Final Report

Improving outcomes of hospitalization for geriatric pneumonia

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Executive Summary

At Western Health, our organizational strategic plan explicitly prioritizes the development of expertise in **health services research** as our **leading research objective**. In practical terms, we realise that this involves more than just descriptive analysis of our health service - we also need to be capable of carefully evaluating new health service interventions in a suitably robust fashion, so that we can **see clearly what works and what doesn't**. However, generating information that answers these questions in an unambiguous way is challenging. We think the issues can be distilled into two major problems:

1. **Commonly used evaluation frameworks for health services interventions have major methodological flaws, being prone to bias and confounding that leads to uncertainty and potentially very misleading conclusions.** The commonest example is the "before vs after" evaluation that has major problems related to its use of historical controls. Ideally, health systems interventions should be evaluated with the same rigour that we apply to testing new drugs in the clinical trial setting. However, several factors make this challenging. Whilst clinical trials minimize bias through randomization, doing so at an individual patient level is impractical with health systems interventions (which are often delivered at scale), and ethically challenging for treatments already well-supported by evidence. Therefore, novel approaches utilising alternative evaluation framework designs are needed in interventional health services research.
2. **Our current processes fail to record and evaluate the outcomes that matter most to patients.** We generate information on utilization and expenditure, but little on the things that patients tell us they want from their healthcare. This is especially so as our population ages and the prevalence of chronic diseases escalates. It is vital that we evaluate the performance of our health system in terms of how it meets patients' needs to control symptoms, maintain independence and achieve good overall quality of life. Valid tools exist that could potentially be used as metrics for evaluating aggregate health systems outcomes, but these have not been widely implemented in practice.

We therefore aimed to design a project that would address these issues and therefore provide a "proof of principle" to demonstrate a feasible approach for prosecuting high-quality interventional health services research in our setting. Our broad objectives were as follows:

1. To examine a high burden condition that contributes substantively to health service utilization both at our own centre and Australia-wide.
2. To develop and evaluate a novel health services intervention that was practical, relatively simple and that could plausibly improve health outcomes in a significant patient cohort.
3. To evaluate *effectiveness* (rather than *efficacy*) in a suitably representative population and in a "real-world" setting.

4. To employ a scientifically robust evaluation design that minimized potential for bias.
5. To embed the evaluation framework into routine clinical practice, thereby removing parallel administrative processes and greatly reducing trial costs.
6. To include some evaluation of Patient Reported Outcome Measures (PROMs).

We chose to look at community-acquired pneumonia (CAP) as this is the leading non-obstetric cause of hospitalization in Australia. We recognized that high-level evidence now supports numerous interventions for improving patient outcomes but that these were being poorly applied in practice, possibly reflecting uncertainty as to whether "efficacy" in clinical trials translates to "effectiveness" in the real world. We therefore designed a novel model of care to improve compliance with evidence-based management of CAP. In order to evaluate the effectiveness of this in a representative population, in a way that minimized risks of confounding and bias, we obtained approval from our supervising Human Research Ethics Committee (HREC) for a "waiver of consent" and utilized a "stepped wedge" cluster randomized control trial approach. This involved partitioning our general internal medical (GIM) service into eight clusters (based on existing separate operational units), and rolling out our intervention into each unit by a randomly determined sequence over five time periods; a phased introduction of the intervention that would allow analytically robust comparisons of outcomes between intervention and control groups. The waiver of consent ensured a representative sample.

Over our 12-month enrolment period, 415 and 401 individuals were enrolled in control and intervention groups, respectively. Baseline data suggested the two groups were well-matched and representative of the burden of disease in the Australian hospital system. We found no benefit from the intervention, including when comparing our primary outcome, length of stay, between the two treatment arms (unadjusted geometric mean ratio of 0.95 [95% confidence interval (CI): 0.78, 1.16]). Similarly, no significant differences were observed for the secondary outcomes; mortality and readmission. As well as not demonstrating any benefits from the intervention, we also saw slightly higher than expected proportions of gastrointestinal bleeding in our intervention arm (9, 2.2%) compared to the controls (3, 0.7%) that was statistically significant (estimated difference in mean proportions of 0.008 [95% CI: 0.005, 0.010]). Our novel model of care cannot, therefore, be recommended within routine clinical practice.

Our study has therefore yielded a "negative" result, but one with very significant implications. It demonstrates how "efficacy" as demonstrated under ideal clinical trial conditions may not necessarily translate into "effectiveness" when implemented at scale under routine clinical conditions in a population representative of the realities of modern healthcare. It has demonstrated that had we invested in routine application of evidence-based treatments for CAP without concurrent evaluation, this would in fact have been a futile use of health system resources.

We wonder how many other "evidence-based" treatment approaches have been implemented without the sort of scrutiny we applied to assessing effectiveness under conditions of routine care as we have done. How many of these are, unbeknown to clinicians, actually failing to benefit patients whilst consuming scarce health resources? The significance of our study's findings was borne out when it was accepted recently for publication in one of the world's leading medical journals (JAMA Internal Medicine). The interest generated in social and mainstream media saw it ranked in the top 2% of all research outputs by Altmetric. Several additional minor publications including those examining the use of patient reported outcomes (PROMS) have also arisen through this work, and 12 abstracts to date have been accepted for presentation at various scientific meetings.

Our project was a large, and logistically complex one. Its novel methods utilizing a waiver of consent approach required resource-intensive administrative work in securing ethical and contractual approvals, data linkage and highly complex statistical analysis. For these reasons, although the enrolment and data collection were conducted over a 15-month period, the study in its entirety now represents a total of 3-years' work. Studies requiring the sample size we achieved usually require a network of multiple sites and many years to enrol the necessary number of participants. Costs of conducting clinical trials are now estimated to average over $US16,000 per-participant in the USA. However, in our study, the novel approaches used meant that we were able to enrol 816 participants over 1 year at a single health service, with per-participant costs of approximately $AUD350. This sets an important precedent for evaluation of health care interventions in a rapid timeframe and at a low cost.

Our approach has therefore exemplified the concept of "implementation research" and provides proof of principle that this is feasible for assessing the impact of health systems interventions in representative multi-morbid populations in the Australian hospital system. Together with other work being conducted by the Western Health Chronic Disease Alliance, the HCF Research Foundation's support of this study has helped position us as a national leader in the science of evaluating new models of healthcare.

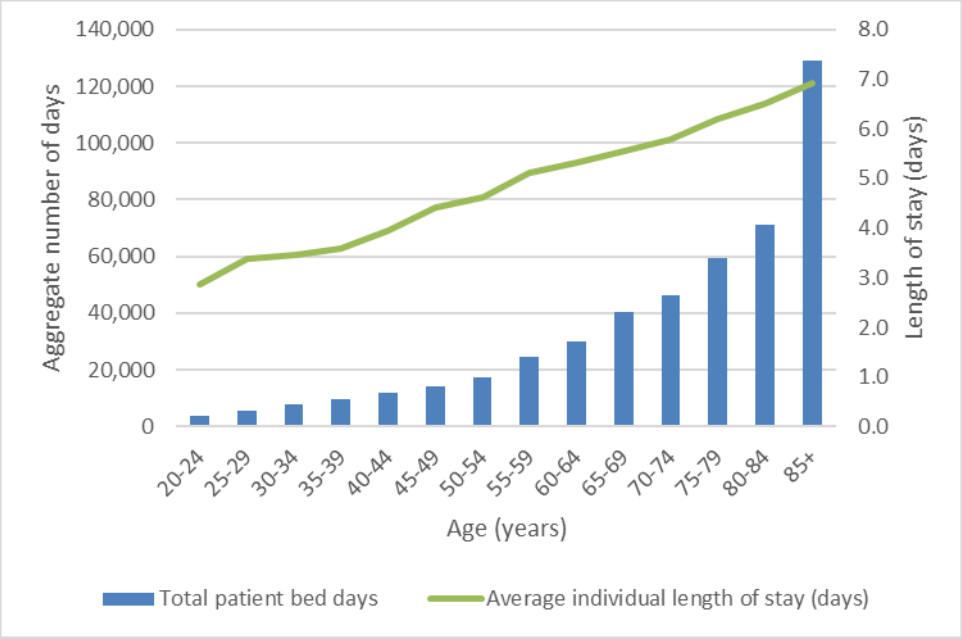
Contents

Chapter 1 - Why did we decide to evaluate a new health systems approach to managing CAP?

1.1 The healthcare burden associated with hospital care for CAP is very high

Lower respiratory tract infection, including community-acquired pneumonia (CAP), is the leading non-obstetric primary diagnosis for hospitalizations in Australia[1] and the third leading contributor to lost disability adjusted life years worldwide[2]. In Australia and other high-income countries, CAP incidence and healthcare burden is primarily concentrated in the elderly[3-6] (Figure 1). Frequent requirements for intensive clinical support and prolonged hospital length of stay (LOS) contribute to high healthcare expenditure[7-9]. CAP often occurs in the context of overlapping comorbidities, where there are pre-existing deficiencies in physical function[10], and cardiac, gastrointestinal and neurologic complications are common[11,12]. Therefore, CAP can be considered a multisystem disease, leading to further significant deconditioning and loss of independent function and wellbeing. These sequelae may persist for many months, especially when prolonged hospitalization occurs[13,14], and drive high rates of readmission.

Figure 1. *Relationship between total patient bed days, length of hospital stay and age for Australian adults hospitalised with influenza and pneumonia (ICD-10 codes J09-J18, 2014-15).*

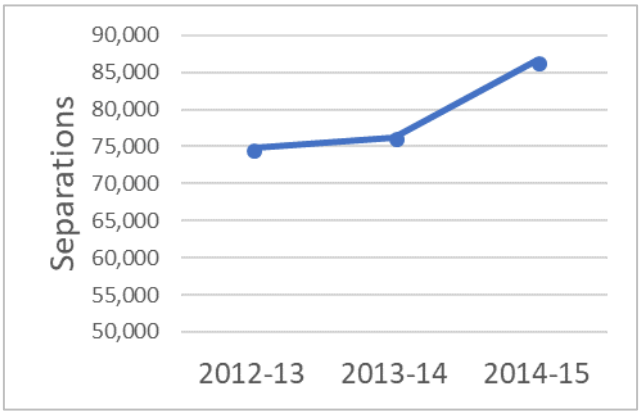


Source: Australian Institute of Health and Welfare, 2018; *Hospital data cubes: Principal diagnosis data cubes 2014-15.* Accessed 15/01/2018, https://www.aihw.gov.au/reports/hospitals/principal-diagnosis-data-cubes/contents/data-cubes.

1.2 The already high healthcare burden from CAP is continuing to rise as our population ages

Hospitalizations, bed stays and costs for CAP are continuing to rise[15], even after accounting for population growth. This is likely to reflect overall population ageing and the proportionately higher prevalence of co-morbidity in the Australian population. This trend is therefore likely to continue (Figure 2).

Figure 2. *Australian hospital admissions with a primary diagnosis of lower respiratory infection (pneumonia or influenza) over time (ICD10 primary diagnosis codes: J12-18).*



Source: Australian Institute of Health and Welfare, 2018; *Hospital data cubes: Principal diagnosis data cubes 2012-13, 2013-14, 2014-15.* Accessed 15/01/2018, https://www.aihw.gov.au/reports/hospitals/principal-diagnosis-data-cubes/contents/data-cubes.

1.3 CAP occurs in patients with complex needs and requires a system of well-coordinated multi-disciplinary expertise to ensure optimal care

CAP management can involve numerous clinical craft groups and ancillary care. A single patient's clinical journey through the hospital system may involve initiation of care by Emergency Medicine physicians, high-level support by intensivists or respiratory physicians in an intensive care unit (ICU), high dependency unit (HDU) or intensive respiratory care unit (IRCU), further nursing on a general medical ward, followed by time in an inpatient rehabilitation facility. During these phases of care there will also be requirements for allied health support from physiotherapists, occupational therapists and dieticians and other sub-specialist input into the management of co-morbidities and complications. What is more, multimorbidity increases complexity of care that makes it more difficult to maintain compliance with evidence-based guidelines, apply clinical pathways and standardize outcomes frameworks. Complexity creates risks of fragmented "disease-centric", rather than "patient-centred" care. This is exemplified by management guidelines for CAP formulated by sub-specialist practitioners

that can tend towards a less than holistic approach to management. For example, therapeutic guidelines written by infectious diseases physicians can concentrate largely on the issue of antibiotic choice, whilst ignoring very important aspects of ancillary care provided by allied health practitioners.

1.4 There are large "gaps" between evidence and practice in the management of CAP

Despite high-level evidence supporting efficacy in improving outcomes, many interventions are poorly or not routinely deployed in routine clinical practice[16]. Therefore, they represent areas where there is significant scope to improve the translation of evidence into clinical practice, demonstrating a clear "evidence-practice gap". The notoriously poor adherence to consensus guidelines for CAP is consistent with a broader general problem of widespread delays and inconsistency in translation of evidence into healthcare practice in a variety of fields[17]. Reducing this gap has been recognised as a leading priority for the medical research establishment in Australia and elsewhere[18]. Innovative health services approaches, including alternative models of care will be required to accelerate research translation, and it will be important that their effectiveness is measured in a suitably robust fashion.

One reason that clinicians may be reluctant to incorporate scientific evidence into clinical decision making may be scepticism regarding the generalizability of clinical research conducted under highly regulated conditions in very selected patient populations. Elderly individuals with complex health needs are often excluded from clinical trials, calling into question the extent to which study results can be generalized to this population[19]. This supports a need for "effectiveness" studies conducted in real-world settings with representative populations, rather than the rarefied atmosphere of the conventional clinical trial.

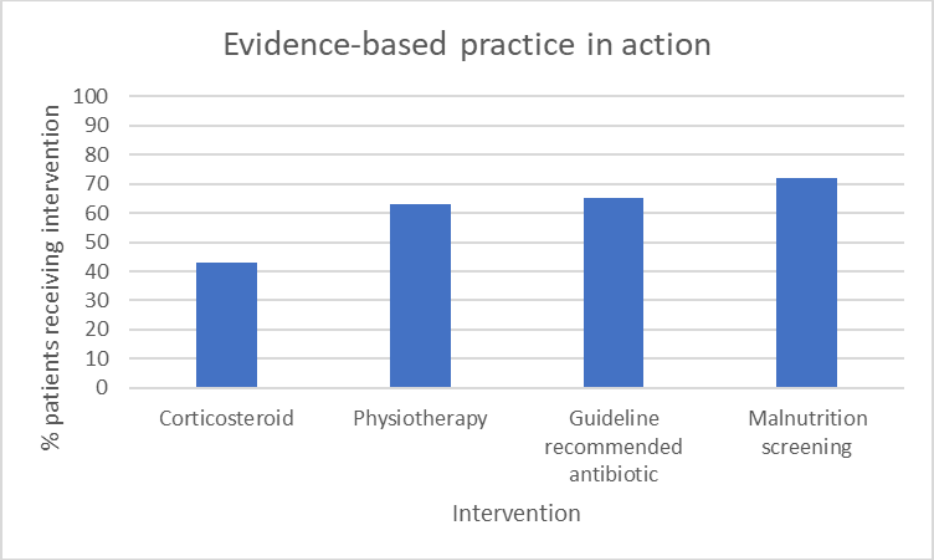
Chapter 2 - Designing a health-systems intervention to improve CAP management and evaluating this intervention: The IMPROVE-GAP project

2.1 Designing a novel health systems intervention

We identified four key interventions (adjunctive corticosteroids, early switching to oral antibiotics, early mobilisation and routine malnutrition screening) that are now supported by Level 1 or 2 evidence demonstrating improvement in clinical outcomes (including time to recovery, length of hospitalization and readmission rates) in patients with CAP. At the time this study was designed, a body of evidence had accrued supporting the efficacy of adjunct corticosteroids including results from two large randomised controlled trials (RCTs) showing that they (1) reduced treatment failure in severe CAP[20] and (2) shortened time to clinical stability and time to effective hospital discharge without an increase in adverse complications[21]. Although there was a slightly higher risk of hyperglycaemia, this can be effectively treated with insulin with no long-term adverse effects[21,22]. Meta-analyses including a subsequent Cochrane review have also confirmed these findings and demonstrated an overall lower rate of complications in corticosteroid-treated CAP patients, including a reduction in the need for vasopressors or mechanical ventilation, and shorter LOS[23,24]. Early mobilisation safely and effectively reduces LOS[25] as does an early switch from intravenous to oral antibiotics[26]. A recent randomised trial of both these interventions found a shortened LOS by two days compared to standard care[27]. In a recent meta-analysis of malnourished medical inpatients (including those admitted with CAP), systematic screening for malnutrition risk and targeted nutritional therapy reduced non-elective readmission rates[28].

A clinical audit conducted at our health service in 2013 revealed inconsistent application of evidence-based practice in the management of CAP admissions within the General Medicine units across all four of the target interventions (Figure 3).

Figure 3. *Proportion of patients admitted under General Medicine units with a primary diagnosis of community-acquired pneumonia receiving evidence-based interventions (2013).*



Source: Unpublished data from a 2013 Western Health clinical audit.

A key barrier to translation is changing clinician behaviour, we therefore hypothesised that an effective way to meet the challenge of improving compliance with a number of evidence-based interventions simultaneously in a complex patient group would be to utilize an independent syndrome-based clinical service for CAP, analogous to those applied in other areas (e.g. stroke services)[29]. Our proposed CAP Service would have core responsibility for ensuring comprehensive and rigorous current evidence-based best practice by recommending that treating clinical teams align treatment with a standardized set of management algorithms incorporating interventions supported by at least Level-2 evidence. This novel service delivery approach would therefore represent the intervention we sought to test.

2.2 Using a suitably representative population and setting generalizable to the healthcare burden in Australia

We identified a fundamental issue of **representativeness and generalizability** as a key shortcoming of existing data in this field. Recognizing that concerns about the generalizability of previous clinical research to the "real world" have impeded application of evidence to practice, **we were anxious not to repeat past mistakes of enrolling a highly selected patient population that was not representative, and therefore would fail to change practice in the real world.** We therefore decided

to study a cohort of patients admitted under a General Internal Medical (GIM) service in a large metropolitan health service because:

1. In Australia, acute unplanned non-surgical hospital admissions in multimorbid patients are largely managed by GIM units, who therefore now manage the largest proportion of patients hospitalised with CAP. With population ageing, the elderly and highly multimorbid population treated by GIM units is likely to constitute the bulk of Australia's future health service burden for CAP[30]. At our service, approximately 50% of the 2000 annual admissions given a primary diagnosis of pneumonia are admitted under GIM units and comprise 20% of the total GIM inpatient service workload.
2. Benchmarking data obtained from our health service in 2012 revealed a demographic cohort similar to that described by AIHW data. In particular, the mean age of CAP patients in our GIM service (75 years) was similar to that described by AIHW (74 years) for all adult CAP admissions in Australia[31].

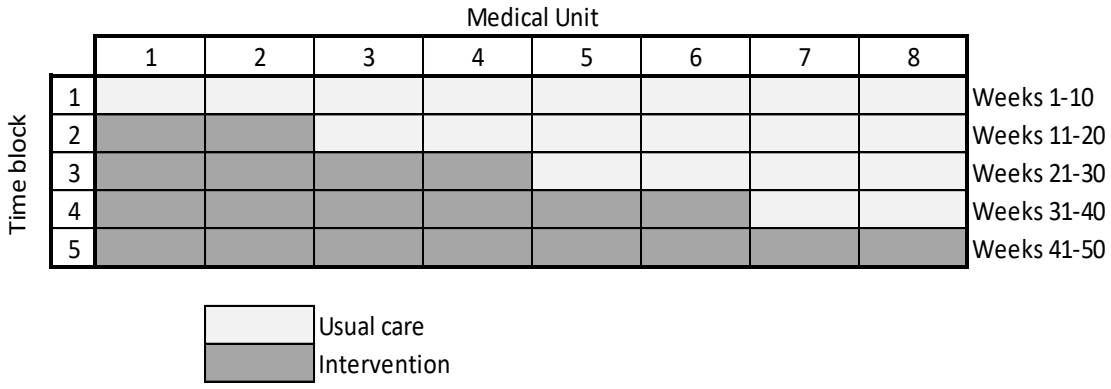
We also recognized that conventional clinical research studies are prone to selection bias because they often exclude patients with issues that make informed consent difficult, including cognitive impairment, confusion or drowsiness, general frailty, severe or life-threatening illness, hearing or visual impairment and linguistic difficulties[32-35]. In a modern Australian setting that is culturally and linguistically diverse (CALD) and has an ageing population with high rates of frailty, dementia and other co-morbidities, these factors may, collectively, affect a very large proportion of the population. We therefore needed a strategy that would enable inclusive enrolment, and avoid excluding patients with these common issues, to ensure that we were working with a truly representative sample.

2.3 How will we know whether the intervention works or not? Designing a robust evaluation framework

Our next challenge was to design a robust evaluation framework that would provide us with an unambiguous assessment of whether the intervention was worthwhile continuing. Most importantly we were aware of the very significant limitations of "before vs after" evaluations that, through their use of a historical control group, are subject to problems of confounding and bias that can undermine study validity and can lead to very misleading conclusions being drawn[36]. In conventional clinical research, these issues of bias and confounding are dealt with through the use of the randomized controlled trial (RCT), whereby allocating treatment to individuals on a random basis, one minimizes potential for confounding. However, we also recognized that health services interventions are

fundamentally designed to be deployed at scale (e.g. organisation-wide), meaning that deployment based on individual randomisation is impractical. Therefore, the most appropriate designs for us to use would be one where the unit of randomisation is larger – ideally based on a practical sub-division of the existing health system that can then be used as the unit for randomisation. We decided that the relatively recent development of stepped-wedge methodology could provide a very effective tool in this context. Stepped-wedge studies are a modified type of cluster RCT. However, unlike conventional cluster RCTs, under the stepped-wedge methodology, after a baseline period during which none of the clusters receive the intervention, the intervention is progressively "rolled-out" in constant increments in several clusters over time so that by study conclusion, all clusters are receiving the intervention (Figure 4). This design is therefore analogous to an "upscaling" that effectively mimics the way an intervention may be deployed in practice and is therefore particularly well-suited to implementation and health services research[37,38]. Statistical analysis principles have now been established to ensure that variation in outcomes across clusters and time periods are appropriately modelled and accounted for when developing estimates of treatment effect from these designs[39]. This approach has significant logistic, financial and ethical advantages over conventional cluster- and individual-RCT approaches, particularly where collected outcomes are part of usual care, minimizing additional burden to researchers and participants[37,38,40,41].

Figure 4. *Stepped-wedge roll out of CAP Service by Medical Unit*



2.4 What would we like to see our intervention achieve? Which outcomes should we evaluate and how?

The purpose of implementing the new CAP Service intervention model was to improve outcomes for both the patient and the health service. Ideally, measurement of effectiveness therefore required a combination of health service outcomes (such as length of hospital stay and readmissions), clinical outcomes, and patient-reported outcomes. Early in the project design process, however, it became apparent that a compromise needed to be struck between optimizing the outcome measurement framework, maximising the generalizability of the results, managing the data collection costs associated with the study, and operating in accordance with certain ethical and regulatory constraints. In order to ensure our sample was representative and that our study would assess *effectiveness*, rather than *efficacy*, we felt that conducting our study under conditions of a waiver of individual consent was vital if we were to meet our primary objectives. However, a consequence of the waiver of consent approach was that we were limited to the use of routinely collected outcomes, as, consistent with NHMRC guidelines, the project investigators were not permitted to impose additional tests or measurements above that which constituted "standard care". In essence, the choice had to be made between recruitment of a large and representative sample using routinely available outcomes, or measurement of an "ideal" outcome set in a highly selected, non-representative population. The decision was made to pursue the former, given the primary purpose of this study was to establish proof in principle that the novel methodologies were a robust and feasible method for health service evaluation.

As patient-reported instruments are not routinely used by General Medicine clinicians at our institution, these were not able to be included as primary or secondary outcomes for the IMPROVE-GAP study. However, in recognising the value of these types of outcome measures, a compromise was reached where it was decided to recruit a nested sub-sample of individuals and obtain separate informed written consent to collect the additional PROMs in a pilot feasibility trial. Because the processes of individual consent and outcome evaluation are relatively labour intensive, given our funding constraints and staffing commitments to meeting the primary objectives of IMPROVE-GAP, recruitment to this sub-study (the CAP-PROMS study) was limited to a pilot feasibility trial conducted over a 10-week period at a single site (Sunshine Hospital). Nonetheless, the investigators were able to collect useful data from this sub-study to inform design of a future standardised outcomes model that we hope to integrate into routine clinical practice.

2.5 Summary of key design elements of IMPROVE-GAP

With these considerations in mind we designed a combined implementation / evaluation framework based on the stepped-wedge cluster randomized controlled trial approach. The methodology of this is described in detail elsewhere, including in a clinical trial registry (www.ClinicalTrials.gov registry number: NCT02835040) and a standalone methods paper published recently in the journal, *Trials* (see Appendix A). To summarize, the key design elements were as follows:

a) CAP Service intervention

Participants admitted under the experimental arm of the study were to be reviewed daily by the multi-disciplinary physiotherapist-led CAP Service who routinely advised treating teams using algorithm-based guidelines for the medical interventions (corticosteroids, early switch to oral antibiotics) and directly instituted the allied health interventions (early mobilisation out of bed and malnutrition screening with targeted nutrition management). Algorithms incorporated contraindications to the specific interventions and screening criteria to optimize safety.

b) Stepped wedge design

8 medical units and 5 time periods (representing a total of 40 separate time-unit clusters) were utilized, with the sequence by which each unit was rolled into the intervention determined by randomization performed prior to study commencement.

c) Waiver of consent

Our supervising HREC (Melbourne Health) approved a waiver of individual informed consent for the study, enabling an inclusive and representative sample to be enrolled while minimizing the administrative burden, and ultimately the cost of the study. We regard this as a crucial element that was fundamental to the project's success.

d) Primary and secondary outcomes

The primary outcome was hospital length of stay. This and key secondary outcomes (readmission to hospital at 30- and 90-days, and operational costs) were obtained through data extraction from Western Health's Health Performance Unit. 30- and 90-day mortality were obtained through data linkage with the Victorian Death Index via the State Department of Health and Human Services. Other secondary outcomes (protocol adherence, adverse events and complications) were extracted from the patient medical records by project investigators.

e) CAP-PROMS sub-study

Collected additional patient-reported outcome data, including validated instruments for measuring quality of life (EuroQoL EQ-5D-5L), independent function (Late-Life Function and Disability Instrument (LLFDI)) and pneumonia-specific symptoms (the CAP-Sym Questionnaire) at

admission, discharge, 30- and 90-days for a nested subset of individuals who provided written consent to participate.

Chapter 3 - Implementing the IMPROVE-GAP project

3.1 Pre-implementation planning

The pre-implementation phase of the study involved a lengthy ethics and governance application process, development of an extensive communication plan, registration of the clinical trial and publication of a methods paper.

The IMPROVE-GAP interventions were to be implemented across eight medical units treating patients in 12 different hospital wards, and would involve staff from four clinical professions. The complexity of the health service operating structure required the investigators to instigate a lengthy and inclusive communication strategy encompassing staff from senior managers to junior clinicians. Early meetings and written communications were complemented by regular updates throughout the study to maintain interest and momentum. This was a key factor in the project's subsequent successful implementation.

3.2 Implementation phase

Participant recruitment commenced on 1 August 2016 and continued for 50-weeks with a 2-week hiatus over the Christmas holidays to allow for staff absence during this time. Seasonality of pneumonia presentations meant that recruitment peaked during Winter and Spring seasons at both the beginning and end of the study. Statistical methodologies employed in the step-wedge analysis account for these seasonal variations and other time-period specific factors.

Despite widespread senior clinician support and our sophisticated communication plan, the implementation phase was not without challenges of a political nature. Given the novel evaluation framework, many clinical staff struggled to reconcile the project with their experience of traditional randomized clinical trials, and constant vigilance was required from the investigators to ensure the integrity of the ascertainment process and intervention protocols was maintained.

3.3 CAP-PROMS sub-study

Throughout the 10-week second block of IMPROVE-GAP implementation, all CAP patients admitted to Sunshine Hospital were invited to participate in the CAP-PROMs sub-study. This involved completion of three patient questionnaires to explore the impact of the CAP illness on symptoms (CAP-Sym

Questionnaire[42]), physical function (Late-Life Function and Disability Instrument[43]) and health-related quality of life (EuroQol EQ-5D-5L[44]) from the perspective of the individual patient. The purpose of this study was to determine whether routine use of patient-reported outcomes is feasible in the target population. Data was collected at admission and discharge from hospital, and via phone at 30- and 90-days post-discharge by trained research assistants. The feasibility of routinely applying this outcome framework was measured by the number of patients willing and able to participate, attrition rates and the time burden of measurement for clinicians. Established methods for determining instrument quality, such as missing data, floor and ceiling effects and responsiveness to change were also explored.

3.4 Post-implementation phase – ancillary data collection and aggregation

Multiple outcomes of the study required measurement to 90-days post enrolment. Primary outcome data was obtained from the Western Health Performance Unit. Mortality data was obtained via data linkage with the Victorian Death Index. While this resulted in a highly accurate data source, the data linkage process was lengthy and required contractual approval from both our organisation and the Department of Health, approval from the data custodian (Department of Justice) and establishment of a secure data sharing repository. External data linkage was completed in February 2018, with the final study database cleaned, finalised and delivered to the Biostatistician in early-May 2018.

3.5 Post-implementation phase – data analysis

Analysis of the final dataset took place between May and November 2018. Budget provision for biostatistics support was essential in ensuring appropriate resources were available for this challenging phase of the project, and that the analysis was completed to a high standard.

Chapter 4 - What have we learned? Results of the IMPROVE-GAP Project

4.1 Proof of principle

The IMPROVE-GAP study demonstrates that, in principle, it is possible to conduct robust interventional health services research in complex, elderly populations using stepped-wedge methodology. In particular, the precedent set from the successful completion of this study includes:

a) Granting of the waiver of consent

Provision of a waiver of informed consent for study participants for a prospective interventional trial presented a degree of risk for the governing Human Research Ethics Committee, and the precedent established by this decision is extremely important for future studies seeking to employ similar methodologies.

b) Reduced cost of clinical research

The cost of participant recruitment and monitoring throughout the IMPROVE-GAP study was constrained to an average of $350 / participant, which compares extremely favourably to published clinical trial data suggesting that average industry costs now total over $16, 000 per participant (2011 data)[45].

c) Established framework for effective data linkage

The successful IMPROVE-GAP data linkage framework included hospital administrative data, and the Victorian Births, Deaths and Marriages database. Established processes can now be applied efficiently in future studies.

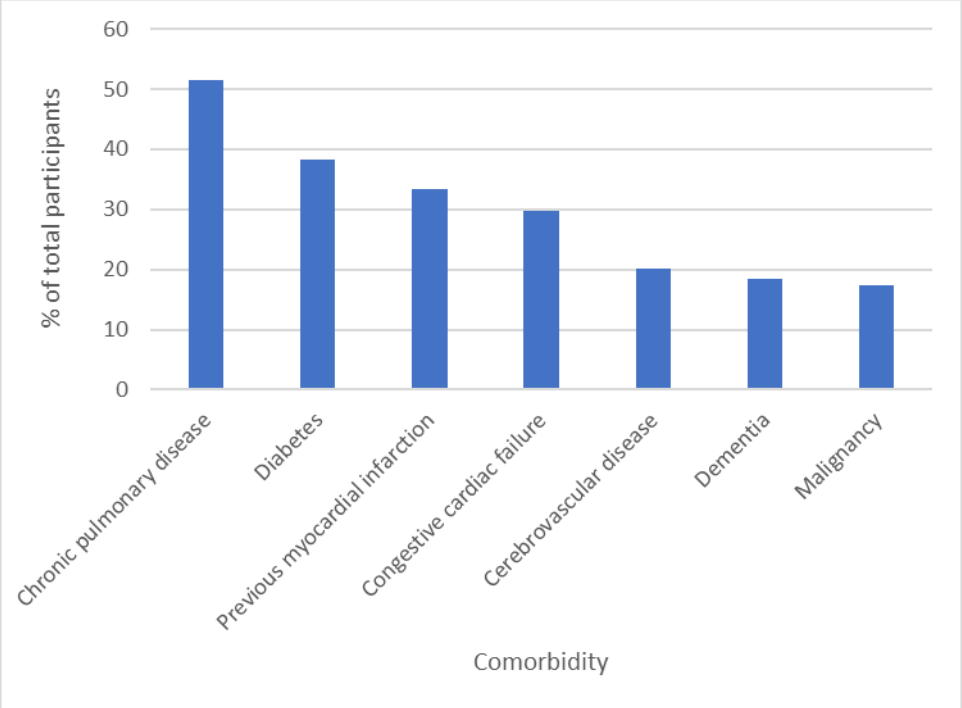
4.2 What are the characteristics of our representative cohort?

Aggregate baseline data provides an Illuminating picture of the IMPROVE-GAP cohort and, given the representative recruitment strategy employed, this information may be readily extrapolated to the broader General Medicine and community-acquired pneumonia populations. A snapshot of participant characteristics is provided here (Table 1 and Figure 5).

Table 1: *Baseline characteristics of individuals admitted under General Medicine units meeting standardized diagnostic criteria for community-acquired pneumonia (Footscray and Sunshine Hospitals, August 2016 to July 2017, n=816)*

Site *n (%)*:	
Sunshine	414 (50.7)
Footscray	402 (49.3)
Age *mean (SD)*	76.12 (13.3)
Sex (male) *n (%)*	465 (57.0)
Residential status *n (%)*:	
Independent living	637 (78.1)
Supported accommodation	25 (3.1)
Residential aged care	154 (18.9)
Language status (English spoken at home) *n (%)*	610 (74.8)
Baseline number medications, *median [interquartile range]*	7 [4-11]

Figure 5: *Comorbidities documented in the medical record of individuals admitted under General Medicine units meeting standardized diagnostic criteria for community-acquired pneumonia (Footscray and Sunshine Hospitals, August 2016 to July 2017, n=816)*



4.3 Adherence to evidence-based practice under the new model of care

The multi-disciplinary CAP team was highly successful in improving adherence to evidence-based practice across all four target interventions (Table 2).

Table 2: *Compliance with evidence-based interventions by exposure group*

Intervention component	Control n, (%)	Intervention n, (%)
Corticosteroids		
Prescription of 50mg corticosteroid daily within 36-hours of arrival in ED	105 (25.3%)	292 (72.8%)
Minimum 7-day duration corticosteroid prescription	14 (3.4%)	225 (56.1%)
Number compliant with protocol dosage and duration	8 (1.9%)	214 (53.4%)
Number ineligible (met pre-specified criteria for corticosteroid prescription contraindicated)	15 (3.6%)	16 (4.0%)
Antibiotics		
Switch to oral therapy made within 24-hours of stability criteria reached	287 (69.2%)	310 (77.3%)
Early mobilization		
Sit out of bed for >20 minutes with physiotherapist in first 24-hours of admission	119 (28.7%)	299 (74.6%)
Progressive movement achieved with physiotherapy on >70% eligible days	98 (23.6%)	329 (82.0%)
Number compliant with early mobilization protocol	80 (19.3%)	287 (71.6%)
Number ineligible (SOOB Day 1 contraindicated)	77 (18.6%)	74 (18.5%)
Nutrition		
MST score documented within 24-hours of admission	328 (79.0%)	387 (96.5%)
Appropriate nutrition therapy initiated in response to MST score	228 (54.9%)	333 (83.0%)
Patients receiving all interventions	0 (0.0%)	115 (28.7%)

Abbreviations: ED: Emergency Department; SOOB: sit out of bed; MST: Malnutrition screening tool.
Source: Reproduced from Lloyd M et al *JAMA Internal Medicine* 2019;179(8):1052-1060.

4.4 Effectiveness of the new evidence-based model of care

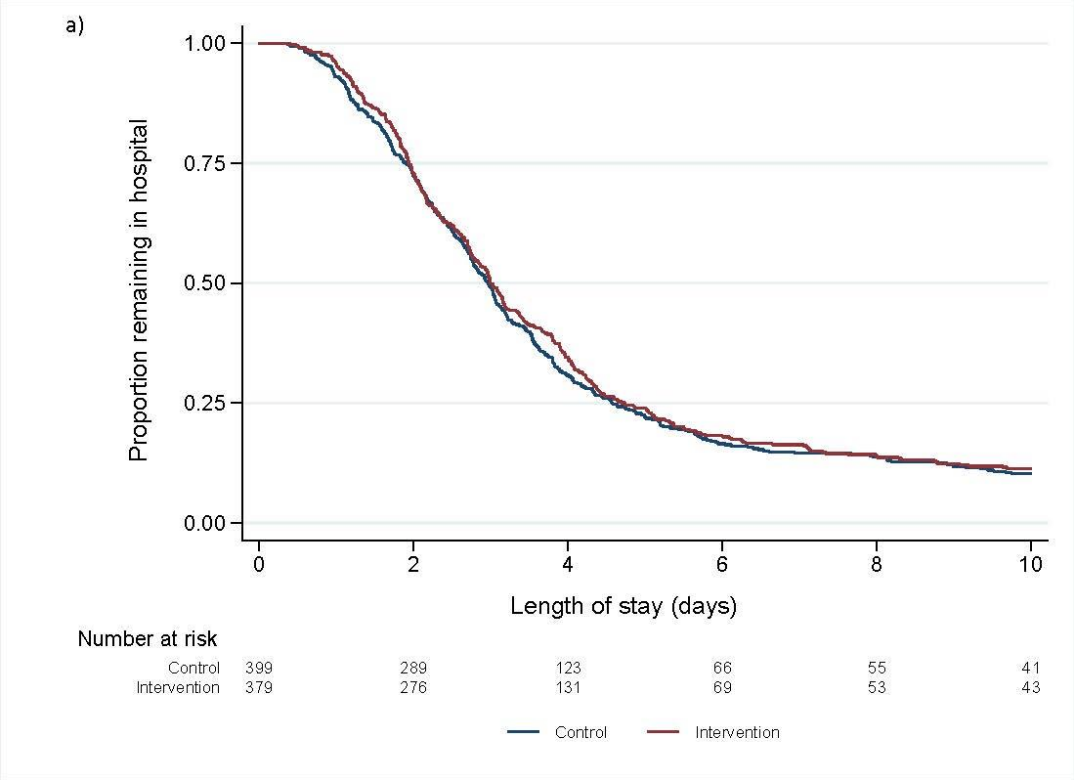
The results of the study are presented in detail in the published manuscript (Lloyd M, et al. JAMA Internal Medicine – see Appendix B) with a brief summary provided below.

Primary Outcome

Distributions of LOS were similar in control and intervention arms (Figure 6). We observed a geometric mean ratio [95% confidence interval] of 0.95 [0.78, 1.16] and an odds ratio [95% confidence interval] of

0.95 [0.57, 1.59] when LOS was analyzed as continuous and binary (LOS>3) variables, respectively. Therefore, no difference in the primary outcome of LOS between control and intervention arms was observed. This remained unchanged after adjustment for age and sex.

Figure 6: *Length of stay in hospital compared between study arms.*



Source: Reproduced from Lloyd et al. *JAMA Internal Medicine*. 2019; 179(8):1052-1060.

Secondary Outcomes

Minimal non-statistically significant differences between intervention and control arms were observed for mortality and readmission at all timepoints (inpatient, 30- and 90-days). Small proportions required ICU support (5.5% total) or mechanical ventilation (≤1%) with minimal differences between intervention and control arms.

A two-fold increase in new insulin prescription was observed in patients with diabetes in the intervention arm (unadjusted odds ratio: 1.96 [0.73, 5.25]). Number of gastrointestinal bleeding events, whilst small, was marginally higher for the intervention arm (nine events, 2.2%) compared to the control arm (three events, 0.7%: unadjusted estimated difference in mean proportions of 0.008 [95% CI: 0.005, 0.010]). None resulted in death.

Some interesting trends were observed in the mortality data for the study which will form an important basis for further work. In particular, we were interested in the strong associations between comorbidity incidence and residential status, and 6-month mortality in our cohort (see Figures 7 and 8 below).

Figure 7: *Mortality in the six-months following admission according to Charlson Comorbidity Index (CCMI) risk groups for individuals admitted under General Medicine meeting the standardized diagnostic criteria for community-acquired pneumonia (Footscray and Sunshine Hospitals, August 2016 to July 2017, n=816)*

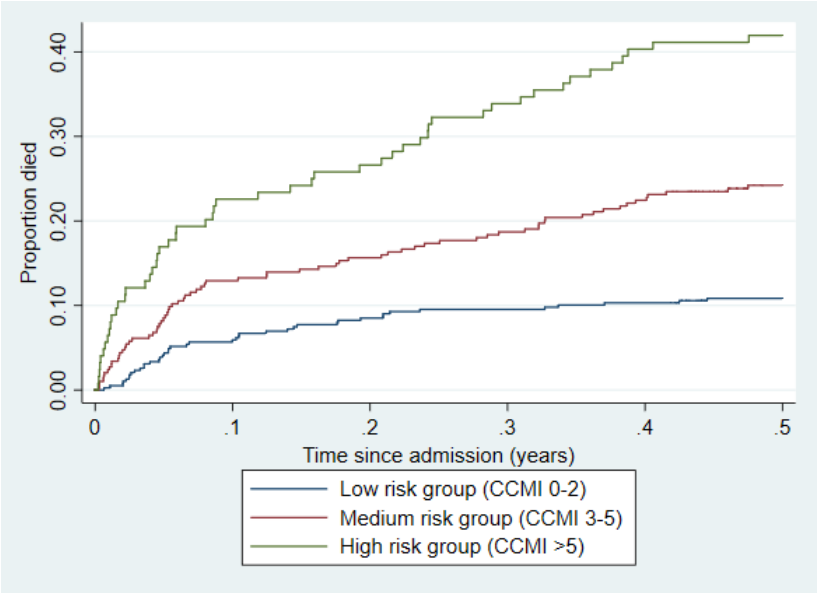
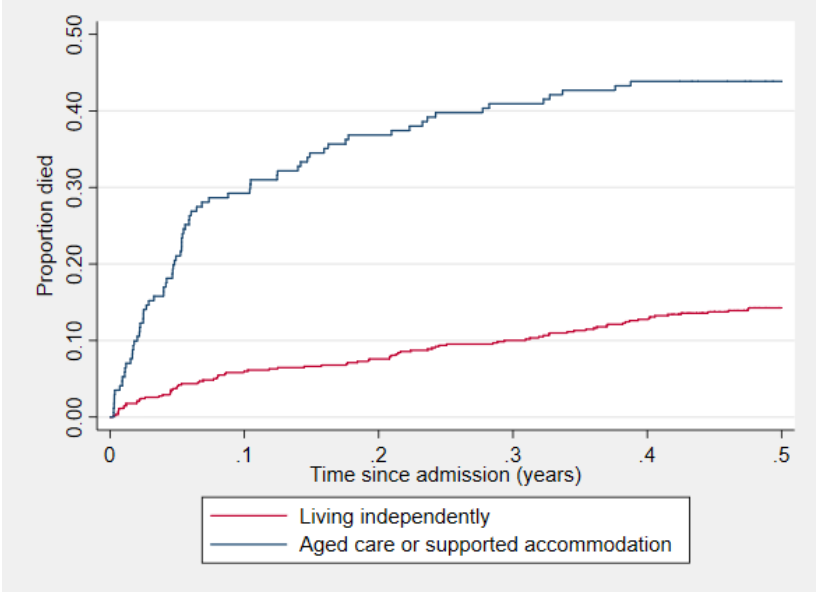


Figure 8: *Mortality in the six-months following admission according to residential status for individuals admitted under General Medicine meeting the standardized diagnostic criteria for community-acquired pneumonia (Footscray and Sunshine Hospitals, August 2016 to July 2017, n=816)*



4.5 Feasibility of routine application of patient-reported outcome measures

The CAP-PROMs pilot study reinforced that routine application of three short instruments to measure burden of symptoms, physical function and health related quality of life can provide valuable information relating to clinical recovery from the perspective of the individual patient. However, the heterogenous demographic characteristics, acuity of illness and complex underlying health status of the CAP population introduced challenges to feasibility and interpretability of these instruments. In particular, limited English language proficiency, cognitive impairment and acute confusion precluded participation for a significant proportion of the target patient group. Patients who participated in PROMs assessments were more likely to be younger, living independently in the community, and able to walk independently. Additionally, despite the concerted efforts of investigators, 40% of participants were lost to follow-up by 90-days post-discharge. The methodology and detailed results of the CAP-PROMs sub-study are provided in Appendix C.

The PROMs data collected also demonstrated that care must be taken when using symptom questionnaires in populations with a different demographic profile to the validation cohort used during psychometric testing of the instrument. There was a trend for younger participants to report a higher burden of symptoms at admission consistent with results of prior studies[46,47]. The impact of age on outcomes was less problematic for the health-related quality of life instrument.

Our sub-study demonstrates that further research is required to maximize efficiency of routine patient-reported data collection in complex multimorbid populations, without compromising sensitivity and specificity of that data. Modified approaches should also be developed for the large and growing proportion of patients for whom traditional PROMs are not feasible.

Chapter 5 – Implications for clinical practice

This study found no evidence that routine application of evidence-based interventions for CAP improved duration of hospitalization or other clinical outcomes. It was also associated with increased incidence of gastrointestinal bleeding.

Prior to this study, evidence supporting all interventions used in our bundle appeared sound. Routine early mobilisation has been shown to safely reduce duration of hospitalisation,[25] and when applied in conjunction with early switch to oral antibiotics achieved a 2-day reduction in LOS.[27] Systematic screening for malnutrition risk and targeted nutritional therapy has been shown to reduce readmission rates in malnourished medical inpatients. Although the issue of adjunctive corticosteroid has continued to be somewhat contentious, at least 17 RCTs (with >2000 participants) have now been performed and subjected to numerous meta-analyses by separate research groups yielding consistent results interpreted in a similar fashion.[23,24,48-51] The recent Cochrane review states that "people with CAP treated with corticosteroids had lower clinical failure rates (death, worsening of imaging studies, or no clinical improvement), shorter time to cure, shorter hospital stay, and fewer complications."[48] Meta-analyses suggested overall serious adverse event rates are no higher or even reduced with corticosteroids.[24,48,49] However this has not allayed concerns of many.[52-54] Our finding of increased gastrointestinal bleeding reinforces these concerns. Although this comes in the context of a bundle with three other interventions, it is difficult to see how the non-corticosteroid components of the intervention (early mobilization, antibiotic switch rules or dietary assessment and intervention) could have contributed to this. This is especially so given the magnitude of the effect was similar to the increased rates of gastrointestinal bleeding seen with corticosteroid use more broadly.[55]

Our study was carefully designed to enrol a study sample most representative of the overall burden of disease in our population and to deploy the intervention as it might realistically be implemented in "real life" as part of a guideline-package designed to improve routine care. It therefore aimed to measure *effectiveness*, rather than *efficacy*. We hoped this would resolve the uncertainty that has prevented the large existing body of clinical trial evidence from translating into clinical practice. A particular strength was that it circumvented the ascertainment bias problematic in previous RCTs.[56] For instance the largest previous RCT of adjunctive corticosteroids by Blum *et al*. (n=785) recruited 27% of screened patients with CAP, requiring a 4.5 year enrolment period at 7 hospitals.[21] By comparison, 89% of CAP patients were recruited to our study (n=816) over 12 months. The stepped-wedge cluster-randomized design was an additional strength that enabled robust analytical methods, minimizing potential for bias or confounding, whilst enabling a pragmatic "roll-out" of the intervention. It is especially well-suited for experimental evaluations of health system interventions' effectiveness.[57]

Previous corticosteroid, early mobilization and antibiotic stopping rule studies are notable for consistently demonstrating LOS reductions.[25,27,48] This stark difference from the findings of our own study could relate to previous studies' aforementioned issues of ascertainment bias, but also to other health system factors influencing LOS. For instance the 3 day median LOS in our study compares with 6-7 days in the adjunctive corticosteroid study by Blum *et al.*[21] Another explanation is that the manner in which we deployed the intervention may have diluted any effect (whether advantageous or disadvantageous). For instance, a small percentage in our control arm (mostly patients with co-existing chronic lung disease) received some corticosteroid – albeit generally at much lower doses and shorter courses than recommended in our intervention arm. Adherence to corticosteroid prescribing in the intervention arm was also incomplete. However, our design was valid as a means of measuring effectiveness (rather than efficacy) as it reflects a "real-life" scenario whereby guideline adherence is likely to be incomplete and subject to a variety of factors.

Chapter 6 - Lessons learned from the IMPROVE-GAP project

6.1 Challenges

The IMPROVE-GAP study highlighted a number of challenges faced by researchers seeking to implement health service evaluation studies. These are discussed below.

a) The administrative burden associated with ethical review, governance submissions, project staff recruitment and data linkage is considerable. A large proportion of Project Manager time was devoted to administration, at the expense of time spent pursuing scientific enquiry.
b) The waiver of consent, while approved by our governing HREC, remained controversial and was challenged in its legitimacy by senior clinical staff on a number of occasions. This required clear and open communication from the Principal Investigators to maintain the integrity of the project and clinician support.
c) Novel methodologies that divert from the traditional RCT model can be difficult to implement due to the additional training and oversight required, and the difficulty in overcoming preconceived ideas held by clinical staff about the way research should be conducted. Again, this required a comprehensive communication plan.
d) There is a strong need for adequate data management, biostatistics and analytical support ongoing throughout the project in order to secure timely results. The current Australian skill shortage in this area led, in our case, to a delay in analysis and dissemination of the final results.

6.2 Successes

Despite the challenges, the project investigators can celebrate a number of significant successes. In particular, effectively completing recruitment for a clinical trial with more than 800 participants within year and with a budget of $350/participant is more or less unprecedented under current conditions. In the Australian medical research industry, competition for funding demands that teams increasingly set more ambitious output targets. The scientific, ethical and administrative precedent set by studies such as IMPROVE-GAP, has the potential to revolutionise the way health services evaluate clinical practice in the context of significant funding constraints.

6.3 Additional resources leveraged due to IMPROVE-GAP funding

In order to leverage the opportunities created by the HCF Foundation Grant and maximise the research output of the study, additional sources of funding were pursued during the project, mostly to support staff salaries for the sub-analyses. These included:

1. An Australian Government Research Training Scheme Scholarship 2017-2020 ($94,000) was awarded to the project research manager (Melanie Lloyd) to support her in PhD studies over 3 years to continue work on data collected during IMPROVE-GAP and generate further scientific value from this project.
2. A medical student was recruited to work full-time on the project for 6 months, as part of a University of Melbourne final year research module. This augmented data collection and has facilitated additional research papers (Appendix C) and presentations arising from the project.

Chapter 7 – Dissemination of study findings: Publications and presentations

The primary results paper was accepted for publication in JAMA Internal Medicine (a world leading medical journal with an Impact Factor of 19.9) in March 2019 and published in its 8 July 2019 Edition. It is currently ranked in the top 2% of all research outputs, according to Altmetric, based on its social and mainstream media impact. Current commentary suggests that it is likely to have an effect on policy and practice at a global level, especially in regard to the question of whether or not to administer adjunctive corticosteroids for pneumonia. This landmark publication has also been supplemented by the publication of the trial protocol in 2018 and three additional sub-studies in 2019. These are listed below and abstracts are included in the Appendices.

Members of the research team have also presented project findings at a number of prestigious national conferences including the BMJ Quality and Safety Forum (Melbourne, September 2018), the NHMRC Research Translation Symposium (Sydney, November 2018), the Australasian Society of Infectious Diseases (ASID) Annual Scientific Congress (Darwin, May 2019) and the Australian Physiotherapy Conference (Sydney, October 2017). Additional conference papers have been accepted for presentation at the Internal Medicine Society of Australia and New Zealand Conference (5 abstracts accepted for this meeting being held in Melbourne, in September 2019) and the ACTA International Clinical Trials Conference (Sydney, October 2019). These are listed below, with selected conference abstracts also included in Appendix F. Awards presented to members of the research team in recognition of this work are documented in Appendix G.

List of Publications:

1. Lloyd M, Janus E, Karahalios A, Callander E, Tang C, Lowe S, Skinner E, Karunajeewa H. Effectiveness of a bundled intervention including adjunctive corticosteroids on outcomes of hospitalized patients with community-acquired pneumonia: A stepped-wedge randomized clinical trial. *JAMA Internal Medicine*. 2019; 179(8):1052-1060.
2. Skinner, E, Lloyd, M, Janus, E, Ong, ML, Karahalios, A, Haines, TP, Kelly, AM, Shackell, M, and Karunajeewa, H, 2018, The IMPROVE-GAP Trial aiming to improve evidence-based management of community-acquired pneumonia: study protocol for a stepped-wedge randomised controlled trial. *Trials*. 2018;19:88. doi.org/10.1186/s13063-017-2407-4.
3. Lloyd M, Janus E, Karahalios A, Callander E, Tang C, Lowe S, Skinner E, Karunajeewa H. Patient-reported outcome measurement in community-acquired pneumonia: Feasibility of routine application in an elderly hospitalized population. *BMC Pilot and Feasibility Studies*. 2019; 5:97.

4. Lloyd M, Callander E, Karahalios A, Desmond L, Karunajeewa H. Patient-reported outcome measures in community-acquired pneumonia: a systematic review of application and content validity. *BMJ Open Respiratory Research*. 2019; 6:e000398.
5. Desmond L, Janus E, Lloyd M, Ryan S, Karunajeewa H. Respiratory viruses in adults hospitalised with community-acquired pneumonia during the non-winter months in Melbourne: Routine diagnostic practice may miss large numbers of influenza and respiratory syncytial virus infections. *Communicable Diseases Intelligence*. 2019; 43. doi.org/10.33321/cdi.2019.43.12.

List of Abstracts accepted for presentation at Scientific Conferences:

1. Lloyd M, Karahalios A, Skinner E, Lowe S, Shackell M, Ko S, Desmond L, de Silva A, Haines T, Janus E, Karunajeewa H. A stepped-wedge cluster randomized controlled study assessing the effectiveness of an adjunctive corticosteroid-based intervention in hospitalized patients with community-acquired pneumonia. Australasian Infectious Diseases Society Annual Scientific Congress, Darwin, May 2019.
2. Karunajeewa H, Lloyd M, Karahalios A, Skinner E, Ong ML, Shackell M, Kelly AM, Harrison R, Haines T, Janus E. Utilizing the stepped wedge cluster randomized controlled trial design to test the effectiveness of health systems interventions: A "real-world" implementation research study to assess the effectiveness of a new model of care for community-acquired pneumonia. NHMRC Research Translation Symposium, Sydney, November 2018.
3. Karunajeewa H, Lloyd M, Karahalios A, Janus E, Haines T, Skinner E, De Silva A, Lowe S, Shackell M, Desmond L, Ko S. Integrating implementation and evaluation using the "stepped wedge" framework: A research study to assess the effectiveness of a new model of care for community-acquired pneumonia. BMJ Quality and Safety Forum, Melbourne, October 2018.
4. Lloyd M, Janus E, Karahalios A, Callander E, Tang C, Karunajeewa H. Patient-reported outcome measures in adult community-acquired pneumonia: A pilot study to determine feasibility and acceptability of routine use in elderly hospital populations. BMJ Quality and Safety Forum, Melbourne, October 2018.
5. Lloyd M, Janus E, Lowe S, Tang CY, Shackell M, Haines T, Skinner E, Karahalios A, Callander E, Haines K, Bali P, Ko S, Kelly AM, Karunajeewa H. Connecting the Silos: Physiotherapist leadership in promoting multidisciplinary evidence-based management of community-acquired pneumonia. Australian Physiotherapy Conference, Sydney, October 2017.
6. Lloyd M, Karunajeewa H, Janus E, Tang C, Skinner E, Haines T, Haines K, Lowe S, Shackell M, Karahalios A, Callander E. Defining Patient-Reported Outcomes in Community-Acquired Pneumonia: A pilot study to determine feasibility of routine application in an elderly, multimorbid population. Australian Physiotherapy Conference, Sydney, October 2017.

7. Lloyd M, Karunajeewa H, Karahalios A, Janus E, Haines T, Skinner E, De Silva A, Lowe S, Shackell M, Desmond L, Ko S. The IMPROVinG Evidence-based interventions and outcomes in community-Acquired pneumonia trial. ACTA International Clinical Trials Conference, Sydney, October 2019.
8. Lloyd M, Janus E, Karahalios A, Callander E, Tang C, Karunajeewa H. Patient-reported outcome measures in adult community-acquired pneumonia: A pilot study to determine feasibility and acceptability of routine use in elderly hospital populations. Internal Medicine Society of Australia and New Zealand Annual Conference, Melbourne, September 2019.
9. Ko S, Lloyd M, Karunajeewa H, Karahalios A, Janus E, Haines T, Skinner E, De Silva A, Lowe S, Shackell M, Desmond L. The IMPROVinG Evidence-based interventions and outcomes in community-Acquired pneumonia trial. Internal Medicine Society of Australia and New Zealand Annual Conference, Melbourne, September 2019.
10. Skinner E, Lloyd M, Janus E, Karunajeewa H. Community-acquired pneumonia in the 21st century: Disaggregating the clinical phenotype. Internal Medicine Society of Australia and New Zealand Annual Conference, Melbourne, September 2019.
11. Milevski S, Lloyd M, Maguire G, Janus E, Karunajeewa H. Weekend admissions and changes in treating physician are associated with poorer outcomes in patients admitted with community-acquired pneumonia. Internal Medicine Society of Australia and New Zealand Annual Conference, Melbourne, September 2019.
12. Vadher G, Maguire G, Lloyd M, Janus E, Karunajeewa H. Intertwining of heart disease and community-acquired pneumonia. Internal Medicine Society of Australia and New Zealand Annual Conference, Melbourne, September 2019.

Chapter 8 - Where to now? Opportunities and Next Steps

We believe that we have succeeded in demonstrating a highly successful proof of principle for a novel approach to prosecuting health services implementation research in the modern Australian hospital system. We would now like to take this further by expanding this framework into what we term a "learning health system" that uses methodologies such as our stepped-wedge approach to concurrently measure effectiveness during implementation and optimise translation of scientific evidence into clinical practice. This would represent a means by which our hospitals could evaluate a variety of health services interventions in a practical, robust, timely and cost-effective way.

At a local level, IMPROVE-GAP has built capacity within our own health service with personnel, expertise and infrastructure to expand and extend our work. In particular, development of capacity in this field has proven timely, as the platform is especially well aligned with the strategic goals of new funding avenues, such as the Australian Medical Research Future Fund (MRFF) which lists the following amongst its priority areas[18]:

a) *"Support stronger partnerships between researchers, healthcare professionals, governments and the community.*
b) *Make better use of existing data and infrastructure to help improve our health and medical research.*
c) *Strengthen our health services and systems research to make healthcare more efficient and affordable.*
d) *Develop the skills of researchers and healthcare professionals and encourage collaboration across health and medical research disciplines and sectors.*
e) *Support new and existing clinical trial networks to guide the development of new drugs and devices, new models of care, and improved clinical practice."*

Our aims now are, therefore, to build upon this and other work conducted by the Western Health Chronic Disease Alliance to leverage funding support, including from government bodies (such as Victorian State Government, NHMRC, MRFF), to enable further hospital-based implementation research and realize our strategic vision of becoming Australia's leading institution for scientific evaluation of novel models of healthcare. As a result of the HCF Foundation's support for the IMPROVE-GAP study, we can now define our strengths and capabilities as follows:

a) Proof that we can effectively access a very large population substrate through General Internal Medical services at tertiary hospitals and utilise this population for high quality health services research.

b) Demonstrated track record in dealing with representative populations that have “priority” problems of multi-morbidity, frailty, end-of-life care and complex multi-disciplinary care needs.
c) Experience in performing research with a heavy emphasis on cost-effectiveness.
d) Demonstrated track record in successfully deploying cluster randomized / stepped-wedge methodologies made feasible by waiver of, or limited consent, frameworks.
e) Track record of successful cost-minimising multi-disciplinary collaboration that brings together a team of health professionals from a number of craft groups, and scientific collaborators with key specialized expertise in clinical trials statistics and health economics.

List of Abbreviations

CALD: culturally and linguistically diverse
CAP: community-acquired pneumonia
CAP-PROMs: Patient-reported outcomes in community-acquired pneumonia pilot study
ICU: Intensive Care Unit
IMPROVE-GAP: The Improving Evidence-based GAPs and outcomes in community-acquired pneumonia trial
IRCU: Intensive Respiratory Care Unit
GIM: General Internal Medicine
HDU: High Dependency Unit
LOS: length of stay
PhD: Doctor of Philosophy degree
PROMs: patient-reported outcome measures
RCT: randomized controlled trial
WH: Western Health

Appendices

Publications, submitted manuscripts, abstracts submitted for conference / symposium presentations and a list of awards arising from this work are included in the following appendices.

Appendix A – IMPROVE-GAP Protocol publication

Skinner E, et al. *Trials.* 2018;19:88. doi.org/10.1186/s13063-017-2407-4.

Skinner *et al. Trials* (2018) 19:88
DOI 10.1186/s13063-017-2407-4

Trials

STUDY PROTOCOL Open Access

The IMPROVE-GAP Trial aiming to improve evidence-based management of community-acquired pneumonia: study protocol for a stepped-wedge randomised controlled trial

Elizabeth H. Skinner[1,2,3*], Melanie Lloyd[1], Edward Janus[4,5], May Lea Ong[4], Amalia Karahalios[6], Terry P. Haines[3], Anne-Maree Kelly[5,7], Melina Shackell[1,2] and Harin Karunajeewa[4,5,8]

Abstract

Background: Community-acquired pneumonia is a leading worldwide cause of hospital admissions and healthcare resource consumption. The largest proportion of hospitalisations now occurs in older patients, with high rates of multimorbidity and complex care needs. In Australia, this population is usually managed by hospital inpatient general internal medicine units. Adherence to consensus best-practice guidelines is poor. Ensuring evidence-based care and reducing length of stay may improve patient outcomes and reduce organisational costs. This study aims to evaluate an alternative model of care designed to improve adherence to four Level 1 or 2 evidence-supported interventions (routine corticosteroids, early switch to oral antibiotics, early mobilisation and routine malnutrition screening).

Methods/Design: The IMPROVing Evidence-based treatment Gaps and outcomes in community-Acquired Pneumonia (IMPROVE-GAP) trial is a pragmatic, investigator-initiated, stepped-wedge randomised trial. Patients hospitalised under a general internal medicine unit who meet a standard case definition for community-acquired pneumonia will be included. Eight general internal medicine units at two Australian hospitals in a single health service will be randomised using concealed allocation to: (i) usual medical, nursing and allied health care delivered according to existing organisational practice or (ii) care supported by a dedicated "community-acquired pneumonia service": a multidisciplinary team deploying algorithm-based implementation of a bundle of the four evidence-based interventions. The primary outcome measure will be length of hospital stay. Secondary outcome measures include inpatient mortality, 30 and 90 day readmission rates and mortality and health-service utilisation costs. Protocol adherence will be measured and reported, and serious adverse events (rates of hyperglycaemia requiring new insulin; falls during mobilisation) will be collected and reported.

Discussion: IMPROVE-GAP represents an important and unique precedent for testing a new service-delivery model for improving compliance with a number of evidence-based interventions. Its stepped-wedge randomised controlled trial design provides a means to address some significant ethical, organisational and other methodological challenges to evaluating the effectiveness of health-service interventions in complex hospital populations. The new service-delivery model will effectively be fully implemented by trial completion, facilitating rapid, seamless translation into practice should care outcomes be superior. This trial is currently recruiting.

Trial registration: ClinicalTrials.gov, NCT02835040. Prospectively registered on 22 May 2016.

Keywords: Community-acquired pneumonia, Randomised controlled trial, Corticosteroids, Antibiotic, Early mobilisation, Malnutrition

Appendix B – IMPROVE-GAP Main Paper

Lloyd M, et al. *JAMA Internal Medicine.* 2019; 179(8):1052-1060. doi:10.1001/jamainternmed.2019.1438

JAMA Internal Medicine | Original Investigation

Effectiveness of a Bundled Intervention Including Adjunctive Corticosteroids on Outcomes of Hospitalized Patients With Community-Acquired Pneumonia
A Stepped-Wedge Randomized Clinical Trial

Melanie Lloyd, MPhtySt; Amalia Karahalios, PhD; Edward Janus, MD, PhD; Elizabeth H. Skinner, PhD; Terry Haines, PhD; Anurika De Silva, PhD; Stephanie Lowe, MPH; Melina Shackell, BPty; Soe Ko, MBBS; Lucy Desmond, MD; Harin Karunajeewa, MBBS, PhD; for the Improving Evidence-Based Treatment Gaps and Outcomes in Community-Acquired Pneumonia (IMPROVE-GAP) Implementation Team at Western Health

IMPORTANCE Community-acquired pneumonia remains a leading cause of hospitalization, mortality, and health care costs worldwide. Randomized clinical trials support the use of adjunctive corticosteroids, early progressive mobilization, antibiotic switching rules, and dietary interventions in improving outcomes. However, it is uncertain whether implementing these interventions will translate into effectiveness under routine health care conditions.

OBJECTIVE To evaluate the effectiveness of a bundle of evidence-supported treatments under conditions of routine care in a representative population hospitalized for community-acquired pneumonia.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, stepped-wedge, cluster-randomized clinical trial with 90-day follow-up was conducted between August 1, 2016, and October 29, 2017, in the general internal medicine service at 2 tertiary hospitals in Melbourne, Australia, among a consecutive sample of patients with community-acquired pneumonia. The primary analysis and preparation of results took place between May 14 and November 25, 2018.

INTERVENTIONS Treating clinical teams were advised to prescribe prednisolone acetate, 50 mg/d, for 7 days (in the absence of any contraindication) and de-escalate from parenteral to oral antibiotics according to standardized criteria. Algorithm-guided early mobilization and malnutrition screening and treatment were also implemented.

MAIN OUTCOMES AND MEASURES Hospital length of stay, mortality, readmission, and intervention-associated adverse events (eg, gastrointestinal bleeding and hyperglycemia).

RESULTS A total of 917 patients were screened, and 816 (351 women and 465 men; mean [SD] age, 76 [13] years) were included in the intention-to-treat analysis, with 401 patients receiving the intervention and 415 patients in the control group. An unadjusted geometric mean ratio of 0.95 (95% CI, 0.78-1.16) was observed for the difference in length of stay (days) between the intervention and control groups. Similarly, no significant differences were observed for the secondary outcomes of mortality and readmission, and the results remained unchanged after further adjustment for sex and age. The study reported higher proportions of gastrointestinal bleeding in the intervention group (9 [2.2%]) compared with the controls (3 [0.7%]), with an unadjusted estimated difference in mean proportions of 0.008 (95% CI, 0.005-0.010).

CONCLUSIONS AND RELEVANCE This bundled intervention including adjunctive corticosteroids demonstrated no evidence of effectiveness and resulted in a higher incidence of gastrointestinal bleeding. Efficacy of individual interventions demonstrated in clinical trials may not necessarily translate into effectiveness when implemented in combination and may even result in net harm.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT02835040

JAMA Intern Med. doi:10.1001/jamainternmed.2019.1438
Published online July 8, 2019.

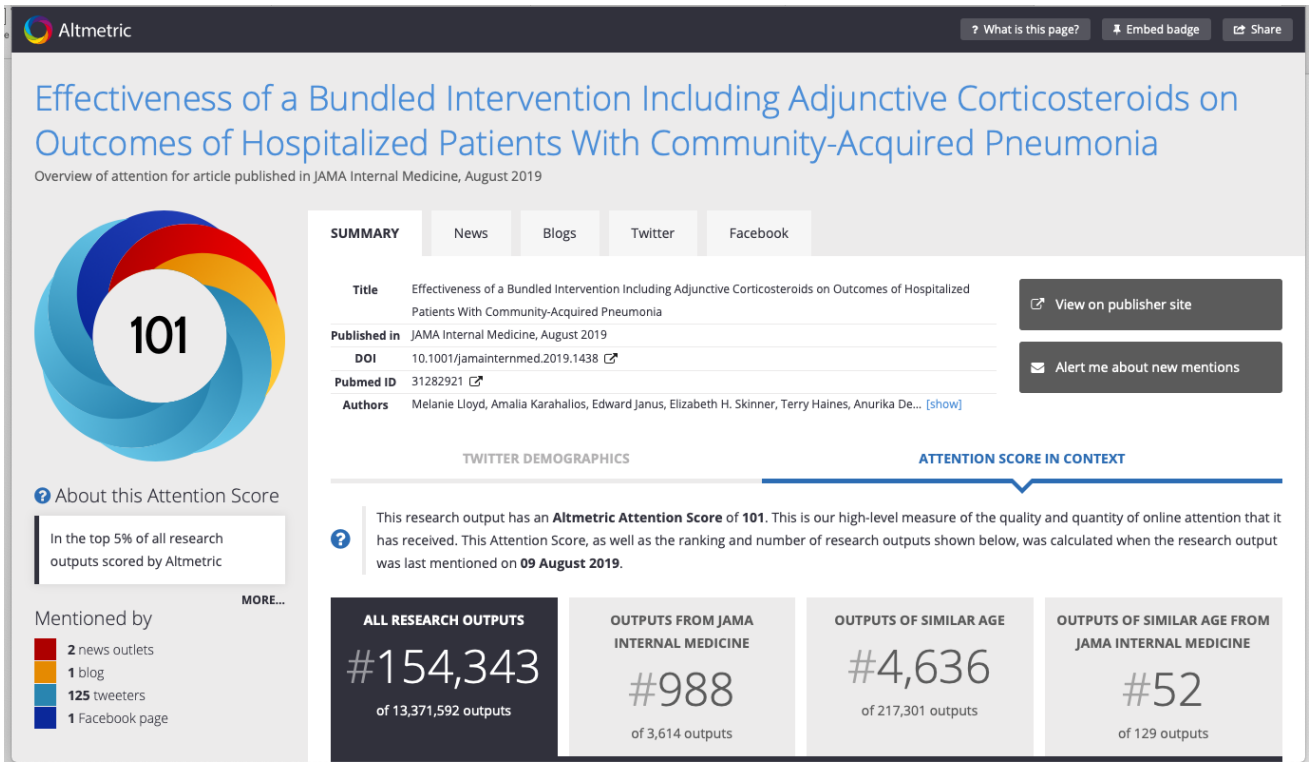
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Improving Evidence-Based Treatment Gaps and Outcomes in Community-Acquired Pneumonia (IMPROVE-GAP) Implementation Team at Western Health appear at the end of the article.

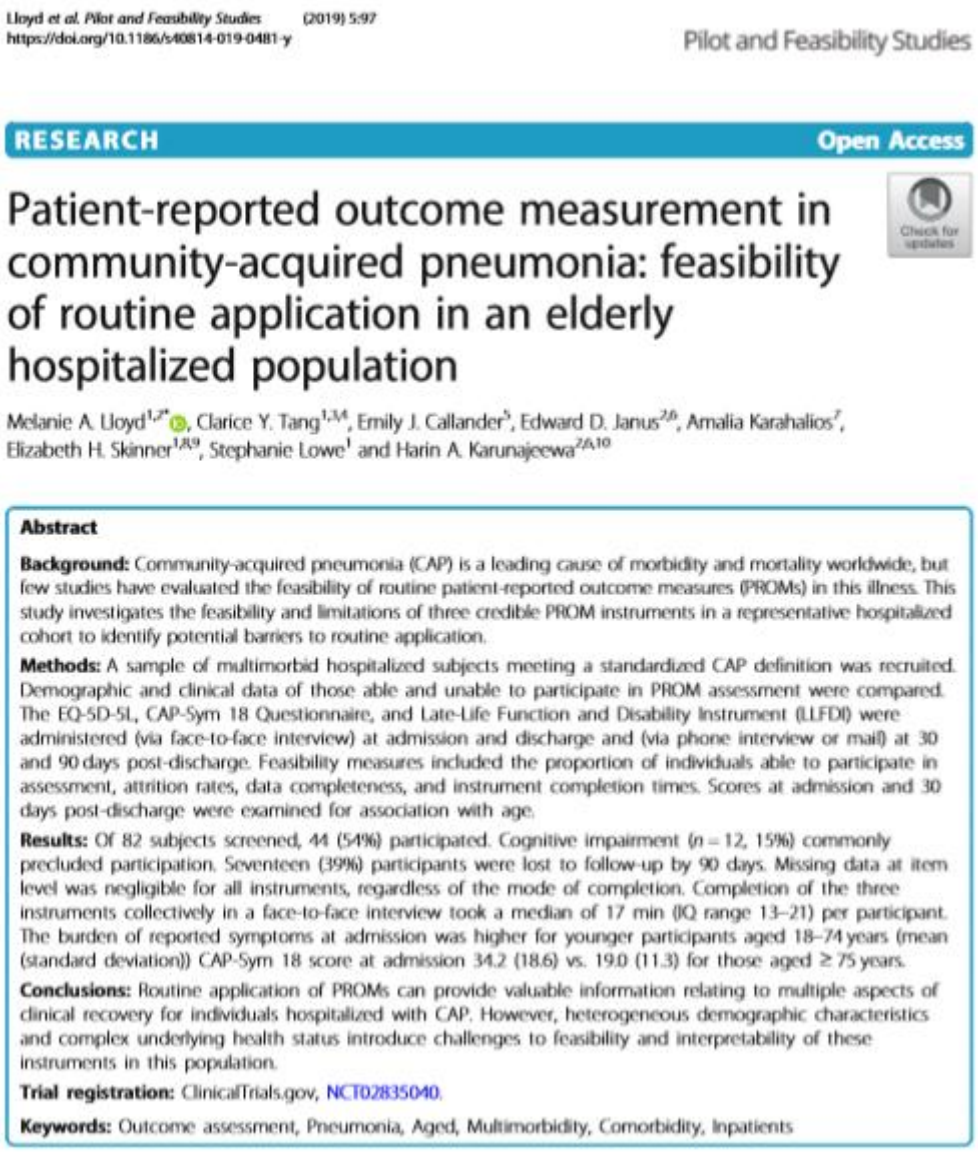
Corresponding Author: Harin Karunajeewa, MBBS, PhD, General Internal Medicine Unit, Western Health, The University of Melbourne, Melbourne, Australia (harin.karunajeewa@wh.org.au).

Appendix B (2) Altmetric Research Metrics for main IMPROVE-GAP paper (as of August 15)



Appendix C – PROMs sub-study

Lloyd M, et al. *BMC Pilot and Feasibility Studies*. 2019; 5:97. https://doi.org/10.1186/s40814-019-0481-y



Lloyd et al. Pilot and Feasibility Studies (2019) 5:97
https://doi.org/10.1186/s40814-019-0481-y

Pilot and Feasibility Studies

RESEARCH Open Access

Patient-reported outcome measurement in community-acquired pneumonia: feasibility of routine application in an elderly hospitalized population

Melanie A. Lloyd[1,2*], Clarice Y. Tang[1,3,4], Emily J. Callander[5], Edward D. Janus[2,6], Amalia Karahalios[7], Elizabeth H. Skinner[1,8,9], Stephanie Lowe[1] and Harin A. Karunajeewa[2,6,10]

Abstract

Background: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide, but few studies have evaluated the feasibility of routine patient-reported outcome measures (PROMs) in this illness. This study investigates the feasibility and limitations of three credible PROM instruments in a representative hospitalized cohort to identify potential barriers to routine application.

Methods: A sample of multimorbid hospitalized subjects meeting a standardized CAP definition was recruited. Demographic and clinical data of those able and unable to participate in PROM assessment were compared. The EQ-5D-5L, CAP-Sym 18 Questionnaire, and Late-Life Function and Disability Instrument (LLFDI) were administered (via face-to-face interview) at admission and discharge and (via phone interview or mail) at 30 and 90 days post-discharge. Feasibility measures included the proportion of individuals able to participate in assessment, attrition rates, data completeness, and instrument completion times. Scores at admission and 30 days post-discharge were examined for association with age.

Results: Of 82 subjects screened, 44 (54%) participated. Cognitive impairment ($n = 12$, 15%) commonly precluded participation. Seventeen (39%) participants were lost to follow-up by 90 days. Missing data at item level was negligible for all instruments, regardless of the mode of completion. Completion of the three instruments collectively in a face-to-face interview took a median of 17 min (IQ range 13–21) per participant. The burden of reported symptoms at admission was higher for younger participants aged 18–74 years (mean (standard deviation)) CAP-Sym 18 score at admission 34.2 (18.6) vs. 19.0 (11.3) for those aged ≥ 75 years.

Conclusions: Routine application of PROMs can provide valuable information relating to multiple aspects of clinical recovery for individuals hospitalized with CAP. However, heterogeneous demographic characteristics and complex underlying health status introduce challenges to feasibility and interpretability of these instruments in this population.

Trial registration: ClinicalTrials.gov, NCT02835040.

Keywords: Outcome assessment, Pneumonia, Aged, Multimorbidity, Comorbidity, Inpatients

Appendix D – PROMs systematic review

Lloyd M, et al. *BMJ Open Respiratory Research*. 2019;6:e000398. http://dx.doi.org/10.1136/bmjresp-2018-000398

Respiratory research

BMJ Open Respiratory Research

Patient-reported outcome measures in community-acquired pneumonia: a systematic review of application and content validity

Melanie Lloyd,[1,2] Emily Callander,[3] Amalia Karahalios,[4] Lucy Desmond,[5] Harin Karunajeewa[1,5]

To cite: Lloyd M, Callander E, Karahalios A, *et al*. Patient-reported outcome measures in community-acquired pneumonia: a systematic review of application and content validity. *BMJ Open Resp Res* 2019;**6**:e000398. doi:10.1136/bmjresp-2018-000398

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2018-000398).

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ABSTRACT

Introduction Patient-reported outcome measures (PROMs) are a vital component of patient-centred care. Community-acquired pneumonia (CAP) is a significant contributor to morbidity, mortality and health service costs globally, but there is a lack of consensus regarding PROMs for this condition.

Methods We searched MEDLINE, EMBASE and Cochrane Collaboration for studies, both interventional and observational, of adult recovery from CAP that applied at least one validated PROM instrument and were published before 31 December 2017. The full text of included studies was examined and data collected on study design, PROM instruments applied, constructs examined and the demographic characteristics of the populations measured. For all CAP-specific PROM instruments identified, content validity was assessed using the COnsensus based Standards for selection of health Measurement INstruments guidelines (COSMIN).

Results Forty-two articles met the inclusion criteria and applied a total of 17 different PROM instruments including five (30%) classified as CAP specific, six (35%) as generic and six (35%) that measured functional performance or were specific to another disease. The 36-Item Short Form Survey (SF-36) was the most commonly used instrument (15 articles). Only one of 11 (9%) patient cohorts assessed using a CAP-specific instrument had a mean age ≥70 years. The CAP-Sym and CAP-BIQ questionnaires had sufficient content validity, though the quality of evidence for all CAP-specific instruments was rated as very low to low.

Discussion PROM instruments used to measure recovery from CAP are inconsistent in constructs measured and have frequently been developed and validated in highly selective patient samples that are not fully representative of the hospitalised CAP population. The overall content validity of all available CAP-specific instruments is unclear, particularly in the context of elderly hospitalised populations. Based on current evidence, generic health instruments are likely to be of greater value for measuring recovery from CAP in this group.

Key messages

- What patient-reported outcome measures (PROMs) have been used in studies of community-acquired pneumonia (CAP), what constructs do they measure and do they have adequate content validity?
- PROMs are a vital valuation tool in the current era of unsustainable growth in health costs; however, there is little consistency in the instruments used and constructs measured in studies of CAP, and no CAP-specific instrument has high-quality evidence to support its content validity.
- The limited evidence supporting existing instruments developed to measure patient-reported recovery from CAP must be addressed if we are to reduce the considerable health burden associated with this disease.

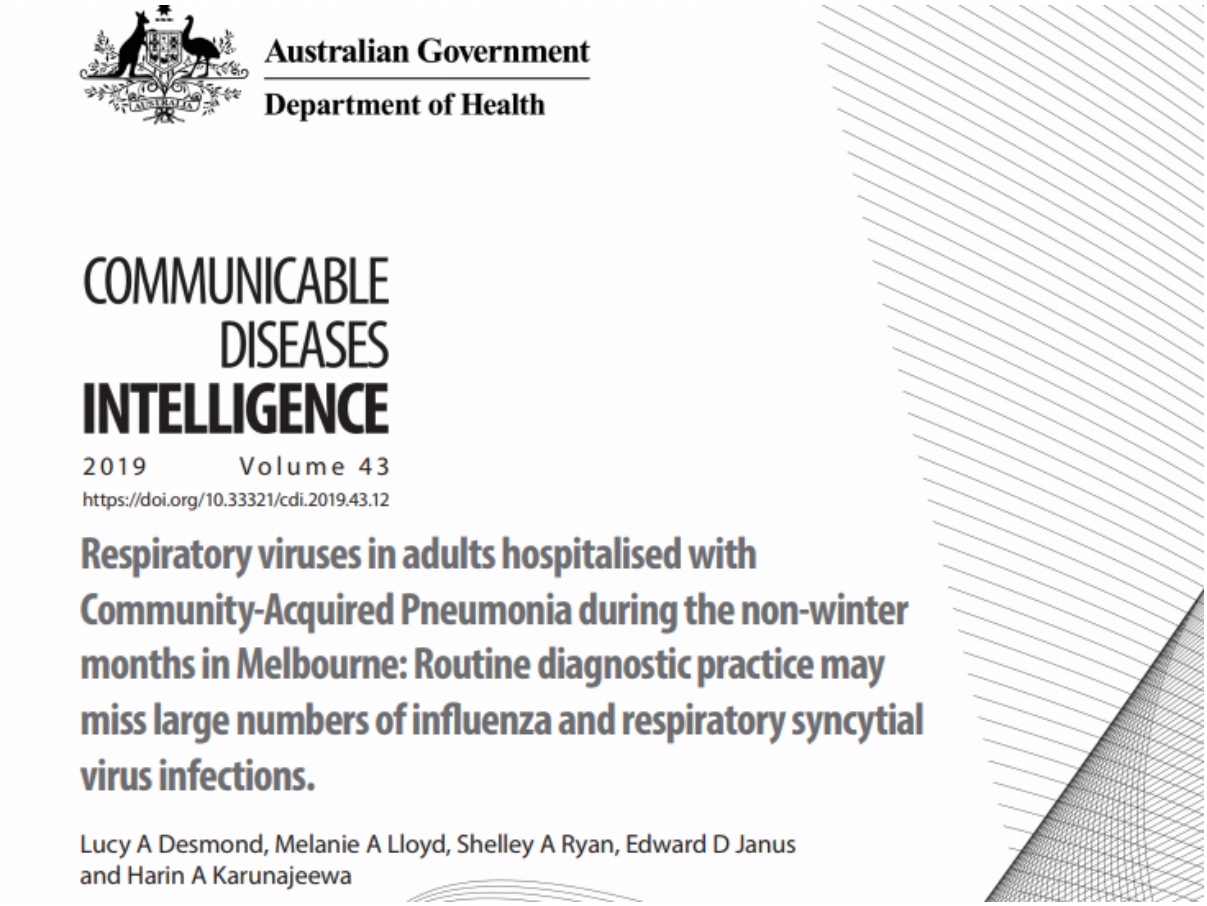
INTRODUCTION

Patient-reported outcome measures (PROMs) are critical endpoints for assessing the effectiveness of patient care, and their purpose is a more sensitive and meaningful evaluation of the patient illness experience,[1] thereby quantifying and identifying changes in health.[2] This defining characteristic is of crucial importance as it offers a departure from system or process metrics that have historically been relied on for performance measurement.[3] PROMs are therefore integral to determining value in the allocation of health resources as they measure the actual health outcomes produced.[4] Their role is particularly relevant for conditions that are generating large and increasing health service costs, as PROMs help quantify the actual health outcomes that are achieved relative to monetary investment. The momentum surrounding PROMs usage has grown in recent years with the establishment of international collaborations for standardisation of outcome measurement[5 6] and increasing integration of PROMs into routine clinical care within national health systems.[7]

Community-acquired pneumonia (CAP) is a common and complex disease with high

Appendix E – Diagnostic sub-study

Desmond L, et al. *Communicable Disease Intelligence*. 2019;43. doi.org/10.33321/cdi.2019.43.12



Appendix F – Abstracts accepted for presentation at Scientific Conferences arising from the IMPROVE-GAP study

1. Abstract presented at Australian Physiotherapy Conference (Sydney 2017)

Authors: Lloyd M**,** Janus E, Lowe S, Tang CY, Shackell M, Haines T, Skinner E, Karahalios A, Callander E, Haines K, Bali P, Ko S, Kelly AM, Karunajeewa H.

Connecting the Silos: Physiotherapist leadership in promoting multidisciplinary evidence-based management of community-acquired pneumonia

Aim: To evaluate an alternative physiotherapist-led model of care for community-acquired pneumonia (CAP), designed to improve adherence to levels-1 and -2 evidence-supported interventions (early mobilisation, routine corticosteroids, early switch to oral antibiotics, and routine malnutrition screening).

Design: Pragmatic, investigator-initiated, stepped-wedge randomised trial, with waiver of prior informed consent.

Method: All patients hospitalised under a General Internal Medical (GIM) unit meeting a standard case-definition for CAP were included. Eight GIM units at two Australian hospitals were randomised using concealed allocation to either: i) usual medical / allied health care delivered according to existing organisational practice, or ii) care supported by a dedicated physiotherapist-led "CAP Service": a multidisciplinary team deploying algorithm-based implementation of four evidence-based interventions. Outcome measures include: i) length of hospital stay, ii) mortality, iii) 30- and 90-day readmission rates, iv) compliance with evidence-based practice, and v) adverse events. Target sample size for the study is 640, with 520 recruited at Week 30 of 50.

Results: This trial is recruiting until 31-07-2017. Preliminary results relating to compliance with evidence-based practice and adverse events are expected by September 2017.

Conclusion: This study demonstrates an innovative, analytically robust approach to prosecuting translational health services research, where the aim is to improve adherence to treatments already well-supported by existing evidence in a generalisable "real-world" setting. The novel model of care being evaluated places physiotherapists as leaders of a multidisciplinary approach to managing one of the highest burden conditions in our health system.

2. Abstract presented at Australian Physiotherapy Conference (Sydney 2017)

Authors: Lloyd M**,** Karunajeewa H, Janus E, Tang C, Skinner E, Haines T, Haines K, Lowe S, Shackell M, Karahalios A, Callander E.

Defining Patient-Reported Outcomes in Community-Acquired Pneumonia: A pilot study to determine feasibility of routine application in an elderly, multimorbid population

Aim: To evaluate the feasibility of routine application of patient-reported outcome measures (PROMs) in a representative sample of hospitalized adults with community-acquired pneumonia (CAP).

Design: Investigator-initiated, prospective, pilot feasibility study.

Method: All patients hospitalised under a General Internal Medical (GIM) unit at two Australian hospitals over a 10-week period, meeting a standard case-definition for CAP, were screened for eligibility. Exclusion criteria included: i) cognitive impairment, ii) acute delirium, iii) insufficient English language proficiency, and iv) impaired conscious state. A total of 44 patients were recruited to participate in assessment at admission, discharge, and via telephone at 30- and 90-days post-discharge. Three PROMs tools were selected for the pilot trial. Feasibility outcomes included: i) eligibility, recruitment, and retention rates, ii) process efficiency, and ii) measures of centrality and variance for the chosen metrics.

Results: 52% of patients meeting the CAP case-definition were eligible for the pilot study, of which 76% were recruited. 100% successfully completed inpatient assessments with 77% retained for participation in outcome assessment at 30-days post-discharge. The PROMs tools were completed quickly (completion time per tool: median 3 mins, IQ range 2-5) in the inpatient setting. 90-day post-discharge assessments will be completed in April 2017.

Conclusion: PROMs can provide useful information to inform patient-centred care, and are efficient and simple to apply in the acute hospital setting. Routine application of PROMs should be considered for patients hospitalised with CAP, which represents one of the highest burden conditions in our health system.

3. Abstract accepted for poster presentation at BMJ International Quality and Safety Forum (Melbourne, 2018)

Karunajeewa H, Lloyd M, Karahalios A, Janus E, Lowe S, Shackell M.

Integrating implementation and evaluation using the "stepped wedge" framework: A research study to assess the effectiveness of a new model of care for community-acquired pneumonia

1) Conflicts of interest statement:

Funded by the HCF Research Foundation. HCF, an Australian not-for-profit private health insurance fund, had no role in design, analysis, or presentation of this work. No other competing interests to declare.

2) Context:

Western Health is a multi-site metropolitan health service in Melbourne, Australia. Its General Internal Medical (GIM) service manages approximately 5000 inpatient admission episodes per year including approximately 20% with community-acquired pneumonia (CAP). Inpatients are predominantly elderly with high rates of co-morbidity and complex care needs.

3) Problem:

CAP is the leading non-obstetric cause of hospital admission in Australia (>300,000 hospital bed-days/year). High-level evidence now supports numerous medical and allied health interventions for improving patient outcomes, including reducing hospital length of stay (LOS), in CAP. However, these are poorly applied in practice and there is ongoing uncertainty as to whether "efficacy" in clinical trials translates to "effectiveness" in the real world.

4) Assessment of problem and analysis of its causes:

We aimed to evaluate the effectiveness of a systems approach in improving compliance to evidence-supported interventions in CAP, however, we faced methodological, logistical and ethical challenges. We were concerned that the legitimacy of our evaluation could be undermined by potential for bias and confounding. For example, a binary "before versus after" evaluation would be prone to observer bias and confounding by dynamic changes at the health system and population level (e.g. an influenza epidemic occurring during the intervention phase). Clinical trials eliminate these problems through randomization, but randomizing interventions at patient level is impractical with health systems evaluations (which are delivered at scale) and ethically challenging for treatments already well-supported by evidence. An alternative approach was required.

5) Intervention:

The "stepped wedge" combined implementation-evaluation design is well-suited to health systems research. If the health service can be "partitioned" into a defined number of clusters, the intervention can be rolled out throughout these clusters in a randomly determined sequence. This is a practical way of introducing the intervention gradually over time while also allowing analytically robust comparisons between intervention and control groups in a way that minimizes potential for bias and confounding. It exemplifies the concept of "implementation research". The novel intervention consisted a

multidisciplinary team (the “CAP service”), who assessed all patients daily, routinely initiated early mobilization and nutritional assessment, and applied clinical decision algorithms to advise treating teams regarding the use of corticosteroid and antibiotic cessation.

6) Strategy for change:

Our GIM service has eight separate operational units. These constituted the eight clusters in our stepped wedge framework. Following a 10-week baseline period, the intervention was rolled into two new medical units every 10 weeks in a randomly determined sequence. By week 41, all eight units were receiving the intervention.

7) Measurement of improvement:

Primary pre-defined outcomes were LOS, 30- and 90-day readmission, mortality and clinical costing. We also measured process improvements, including compliance with evidence-based best-practice.

8) Effects of changes:

We successfully implemented the stepped wedge program over 12-months, with 415 and 401 individuals in the control and intervention groups, respectively. Clear process improvements occurred in most domains, including mobilization within 24 hours (19% to 72%), use of corticosteroid (2% to 55%) and appropriate nutritional assessment and management (55% to 83%), though were marginal in the application of antibiotic stopping rules which were already being well-applied (69% to 77%).

9) Lessons learnt:

The stepped wedge study design can be used simultaneously to enhance adherence to evidence-based clinical practice and measure patient outcomes. Final analysis of outcomes is expected to be complete by August 2018. These will tell us whether process improvements actually *translate to improved patient outcomes*.

10) Messages for others:

The stepped wedge framework is feasible in the modern hospital system and likely to be far more robust as a means of assessing the impact of health systems interventions than conventional “before vs after” approaches. It generates data quality comparable to clinical trials and is therefore highly publishable - which helps implementers develop broader reputation, recognition and builds their morale.

4. Abstract accepted for poster presentation at BMJ International Quality and Safety Forum (Melbourne, 2018)

Lloyd M, Janus E, Karahalios A, Callander E, Tang C, Karunajeewa H.

Patient-reported outcome measures in adult community-acquired pneumonia: A pilot study to determine feasibility and acceptability of routine use in elderly hospital populations

1) Please declare any conflicts of interest below:

The authors declare they have no competing interests. Funding for this study was provided by a HCF Research Foundation Grant.

2) Context:

Community-acquired pneumonia (CAP) is characterized by high mortality, morbidity and health system costs, and most commonly manifests in elderly individuals with underlying chronic health conditions. We conducted this pilot study in consecutive CAP patients hospitalised under a General Internal Medical (GIM) unit at two Australian hospitals over a 10-week period in 2016.

3) Problem:

Existing quality metrics in CAP focus on expediting time to "clinical stability" and hospital discharge, which can be seen as addressing the needs of the health provider rather than the patient. Patient-reported outcome measures (PROMs) encourage clinicians to implement patient-centred care by driving patient-oriented clinical decision making[58,59], process advancements, and health outcomes. The challenge is applying valid tools with high rates of patient participation, particularly among older and sicker patients. There is a need to determine the feasibility and acceptability of PROMs in routine clinical settings, and proactively identify potential barriers to their uptake.

4) Assessment of problem and analysis of its causes:

Resource limitations (e.g. staff time required to perform assessments) and impediments to patient participation (e.g. reluctance to complete survey instruments) creates potential for data that is incomplete, biased and misleading. A multidisciplinary clinical steering committee selected appropriate putative PROMs instruments for the target patient population, and designed a schedule of assessments to track CAP recovery in a patient-oriented fashion. Feasibility measures were proposed to determine their suitability for routine practice.

5) Intervention:

We devised a "modular" approach to PROMs suitable for complex elderly populations, since hospitalization is generally the result of multiple exacerbated medical conditions, and a single disease-specific tool is unlikely to capture all relevant aspects of patient recovery[60,61]. Three PROMs instruments were selected, each addressing a separate aspect of patient recovery: health-related quality of life (EQ-5D-5L English instrument), physical function (Late Life Function and Disability Instrument (LLFDI)), and

symptoms specifically related to CAP (CAP-Sym Questionnaire). We invited patients to undergo longitudinal PROMs assessments with these tools through face-to-face interview with a study investigator (admission and discharge) and via phone or mail (30- and 90-days post-discharge).

6) Strategy for change:

Data collected during patient interviews included time taken to complete the instrument, difficulties experienced with completing the PROMs and any other barriers to successful completion.

7) Measurement of improvement:

Feasibility outcomes included: i) eligibility, recruitment, and retention rates, ii) questionnaire completion times, and iii) measures of centrality and variance for the chosen metrics. Of 82 CAP patients admitted and screened during the enrolment period, 24 (29%) were unable to participate due to either poor English (21%) or cognitive impairment (14%), and a further 14 (17%) declined to participate. All 44 participants successfully completed required inpatient assessments, but 10 (23%) and 17 (39%) were lost to follow-up at 30- and 90-days respectively. Questionnaires were efficient to complete (median 4 [IQR:1-10] minutes). Hearing impairment, patient availability and poor recall were commonly identified difficulties.

8) Effects of changes:

The PROMs assessment framework evaluated in this pilot study appeared to be efficient and useful in our target population. Inclusive recruitment strategies employed resulted in a representative sample.

9) Lessons learnt:

Three key barriers to participation were identified: i) language barriers, ii) cognitive impairment and iii) follow-up post-discharge from hospital. Further work is therefore required to investigate the use of PROMs in linguistically diverse and cognitively impaired populations, and to explore the opportunities for technology to increase efficiency and participation.

10) Messages for others:

There is a need to promote consistent application of PROMs in routine clinical care as these tools provide valuable information relating to multiple aspects of patient recovery. Increasing age and multimorbidity limit the use and interpretation of disease-specific instruments. Integration of technology that increases the sensitivity and specificity of PROMs data while simultaneously reducing questionnaire complexity should be prioritised.

5. Abstract presented at the NHMRC Symposium on Translational Research (Sydney, November 2018)

Authors: Karunajeewa H**,** Lloyd M, Karahalios A, Skinner E, Ong ML, Shackell M, Kelly AM, Harrison R, Haines T, Janus EJ

Utilizing the stepped wedge cluster randomized controlled trial design to test the effectiveness of health systems interventions: A "real-world" implementation research study to assess the effectiveness of a new model of care for community-acquired pneumonia.

Background

Whilst clinical trials minimize bias through randomization, doing so at an individual patient level is impractical with health systems interventions (which are often delivered at scale) and ethically challenging for treatments already well-supported by evidence. Community-acquired pneumonia (CAP) is the leading non-obstetric cause of hospitalization in Australia. High-level evidence now supports numerous interventions for improving patient outcomes but these are poorly applied in practice, possibly reflecting uncertainty as to whether "efficacy" in clinical trials translates to "effectiveness" in the real world.

Objectives

We designed a novel model of care to improve compliance with evidence-based management of CAP. We aimed to evaluate the effectiveness of this in a representative population and in a way that minimized risks of confounding and bias.

Method

By partitioning our general internal medical (GIM) service into 8 "clusters" (based on existing separate operational units), and rolling out our intervention into each unit by a randomly determined sequence over 5-time periods, we implemented a phased introduction of the intervention that would also allow analytically robust comparisons of outcomes between intervention and control groups. A waiver of consent ensured a representative sample.

Results

Over 12-months, 415 and 401 individuals were enrolled in control and intervention groups, respectively. Completion of final outcomes analysis is expected by August 2018.

Conclusions

Our approach exemplifies the concept of "implementation research" and provides proof of principle that this is feasible for assessing the impact of health systems interventions in representative multi-morbid populations in the Australian hospital system.

6. Abstract presented at the Australasian Society of Infectious Diseases Annual Scientific Congress (Darwin, May 2019)

A STEPPED WEDGE CLUSTER RANDOMIZED CONTROLLED STUDY ASSESSING THE EFFECTIVENESS OF AN ADJUNCTIVE CORTICOSTEROID-BASED INTERVENTION IN HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA.

Authors: Lloyd ML[1,2], Karahalios A[2], Skinner E[1], Lowe S[1], Shackell M[1], Ko S[1], Desmond L[1], de Silva A[3], Haines T[3], Janus, E[1,2], Karunajeewa H[1,2]

[1]*Western Health,* [2] *University of Melbourne,* [3]*Monash University*

Introduction: A Cochrane Review now supports adjunctive corticosteroids as safe and efficacious for community-acquired pneumonia (CAP). However a reluctance to incorporate into clinical guidelines may reflect skepticism as to whether "efficacy" in clinical trials will translate to "effectiveness" in the "real world". To resolve this uncertainty we designed an implementation research study in a population representative of Australia's current hospital CAP burden.

Methods: A stepped wedge cluster randomized controlled trial design was implemented by partitioning a General Internal Medical service at two hospitals into 8 "clusters" (based on existing distinct operational units). A bundled guideline-based intervention including 7-days 50mg prednisolone was rolled into each unit in a randomly determined sequence over 5 time periods. Outcomes included length of stay (LOS), readmission, mortality (both to 90 days) and adverse event rates.

Results: Of 917 CAP patients screened 816 (89%), including 401 intervention and 415 control patients, were included. A geometric mean ratio of 0.94 [95% confidence interval (CI): 0.77, 1.14] was observed for LOS (days) in intervention vs control arms. Similarly, no significant differences were observed for mortality and readmission. Significantly higher proportions of gastrointestinal bleeding occurred in intervention (9, 2.2%) compared to control patients (3, 0.7%).

Conclusion: An intervention including adjunctive corticosteroid demonstrated no evidence of effectiveness and a higher risk of gastrointestinal bleeding. Efficacy in clinical trials may not necessarily translate into effectiveness and can even result in net harm under conditions of routine care. Adjunctive corticosteroids cannot be recommended for routine treatment of inpatient CAP.

Disclosure of Interest Statement: This study was supported by an HCF Research Foundation grant. The funder had no role in the design or analysis of this study.

Appendix G. List of awards to date arising from the IMPROVE-GAP project

Best Allied Health Research Presentation – Western Health Research Week 2018

Melanie Lloyd

"Early mobilisation in community-acquired pneumonia"

Finalist – Western Health Best Care Awards 2017

Melanie Lloyd

"Defining patient-reported outcome measures in community-acquired pneumonia: A pilot study to investigate the feasibility of routine use in an elderly multi-morbid population".

Australian Government Research Training Scheme Scholarship 2017-2020 ($94,000)

Melanie Lloyd – PhD candidate, The University of Melbourne

"Recovery from Community-Acquired Pneumonia: Translating the evidence in an elderly, multimorbid population".

Melbourne Medical School Student Research Prize 2017 and Melbourne University Student Research Conference Peoples' Choice Award for Best Presentation 2017

Lucy Desmond

"Respiratory viruses in adults hospitalized with Community-Acquired Pneumonia during the non-winter months in Melbourne: Routine diagnostic practice may miss large numbers of notifiable infections".

Appendix H: Budget expenditure

Item	Expenditure
Staff salaries (including on-costs): Research coordinator (0.6 EFT – 2.5 years) Physiotherapy site lead (0.6 EFT – 1 year) Research nurse (0.6 EFT – 0.5 year) Weekend casual project physiotherapists (0.4 EFT - 1 year) Casual research assistant (0.4 EFT – 0.25 year) Biostatistician (0.4 EFT – 0.25 year)	 $150,000 $55,000 $22,000 $40,000 $5,000 $10,000
Sub-total (salaries):	*$282,000*
Equipment: Research tablet computers x 2 Stationary and Incidentals	 $3000 $1000
Ethics submissions and amendments:	$1000
Data linkage costs	$300
Research Dissemination: Open access journal fees (x3) Australian Physiotherapy Conference registration and travel costs to Sydney (x1 speaker) BMJ International Quality and Safety Forum registration (x2 speakers) Internal Medical Society of Australia and New Zealand conference registration (x3 speakers)	 $8600 $900 $1500 $2100
Total	**$299,500**

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