Reducing Medical Admissions and Presentations Into Hospital through Optimising Medicines (REMAIN HOME) Study: a stepped-wedge cluster randomised controlled trial

Abstract

Objective

To investigate whether a pharmacist integrated into the general practice team reduces unplanned readmissions after hospitalisation.

Design and Setting

Stepped wedge cluster randomised trial involving 14 general practices across South-East Queensland, Australia.

Participants

Hospitalised patients prescribed five or more medicines or having a primary discharge diagnosis of either congestive heart failure or exacerbation of chronic obstructive pulmonary disease.

Intervention

Face-to-face comprehensive medicine management consultation with an integrated practice pharmacist within seven days of discharge, followed by a consultation with their GP and further pharmacist consultations as needed.

Outcomes

Rate of unplanned, all-cause hospital readmissions and emergency department (ED) presentations at 30 days to 12 months after hospital discharge, with differences between rates expressed as incidence rate ratios (IRR), and incremental net monetary benefit.

Results

At 12 months, there were 282 readmissions among 177 control patients (IR 1.65 per person years) and 136 readmissions among 129 intervention patients (IR 1.09 per person years) [IRR 0.74 (95%CI: 0.50 to 1.08) adjusted for time and 0.79 (95%CI: 0.52 to 1.18) when fully adjusted for co-variates]. At 12 months, ED presentations and the composite of both readmissions and ED presentations were reduced by 54% (IRR=0.46, 95%CI: 0.22 to 0.94) and 31% (IRR=0.69, 95%CI: 0.48 to 0.99) respectively. The incremental net monetary benefit of the intervention was $5,072 per patient, which represents a benefit-cost ratio of 32.

Conclusion

A collaborative pharmacist-GP model of care is likely to reduce hospital and ED presentations and to confer substantial health-system savings.

Trial registration

Australian New Zealand Clinical Trials Registry: ACTRN12616001627448. Universal trial number: U1111-1182-7390.

- **The known**

  Pharmacists who are integrated into general practice teams improve a number of clinical and non-clinical patient outcomes, but the impact on hospital readmissions and ED presentations in recently hospitalised patients is unknown.

- **The new**

  The REMAIN HOME trial was a multi-centre study that integrated pharmacists into 14 general practice teams to review medicine management of patients shortly after hospital discharge and to provide recommendations to GPs.

- **The implications**

  Given the potentially significant return on investment, policy measures should be implemented to support this model of practice as routine care following hospital discharge.

Introduction

Patients recently discharged from hospital following acute illness are at high risk of re-hospitalisation.[1] A major contributory cause is failure of patients to follow medication changes initiated in hospital (as high as 44%[2]), comprising unintentional continuation of discontinued medicine, omission of newly prescribed medicine, or non-implementation of dose changes.[3, 4] Patients with chronic conditions and those receiving polypharmacy (≥5 chronic medicines) are most vulnerable to readmission.[1, 3]

Several pharmacist-led interventions have aimed to reduce readmissions by improving medicine management during transition from hospital to primary care.[3, 5-11] Most involve hospital-based pharmacists conducting medicine review and reconciliation within 14 days of hospital discharge, either face to face in the patient's home, [5-7] in an outpatient clinic,[8] or via telephone.[9] While study pharmacists were purported to have communicated with the patient's primary care provider, this usually occurred on an *ad-hoc* basis and rarely involved close, formalised relationships. The effects of these interventions on readmissions have been variable[5-7] and few studies have involved primary care-based pharmacists. A US study reported decreased readmissions at 30 and 180 days in patients reviewed by a pharmacist in a primary care clinic shortly after discharge, compared to those who did not.[11]

In Australia, the model of pharmacists working within general practice and providing medicine management services in a collaborative and integrated manner is slowly gaining traction.[12, 13] A survey conducted in 2013 reported only 26 pharmacists working from this setting with this number having grown recently, stimulated through activity from Primary Health Networks (PHNs).[13] While this model can optimise management of hypertension,[14] and improve implementation of post-discharge treatment plans,[15] whether it prevents hospital readmissions and emergency department (ED) presentations remains unclear. The REMAIN HOME trial aimed to identify the effects of an integrated general practice pharmacist role on hospital utilisation.

Methods

REMAIN HOME was a stepped wedge cluster randomised controlled trial (RCT) involving 14 general practices and patients discharged from eight public hospitals across South-East

Queensland, Australia. The primary outcome of the REMAIN HOME study was the rate of unplanned, all-cause, hospital readmissions over 12 months following discharge. Secondary outcomes were readmissions at 30 days, 3 and 6 months, ED presentations, and cost savings associated with the model of care. The protocol was reported previously[16] and findings follow the CONSORT statement extension for stepped wedge RCTs.[17]

Trial design and context

General practices (clusters) were randomised to one of seven different steps in the stepped-wedge design (Figure 1). All practices began in the control phase for at least one month. Each month thereafter, two practices switched to the intervention phase and a pharmacist began working in the practice and conducting the intervention with recruited patients. All patients, both intervention and controls, were subject to follow-up at 30 days, 3, 6 and 12 months from the date of discharge from the index hospitalisation. All practices had a one month lead-in phase for embedding the intervention into the practice during which any data collected from recruited patients did not contribute to the analysis.

Ethics approval

Ethics approval was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/16/QRBW/410) and all study patients provided written consent.

Recruitment

General practices located within catchment areas with high rates of potentially preventable hospitalisations were identified using publically available data.[18] Facilitated by local PHNs, these practices were invited by email to express their interest in participating. Only practices without an existing co-located pharmacist were eligible for recruitment. Interested practices were visited by the trial coordinator who, after discussion, obtained consent to participate from practice principals. Practice pharmacists were recruited through online advertisements from national pharmacy organisations. Study pharmacists received one day of training in intervention processes, procedures for documenting drug-related problems (DRPs), and data collection. Each practice was allocated one pharmacist providing 12 hours per week of remunerated consultation time.

Patients aged 18 years or older, discharged within the previous seven days from a study hospital, could participate if they: 1) had nominated a GP working in an enrolled general

practice as their regular GP; and 2) were prescribed five or more long-term regular medicines on discharge OR received a primary discharge diagnosis of either congestive heart failure or an exacerbation (infective or non-infective) of chronic obstructive pulmonary disease (COPD).

Patients were excluded if receiving active radiation therapy or chemotherapy for malignant conditions, renal dialysis, or palliative care.

Intervention phase

The intervention comprised a face-to-face medicine management consultation between patient and practice pharmacist, followed by a consultation between patient and their GP, preferably within a week, after hospital discharge. The pharmacist-patient consultation comprised a comprehensive medicine review to identify DRPs, review of discharge medicines lists and their reconciliation with practice records, and discussion about any changes to usual medicines during hospital admission.

The pharmacist then discussed consultation outcomes with the patient's GP following which each patient had a consultation with their regular GP, on the same day (where possible).

Pharmacists had follow-up visits with each patient in person or via the telephone and also liaised with the patient's community and hospital pharmacists, and other prescribers, if indicated, to clarify medicine issues or discrepancies, and to communicate changes to medicines made in hospital.

Control phase

Patients recruited during control phases received usual care at their general practice, with no practice pharmacist review or routinely scheduled GP appointments.

Randomisation and blinding

After completing practice recruitment, each practice was randomised by the study statistician using a computer-generated random list of numbers. Personnel recruiting patients were blinded to the practice randomisation schedule, and had no contact with practice pharmacists or other providers. Blinding of general practice staff and of patients to the intervention was not possible.

Statistical methods

The primary outcome measure used to estimate the sample size was the rate of readmissions at the 12 month time point, which was compared between groups and expressed as incidence rate (IR) ratios (IRR). Described in more detail elsewhere,[16] based on a hypothesised 10% absolute reduction in unplanned readmissions, an anticipated drop-out rate of 20% at the level of the individual, intracluster coefficients (ICC) ranging from 0.05 to 0.15 and 5% significance levels, sample size was estimated at 2,240 patients to lend 80% to 90% power in detecting the hypothesised effect size. Secondary outcomes were readmissions at 30 days, 3 and 6 months, ED presentations and composite of readmissions and ED presentations, time to first readmission (expressed as median and interquartile range [IQR]), and cost savings associated with the model of care.

Analysis of outcomes was by intention-to-treat (ITT) and comprised all participants except those recruited in the lead-in phase. In a per-protocol analysis a small number of participants who did not receive the full intervention were excluded.

The planned analysis involved fitting a generalised mixed model to allow for clustering of data and adjustment for secular trends. However, when attempting to fit mixed-effects models, many failed to converge because variance of the random effects components were very close to zero, with very small numbers of events in many cluster-periods. In such situations we therefore fitted generalised linear models. All models include fixed effects for time periods (time-adjusted), and additional adjustments for age, gender, days to GP visit, length of stay, planned or unplanned admission, number of medications, and number of comorbidities (fully-adjusted). Models were fitted with log links and using the Poisson distribution offset for number of person-months at risk. For mixed models that converge we present variance components.

Post-hoc analyses considered sensitivity to exchangeability assumption for clustering by additionally including cluster by period random effects and to identify if mixed models would converge in SAS (for the primary outcome at the primary assessment point). We also considered sensitivity to the Poisson distribution by additionally fitting models negative-binomial, zero inflated negative binomial, and zero inflated Poisson distributions (again for

the primary outcome at the primary assessment point). Most analysis was conducted in Stata v16, with some sensitivity analyses conducted in SAS.

Economic evaluation

A cost-benefit analysis of the intervention from an Australian healthcare system perspective was conducted. Intervention costs (pharmacist and Medicare Benefits Schedule [MBS] use) were compared to savings from reduced hospital and ED utilisation over the 12 month follow-up period.

Results

Each of the fourteen general practices achieved crossover from control to intervention phase at the pre-specified time (Figure 1 and Supplementary table 1). Recruited pharmacists were experienced and often held post-graduate qualifications and accreditations (Supplementary table 2).

Figure 1 shows patient recruitment over time for each practice. The pre-specified target sample size was not achieved. Of 561 patients referred to onsite research assistants, 477 met eligibility criteria with 353 providing consent. Excluding 47 patients recruited during the lead-in phase, 177 control patients and 129 intervention patients were included in the analysis. Patient characteristics were similar between groups (Table 1).

The proportions of patients consulting their GP within a week of discharge was similar between groups: 103 (58%) control versus 79 (61%) intervention patients.

In the intervention group, 28 patients did not receive the full intervention for various reasons, although their baseline characteristics were no different to those of the 101 patients who did. Among the latter, the first patient-pharmacist consultation occurred at a median (IQR) of 8.0 (5.0–12.3) days, at either the practice (84 [83%]) or at the patient's home (17 [17%]), and lasted a median (IQR) of 45 (30–60) minutes. After the first pharmacist consultation, 48 (48%) patients had a GP consultation on the same day, 36 (36%) within a week, and 17 (17%) more than one week later.

Intervention patients had, on average, 4 (SD ±2.5) DRPs identified by the pharmacist in the initial consultation, most relating to choice of medication (e.g. duplication), medication adherence, and problems relating to conditions requiring additional management or

prevention. GPs implemented at least one pharmacist recommendation in 81% of patients, with a mean of 1.5 (SD ±1.2) recommendations implemented per patient within one week of initial pharmacist consultation.

Table 2 summarises outcomes for both patient groups across all time points on ITT analysis. At 12 months, 282 readmissions occurred among control patients (IR: 1.65 per person-year) and 136 among intervention patients (IR: 1.09 per person-year). The time-adjusted IRR for all cause hospital readmissions was 0.74 (95%CI: 0.50 to 1.08) and 0.79 (95%CI: 0.52 to 1.18) when fully-adjusted.

At 12 months, ED presentations and the composite measure of both readmissions and ED presentations were reduced by 54% (IRR=0.46, 95% CI: 0.22 to 0.94) and 31% (IRR=0.69, 95% CI: 0.48 to 0.99) respectively when fully-adjusted.

At 30 days, the incidence rate of readmissions among intervention and control patients were 0.12 and 0.33 per person-months respectively, equalling a fully adjusted IRR of 0.35 (95%CI: 0.14 to 0.90).

Sensitivity analyses using the best-fitting random effects models supported our main results (Supplementary Table 3). Several models (Poisson, negative-binomial, zero inflated negative binomial, and zero inflated Poisson distributions with and without robust standard errors) would not converge with random effects, but fixed-effect models for cluster and fixed-period effects each gave similar results (Supplementary Table 4). Variance components for the random effects that would converge are provided (Supplementary Table 5)

Per-protocol analysis of patients completing the full intervention (Supplementary table 6) showed similar results at 12 months, with IRR of 0.78 (95% CI: 0.51 to 1.19) for hospital readmissions, 0.45 (95% CI: 0.21 to 0.96) for ED presentations and 0.74 (95% CI: 0.52 to 1.05) for the composite of both.

For re-admitted patients, median time from discharge to first re-admission was 46 (IQR 16 – 158) days among control patients and 98 (39 – 236) days among intervention patients. Both groups had the same length of hospital stay (median [IQR] 3 [1–7] days).

The most common reasons for readmission, defined by AR-DRG codes, are shown in Table 3, with '*Chronic Obstructive Airways Disease, Major Complexity*' occurring most frequently.

Economic evaluation

In total, pharmacists spent 101 hours, 3 minutes with intervention patients, totalling $6,678 ($51.77 per patient). MBS use was similar in both groups (Table 4). The cost of hospital readmissions and ED presentations was estimated as $8,138 per intervention patient versus $13,374 per control patient (a difference of $5,236). The estimated incremental net monetary benefit (or overall health service cost saving) of the intervention at 12 months was $5,072 per patient. Since the incremental cost per patient of the intervention was estimated to be $164, this represents a benefit-cost ratio of approximately 32. Sensitivity analysis (using increased pharmacist wages of $69/hr inclusive of on-costs[19]) determined total intervention cost as $1,666 per patient, equalling an incremental cost per patient of $182 (calculation not shown in Table 4), resulting in an estimated incremental net benefit per patient of $5,054 and a benefit cost-ratio of 28.8.

Discussion

In the REMAIN HOME trial, pharmacists integrated into general practice teams providing medicine management consultation to patients recently discharged from hospital resulted in a 21% reduction in all cause, unplanned 12 month hospital readmissions. Whilst not reaching statistical significance, the values supported by the confidence interval do signal a likely benefit from the intervention. Moreover, ED presentations and the composite of both hospital readmissions and ED presentations were both significantly reduced by 54% and 31% respectively.

The decline in effect from 30 to 90 days and beyond to 12 months suggests additional intervention is required between these time points by the pharmacist and GP team.

Our report adds to the literature which, to date, reports mixed results of medication review and reconciliation involving collaboration between pharmacists and GPs.[20] The benefits of our intervention may relate to timely and coordinated care provided by the pharmacist consultation, linked closely with GP review and engagement whereby the clinical rapport and trust between these co-located individuals, missing in other studies,[21] improves uptake of pharmacist recommendations.[22-24] Our intervention also enabled pharmacist reconciliation of accessible general practice records with the hospital discharge medicine list, absent in most published studies reliant on hospital discharge medicine lists being forwarded to the GP for

reconciliation. DRPs identified by pharmacists during the intervention, particularly issues with medication adherence, constitute a common cause of patients representing to hospital following discharge.[2-4] The additional clinical information and tacit knowledge the GP has of the patient may also contribute.

Importantly, as the percentage of patients seeing their GP within a week of discharge was similar for both groups (58% vs 61%), pharmacist consultation, rather than early GP review by itself, was probably primarily responsible for the reduction in hospital utilisation.

A substantial net benefit to the healthcare system accrued from the intervention, with a return on investment (ROI) of AUD$32 for every dollar invested over 12 months, which compares to AUD$1.56 estimated in a previous review however only considered adverse drug event-related hospitalisations, not all-cause readmissions.[25] Our ROI was also higher than the AUD$23 ROI for pharmacist-initiated changes in drug therapy or management within the public hospital setting.[26]

Limitations

We were unable to ascertain the extent to which re-admissions were attributable to medicine-related adverse events, because of anticipated inaccuracy in retrospectively identifying preventable and/or medicine-related readmissions, insensitive hospital coding, and limited researcher time.[27] Under-recruitment was due to several reasons including delays in obtaining ethics and governance approvals from multiple hospitals[28]; inconsistent identification and referral to researchers of potentially eligible patients; high patient turnover due to hospital bed pressures such that target patients were discharged before recruitment; patients having no regular GP recorded; and restriction of researchers to working hours for consenting patients. We observed a 22% drop-out rate among intervention patients although this was similar to fail-to-attend rates of a general medical outpatient clinic providing a pharmacist review service,[29] and reflects real world conditions in which the study was conducted. Drop-out patients were no different in their baseline characteristics to those who remained in the study, and results of intention to treat and per-protocol analyses were similar.

Conclusion

Pharmacists integrated into general practice teams, reviewing medicine management of patients shortly after hospital discharge, and providing recommendations to GPs for future management, can reduce hospital utilisation, resulting in significant cost savings to the health system. Larger-scale studies of this model of care on different clinical and non-clinical outcomes are warranted.

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Table 1: Patient baseline characteristics

Baseline Characteristics	**Control** **n = 177**	**Intervention** **n = 129**
Sex, female (%)	98 (55.4)	69 (53.4)
Mean (±SD) age, years	69.3(±13.7)	70.8 (±12.4)
Median (IQR) number of co-morbidities	5 (3–8)	5 (4–7)
Median (IQR) number of regular medicines	9 (6–11)	8 (6–11)
Index admission, unplanned (%)	138 (78.0)	98 (76.0)
Median (IQR) length of stay for index admission, days	5 (3–8)	4 (3–8)
Most frequent primary diagnoses (DRGs) for index admission (%)		
I04B: Knee Replacement, Minor Complexity	9 (5.1)	3 (2.3)
F62A: Heart Failure and Shock, Major Complexity	6 (3.4)	2 (1.6)
D63A: Otitis Media and Upper Respiratory Infections, Major Complexity	4 (2.3)	2 (1.6)
G70A: Other Digestive System Disorders, Major Complexity	4 (2.3)	2 (1.6)
J64A: Cellulitis, Major Complexity	3 (1.7)	3 (2.3)

DRG, diagnostic-related group; IQR, interquartile ranges; SD, standard deviation.

Table 2: Evaluation of intervention on outcomes at different time points.

	No. of events (incidence rate)		Time adjusted		Fully adjusted*	
30 Day Outcomes	**Control (ET=176.13 person-months)**	**Intervention (ET=129.00 person-months)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
30 day hospital readmissions	59 (0.33)	15 (0.12)	0.30 (0.12 to 0.72) [$]	0.008[$]	0.35 (0.14 to 0.90)[$]	0.029[$]
30 day non-admitted ED presentations	15 (0.09)	5 (0.04)	0.43 (0.05 to 3.68) [$]	0.437[$]	0.43 (0.03 to 6.64)[$]	0.547[$]
30 day hospital readmission and ED presentation (composite measure)	74 (0.42)	20 (0.16)	0.31 (0.14 to 0.71)[$]	0.005[$]	0.36 (0.15 to 0.87)[$]	0.023[$]
90 Day Outcomes	**Control (ET=43.0 person-years)**	**Intervention (ET=31.6 person-years)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
90 day hospital readmissions	105 (2.4)	38 (1.2)	0.53 (0.27 to 1.01)	0.055	0.57 (0.31 to 1.06)[$]	0.075[$]
90 day non-admitted ED presentations	27 (0.63)	12 (0.38)	0.40 (0.15 to 1.09)[$]	0.074[$]	0.54 (0.18 to 1.59)[$]	0.262[$]
90 day hospital readmission and ED presentation (composite measure)	132 (3.07)	50 (1.58)	0.51 (0.29 to 0.90)	0.020	0.57 (0.33 to 0.96)[$]	0.036[$]
180 Day Outcomes	**Control (ET=85.4 person-years)**	**Intervention (ET=62.7 person-years)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
180 day hospital readmissions	156 (1.83)	72 (1.15)	0.73 (0.44 to 1.23)	0.244	0.76 (0.47 to 1.23)[$]	0.267[$]
180 day non-admitted ED presentations	52 (0.56)	22 (0.35)	0.26 (0.11 to 0.61)[$]	0.002[$]	0.32 (0.13 to 0.80)[$]	0.015[$]
180 day hospital readmission and ED presentation (composite measure)	208 (2.44)	94 (1.50)	0.58 (0.38 to 0.91)	0.018	0.63 (0.42 to 0.97)[$]	0.034[$]
12 Month Outcomes	**Control (ET=170.6 person-years)**	**Intervention (ET=125.1 person-years)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
12 month hospital readmissions	282 (1.65)	136 (1.09)	0.74 (0.50 to 1.08)	0.122	0.79 (0.52 to 1.18)	0.249
12 month non-admitted ED presentations	88 (0.52)	45 (0.36)	0.37 (0.19 to 0.73)	0.004	0.46 (0.22 to 0.94)	0.033
12 month hospital readmission and ED presentation (composite measure)	370 (2.17)	181 (1.45)	0.63 (0.45 to 0.90)	0.010	0.69 (0.48 to 0.99)	0.044

CI, Confidence Interval; ED, Emergency Department; ET, Exposure Time; IRR, Incident Rate Ratio. Note: All models contain adjustment for time period. [$]: Calculated without allowance for clustering of observations due to convergence problems with the random effects (see main text). *Adjusted for age, gender, days to GP visit, LOS, planned or unplanned, number of medications, and number of comorbidities.

Table 3: Most common reasons for readmission, defined using AR-DRG codes.

Control (n=177)		Intervention (n=129)	
AR-DRG	**n (%)**	**AR-DRG**	**n (%)**
E65A – Chronic Obstructive Airway Disease, Major Complexity	13 (7.3)	E65A - Chronic Obstructive Airway Disease, Major Complexity	10 (7.8)
E62A – Respiratory Infections and Inflammations, Major Complexity	11 (6.2)	G70A - Other Digestive System Disorders, Major Complexity	5 (2.8)
F62A (Heart Failure and Shock, Major Complexity,	10 (5.6)	E62A - Respiratory Infections and Inflammations, Major Complexity	4 (2.3)
F62B – Heart Failure and Shock, Minor Complexity	9 (5.1)	F62A - Heart Failure and Shock, Major Complexity	4 (2.3)
F65A – Peripheral Vascular Disorders, Major Complexity,	7 (4.0)		

Table 4: Incremental costs and benefits of the intervention and control phases at 12 months.

	Control (n=177)	**Intervention (n=129)**	**Difference**
COSTS			
MBS[1]	$262,678	$206,017	
Pharmacist Consultations[2] Initial Follow-up	 N/A N/A	 $5107 $1571	
TOTAL for cohort	**$262,678**	**$212,695**	
TOTAL per patient	**$1484**	**$1648**	**$164**
BENEFITS			
Readmissions[3]	$2,321,084	$1,026,243	
ED presentations	$46,112	$23,580	
TOTAL for cohort	**$2,367,196**	**$1,049,823**	
TOTAL per patient	**$13,374**	**$ 8,138**	**$5,236**

AR-DRG, Australian Refined Diagnosis Related Groups; ED, Emergency Department; MBS, Medical Benefits Scheme; QEP, Queensland Efficient Price.

[1] Patients with missing data (n=30 control group and n=23 for intervention group) were costed at the average cost of MBS use for their cohort. [2] Patients who were allocated intervention but did not receive the intervention (n=28) were costed at the average pharmacist time for the cohort. [3] Patients with missing data (n=9 control group and n=7 for intervention group) were costed at the average cost of readmissions for their cohort

Figure 1: Patient recruitment into the stepped wedge design.*

General practice	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9
1	Eligible (n=2) **Consented (n=2)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=2) **Consented (n=1)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=2) **Consented (n=1)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=2) **Consented (n=1)**	Eligible (n=3) **Consented (n=2)**
2	Eligible (n=1) **Consented (n=0)**	Eligible (n=2) **Consented (n=0)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=0) **Consented (n=0)**	Eligible (n=4) **Consented (n=4)**	Eligible (n=0) **Consented (n=0)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=2) **Consented (n=2)**
3	Eligible (n=3) **Consented (n=2)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=6) **Consented (n=4)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=5) **Consented (n=5)**	Eligible (n=3) **Consented (n=3)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=3) **Consented (n=1)**
4	Eligible (n=2) **Consented (n=1)**	Eligible (n=4) **Consented (n=3)**	Eligible (n=3) **Consented (n=3)**	Eligible (n=3) **Consented (n=1)**	Eligible (n=4) **Consented (n=4)**	Eligible (n=8) **Consented (n=6)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=5) **Consented (n=4)**	Eligible (n=5) **Consented (n=5)**
5	Eligible (n=5) **Consented (n=3)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=3) **Consented (n=1)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=3) **Consented (n=3)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=3) **Consented (n=1)**	Eligible (n=5) **Consented (n=1)**
6	Eligible (n=6) **Consented (n=3)**	Eligible (n=3) **Consented (n=3)**	Eligible (n=7) **Consented (n=6)**	Eligible (n=4) **Consented (n=4)**	Eligible (n=4) **Consented (n=3)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=6) **Consented (n=5)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=3) **Consented (n=2)**
7	Eligible (n=10) **Consented (n=9)**	Eligible (n=6) **Consented (n=4)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=7) **Consented (n=6)**	Eligible (n=5) **Consented (n=4)**	Eligible (n=5) **Consented (n=3)**	Eligible (n=4) **Consented (n=3)**	Eligible (n=6) **Consented (n=5)**	Eligible (n=6) **Consented (n=5)**
8	Eligible (n=7) **Consented (n=5)**	Eligible (n=11) **Consented (n=7)**	Eligible (n=10) **Consented (n=8)**	Eligible (n=16) **Consented (n=15)**	Eligible (n=11) **Consented (n=9)**	Eligible (n=6) **Consented (n=5)**	Eligible (n=5) **Consented (n=4)**	Eligible (n=5) **Consented (n=4)**	Eligible (n=4) **Consented (n=3)**
9	Eligible (n=6) **Consented (n=6)**	Eligible (n=6) **Consented (n=5)**	Eligible (n=6) **Consented (n=5)**	Eligible (n=4) **Consented (n=4)**	Eligible (n=2) **Consented (n=1)**	Eligible (n=6) **Consented (n=5)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=4) **Consented (n=3)**	Eligible (n=5) **Consented (n=4)**
10	Eligible (n=3) **Consented (n=0)**	Eligible (n=4) **Consented (n=3)**	Eligible (n=4) **Consented (n=4)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=5) **Consented (n=4)**	Eligible (n=4) **Consented (n=2)**	Eligible (n=2) **Consented (n=1)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=2) **Consented (n=2)**
11	Eligible (n=10) **Consented (n=7)**	Eligible (n=7) **Consented (n=6)**	Eligible (n=4) **Consented (n=4)**	Eligible (n=10) **Consented (n=7)**	Eligible (n=8) **Consented (n=5)**	Eligible (n=13) **Consented (n=10)**	Eligible (n=10) **Consented (n=8)**	Eligible (n=6) **Consented (n=4)**	Eligible (n=8) **Consented (n=2)**
12	Eligible (n=4) **Consented (n=1)**	Eligible (n=0) **Consented (n=0)**	Eligible (n=5) **Consented (n=3)**	Eligible (n=3) **Consented (n=1)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=1) **Consented (n=1)**
13	Eligible (n=2) **Consented (n=2)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=5) **Consented (n=3)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=2) **Consented (n=0)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=3) **Consented (n=2)**
14	Eligible (n=1) **Consented (n=1)**	Eligible (n=0) **Consented (n=0)**	Eligible (n=2) **Consented (n=2)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=1) **Consented (n=0)**	Eligible (n=3) **Consented (n=2)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=1) **Consented (n=1)**	Eligible (n=3) **Consented (n=3)**

*Blue, white and green cells represent months that the general practice was in the control phase, lead-in phase and intervention phase, respectively

Supplementary Table 1: General practice characteristics

General practice	Dominant Billing Type	Number of FTE GPs	Number of GP registrars	Number of active patients[1]	SWPEs	Number Practice nurses	Number of Medical Specialist and Allied Health Professionals	Number of pharmacies within 5km radius	SEIFA
1	Mixed billing	12	6	8452	5587	5	9	12	95
2	Private billing	5.2	1	15593	4773	4	2	4	59
3	Private billing	7	0	11297	5073	6	14	8	61
4	Mixed billing	10	4	9893	6752	5	2	4	80
5	Bulk Billing	7	0	9400	5431	4	9	8	15
6	Bulk Billing	8	2	3500	2405	4	8	8	4
7	Bulk Billing	9	2	8693	5290	3	5	6	75
8	Mixed billing	16	2	100868	14512	5	1	18	68
9	Mixed billing	8	2	10902	7506	4	6	6	74
10	Bulk Billing	10	6	18762	4588	4	12	4	33
11	Mixed billing	9	3	11103	8182	4	7	14	71
12	Bulk Billing	8	0	26512	9248	5	3	10	4
13	Bulk Billing	2.3	1	n/a	2000	1	1	2	80
14	Mixed billing	6	1	6134	4586	2	0	4	75

FTE, Full-Time Equivalent; GP, General Practitioner; SEIFA, Socio-Economic Indexes for Areas; SWPE, Standardised Whole Patient Equivalent.
[1]≥3 visits within 2 years.

Supplementary Table 2: Practice pharmacist characteristics

Characteristic (n=11)	**Value**
Gender, female, n (%)	10 (91%)
Mean (±SD) years with registrable pharmacy degree	25.6 (11.1)
Postgraduate qualifications, n (%)	9 (82%)
Previous field of employment, n (%) Independent consultant Community Academia Hospital	 9 (82%) 6 (55%) 2 (18%) 1 (9%)
Accreditation with the Australian Association of Consultant Pharmacy (AACP), n (%)	11 (100%)
Mean (±SD) years accredited with AACP	10.5 (4.4)

*Two pharmacists did not complete questionnaire

Supplementary Table 3: Comparison of treatment effects across different software packages

12 month hospital readmission		**IRR (95% CI)**
Software	**Random effects**	**P-value**
Stata	Random cluster and cluster by period	DNC
	Random cluster	0.74 (0.50 to 1.08) 0.122
	None	0.69 (0.49 to 0.96) 0.03
SAS	Random cluster and cluster by period	DNC
	Random cluster	DNC
	None	0.69 (0.49 to 0.97) 0.034

DNC, Did not converge or fitted model was unstable. Note: Stata commands used are: mepoisson for IRR with random effects and poisson for IRR without random effects; In SAS, a Poisson distribution was specified for IRR. All models contain adjustment for time period.

Supplementary Table 4: Comparison of treatment effect on the primary outcome (12 month hospital readmission)

Model	Random effect	IRR	CI Lower bound	CI Upper bound
Poisson	Cluster and cluster by time	DNC	DNC	DNC
	Cluster	0.74	0.50	1.08
	None	0.69	0.49	0.96
Negative Binomial	Cluster and cluster by time	DNC	DNC	DNC
	Cluster	DNC	DNC	DNC
	None	0.65	0.33	1.26
Poisson with zero inflation	None	0.66	0.45	0.96
Negative Binomial with zero inflation	None	0.61	0.32	1.17

DNC, Did not converge or fitted model was unstable. IRR: Incidence rate ratio. CI: Confidence interval.

Supplementary Table 5: Comparing model convergence and random effect components in STATA and SAS for all outcomes and time points

		Time adjusted				Fully adjusted*				
		Apparent convergence	Random effect		Stable model	Apparent convergence	Random effect		Stable model
			Coefficient	95% CI			Coefficient	95% CI	
30 day									
Readmission	Stata	Yes	0.000	- -	No[1]	Yes	0.000	- -	No[1]
	SAS	Yes	0.000	- -	No [2]	Yes	0.000	- -	No[2]
ED presentation	Stata	Yes	0.000	- -	No[1]	Yes	0.000	- -	No[1]
	SAS	No	-	- -	-	No	-	- -	-
Composite	Stata	Yes	0.000	- -	No[1]	Yes	0.000	- -	No[1]
	SAS	Yes	0.000	- -	No[2]	Yes	0.000	- -	No[2]
90 day									
Readmission	Stata	Yes	0.033	0.001 0.807	Yes	Yes	0.000	- -	No[1]
	SAS	Yes	0.001	0.001 0.001	No[2]	No	-	- -	-
ED presentation	Stata	Yes	0.000	- -	No[1]	Yes	0.000	- -	No[1]
	SAS	No	-	- -	-	No	-	- -	-
Composite	Stata	Yes	0.061	0.007 0.538	Yes	Yes	0.012	0.000 50.729	No
	SAS	Yes	0.002	0.002 0.002	No[2]	Yes	0.001	0.001 0.001	No[2]
180 day									
Readmission	Stata	Yes	0.015	0.000 1.191	Yes	Yes	0.000	- -	No[1]
	SAS	No	-	- -	-	Yes	0.000	- -	No[1]
ED presentation	Stata	Yes	0.000	- -	No[1]	Yes	0.000	- -	No[1]
	SAS	No	-	- -	-	Yes	0.000	- -	No[1]
Composite	Stata	Yes	0.022	0.001 0.399	Yes	Yes	0.000	- -	No[1]
	SAS	Yes	0.000	0.000 0.000	No[2]	Yes	0.000	- -	No[1]

1 year											
Readmission	Stata	Yes	0.038	0.007	0.198	Yes	Yes	0.064	0.014	0.282	Yes
	SAS	Yes	0.000	-	-	No[1]	No	-	-	-	-
ED presentation	Stata	Yes	0.120	0.015	0.946	Yes	Yes	0.171	0.026	1.101	Yes
	SAS	Yes	0.001	0.001	0.001	No[2]	Yes	0.000	-	-	No[1]
Composite	Stata	Yes	0.066	0.020	0.218	Yes	Yes	0.080	0.025	0.262	Yes
	SAS	No	-	-	-	-	No	-	-	-	-

CI: Confidence Interval. A "-" indicates that a value could not be obtained. All models have included cluster as a random effect. * Adjusted model contains adjustment for: age, gender, days to GP visit, LOS, planned or unplanned, number of medications, and number of comorbidities. [1]: Deemed unstable as confidence interval for random effect not reported. [2]: Deemed unstable as confidence interval is the same as the point estimate

Supplementary Table 6: Per Protocol Evaluation of intervention on outcomes at different time points.

	No. of events (incidence rate)		Time adjusted		Fully adjusted*	
30 Day Outcomes	**Control (ET=176.13 per person-month)**	**Intervention (ET=101.00 per person-month)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
30 day hospital readmissions	59 (0.33)	14 (0.14)	0.35 (0.14 to 0.86)	0.022	0.38 (0.15 to 0.98)	0.045
30 day non-admitted ED presentations	15 (0.09)	4 (0.04)	0.60 (0.06 to 5.63)	0.654	0.52 (0.03 to 8.26)[1]	0.644
30 day hospital readmission and ED presentation (composite measure)	74 (0.42)	18 (0.16)	0.38 (0.17 to 0.86)	0.02	0.41 (0.17 to 0.98)[1]	0.044
90 Day Outcomes	**Control (ET=43.0 per person-year)**	**Intervention (ET=24.7 per person-year)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
90 day hospital readmissions	105 (2.4)	31 (1.26)	0.55 (0.30 to 1.00)	0.051	0.59 (0.32 to 1.11)	0.104
90 day non-admitted ED presentations	27 (0.63)	11 (0.45)	0.49 (0.18 to 1.32)	0.158	0.59 (0.20 to 1.74)	0.341
90 day hospital readmission and ED presentation (composite measure)	132 (3.07)	42 (1.70)	0.53 (0.31 to 0.89)	0.016	0.60 (0.35 to 1.03)	0.065
180 Day Outcomes	**Control (ET=85.4 per person-year)**	**Intervention (ET=48.9 per person-year)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
180 day hospital readmissions	156 (1.83)	57 (1.17)	0.71 (0.44 to 1.15)	0.164	0.75 (0.46 to 1.22)	0.251
180 day non-admitted ED presentations	52 (0.56)	16 (0.33)	0.29 (0.12 to 0.69)	0.005	0.31 (0.12 to 0.80)	0.015
180 day hospital readmission and ED presentation (composite measure)	208 (2.44)	73 (1.49)	0..57 (0.38 to 0.87)	0.009	0.62 (0.41 to 0.96)	0.033
12 Month Outcomes	**Control (ET=170.6 per person-year)**	**Intervention (ET=97.9 per person-year)**	**IRR (95% CI)**	**P-value**	**IRR (95% CI)**	**P-value**
12 month hospital readmissions	282 (1.65)	109 (1.11)	0.70 (0.49 to 1.00)	0.048	0.71 (0.50 to 1.01)	0.055
12 month non-admitted ED presentations	88 (0.52)	37 (0.38)	0.40 (0.22 to 0.74)	0.004	0.45 (0.23 to 0.87)	0.017
12 month hospital readmission and ED presentation (composite measure)	370 (2.17)	146 (1.49)	0.61 (0.45 to 0.83)	0.002	0.64 (0.47 to 0.87)	0.005

*Adjusted for age, gender, days to GP visit, LOS, planned or unplanned, number of medications, number of comorbidities.