$ or $<90$, OR $\leq 10$ mm Hg than normal systolic or diastolic pressure in patients with renal disease
- HR $<50$ or $>110$ bpm +/- new arrhythmia
- vasopressor support
- RR $>25$ breaths per minute
- $\text{FiO}_2 >0.6$ with $\text{PaO}_2 <70$ mm Hg OR $\text{SpO}_2 <90\%$ ($<88\%$ for patients with respiratory disease where a modification is documented on the observation chart); PEEP $>8$ cm H$_2$O (for intubated patients);
- acute clinical deterioration since last mobilization session
- patient drowsy and unable to follow commands
- recent fall not yet assessed by medical staff
- new onset chest pain.

In the event of any of the following patient observations, the patient will be directed to take a seated rest. If observations recover to within normal limits within 2-minutes the patient may continue with their mobilization session. If the patient does not recover
within 2-minutes, physiotherapy will cease for that day, the patient’s nurse will be notified of observations recorded outside normal range and asked to monitor the patient, and these will be documented in the patient’s medical record.

- Systolic blood pressure >180 or <90, OR ≤10mm Hg than normal systolic or diastolic pressure in patients with renal disease
- decrease in SpO2 >10% or SpO2 <85% during mobilization
- RR > 25
- HR <50 or >110 bpm
- Patient becomes breathless and unable to speak in sentences.

In the event any of the following occur during mobilisation an urgent medical review, MET call or Code Blue will be activated in accordance with Western Health procedures:

- New onset chest pain or patient becomes pale and sweaty, drowsy or has a change in conscious state,
- Sustained (after >5 minutes rest):
  - Systolic BP >180 or <90 OR ≤10mm Hg than normal systolic or diastolic pressure in patients with renal disease, or
  - HR <50 or >140, or
  - SpO2 <90% (<88% for patients with respiratory disease where a modification is documented on the observation chart) despite appropriately titrated O2 therapy, or
  - RR >25.
- Patient has a fall with associated injury.

Early mobilization will be defined as movement out of bed with change from horizontal to upright position for at least 20 minutes during the first 24 hours of hospitalization (a minimum score of 2 on the ICU Mobility Scale31), and progressive movement each subsequent day14. Patient movement either upright in bed or to the commode for toileting alone is insufficient14 and the patient mobilization intervention will be progressed daily by the treating physiotherapist, with the aim of achieving the patient’s pre-morbid mobility level as soon as possible. “Progressive movement” is defined as achieving a higher score on the ICU Mobility Scale when compared to the preceding day, or an increase in the total distance mobilized during the session. Premorbid mobility will be categorized according to the ICU Mobility Scale31.
Specialised daily physiotherapy intervention by the CAP Service physiotherapists will continue until the patient meets the CAP IV antibiotic stopping rules (above), and then cease when one of the following physiotherapy stopping rules is achieved:

1. Patient achieves self-reported pre-morbid functional status and exercise tolerance. In this case the patient will be encouraged to continue a general functional maintenance program with an Allied Health Assistant\textsuperscript{32} if their admission on the acute medical ward is to be prolonged for some reason.
2. Patient is transferred to the sub-acute setting (or waitlisted). If ongoing physiotherapy is indicated, this will be provided in accordance with usual practice in the sub-acute setting (and waitlist).
3. Patient is discharged home.
4. Patient refuses to participate in CAP Service physiotherapy for three consecutive days. In these cases, ongoing physiotherapy input and discharge planning will be referred back to the unit physiotherapist assigned to that GIM unit, and patient treatment will be prioritised in accordance with usual care.

Intervention 3 protocol adherence will be met if:

1. Pt SOOB >20 minutes during a physiotherapy session in first 24 hours of admission to a GIM unit, and
2. On >70% of admission days where CAP Service physiotherapy review is not contraindicated, progressive movement is achieved (increase in ICU mobility scale score or increase in total distance mobilised).

**Intervention 4**

Standardized malnutrition screening, using the Malnutrition Screening Tool (MST)\textsuperscript{33} and measurement of patient body weight (in kilograms) will be completed for all patients admitted into the intervention group. The score obtained with this tool will be used to guide implementation of appropriate nutritional therapy as follows\textsuperscript{34}:

- 0-1: Nil nutrition therapy intervention indicated,
- 2-3: Initiation of a high energy high protein (HEHP) diet by nursing staff,
- 4-5: Referral to the WH Dietetics Service for urgent review and implementation of an individually tailored malnutrition intervention. The Dietetics Service will review patients within 24-hours of referral.

Protocol compliance for Intervention 4 will be measured by completion of MST-score within 24-hours of admission to a GIM unit, and implementation of appropriate nutrition therapy in response to MST score (none, high-energy-high-protein diet, or dietician referral and review within 24-hours).
Usual care
During the non-interventional control periods (as determined by the stepped-wedge roll-out schedule) CAP patients will receive usual care as currently practiced by the treating GIM multi-disciplinary team.

See also the detailed outline and description of the two study groups as per the Template for Intervention Description and Replication (TIDieR) criteria in Table 1.35

Intervention roll-out

Following a 10-week baseline data collection phase, 2 GIM units will be randomized to roll into the intervention every 10-weeks for a total study duration of 50 weeks (as per Figure 1 above).

Study endpoints

The primary outcome will be hospital length of stay (LOS) calculated from arrival in the emergency department until discharge from the health service. Western Health already routinely collects this data for all inpatients.

Secondary outcomes will include:
1. Total individual per-separation clinical costing as determined by Western Health’s dedicated clinical costing unit using the Power Performance Manager™ software platform. Western Health already routinely collects this data in all inpatients.
2. 30-day and 90-day readmission rates. Western Health already routinely collects this data.
3. Inpatient, 30- and 90-day mortality. Western Health already routinely collects this data in all inpatients.
4. Process and organizational outcome measures: Protocol adherence will be measured by the proportion of evidence-based treatment recommendations that are delivered in each group and the proportion of patients that received the whole bundle. Reasons for failure to adhere to protocol will be documented.
5. Adverse events: Rates of hyperglycaemia requiring insulin, falls or clinical deterioration during mobilisation. This information is already routinely collected and documented in the patient medical record.
6. Admission to the ICU from the inpatient wards and duration of mechanical ventilation (if applicable).

**Ascertainment**

Ascertainment will be conducted in a prospective manner in order to identify eligible participants in “real time” and so that identical methods of ascertainment are employed for both usual and CAP Service groups. To do this, a CAP Service team-member will attend each GIM morning handover meeting to review the list of admissions over the previous 24 hours in order to identify potential participants noted by the admitting team as having possible respiratory infection. Either the Chief Medical Register (CIs Bali and Ko) or treating Medical Registrar will then review the medical record and chest X-ray of all potential participants in order to assess eligibility (according to inclusion and exclusion criteria, above). As all information for inclusion and exclusion criteria is routinely collected, the patient will not need to be approached directly to assess eligibility. Those meeting the standardised CAP case definition and eligibility criteria will be enrolled. This will apply in both models of care (i.e. 1. usual care and 2. best-practice CAP Service). In situations where the CXR or CAP diagnosis are not definitive, the treating Medical Consultant will determine eligibility.

**Enrolment and waiver of consent**

As with our previous stepped wedge implementation studies, we will seek HREC approval for waiver of consent as our intervention represents the implementation of an optimized care model (in this case systematic implementation of standardized evidence-based practice, rather than the introduction of an unproven novel treatment) and our study outcome measures are already routinely collected by the health service. It is therefore intended that all patients presenting to Sunshine and Footscray Hospitals during the study period who meet the inclusion criteria will be enrolled in the study.

**Allocation**

As previously described (See Figure 1), Western Health has 4 GIM units at each campus (Footscray and Sunshine) meaning a total of 8 units that would constitute the 8 separate clusters used in the step wedge. Patients will be assigned to usual care or
CAP Service intervention. After a period of baseline data collection (during which all 8 units receive conventional care), the CAP Service intervention would be rolled out throughout the 8 GIM units, with two units each assigned (by pre-determined randomization schedule) to commence the intervention at either 11, 21, 31, or 41 weeks. All 8 GIM units would therefore receive the intervention for the final 10 weeks of the study (Weeks 41-50).

Patients will not be recruited into the study for two weeks (19 December 2016-2 January 2017), though interventions for those already admitted will continue as per the randomization schedule. This is to allow for bed closures and staff absence over the Christmas holiday period. As a result, the study will be completed over a 52-week period to account for the 2-week shutdown.

The random allocation sequence will be generated by a statistician not involved with the study, using Stata version 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

**Blinding**

Outcomes (length of stay, clinical costing, readmission and mortality) are defined routinely within the organization by staff who have no role in this project and who would be unaware of which arm participants in this study would have been allocated to. Therefore, there is little or no potential for bias in outcome assessments.

A statistician who is blinded to the allocation sequence, will carry out the data analysis and interpretation of the results.

It will not possible to blind clinicians providing patient interventions, although participants will be effectively blinded if the waiver of consent is granted.

**Withdrawal from trial**

Participants will be withdrawn if they are transferred to a non-GIM treating unit (eg. Specialist Respiratory, Cardiology, Surgical) or another health service within 48-hours of admission, or are no longer considered to meet the CAP case definition on consultant review. All withdrawals and reasons will be reported.
**Sample size**

Following a 10-week baseline data collection phase, 2 GIM units will be randomized to roll into the intervention every 10 weeks for a total study duration of 50 weeks. Using a stepped wedge cluster randomised trial with the 8 discharge units, over 5 time periods/steps (i.e. baseline + 4 intervention steps), a sample size of 80 patients per GIM unit (640 patients total) will be sufficient to detect a clinically important decrease in the proportion of patients with a length of stay greater than the median length of stay from 36% to 20%, assuming an intra-cluster correlation of 0.01, with 75% power and a 5% significance level. This will also be sufficient to estimate absolute and relative reductions in mean LOS between the intervention and control periods.

Using 2014/15 admission data, the Western Health Performance Unit calculated the total number of annual separations with an ICD-10 diagnosis code of Pneumonia (J12-J18, excluding J35) admitted to a GIM unit at either Footscray or Sunshine Hospital to be 1008 patients. It is therefore expected that there will be an adequate number of admissions during the 50-week period to satisfy the sample size requirements, allowing for an exclusion rate of 20%.

**DATA COLLECTION METHODS AND DATA MANAGEMENT**

All data will be captured in the patient medical file, and stored electronically on Bossnet, and the hospital admission information systems (iPM and EDIS). Data from the medical file will extracted by study investigators throughout admission and after the patient is discharged from hospital. iPM and EDIS data will be extracted by the Western Health Performance Unit after the patient has been discharged. Study data will be collected and managed using REDCap electronic data capture tools hosted at The University of Melbourne. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Relevant case report forms have been included in the submission. Any paper forms generated will be stored in a locked cabinet in a locked office, and electronic data will be stored in a password-protected file, accessible only to investigators. Only investigators will be able to access data.

A summary of the information to be collected during the study is listed below.
At enrolment (review of medical record):

- All eligibility criteria (age, chest X-ray findings, cough, dyspnoea, temperature, chest auscultation findings, sputum leucocyte count)
- Vital signs on admission (temp, heart rate, blood pressure, respiratory rate)
- eGFR
- Residential care status (home vs low-level vs high level supported care)
- Pre-morbid mobility, function and exercise tolerance
- CORB score (derived from confusion, oxygenation, respiratory rate and blood pressure)
- Any relevant comorbidities (eg. Diabetes, immunosuppression, adrenal insufficiency, COAD, CCF, malignant process)
- Initial antibiotic prescribed (<24 hour).
- MST score, body weight and nutrition intervention initiated
- Number of routine medications used by the patient, including baseline corticosteroid dose (if any), baseline insulin usage and relevant drug allergies,
- Enrolment in a concurrent inpatient research trial,
- Any decision to initiate palliative care on admission.

Throughout admission for patients in the CAP Service arm (during each daily CAP Service review):

- Any adverse events relating to the CAP Service interventions (see monitoring below)
- Daily vital signs (SpO2 and supplementary O2 requirements, heart rate, respiratory rate, blood pressure, temperature, blood sugar readings (for diabetic patients) and oral intake status).
- Weekly body weight
- Any decision to palliate
- Compliance with protocol for Intervention 1 (corticosteroid) including any applicable contraindications
- Compliance with protocol for Intervention 2 (antibiotic) including drug and route, and adherence to IV antibiotic stopping rules.
- Compliance with protocol for Intervention 3 (early mobilization) including adherence to <24-hour mobilization, physiotherapy outcomes measures and adherence to stopping rules for CAP Service physiotherapy
- Compliance with protocol for Intervention 4 (malnutrition management) including completion of MST and implementation of appropriate nutrition therapy.
- Blood glucose readings as clinically indicated and requested by the treating team.
- Admission to the Intensive Care Unit and duration of mechanical ventilation.
At discharge (review of medical record):
- Chest X-ray as reported by radiologist
- Other diagnostic test results (respiratory PCR, legionella urinary antigen, sputum culture, blood culture, serology)

At 3 months following discharge the following data will be extracted directly from the Western Health data warehouse and linked to the study dataset by unique identifier (admission episode number):
- Age
- Sex
- Marital status
- Language status
- Primary ICD-10 discharge code and allocated DRG
- ICD-10 co-morbidity groupings used in the Charlson’s co-morbidity index (derived using an existing algorithm that interrogates ICD-10 coding data).
- Total length of stay (broken down to emergency department, inpatient ward, rehabilitation/sub-acute care and hospital in the home)
- ICU length of stay
- Clinical costing
- Readmission within 30 and 90 days.
- Date of death (if applicable).
Table 1. Study outcome measures – routinely collected data

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Pre-morbid status</th>
<th>At admission</th>
<th>Throughout admission</th>
<th>At discharge</th>
<th>90-days post-discharge</th>
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<tbody>
<tr>
<td>ICU Mobility Score</td>
<td>X (CAPS)</td>
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<td>X (CAPS)</td>
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<td>MST</td>
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<td>Body weight</td>
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<td>Compliance with intervention protocols</td>
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<td>X (CAPS)</td>
<td>X (UC)</td>
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<td>Adverse events</td>
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<td>X (CAPS)</td>
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<td>Demographic data</td>
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<td>Readmissions</td>
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<td>Mortality</td>
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</table>

CAPS – CAP Service group       UC – Usual care group

CI Skinner will randomly audit data collection of one patient per each ten recruited to ensure data quality and data entry will be randomly checked and cleaned by an investigator, either CI Skinner or supervised by CI Skinner.

Once the complete database has been compiled from all relevant data sources, the information will be de-identified and retained in a Databank in accordance with procedures outlined in the Western Health “Data Management in Research” Guideline document. Ownership of the databank will remain with WH under the custodianship of Professor Janus. The databank, called the “IMPROVe-GAP Databank” will be entered onto the Departmental Register of Databanks for General Internal Medicine, and registered with the WH Office for Research.
STATISTICAL ANALYSES

Participants included in the final analysis will be those that meet the CAP case definition.

Randomization is used to reduce bias and balance community covariates at baseline. In a stepped wedge design clusters contribute different amounts of time to the intervention and control periods, making traditional measures of covariate balance between intervention arms difficult to use.\textsuperscript{38} In this study, we used a method to assess covariate balance by calculating a weighted average of each baseline characteristic for control and intervention periods; cluster\textsuperscript{14} characteristics were weighted by the amount of person-time they contributed to control and intervention periods (i.e., a cluster that crossed over in Step 2 contributed baseline covariates to two control periods (Steps 0–1) and three intervention periods (Steps 2–4)).\textsuperscript{39}

Demographic and clinical characteristics of participants in the study will be described with means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

Primary and secondary analyses will be by intention to treat using a multi-level, mixed effects generalised linear model. The effect of the intervention and time period will be considered as fixed effects while the effect of treating GIM unit and patient will be considered as a random effects. We will also adjust for sex and age of the patients. This will include adjustment for block and time period of the design, seasonal variation in the outcomes (based on the previous 2 years of data), age and gender of the patient admissions.\textsuperscript{21,23,24}

We will make every effort to minimize missing outcome data at each wave. As well, sensitivity analyses will be conducted to assess the robustness of the missing data assumption made in the primary analysis. A detailed analysis plan will be developed for secondary and sensitivity analyses. Statistical analyses will be carried out using Stata® (StataCorp. 2013.)

The detailed statistical analysis plan is included as a stand alone document at the end of this protocol.
Economic analysis
Economic analysis and reporting will be consistent with published frameworks. The primary economic analysis within this study will analyse the difference in total direct costs in AUD (2016 prices) from the health service perspective. Total per episode costings will be obtained, as well as individual item costs to identify the elements of patient care that underpin any significant cost differences between the two intervention models. Costings will include the 90-day post-discharge period to capture outpatient specialist, allied health, pathology and radiology services, as well as any readmission to hospital.

A cost-effectiveness analysis from the health service perspective will also be completed, with the incremental cost for each life year saved to be compared between the CAP Service best-practice intervention and usual care groups. This analysis will only consider inpatient costs and mortality associated with the original admission to hospital, as mortality once the patient has been discharged from the health service is not routinely collected. Depending on the outcomes of preliminary analysis, appropriate analysis of uncertainty, such as use of non-parametric bootstrapping methods to calculate 95% confidence intervals with a corresponding cost-effectiveness plane and acceptability curves, will be explored.

MONITORING

Adverse Events (AEs) and Adverse Drug Reactions (ADRs) considered to be associated with the delivery of the CAP Service protocolized interventions will be reported by the GIM Chief Registrar to the Principal Investigator within 72-hours. In particular, known diabetics will have monitoring and control consistent with WH processes and procedures, and will mirror the approach used for COPD patients. Patients receiving routine corticosteroids as a component of the CAP Service interventions will be reviewed daily and record kept of any hyperglycaemia requiring new insulin treatment. A log of AEs and ADRs will be kept and reported to the project steering committee at quarterly meetings, and the Melbourne Health HREC at three-monthly intervals.

Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the Melbourne Health HREC within 72 hours. These may include (but are not limited to):
- Unexpected death;
• Serious drug-related adverse event (directly linked to either antibiotic or corticosteroid dose) where it is required that the drug is stopped;
• A fall with associated patient or clinician injury during physiotherapy;
• Patient deteriorating clinically within 60 minutes of a physiotherapy session requiring a MET call or Code Blue (as defined by Western Health procedures).

The project steering committee will meet quarterly to report enrolment numbers, protocol adherence/violations, adverse events and feeding those to the HREC. A data monitoring committee was not deemed necessary because outcome measures (e.g. LOS) are 1) objective, 2) unambiguous and 3) were collected through existing routine validated measures (and were therefore not prone to data integrity issues).

ETHICS AND DISSEMINATION

High-risk HREC approval will be sought from the Melbourne Health Human Research Ethics Committee. Protocol amendments will be communicated to relevant registries or journals if and as they arise.

The study protocol and results will be disseminated via peer-reviewed manuscripts and oral/written poster format at national/international conferences. Authorship eligibility guidelines will be as per the ICMJE and no professional writers will be used.

Confidentiality will be protected by de-identifying and pooling data; data will be coded during the trial and re-identifiable data accessible only to investigators. Paper data records will be stored in locked offices and electronic data records will be stored in password-protected files, accessible only to named investigators and research personnel. No significant competing interests are present or perceived. All trial investigators will have access to the final dataset; limitations on dataset access or restrictions on publication/presentation are not anticipated and it is not anticipated that the full dataset will be released to public access.
ANTICIPATED OUTCOMES AND IMPACTS

Although evidence-based intervention for community-acquired pneumonia improves health outcomes, such management is not currently consistently delivered to all relevant patients. This project aims to:

1. improve the delivery of evidence-based practice to patients with community-acquired pneumonia;
2. streamline disease management across the continuum of care;
3. improve health outcomes and reduce resource utilisation for this population;
4. allow implementation of the developed model nationally and internationally to optimise efficiency and cost-effectiveness of care.

Outcomes will include final and interim reports to the funder (HCF) as required by the funder/sponsor, submission of relevant manuscripts to peer-reviewed journals, conference presentations and a CAP Service model for dissemination and translation both nationally and internationally.

SCOPE

This research will be conducted at Western Health over a 24-month period (including trial setup and analysis). The program scope will include any patients admitted to Western Health under General Internal Medicine Services with community-acquired pneumonia as previously defined.\(^{27}\)
## BUDGET ($300,000 FUNDING CONFIRMED)

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study co-ordinator/Physiotherapist 1</td>
<td>2 years 1 FTE</td>
<td>$144,718</td>
</tr>
<tr>
<td>Physiotherapist 2</td>
<td>1 year 0.6 FTE</td>
<td>$39,483</td>
</tr>
<tr>
<td>Research nurse / Physiotherapist 3</td>
<td>1 year 0.5 FTE</td>
<td>$36,180</td>
</tr>
<tr>
<td>Statistician</td>
<td>1 year 0.25 FTE</td>
<td>$18,090</td>
</tr>
<tr>
<td>Salary on-costs</td>
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<td>$35,771</td>
</tr>
<tr>
<td>Database design</td>
<td></td>
<td>$10,000</td>
</tr>
<tr>
<td>Tablet computers x 3 for data entry</td>
<td></td>
<td>$3,000</td>
</tr>
<tr>
<td>Ethics submission, fees, stationery, sundries</td>
<td></td>
<td>$3,000</td>
</tr>
<tr>
<td>Conference presentations</td>
<td></td>
<td>$9,000</td>
</tr>
<tr>
<td>Open access publication fees</td>
<td></td>
<td>$3,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>$302,242</strong></td>
</tr>
</tbody>
</table>
# MILESTONES AND TIMELINES

<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective/goal</th>
<th>Planned completion date</th>
</tr>
</thead>
</table>
| Planning, ethics and governance (1) | Ethics submission to Melbourne Health HREC  
Governance submission to Western Health research office  
Stakeholder liaison (Allied Health, Director of Medical Services, Executive) | May 25 2016 |
| Planning, ethics and governance (2) | Replies to HREC and research office re ethics submission | June 15 2016 |
| Pre-implementation | Procurement, preparation of study materials (including design of tablet-based decision support and data collection tools).  
Database design and set up.  
Full ethics and governance approvals obtained | June 30 2016 |
<p>| Implementation (baseline) | Baseline data collection (no units receiving intervention) | September 15 2016 |
| Implementation (step 1) | First 2 units rolled into intervention | November 30 2016 |
| Implementation (step 2) | Second 2 units rolled into intervention | February 15 2016 |
| Implementation (step 3) | Third 2 units rolled into intervention | April 31 2017 |
| Implementation (step 4) | Fourth 2 units rolled into intervention | July 15 2017 |
| Analysis and post implementation phase | 1. All units now receiving intervention. Outcome data | October 31 2017 |</p>
<table>
<thead>
<tr>
<th>Collection to continue for a further 90 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Preliminary data analysis (on outcomes available by April 31)</td>
</tr>
<tr>
<td>3. Preliminary cost-effectiveness analysis (based on outcomes available by April 31)</td>
</tr>
<tr>
<td>4. Decision as to whether to continue intervention or whether to disinvest (roll back) based on 2. and 3. (above)</td>
</tr>
</tbody>
</table>

**Final analysis**

| Complete dataset cleaned and formal *a priori* analysis complete. |
| Internal (Western Health) dissemination of results – (research week, report to CEO and Western Health board) |
| Report prepared for HCF |
| December 31 2017 |

**Dissemination of results**

| Preparation of abstracts for conference presentation |
| Preparation of manuscripts for publication. |
| Submission to Victorian Health Department |
| Follow-up funding applications (eg to NHMRC) |
| March 31 2018 |

**SIGNIFICANCE**

The comprehensive range of information generated all in a relatively short (2-year) timeframe could build a highly persuasive case for this model of care applicable to a wide range of stakeholders (including clinicians, hospital administrators, health department and health system end-users). This could also support similar evaluations of cost-cutting syndrome-based service models for other high service-burden conditions (e.g. CCF) in the elderly multi-morbid population.
In addition to internal reports to our executive, conference presentation and peer-reviewed publication, the Victorian Health Department will also be provided with a report of the results (positive or negative) to facilitate broader policy implementation (see translation section above).

We also hope the research infrastructure and scientific outcomes generated will provide a platform for subsequent funding applications (e.g. NHMRC) for future CAP and health services research at Western Health. This is supported by our team members’ existing track record in attracting NHMRC funding in other areas (EJ, HK and TH). Potential to build capacity in health services research at Western Health and to develop and consolidate strategic partnerships with marquee research bodies (Monash and Melbourne Universities, WEHI) further increases stakeholder engagement.

FEASIBILITY AND TEAM EXPERTISE

Key stakeholders at Western Health are the GIM Unit, Allied Health and the Western Health Executive, all of whom have senior representatives as co-investigators on this proposal.

**GIM:** Principal Investigator EJ is Head of GIM across both Hospitals (Footscray and Sunshine) and over the last 5 years in collaboration with co-investigator HK, the other GIM physicians and registrars, has implemented service-wide evidence-based improvements in patient care for CAP and other common conditions resulting in presentations and publications\(^3\), demonstrating that further work in this space will continue to be strongly supported by front-line clinicians.

**Allied health:** Co-investigators ES, TH and MS recently completed a stepped wedge design improvement project for weekend physiotherapy services that received excellent organizational support and now been implemented as policy. ES is a senior clinical physiotherapist at Western Health and has had substantial input in this proposal. MS is the Physiotherapy Manager at Western Health and has substantial expertise in the organisation.

**Executive:** Western Health’s CEO has specifically articulated that development of capacity in health services research as a key organizational strategic objective. Russell Harrison, WH Director of Operations, will act as Executive sponsor for the
project. Dr A Wake (Executive Director of Community Services and Allied Health) has been briefed and is strongly supportive.

CI Karunajeewa is a specialist physician and NHMRC Career Development fellow; CI Karahalios is the trial biostatistician from The University of Melbourne and CI Haines has a Grad Cert in Health Economics.

**ROLES AND RESPONSIBILITIES**

Professor Edward Janus: Will have primary responsibility for all aspects of research governance, including financial management and budgeting. He will have a key role in engagement of internal stakeholders at Western Health and will provide intellectual input into trial design, conduct of the project, data collection/analysis/interpretation, manuscript contribution.

A/Prof Harin Karunajeewa: Conceived the study and its overall design and lead the preparation of the funding proposal. He will continue to have a leading role providing intellectual input into trial design, conduct of the project, data collection/analysis/interpretation. He will have the leading senior role in developing a publication plan, and supervising manuscript preparation.

Ms Melanie Lloyd: Trial co-ordinator. Will assist LS in protocol development and HREC and governance submissions. She will have ongoing intellectual input into trial design, conduct of the project, data collection/analysis/interpretation, manuscript contribution. She will have primary responsibility for day to day management and co-ordination of all clinical activities of the study, including leading the CAP Service team and performing the physiotherapy interventions in the intervention patients. She will co-ordinate care in the intervention patients with medical, nursing and allied health staff. She is expected to be first author on the main paper to arise from this study, detailing the effectiveness of the intervention, as well as on additional paper(s) examining health economic analyses in more detail.

Dr Elizabeth Skinner: Will take the leading role in writing the protocol, preparing the HREC submission and will first author a preliminary methods paper outlining the study design. She will have ongoing intellectual input into trial design (especially relating to physiotherapy and other allied health interventions), conduct of the project, data collection/analysis/interpretation, manuscript contribution.

Ms Stephanie Lowe: Will act as project implementation lead at the second site, delivering physiotherapy interventions and co-ordinating care in the intervention patients with medical, nursing and allied health staff. She will have input into manuscript preparation.
Dr Clarice Tang: Has had intellectual input into the study design, and will assist with data analysis and manuscript preparation.

Dr Soe Ko Ko and Dr Parul Bali: As the Chief Medical Registrars at either site will have significant input into the daily operation of the CAP Service, including ascertainment and monitoring of the medical interventions. They will assist with education and training of medical clinicians as they are incorporated into the intervention arm of the study.

Dr Amalia Karahalios: Has had intellectual input into trial design regarding all statistical matters including sample size calculations and development of the a priori analytical plan. She will have primary responsibility for final data analysis, data interpretation, manuscript contribution.

Professor Terry Haines: Intellectual input into trial design, especially in matters pertaining to stepped wedge evaluations. Will have an important role in health economic analysis, data analysis and manuscript contribution.

Professor Anne-Maree Kelly: Intellectual input into trial design, support project conduct, data interpretation, manuscript contribution.

Ms Melina Shackell: Will assist EJ in co-ordination of project governance including especially recruitment and employment of physiotherapists and co-ordination of allied health activities related to the project. Intellectual input into trial design, data interpretation, manuscript contribution.

Mr Russell Harrison: Executive support of the project, stakeholder engagement at Western Health and communication of study findings and their implications to the Western Health executive and board. He will have an important role in building this evaluation into future strategic and policy frameworks at Western Health.

FUNDING

This study has been funded by the HCF Research Foundation. Western Health, The University of Melbourne and Monash University have provided material and other in-kind support.
Table 1. Description of intervention and usual care groups according to TIDieR criteria.35

<table>
<thead>
<tr>
<th>TIDieR criteria</th>
<th>Intervention</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 1. Brief name: Provide the name or a phrase that describes the intervention</td>
<td>Community-acquired pneumonia service (CAP Service)</td>
<td>Usual inpatient hospital care</td>
</tr>
<tr>
<td>Item 2. Why: Describe any rationale, theory, or goal of the elements essential to the intervention</td>
<td>A large randomized controlled trial (RCT) and meta-analysis11,12 demonstrated faster clinical recovery and shorter LOS with adjunct corticosteroids without significant adverse events. Routine adjunctive corticosteroid is now widely supported though as yet not consistently deployed. Early switch to oral antibiotics guided by a set of well-defined basic clinical and laboratory criteria15 also reduces LOS. Recently, a RCT incorporating both measures demonstrated a LOS reduction of 2 days compared to standard care.16 Early mobilization safely and effectively reduces LOS when applied appropriately.14 Routine screening of medical inpatients for malnutrition and appropriate targeted nutrition therapy can reduce unplanned readmissions.17</td>
<td>Usual inpatient hospital care will be delivered as per underlying usual care rationale, theories and goals of CAP management.</td>
</tr>
<tr>
<td>Item 3. What (materials): Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers.</td>
<td>Patient information materials will not apply as a waiver of consent is sought. Intervention providers will be given an intervention algorithm tool to prompt safe, systematic and appropriate initiation of the four evidence-based interventions.</td>
<td>Nil additional to usual care.</td>
</tr>
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<td>---</td>
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</tr>
<tr>
<td>Item 4. What (procedures): Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities</td>
<td>The CAP Service will apply a set of protocols to ensure rigorous application of interventions each with proven efficacy including: (1) routine prescription of 50mg of prednisolone for 7 days (following checklist exclusion of those with contraindications)\textsuperscript{11,12} (2) guideline-consistent antibiotic prescription and constrained parenteral antibiotic duration (using pre-defined “stopping rules”)\textsuperscript{15,16} (3) physiotherapy-led early (&lt;24h) mobilization,\textsuperscript{14} (4) Routine malnutrition screening and implementation of an appropriate nutrition therapy intervention as indicated.\textsuperscript{17,34}</td>
<td>During the non-interventional control periods (as determined by the stepped-wedge roll-out schedule) CAP patients will receive conventional care by the usual treating GIM team: Currently, 43% receive corticosteroids, 63% physiotherapy (median time to initiation 2 days), 65% guideline-compliant antibiotic.\textsuperscript{3} No parenteral antibiotic stopping rules are in place (median 3 days). 72% of inpatients at Western Health currently receive routine malnutrition screening.</td>
</tr>
<tr>
<td>Item 5. Who provided: For each category of intervention</td>
<td>Relevant members of the general</td>
<td>The general internal medicine</td>
</tr>
</tbody>
</table>
provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given

internal medicine multidisciplinary team (doctors, nurses, physiotherapists and dietitians) will deliver the CAP Service intervention. Clinicians treating patients in the intervention arm of the study will be given an education package outlining current evidence-based practice guidelines and the treatment protocols to be applied. Intervention arm clinicians will also have access to a decision-support algorithm to promote consistent application of the protocols.

<table>
<thead>
<tr>
<th>Item 6. How: Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group</th>
<th>Face to face individual intervention.</th>
<th>Face to face individual intervention.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 7. Where: Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features</td>
<td>Acute hospital wards; patients under the care of the general internal medicine unit.</td>
<td>Acute hospital wards; patients under the care of the general internal medicine unit.</td>
</tr>
<tr>
<td>Item 8. When and how much: Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose</td>
<td>Daily during acute hospital admission.</td>
<td>Daily during acute hospital admission.</td>
</tr>
<tr>
<td>Item 9. Tailoring: If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how</td>
<td>The four best-practice interventions will be delivered to all patients meeting the inclusion criteria, except</td>
<td>At the discretion of the treating medical team and allied health clinicians.</td>
</tr>
</tbody>
</table>
in the case of specific contraindication to an intervention as outlined in this protocol. The protocol for each of the interventions also outlines circumstances where treatment can be individualised.

<table>
<thead>
<tr>
<th>Item 10. Modifications: If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)</th>
<th>N/A in protocol</th>
<th>N/A in protocol</th>
</tr>
</thead>
</table>
| Item 11. How well (planned): If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them | Patient proportions receiving:  
  i) Corticosteroids  
  ii) Guidelines consistent antibiotic  
  iii) early mobilization  
  iv) MST application and appropriate nutrition therapy  
  Aim for relevant proportions to exceed 70% for interventions i) and ii), and 85% of interventions iii) and iv). Protocol adherence rates will be available to the project coordinator in real-time, allowing high protocol non-compliance rates to be addressed in a timely fashion. | Patient proportions receiving:  
  i) Corticosteroids  
  ii) Guidelines consistent antibiotic  
  iii) early mobilization  
  iv) MST application and appropriate nutrition therapy.  
  Anticipate existing data on proportions to be maintained. |
| Item 12: How well (actual): If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned | N/A in protocol | N/A in protocol |
Appendix 1. IMPROVE-GAP Statistical analysis plan.
A1. Introduction
This document details the presentation and analysis for the main paper(s) reporting results from the IMPROVing Evidence based treatment Gaps and outcomes in community-Acquired Pneumonia (IMPROVE-GAP) study. Main details of the study are provided in the protocol. It is intended that the results reported in the main papers arising from this study will not divert from the strategy set out here; subsequent papers of a more exploratory nature will not be bound by this strategy though they are expected to follow the broad principles laid down for the main paper(s).

A1.1. Overview design:
The IMPROVE-GAP study is a pragmatic, investigator initiated, stepped-wedge randomized controlled clinical effectiveness study conducted in two participating hospitals located in inner metropolitan Melbourne, Victoria, Australia. The two hospitals have a total of eight general internal medicine units split evenly across the two participating hospitals, which will constitute the eight separate clusters in the stepped-wedge design.

A1.2. Objectives:
The primary objective of study is to estimate the effect that a translation community-acquired pneumonia service delivering four evidence-based interventions has on length of hospital stay, when compared with usual hospital care. Secondary objectives are to evaluate the effect of the community-acquired pneumonia service on inpatient mortality, 30- and 90-day readmission rates and mortality, adverse events and health-service costs.

A2. Study outcomes
A2.1. Primary outcome:
The primary outcome measure will be hospital length of stay (Table A1), calculated from arrival in the emergency department until discharge from the health service, based on date and time (note that data will be collected in minutes but converted to days). This information is routinely collected at the institution for all inpatients.

A2.2. Secondary outcomes:
Secondary outcome measures comprise routinely collected institutional data and include (Table A1):

1. Mortality:
   a. Inpatient mortality: occurring during the index hospitalization (from Health Service data warehouse for the index hospitalization),
   b. 30-day mortality: occurring within 30 days of the index hospitalization admission date (30- and 90-day mortality is derived from the Victorian Death Index),
   c. 90-day mortality: occurring within 30 days of the index hospitalization admission date.

2. Readmission (from Health Service data warehouse):
   a. 30-day readmission: occurring within 30 days of the index hospitalization admission date,
   b. 90-day readmission: occurring within 30 days of the index hospitalization admission date.
3. Requirement for intensive care support (during index hospitalization): from Medical record for the index hospitalization (extracted by a blinded research assistant).
   a. Admission to the intensive care unit from inpatient wards,
   b. Requirement for mechanical ventilation,
   c. Duration of mechanical ventilation,
   d. Number of failed extubations,

4. Adverse events during index hospitalization or requiring representation to hospital within 30-days. Extracted from the medical record for the index hospitalization during daily review by the project clinical team (due to the requirement that the PIs are aware of any adverse events in real time – therefore not blinded). Adverse event data requiring readmission within 30-days were obtained from the medical record by a blinded research assistant. Refer to Table 2 of the published protocol for definitions of additional complications for which data will be collected (and presented descriptively).
   Key adverse events:
   a. Hyperglycemia in known diabetics requiring new insulin prescription during index hospitalization,
   b. Gastrointestinal bleeding not present at admission and occurring within 30 days of admission,
   c. Fall or acute clinical deterioration during physiotherapy intervention requiring urgent medical review,
   d. Adverse drug reaction where it is required that the drug is stopped.

5. Adherence to protocolized interventions (extracted from the medical record by project investigators, not blinded). This outcome and its associated definitions are discussed in detail in the published protocol.

A3. Analytical approach

A3.1. Intention-to-treat (ITT) analysis

The unit of analysis will be the individual participants (see note under statistical models below). The primary analyses will be based on the ITT principle. Each medical unit will be classified as being in the intervention or the control phase based on their pre-specified randomized crossover time, regardless of whether the crossover was achieved at that time. Requirements for an ideal ITT analysis are: full compliance with the randomized intervention, no missing responses and follow-up on all participants. We anticipate no missing responses and complete follow-up on all participants in regards to the primary and most of the secondary outcomes. However, it is important to bear in mind that our study aims to evaluate effectiveness (that incorporates non-adherence as intrinsic to the outcome under real-world conditions), rather than efficacy (that assumes ideal conditions of adherence). Therefore, we expect a degree of non-adherence and our final measures of effectiveness should take this into account. The ITT approach is clearly the most appropriate approach to measuring effectiveness in this instance. In a SW-RCT the potential for non-adherence to the intervention and loss to follow-up are more complex than an individual RCT, since it can occur at multiple levels. For example, in our SW-RCT, the treating clinical care team may not comply with the intervention, or all of the components of the intervention may not be delivered. This can also
happen at the patient level, with interventions being not applicable to some individuals, and the possibility of non-adherence or loss to follow-up.

**A3.2. Missing data**

**A3.2.1. Endpoints**

Whilst high degrees of loss to follow-up can lead to biased estimates of intervention effect (particularly when there is differential drop out between intervention arms, which is related to the intervention) we anticipate complete follow-up with respect to the primary outcome and for secondary outcomes.

**A3.2.2. Covariates**

With respect to the covariates, we anticipate a small (<2%) amount of missing data. As the anticipated amount of missing data is small, we will analyse the data using complete case analysis.

**A3.3. Statistical models**

Primary and secondary analyses will be undertaken using mixed effects generalised linear (continuous outcomes) or logistic (binary outcomes) models, as appropriate. For the primary outcome, length of stay, we will fit two separate models. The first model will assess the change in the proportion of participants staying longer than the average diagnosis-group-related (ICD-10 code J18) length of stay, and the second model will assess the change in the geometric mean length of stay. For all models (i.e. for all outcomes) the effect of the intervention and time period will be considered as fixed effects while the effect of treating general internal medicine unit (cluster) will be considered as a random effect. This will include adjustment for block and time period of the design, age and sex of the patient admissions.21,23,24

Mixed-effects models with a random effect for clusters require a large number of clusters to produce valid estimates and difficulties in convergence, and estimation of variance components and intra-cluster correlations are expected due to the small number of clusters used in this stepped wedge trial. The analysis options are limited for stepped wedge trial designs and we will follow the model proposed by Hussey and Hughes.45 Furthermore, the small number of clusters used in a stepped wedge trial design leads to limited analysis options.46 We will compare the derived estimates with those derived from generalised estimating equations to ensure the validity of the results from the mixed-effects model. Note that effect estimates will be generated using unit-month-level data if effect estimates cannot be calculated using participant-level data (on account of inability to ascertain starting values for models with binary outcomes). We will report the intra-cluster correlation coefficients.

**A3.4. Additional analyses**

**A3.4.1. Sensitivity analyses**

i. We will conduct additional analyses, in which we will adjust for additional pre-specified potential confounders (Table A2). All pre-specified confounders will be included in the
models even when no baseline imbalance exists. We have limited the inclusion of potential confounding variables to those that we surmise to be the most important based on the investigators’ assessment of clinical plausibility (Table A2). This approach has been chosen since confounder selection strategies which are based on collected data, for example selecting confounders using preliminary statistical tests, result in models with poor statistical properties such as incorrect type I error rates.47-49

ii. There is the possibility that a participant can be included in our study on multiple occasions. We will conduct additional analyses where we include participant identifiers as a random-effect in the model.

iii. To account for seasonal variation in the outcome of length of stay, we will conduct an additional analysis for the primary outcome, where we adjust for length of stay based on historical data.

A3.4.2. Subgroup analyses

We will undertake subgroup analyses for the following variables (separately) by fitting an interaction term between the intervention and variable listed below. This will allow us to assess the extent the effect of the intervention on the primary outcome (i.e. length of stay) and the secondary outcome of readmission (at 30 and 90 days) is influenced by these variables. Note that this study was not designed to have sufficient power to test for interaction terms in these subgroup analyses; we will interpret the results with caution.

The following variables will be considered for subgroup analyses:

i. Participants with chronic pulmonary disease (yes/no)
ii. Participants with diabetes mellitus (yes/no)
iii. Charlson’s Co-Morbidity Index sub-groupings (0-1, 2-4, ≥5 for low, medium and high risk, respectively).
A3.5. Presentation of results – Tables and Figures

A3.5.1. Flow chart

The CONSORT diagram for this study will be presented as described in the protocol manuscript for the study. In brief, for each step of the trial we will present the following information:

- # of participants admitted with CAP
- # of participants excluded
- # of participants enrolled
- # of participants withdrawn
- # of participants for which data is collected

A3.5.2. Figures of results

For all primary and secondary outcomes, we will present line graphs based upon whole trial data using time relative to the transition period (see Haines and Hemming 2018).

A3.5.3. Tables of results

See examples tables 1-3 below.
### Table A1: Outcome measurements

<table>
<thead>
<tr>
<th>Study parameter</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Index hospitalization</td>
</tr>
<tr>
<td>Length of stay</td>
<td>X</td>
</tr>
<tr>
<td>Mortality</td>
<td>X</td>
</tr>
<tr>
<td>Readmission</td>
<td>X</td>
</tr>
<tr>
<td>Requirement for intensive care support</td>
<td></td>
</tr>
<tr>
<td>Admission to ICU from ward</td>
<td>X</td>
</tr>
<tr>
<td>Requirement for mechanical ventilation</td>
<td>X</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Number of failed extubations</td>
<td>X</td>
</tr>
<tr>
<td>Requirement for vasopressor support</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia in known diabetics requiring new insulin prescription</td>
<td>X</td>
</tr>
<tr>
<td>Gastrointestinal bleeding not present at admission and occurring within 30 days of admission.</td>
<td>X</td>
</tr>
<tr>
<td>Falls during physiotherapy intervention</td>
<td>X</td>
</tr>
<tr>
<td>Acute clinical deterioration during physiotherapy requiring urgent medical review</td>
<td>X</td>
</tr>
<tr>
<td>Adverse drug reaction where it is required that the drug is stopped</td>
<td>X</td>
</tr>
<tr>
<td>Protocol adherence</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: ICU – Intensive care unit.
Table A2: Potential confounders

<table>
<thead>
<tr>
<th>Level</th>
<th>No.</th>
<th>Confounder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>1</td>
<td>Age (years, continuous)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Sex (Male/Female)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Healthlinks (yes/no)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>CCMI (&lt;2, 2-4, ≥5)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>CORB (0/1, ≥2)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Palliated (yes/no)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>eGFR (mL/minute), continuous</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>ICU admission (yes/no)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Supported accommodation or residential aged care prior to admission (yes/no)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Marital status (Married / De facto, versus Widowed / Single / Separated, binary)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Albumin (g/L, continuous)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>CRP (mg/L, continuous)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Pre-morbid mobility status (≤2 bed or chair bound, ≥9 independently ambulant, indicator variable)</td>
</tr>
<tr>
<td>Medical Unit</td>
<td>14</td>
<td>Day of the week admitted</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Site</td>
</tr>
</tbody>
</table>

Abbreviations: CCMI – Charlson Co-Morbidity Index; CORB – 1-point for each of: Confusion (Acute), Oxygen Saturation ≤ 90%, Respiratory Rate ≥ 30 breaths per minute, Blood Pressure < 90 mm Hg (systolic) or ≤ 60 mm Hg (diastolic); eGFR – glomerular filtration rate; ICU – Intensive Care Unit; CRP – C-reactive protein.
Example Table 1: Characteristics of participants at admission

<table>
<thead>
<tr>
<th></th>
<th>Control (n=)</th>
<th>Intervention (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campus; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age; mean (sd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male); n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential status; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent living</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supported accommodation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential aged care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language status (English spoken at home); n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married / Defacto</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single / Separated / Divorced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid ICU mobility scale; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 (chair or bed-bound)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥9 (independently ambulant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Index; median [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidities; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (any type or severity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy (any)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline number medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORB pneumonia severity score; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR mL/minute; median [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin g/L; median [IQR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP mg/L; median [IQR]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICU – Intensive Care Unit; IQR – Inter-Quartile Range; CORB – Confusion (Acute), Oxygen Saturation ≤ 90%, Respiratory Rate ≥ 30 breaths per minute, Blood Pressure < 90 mm Hg (systolic) or ≤ 60 mm Hg (diastolic); eGFR – glomerular filtration rate; CRP – C-reactive protein.
Example Table 2: Main outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Control (n=)</th>
<th>Intervention (n=)</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length of stay (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 30-days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 90-days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Readmission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 30-days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 90-days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Requirement for intensive care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>support</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admitted to intensive care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>following admission to general ward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mechanical ventilation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requirement for mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed extubation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia in known diabetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requiring new insulin prescription</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding not present at admission and occurring within 30 days of admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall or acute clinical deterioration during physiotherapy requiring urgent medical review</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse drug reaction where it is required that the drug is stopped</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example Table 3: Compliance with evidence-based interventions

<table>
<thead>
<tr>
<th>Intervention component</th>
<th>Control n, (%)</th>
<th>Intervention n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription of 50mg corticosteroid daily within 36-hours of arrival in ED (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum 7-day duration corticosteroid prescription (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number compliant with protocol dosage and duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number ineligible (met pre-specified contraindication criteria for corticosteroid prescription contraindicated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switch to oral therapy made within 24-hours of stability criteria reached (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early mobilisation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sit out of bed for &gt;20 minutes with physiotherapist in first 24-hours of admission (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive movement achieved with physiotherapy on &gt; 70% eligible days (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number compliant with early mobilisation protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number ineligible (SOOB Day 1 contraindicated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nutrition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MST score documented within 24-hours of admission (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate nutrition therapy initiated in response to MST score</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patients receiving all interventions</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ED: Emergency Department; SOOB: sit out of bed; MST: Malnutrition screening tool.
REFERENCES

4. Graf C. Functional Decline in Hospitalized Older Adults: It’s often a consequence of hospitalization, but it doesn’t have to be. AJN The American Journal of Nursing 2006; 106(1): 58-67.


