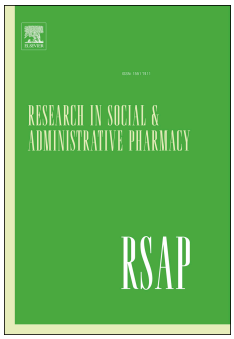

Impact of pharmacist and physician collaborations in primary care on reducing readmission to hospital: A systematic review and meta-analysis

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Impact of pharmacist and physician collaborations in primary care on reducing readmission to hospital: a systematic review and meta-analysis.

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ABSTRACT

Background

Readmissions to hospital due to medication-related problems are common and may be preventable. Pharmacists act to optimise use of medicines during care transitions from hospital to community.

Objective

To assess the impact of pharmacist-led interventions, which include communication with a primary care physician (PCP) on reducing hospital readmissions.

Methods

PubMed, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL and Web of Science were searched for articles published from inception to March 2021 that described interventions involving a pharmacist interacting with a PCP in regards to medication management of patients recently discharged from hospital. The primary outcome was effect on all-cause readmission expressed as Mantel-Haenszel risk ratio (RR) derived from applying a random effects model to pooled data. Sensitivity analysis was also conducted to investigate differences between randomised controlled trials (RCTs) and non-RCTs. The GRADE system was applied in rating the quality of evidence and certainty in the estimates of effect.

Results

In total, 37 studies were included (16 RCTs and 29 non-RCTs). Compared to control patients, the proportion of intervention patients readmitted at least once was significantly reduced by 13% (RR=0.87, CI:0.79–0.97, p=0.01; low to very low certainty of evidence) over follow-up periods of variable duration in all studies combined, and by 22% (RR=0.78, CI:0.67–0.92; low certainty of evidence) at 30 day follow-up across studies reporting this time point. Analysis of data from RCTs only showed no significant reduction in readmissions (RR=0.92, CI:0.80–1.06; low certainty of evidence).

Conclusions

The totality of evidence suggests pharmacist-led interventions with PCP communication are effective in reducing readmissions, especially at 30 days follow-up. Future studies need to adopt more rigorous study designs and apply well-defined patient eligibility criteria.

KEYWORDS

Medication safety; Pharmacy: Quality use of medicines; Meta-analysis: Primary Care

INTRODUCTION

Patients with chronic conditions are often confronted with complex care plans and significant changes to their medication regimen prior to discharge from hospital.[1] For many patients, discontinued medications are unintentionally continued, newly prescribed medications are omitted, and dose changes are not implemented.[2] Readmissions to hospital due to medication-related problems are common and may be preventable.[3] A systematic review found rates of medication-related readmissions varied between 3 – 64% across nine included studies, with a median rate of 21%. On average, 69% of these readmissions were considered preventable. [3] Patients who have a medication discrepancy (a difference between prescribed medication and medication actually taken) following hospital discharge are twice as likely to be readmitted to hospital within 30 days.[4]

Pharmacists play a key role during care transitions from hospital to community through optimising medicine use and reducing medication discrepancies,[5, 6] identifying and rectifying medication errors such as incorrect medication or dosing schedule,[7-9] and improving medication adherence.[7] A commonly performed pharmacist-led intervention is medication reconciliation (matching prescribed medicine with actual medicine use), with a meta-analysis by Mekonnen and colleagues showing that hospital-based pharmacists performing medication reconciliation at admission and/or discharge reduced all-cause readmissions by 19% compared to usual care.[6] In contrast, a review of studies of pharmacist-led medication reconciliation in the community setting shortly after hospital discharge did not demonstrate significant reductions in hospital readmissions.[8] This difference may be explained by the inclusion in the former review of studies that used other components (e.g. medication review, patient follow-up by the pharmacist, or communication with primary care providers) which may have contributed to improved patient outcomes.[6]

A pharmacist-led intervention which involves liaising with the patient, hospital and primary care team after discharge provides an opportunity to improve communication and care during a time that is often associated with medication misadventure and readmission to hospital.[10, 11] Indeed, several studies have described pharmacist-led interventions which involve communication with the primary care provider (physician or nurse practitioner) (PCP) during the transition back into the community after hospitalisation with the aim of reducing readmissions.[12-17] However, between-study differences in interventions and level of PCP involvement do not allow identification of the most effective components. A further

constraint are analyses which use different follow-up time-points. While unplanned readmissions at 30 days is commonly reported as a measure of quality of hospital care transitions, exploring outcomes at later time-points allows better assessment of the duration of intervention effects.

In 2012, Guerts and colleagues undertook a systematic review of interventions of pharmacist and physician collaboration aimed at improving patient outcomes.[7] Only three studies reported readmissions as an outcome and findings were mixed. Since then, pharmacist and GP collaboration in the post-discharge period have increased worldwide, and more studies have likely been published.[12, 17] We undertook a focused systematic review and meta-analysis of the literature relating to any pharmacist-led interventions involving communication with a PCP, with the aim of assessing the impact of these interventions on reducing readmissions to hospital.

Objectives

Specific objectives were to:

1. Investigate whether pharmacist-led interventions which include PCP communication reduce readmission to hospital.
2. Identify and describe the characteristics of included interventions.
3. Explore differences in effectiveness of interventions at different follow-up time-points and between different patient groups.

METHODS

This manuscript was produced in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[18] The protocol for the meta-analysis was registered with PROSPERO (CRD42017047702).

Eligibility criteria

Peer-reviewed original research reports published in English were included if: a) a pharmacist-led intervention (defined as the pharmacist being the main contributor or lead in the intervention for post-discharge care) for adult patients being transitioned from hospital into community care (e.g. home, nursing home) was described, b) participants were recently hospitalised adult patients, c) at least part of the intervention occurred after discharge, d) there was communication (any type) between a registered pharmacist (community, hospital or other) and a PCP or primary care nurse practitioner for other than administrative purposes

(e.g.to request a prescription, that was not identified through a medication review), and d) all-cause hospital readmission at any time-point was measured as an outcome. All study designs that compared an intervention group to a usual care control group were included. Studies involving paediatrics or those not describing collaboration with a PCP were excluded as were conference abstracts and protocols.

Search strategy and selection

A comprehensive search was conducted of PubMed, EMBASE, The Cochrane Central Register of Controlled Trials, CINAHL and Web of Science for relevant articles published from inception to the 19th March 2021. Additional papers were selected from bibliographies of included studies and reviews. Where applicable, Medicine Subject Headings (MeSH) and subject headings were used in the electronic search. Truncation was used to include any variations of terms and Boolean operators 'AND' and 'OR' were used.

For all databases, the following terms were used (or their subject heading substitutes): (hospital readmission OR rehospitali* OR readmission*) AND (pharmacist* OR pharmacy* OR "pharmaceutical service") AND ([general AND practi*] OR [family AND practi*] OR [family AND physician*] OR [general AND physician*] OR [primary AND health] OR [patient AND discharge] OR [ambulatory AND care OR [post AND discharge] OR [outpatient*]).

All articles were retrieved and screened independently by two researchers (HF, KR) for relevance. Any discrepancies were resolved in discussion with another author (CF).

Data extraction

Data were extracted into a standardised form by the first author (HF) and included study design and quality, number and characteristics of participants, descriptions of care provided to the comparison groups, follow-up time-points, and outcome measures. To ensure data accuracy and quality, a random sample of 10 (20%) manuscripts had their data extracted independently by a second author (IS and CF) and this was in perfect agreement with the first author's data extraction.

Descriptive data about the care provided to the intervention group was extracted using the Template for Intervention Description and Replication (TIDieR) checklist, which contains a recommended guide for reporting intervention details sufficient to allow its replication.[19]

Assessment of risk of bias in individual studies

The risk of bias (RoB) in each included study was assessed, using the Cochrane Collaboration's RoB tool for randomised controlled trials (RCTs) [20]and the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for non-RCTs,[21] as rated by the first author (HF).

Data synthesis and meta-analysis

Data were pooled from those studies which reported the number (or percentages) of participants in the intervention and usual care group who were readmitted at a given time-point. For studies with missing data, authors were contacted to request further information. All time-points were included in the primary analyses. For papers reporting readmissions at more than one time-point, results at the 30-day time-point were used in the primary analyses. When both intention-to-treat (ITT) and per-protocol (PP) results were reported, only ITT results were used in the primary analyses.

The primary outcome measure was the difference between intervention and control groups in the proportion of patients who had one or more readmissions over the stated follow-up time period, expressed as the Mantel-Haenszel risk ratio (RR) with 95% confidence intervals (CIs), and derived using random-effects models to account for both within-study and between-study variance (tau-squared [τ^2]). Hedges Q test and the I^2 index were used to identify and quantify study heterogeneity respectively.[22] I^2 values of 30% to 60% were considered moderate heterogeneity, 60% to 100% were considered substantial heterogeneity.

An estimate of absolute risk reduction (ARR) of readmission due to interventions was made by: 1) multiplying the event rate (absolute risk) in the control group of the study with the largest number of patients by the risk ratio, obtained from the meta-analysis, to determine the event rate in the intervention group; and 2) subtracting the intervention event rate from the control event rate.

Secondary outcomes comprised: : 1) proportion of patients readmitted at least once at 30 days, 90 days and 6 months after discharge, using data pooled from studies which reported data for each of these follow-up time-points; and 2) incidence rate of all readmissions for studies that reported total number of readmissions in the intervention and control group over a defined period.

R software version 3.5.1 was used for all statistical analyses, and p values <0.05 denoted statistical significance.

Subgroup analysis

Following detailed characterisation of all patient populations and interventions across all included studies, the primary outcome was re-assessed in post-hoc subgroup analyses to investigate the effect of interventions according to: 1) number of interactions between pharmacists and/or other health professionals and patients; 2) components of the intervention undertaken by pharmacists; 3) type of contact the pharmacist had with the PCP (e.g. face to face; fax; e-mail); and 4) reasons for the pharmacist and PCP interaction.

Substantial between study differences in the eligibility criteria used to select patients into trials precluded subgroup analyses that aimed to explore differences in effect according to patient characteristics.

Sensitivity analyses

Separate meta-analyses compared outcomes from: RCTs versus non-RCTs in determining sensitivity of estimates of effect to risk of bias; and ITT versus PP analyses for studies reporting both types of analysis.

Risk of publication bias across studies

Funnel plots and Egger's test were used to evaluate the effect of publication bias in the primary analysis.[23]

Quality of evidence

The GRADE system was applied in rating the quality of evidence (and hence certainty of the estimates of effect) according to risk of bias, consistency, directness, precision and reporting bias.[24] This system was applied to clinical studies grouped by study type (RCT vs non-RCT) for the primary outcome for each of the time-points (30 days, 90 days, 6 months).

Risk of bias has been previously described. Consistency was assessed using I^2 values and examining sources of heterogeneity among studies (differences in patient eligibility, intervention and control group). Directness was based on recency of studies and concordance with current practice norms. Precision reflected the width of the confidence intervals for the pooled outcome in the meta-analysis and for the outcome in each study. Finally, reporting bias was assessed according to whether positive studies dominated over negative studies.

RESULTS

Study selection

In total, 2170 articles were identified from the literature search and after removing duplicates (n=487), 1683 remained. After screening titles and abstracts, 1187 articles were excluded, leaving 496 of which, after reading full text articles, 45 met inclusion criteria (Figure 1). Corresponding authors of eight studies were contacted for additional information, of whom four did not reply and two were unable to provide further information.

Of the 45 included articles, 38 provided sufficient quantitative data to be included in one or more meta-analyses: 37 articles provided data for only the primary outcome meta-analysis, four studies provided data for both primary and secondary outcomes meta-analysis, and one study provided data for only the secondary outcomes meta-analysis.

Study characteristics

Table 1 describes the characteristics of all 45 included studies. Patient sample sizes varied from 25 to 3690 (mean=492, median=306). Studies were conducted in the USA (n=32),[2, 12, 13, 15-17, 25-50] Australia (n=5),[51-55] UK (n=3),[14, 56, 57] Netherlands (n=1),[58] Denmark (n=1),[59] Sweden (n=1),[60] Northern Ireland (n=1)[61] and Singapore (n=1).[62] Sixteen studies (36%) were RCTs, the remaining 29 (64%) comprised non-RCTs. All patients were recruited during hospital admission in all studies except one, where patients were recruited during hospital admission and within a specialist outpatient heart failure clinic.[58] Most studies (n=35, 78%) recruited patients considered 'at risk' of readmission (as defined by the authors), based most often on age, number of prescribed medications at discharge and/or number of chronic conditions.

Reported follow-up time-points after discharge comprised 7 days (n=2, 4%),[2, 61] 8 days (n=1, 3%),[53] 14 days (n=2, 4%),[2, 61] 30 days (n=34, 76%),[2, 12, 13, 15, 16, 25-50, 55, 59, 61] 45 days (n=1, 3%),[41] 60 days (n=5, 11%),[12, 26, 37, 41, 44] 90 days (n=8, 18%),[17, 29, 44, 52, 53, 55, 57, 61] six months (n=12, 27%)[14, 35, 41, 44, 54-59, 61, 62] and 12 months (n=4, 9%).[31, 55, 60, 61]

Five studies [32, 40, 42, 50, 61] reported results for both ITT and PP analyses.

The most common intervention component, in addition to the pharmacist-PCP communication, was a medication review by a pharmacist following hospital discharge (n=35, 78%). Although different terminology for describing these reviews was used in these studies, most reviews aimed to reconcile any differences between the discharge medication lists and current medication use, identify and rectify any medication-related problems, and

address patient concerns. The remaining ten (22%) studies did not describe undertaking a comprehensive medication review, but instead described a focus on one or two aspects of medication-use, such as educating patients about their medications, promoting adherence to medications, and/or performing a medication reconciliation (e.g. comparing discharge medication list to the medications that the patient was taking at time of consultation).

Most studies (n=38, 84%) aimed to commence the intervention within 14 days after discharge, and eight of these studies initiated the intervention during the patient's hospitalisation. The initial communication between the pharmacist and patient most often occurred face-to-face (n=28, 62%) and this was within the patient's home (n=8, 23%), at the hospital (n=6, 13%), in a primary care clinic (n=8, 18%), at a community pharmacy (n=5, 11%) or in a specialist clinic (n=1, 3%). In 12 (27%) studies, the intervention was conducted completely via telephone and in five (11%) studies conducted face-to-face or via the telephone, depending on the study-assigned risk of readmission or a medicine-related problem of each patient.

All studies stated there was some PCP involvement; however the amount of information given to the PCP from the pharmacist and the method of delivery varied. The information provided to the PCP most frequently was a summary of the intervention (n=17, 38%) and/or recommendations or information about medication-related problems identified as a result of the intervention (n=24, 53%). This was often done indirectly (fax, email, electronic messaging, or surface mail) (n=16, 36%) with no evidence of further interaction between pharmacist and PCP. Five (11%) studies stated the pharmacist had a face-to-face interaction with the PCP, five (14%) studies reported communication with the PCP via telephone and in three (7%) studies, the contact was described as being either indirect or via the telephone. In 16 (36%) studies the method of communication was unclear.

There were 27 (60%) studies that reported at least one additional interaction with patients, either with the pharmacist or PCP, after the initial interaction, but what actually occurred during these interactions was not well described, with eight of these studies only stating there was a follow-up consultation or phone call to the patient.

Pharmacists delivering the service were based in a hospital (n=13, 29%), primary care clinic (n=15, 33%), a community pharmacy (n=6, 13%) or a nursing home (n=1, 3%). In five (11%) studies, the pharmacist was employed specifically for the study. Two (4%) studies had pharmacists based at both the hospital and community pharmacy. It was unclear where the

pharmacist was based in three (7%) studies. In addition to a pharmacist delivering the intervention, four (11%) studies involved other allied health professionals: three (7%) studies involved a nurse, one (3%) study involved a nurse practitioner and one (3%) study involved a social worker. The nurse's role in the intervention was primarily to perform a physical examination,[27, 54] provide in-hospital care to prepare the patient for discharge and create an after-discharge hospital care plan,[33] or relay and coordinate information to other health professionals.[43] The nurse practitioner also used point-of-care testing and had the ability to alter the treatment plan if necessary.[27] The social worker's primary role was to assess the patient's living situation, activities of daily living, mental health and ability to get to medical appointments and obtain medication.[40]

Overall, there were 21 (47%) studies that did not describe at least one item of the TIDieR checklist, with most missing data relating to how the information was delivered from the pharmacist to the PCP (n=14, 67%) (see Table 1).

1 **Table 1: Characteristics of included studies (n=45), using the TIDieR checklist to define the intervention.**

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
Arnold et al., 2015[25]	Non-RCT (pre-post) C: 236 I: 98	≥50 years + >5 medications at discharge	Previous year's data of individuals who received physician only follow-up appointment (usual care)	Medication review and reconciliation Feedback and recommendations to physician (not clear how it was reported)	Hospital pharmacists	Face-to-face	Outpatient primary care teaching clinic; USA	Single interaction ≤ 72 hours after discharge (majority of patients) on the same day as physician visit.
Bingham et al., 2019[43]	Non-RCT C: 116 I: 340	Primary discharge diagnosis of: asthma, pneumonia, diabetes mellitus, HF, COPD, MI, total hip or knee replacement, renal failure, or post-CABG	Those that opted out of the program or were unable to be reached after two phone attempts. Usual care included at least one phone call by hospital's transitional care coordinator within 24-72 hours after discharge (no further details)	Medication review, barriers to adherence, challenges obtaining new prescriptions and transportation issues discussed. Education regarding discharge diagnosis. Within 24 hours of above, nurse relayed relevant information to PCP, specialist and community pharmacy. Pharmacist follow up to address status of any recommendations and/or concerns. Addressed any new issues	Hospital pharmacist	Telephone	Telephone, USA	Two interactions Phone call within 1 week of discharge Follow up 3 weeks post-discharge
Bloodworth et al,. 2019[44]	RCT C: 160 I: 96	Admitted with diagnosis of HF, COPD, pneumonia, or MI	No coordinated outpatient services or supply of discharge medicines	During admission: medication reconciliation, and resolved any issues. Provided with 30 day supply of discharge medications and given	Community pharmacists trained in medication	Face-to-face and via telephone	Community pharmacy; USA	Four interactions Community pharmacy visit: 4-7 days

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				Appointment for outpatient visit at community pharmacy Follow up phone calls and visits: medication review, assessed health status, medication adherence and health education Problems identified were communicated to provider as necessary. Notes from each session were placed in electronic software.	therapy management			postdischarge and 90 days post discharge Phone call: 2, 9, 25 and 190 days and post discharge
Bouvy et al., 2003[58]	RCT C: 78 I: 74	HF and prescribed loop diuretics	No structured interview or monthly follow-up (usual care)	Structured interview to discuss drug use and compliance MEMS used for loop diuretics Report of interview forwarded to GP (not clear how it was reported) Patient follow-up (not clear on content)	Community pharmacists received training (no details provided)	Face-to-face (not clear how follow-up was done)	Community pharmacy; Netherlands	Interacted up to 7 times Interview on first visit to community pharmacy after enrolment Patient contacted monthly for up to 6 months
Brauner et al., 2020[45]	Non-RCT (pre-post) C: 23 I: 23	Patients with a care assessment need of ≥90[a]	Patient from non-intervention team with a care assessment need of ≥90	Medication reconciliation, disease state education, and medication counselling. Communicated medication-related and laboratory blood work recommendation to PCP via electronic record	Pharmacist in primary care clinic	Face-to-face (n=10) and telephone (n=13)	Primary care clinic, USA	Single interaction ≤ 14 days after discharge

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				PCP then accepted or rejected the recommendations				
Budlong et al., 2018 [26]	Non-RCT C: 42,523 I: 1188	Newly diagnosed chronic disease, number of chronic medications, recent hospital admission or documented medication nonadherence[b]	Complexity matched group who did not receive the transition of care clinic service (usual care)	Medication review and reconciliation, with ability to prescribe/change some medications Care plan developed Information documented in electronic record (accessed by PCP) Issues brought to attention of PCP (not clear how it was reported) Follow-up (not clear on content)	Usually pharmacist in patient's usual primary care clinic	Face-to-face where possible (not clear how many via phone)	Primary care clinic (via telephone if unable to travel); USA	Patient eligible for 2 visits ≤ 30 days after discharge
Cheen et al. 2017[62]	Non-RCT C: 402 I: 97	≥ 60 years + > 5 medications + ≥ 2 unplanned hospital admissions in previous 3 months	Intervention by care coordinator only who resolved outstanding 'care' issues	Medication review Pharmacist communicated problems to PCP via letter or telephone	Hospital pharmacists received 6 weeks of training by a pharmacist with experience in the intervention	Face-to-face	Patient's home; Singapore	Single interaction ≤ 14 days after discharge
Cole et al., 2019[46]	Non-RCT C: 12 I: 76	Moderate-to-high risk for hospital readmission and identified as high medication risk patients[c]	Patients who declined services or could not be reached	Medication review and reconciliation. If needed, contacted pharmacy, insurance and made recommendations to PCP via electron record or telephone	Pharmacist working in primary care	Telephone	Telephone, USA	Two interactions Initial within 2 business days of pharmacist receiving referral (but range from

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				Follow up to ensure problems were resolved and no further medication-related concerns existed.				0 – 24 days after referral) Follow-up 14 – 21 days after initial phone call
Donaho et al., 2015[27]	Non-RCT C: NA I: 169	Recently admitted with a diagnosis of HF	Hospitalised patients with HF during same time period at the hospital who received usual care	Physical examination, point-of-care testing, altered treatment plan if needed Medication education and reconciliation, disease education, discharge plan Coordination of outpatient health care resources including communication with PCP (most commonly received full progress notes, identified issues, medication reconciliation reports via electronic records or patient provided copies) Follow-up (not clear on content)	Nurse practitioner (examination) Pharmacist working within clinic	Face-to-face	Pharmacy wellness clinic (facility based clinic) located close to hospital; USA	Two interactions (high risk patients allowed an interim visit between initial and follow-up visits) Initial visit ≤ 7 days after discharge Follow-up 4 – 6 weeks after discharge
Fanizza et al., 2018[28]	Non-RCT C: 22 I: 18	Self-enrolled at community pharmacy if had hospitalisation in last 14 days	Patients that declined the service (did not receive community pharmacy input)	Medication review Mailing of an updated medication list and action plan to patient Cover letter explaining service and identified problems and recommendations faxed to prescriber	Community pharmacist	Initial face-to-face or via telephone (not clear how many in each group)	Community pharmacy or via telephone; USA	Three interactions Initial call ≤ 17 days after discharge 2 follow-ups at least 7 days apart and both within 30 days after discharge

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				Follow-up call to address medication-related questions		Follow-up via telephone		
Farris et al., 2014[29]	RCT C: 313 I: 311	Admitted with diagnosis of cardiovascular related condition, asthma, COPD or receiving oral anticoagulation.	Pharmacist performs medication reconciliation during hospitalisation, nurse provides discharge summary and medication list. Post-discharge usual care not described .	In hospital: medication reconciliation, patient education, discharge list and recommendations faxed to PCP and community pharmacist Post-discharge phone call to evaluate adherence, new side effects and answer questions Report of phone call faxed to PCP and community pharmacist	Hospital pharmacist trained by study investigators on the intervention, strategies to communicate with physicians and community pharmacists and methods to improve medication adherence	Face-to-face during hospitalisation Telephone	Hospital Telephone; USA	Two interactions During hospitalisation Discharge care plan faxed ≤ 24 hours Call at 3 – 5 days after discharge
Fennelly et al., 2020[47]	Non-RCT C:139 I: 159	LACE score ≥13	Eligible patients who were not scheduled	Care navigator phone call (not clear what content was) Medication review and reconciliation, assessed medical stability and documented recommendations for PCP PCP visit	Not clear who made initial call Pharmacist working in clinic PCP	Telephone and PCP visit face-to-face	Telephone, primary care medical centre, USA	Care navigaot call ≤ 2 days Pharmacist call 3 – 7 days PCP visit ≤ 7 days
Fera et al. 2014[30]	Non-RCT C:57 I:118	Admitted with a diagnosis or history of COPD or heart failure	Patients who were enrolled but could not be reached in	Medication review and reconciliation	Care transition pharmacist	Telephone	Telephone; USA	Single interaction

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
		OR > 9 medications OR had another medication problem identified on admission OR physician referral	the follow-up phone call	Review plan of care and address any gaps Reinforced inhaler training and the need for smoking cessation and immunisation PCP was called to resolve issues				≤ 72 hours after discharge
Freeman et al., 2021[55]	RCT C: 177 I:129	Nominated an enrolled GP in the hospital records, ≥ 5 long term, regular medicines on discharge or primary discharge diagnosis of CHF, COPD	No pharmacist involvement in the primary care clinic and no scheduled GP appointment	Medication reconciliation and review, discuss changes to medicines made during hospital admission Pharmacist discussed consultation with GP, then patient had consultation with their GP (same day if possible) Follow up of patients	Pharmacist working in clinic (received one day of training) Patient's regular GP	Face-to-face Face-to-face or telephone	General practice; Australia	Two interactions ≤ 7 days after discharge
Gillespie et al. 2009[60]	RCT C: 201 I: 199	Admitted to one of two acute internal medicine wards	No pharmacist involvement at ward level, discharge summary given, but no changes to medicines recorded (usual care)	In hospital medication review and reconciliation Discharge counselling Information about discharge medicines (rationale for medicines, monitoring needs and expected therapeutic goals, any problems not resolved) faxed to PCP.	Hospital pharmacist	Face-to-face Follow-up via telephone	Hospital Telephone Sweden	Two interactions During hospitalisation Telephone call 2 months after discharge

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				Follow-up call to ensure adequate home management of medicines.				
Haag et al. 2016[31]	RCT C: 12 I: 13	Elders Risk Assessment Index[d] score ≥16 + aged ≥ 60 years	Received an outpatient care transition program (CTP)[e] without pharmacist input	Medication review Electronic medical record searched for potential prescribing omissions Recommendations communicated to PCP via secure messaging function	Tertiary care medical centre pharmacist with certificate in medication management therapy	Telephone	Telephone; USA	Single interaction ≤ 3 – 7 business days after discharge
Hanna et al. 2016[51]	Non-RCT C: 118 I: 398	Concerns regarding carer or patient's ability to manage medications plus one other risk factor identified by hospital specific tool[f]	Patients who were eligible but declined the service	Medication review and reconciliation Report of review (including medication adherence, actions taken and goals) faxed to PCP and community pharmacy. Report also placed in hospital medical records.	Hospital pharmacist who had completed a general-level competency framework	Face-to-face	Patient's home; Australia	Single interaction ≤ 10 days after discharge Report usually faxed same day as review
Hawes et al., 2018[12]	Non-RCT C: 86 I: 86	Discharged from the study hospital and attended a hospital follow-up visit within 30 days of discharge	Seen by PCP at follow-up clinic but not the pharmacist	Medication review and reconciliation Face-to-face "huddle" between pharmacist and PCP immediately after to discuss issues and recommendation. Patient then had consultation with PCP (usual care)	Clinical pharmacist practitioners with prescribing and ordering rights under supervision of a physician	Face-to-face	Primary care unit; USA	Single interaction No pre-specified time, only included in analysis if seen within 30 days of discharge.

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
Heaton et al. 2019[32]	RCT C: 187 I: 213	Patients admitted with primary diagnosis of acute myocardial infarction, pneumonia, heart failure, COPD, or diabetes	No post-discharge care by community pharmacist	Medication review and reconciliation Medication and self-management education Offered adherence aids Personalised medication list and self-monitoring support Referral to social support as needed Communicated recommendations to PCP via fax Follow up not clear	Community pharmacists received training in medication therapy management services.	Face-to-face	Community pharmacy Follow-up at pharmacy or via telephone USA	Two interactions ≤ 7 days after discharge 1 week after initial visit
Hitch et al. 2016[13]	Non-RCT (pre-post) C: 100 I: 164	Moderate (>5 medications OR ≥ 3 diagnoses) or high (:>10 medications OR ≥ 6 diagnoses) risk of readmission on hospital discharge summary	Compared patients retrospectively with same risk category who received usual care (not clear what this involved)	Medication review and reconciliation (not clear how pharmacist communicated with PCP) PCP follow-up including reviewing medication reconciliation and addressed all diagnoses mentioned in discharge summary (not clear if this was also part of usual care)	Clinical (not clear if hospital or primary care) pharmacist with prescribing rights under supervision of a physician	Telephone PCP face-to-face visit	Telephone PCP consultation at primary care clinic USA	Two interactions Telephone call *ideally* occurred before PCP visit PCP visit ≤ 7 days for those at high risk of readmission and within 14 days for those at moderate risk
Holland et al. 2005[14]	RCT C: 435 I: 437	≥80 years, prescribed ≥	Usual care (not described)	Medication review, removed out-of-date drugs	Study pharmacist who held a postgraduate	Face-to-face	Patient's home; UK	Two interactions

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
		2 medications on discharge		Reported drug reactions or interactions to PCP and need for a compliance aid to community pharmacist (not clear how it was reported) Follow-up visit to reinforce original advice	qualification in pharmacy practice or had recent continuing professional development in therapeutics. All received two day training course			Initial visit ≤2 weeks of discharge One follow-up visit 6-8 weeks after discharge
Holland et al. 2007[56]	RCT C: 170 I: 169	Heart failure identified as an important ongoing clinical condition, and ≥ 2 medications on discharge	Usual care (not described)	Patient education on heart failure, medication, basic lifestyle advice. Encouraged completion of symptom monitoring diary. Removed discontinued medication. Fed back recommendations to PCP and local pharmacist (for any need of drug adherence aid) (not clear how it was reported) Follow-up visit to review and reinforce original advice	Community pharmacists who held a postgraduate qualification in pharmacy practice or had recent continuing professional development in therapeutics. Received a 1 – 2 day training course.	Face-to-face	Patient's home; UK	Two interactions Initial visit ≤2 weeks of discharge One follow-up visit 6-8 weeks after discharge
Jack et al. 2009[33]	RCT C: 376 I: 373	Hospitalised adults	Usual care (not described)	Nurse discharge advocates, educated and prepared patients for discharge, provided an after	Nurse discharge advocate (trained in intervention)	Face-to-face Telephone	Hospital Telephone USA	Two interactions During hospitalisation (nurse)

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				hospital action plan. Discharge plan faxed to PCP Medication review and reinforce discharge plan (via telephone) Issues communicated to PCP or back to discharge nurse (not clear how it was reported)	Hospital pharmacist			Telephone 2 – 4 days after discharge
Kilcup et al. 2013[2]	Non-RCT C: 251 I: 243	Patients at higher risk for readmission using hospital specific tool[g]	Nurse follow-up phone call that does not include comprehensive discussion about medication (usual care at a different clinic)	Medication review and reconciliation Any issues sent to PCP. If new prescriptions were needed, the pharmacist pended new orders to the appropriate provider for review and approval	Primary care clinic pharmacist	Telephone	Telephone; USA	Single interaction 3 – 7 days after discharge
Mayzel et al., 2020[48]	Non-RCT (pre-post) C: 50 I: 50	Patients seen at the primary care clinic during the study period (pharmacist present)	Health care professional calls within 48 hours of discharge to complete medication reconciliation, patients consider high risk of readmission are called by care coordinator; moderate risk are called by	In addition to usual care (control group), patients had an additional 20-minute medication reconciliation and review appointment at clinic, prior to PCP visit. Medication related problems were reviewed with PCP (not clear how discussion occurred)	Pharmacist in primary care clinic	Face-to-face	Outpatient primary care clinic, USA	Single interaction 7 to 14 days after discharge

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
			pharmacist. Adherence is assessed and medication problems identified and documented in electronic record. Seen by PCP within 14 days of discharge. Pharmacist did not see patients in clinic					
Miller et al. 2016[34]	Non-RCT (pre-post) C: NA I: 314	Discharged from internal medicine or hospitalist services, ≥ 4 regular medications.	Readmission data from 2 years prior to introduction of program, who received usual care	Medication review, provision of a medication list and action plan Faxing of medication review documents to PCP and mailing medication list and action plan to patient Follow-up to confirm patient received documents sent by mail, assess for any resolutions to previously identified issues, and evaluated for any new or addition problems that may have arisen	Hospital pharmacist	Telephone	Telephone; USA	Two interactions Initial call ≤ 72 hours after discharge Follow-up call 14 – 30 days after initial call.

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
Naunton & Peterson, 2003[52]	RCT C: 64 I: 57	≥60 years, ≥ 2 chronic conditions, ≥ 4 regular medications	Usual care (not described)	Medication review, performed a pill count and asked a single question to assess adherence. Brief letter outlining patient's medication regimen and any suggested changes or monitoring given to patient to provide to PCP Soon after home visit, pharmacist phoned PCP and community pharmacist to inform them of the study and any urgent issues	Study pharmacist	Face-to-face	Patient's home; Australia	Single interaction 5 days after discharge
Nazareth et al. 2001[57]	RCT C: 181 I: 181	≥75 years +≥4 medicines at discharge	Discharge letter to PCP with diagnosis, investigations and current medications (usual care)	Hospital pharmacist: Developed a discharge plan with information on discharge medication and medication support required by the patient. A copy was given to the patient, community pharmacist and PCP. Community pharmacist: Medication review and reconciliation Liaising with PCP (not clear of contents, how it was reported or whether this was mandatory)	Hospital and community pharmacists	Face-to-face	Hospital Patient's home UK	Two interactions During hospitalisation 7 – 14 days after discharge (further follow-up only if required)
Ni et al. 2017[35]	Non-RCT 30 day group C:1005 I: 830	≥1 of the following: high risk determined by specific	Compared patients retrospectively who met high risk	In hospital medication reconciliation	Ambulatory care pharmacist	Telephone Those requiring	Telephone or ambulatory care	Two interactions During hospitalisation

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
	180 day group C: 669 I: 558	algorithm, discharged on ≥5 medications, previous hospital admission in last 45 days	criteria of same algorithm, who received usual care (not described)	Counselled patients to improve adherence, reinforce discharge plan, arrange transport for appointments and working with community pharmacy to resolve insurance-related issues. All information placed in electronic medical records. Pharmacists worked with outpatient providers to resolve medication-related problems and acted as a liaison to bridge communication gaps (no information on how it was reported)		extra assistance invited for face-to-face	pharmacy; USA	Other actions occurred over the 30 days after discharge
Odeh et al., 2020[61]	RCT C: 31 I: 31	Patients admitted with an unplanned hospitalisation with ≥ 1 of the following: ≥4 regular medications, ≥3 changes to medication in hospital, referred to clinic by doctor or pharmacists, prescribed ≥1 high alert medicines or ≥2 prior unplanned	Normal post-discharge care, no follow-up by pharmacist	Medication review and reconciliation, lab test review, general patient education, lifestyle advice, medication adherence assessment, disease management advice and self-management advice (as needed) Documented key points on a take home leaflet, Follow up based on the individual patient's needs Summary of review and recommendations was forwarded to	Hospital pharmacist	Face-to - face Face-to-face or via telephone	Hospital outpatient clinic, Northern Ireland	Two interactions Within 2 weeks after discharge 6-8 weeks after discharge

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
		admissions during last 6 months		the patient's GP and hospital consultant				
Polinski et al. 2015[36]	Non-RCT C: 131 I: 131	Insurance developed algorithm was used to identify patients at high or moderate-to-high risk of readmission[h]	Matched patients who had a hospitalisation during same period that had same risk but attended a hospital without the program	Medication review and reconciliation, personalised adherence education and coaching and made aware of social support and health services available from their insurer. Care plan shared with providers. "Providers" were called to clarify and simplify dosing regimens, report changes in patient's health status, scheduled follow-up appointments and coordinated care between unaffiliated providers.	Community pharmacist	Face-to-face Telephone	High risk: Patient's home Moderate to high risk: telephone USA	Single interaction (pharmacists or patients could initiate telephone contact with each other for 30 days) Phone call ≤ 3 days to invite into study – not clear when consultation actually occurred
Ravn-Nielsen et al. 2018[59]	RCT C: 503 I: 497	≥ 5 regular medications, new acute admission	Usual care (not described)	During hospitalisation: Medication review At discharge: patient interview using motivational interview approach (medication reconciliation, information on changes to medicines, adherence and cost). Any problems not dealt with during hospitalisation was mailed or faxed after discharge to the PCP. Summary note was sent to PCP. The PCP, caregiver and community	Hospital pharmacist trained in medication review and completed a 3-day course in motivational interviewing.	Face-to-face Follow-up telephone calls	Hospital Telephone Denmark	Four interactions At discharge PCP/community pharmacist call approximately 3 days after discharge Two follow-up patient calls at 1 week and 6 months after discharge

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				pharmacy were contacted 3 days after discharge via telephone. Follow-up with PCP and caregiver when changes were made during hospitalisation or problems arose. Follow-up based on motivational interview (not clear on content)				
Rebello et al. 2017[37]	Non-RCT C: 100 I: 100	Veterans ≥ 65 years with acute admission discharged directly home	Matched patients who had a hospitalisation during same period who did not receive the intervention. Each patient was then matched based on risks[i]	Medication reconciliation and review and adherence assessment Recommendations made directly to the primary care team (not clear how it was reported)	Hospital pharmacist with access to a wide network of health services	Telephone	Telephone; USA	Single interaction ≤ 7 days after discharge (follow-up made as needed)
Reidt et al 2016[38]	Non-RCT C: 189 I: 87	Convenience sample of those in skilled nursing facility (transition of care facility between hospital and home) were scheduled for discharge when the pharmacist was available	Nurse practitioner and geriatrician involvement only (usual care)	During hospitalisation: Medication review, reconciliation adherence discussion. Recommendations given to nurse practitioner After discharge: medication review and reconciliation, assess adherence reinforce discharge plan. Updated medication list and summary of home visit documented in electronic medical record and communicated to PCP via fax. If	Pharmacist in a skilled nursing facility	Face-to-face	Hospital Patient's home (skilled nursing facility) USA	Two interactions During hospitalisation ≤7 days after discharge

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				PCP needed urgently, they were paged.				
Sanchez et al., 2015[39]	Non-RCT C:277 I:124	Discharged home	Those who were eligible for service but could not be contacted	Review of current clinical status, medication reconciliation, reminder of follow-up appointments, discussion on what to do if a problem occurred Contacted the PCP via messages through medical records for less acute situations and paged for problems requiring immediate attention	Hospital pharmacist	Telephone	Telephone; USA	Single interaction 2 – 4 days after discharge
Shaya et al., 2015[15]	Non-RCT (pre-post) C: 73 I: 45	Type 1 or 2 diabetes with recent hospitalisation or ED visit	Compared patients retrospectively with same eligibility criteria who received usual care	Medication review and reconciliation, monitoring clinical laboratory results, evaluation response to therapy. Communicating regularly with in practice physician (not clear on contents or how it was reported) Follow-up visits (not clear on content)	Pharmacist (not clear where from)	Face-to-face	Endocrinologist's private practice; USA	Four interactions within 6 months after discharge Soon after discharge, ~ 1, 3 and 6 months later)
Slazak et al., 2020[49]	Non-RCT (pre-post) C: 118 I1: 101 I2: 37	I1: ≥1 medication discrepancy identified by nurse within 24 hours of discharge	Previous year's data of patients at same primary care office (pre-implementation) (No standardised	Medication review and reconciliation Recommendations to PCP (not clear how it was reported)	Primary care pharmacist	Telephone or face-to-face	Primary care clinic, USA	Single interaction (patients saw PCP but no details on interaction)

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
		I2: 2 out of 4 of the following: High-risk discharge diagnosis (acute CVD condition or procedure, acute exacerbation COPD; pneumonia); ≥ 15 scheduled medication at discharge; ≥ 2 discrepancies on initial reconciliation; High risk according to the 'comprehensive primary care plus'.	hospital follow-up)	Follow up if needed Update electronic records (I1 and I2 received same intervention, different eligibility criteria)				Not clear when interaction occurred
Smith et al., 2021[50]	Non-RCT C: 977 I: 507	Hospitalised adults during selected time period and scheduled for a post-discharge follow-up clinic	Outpatient visit with attending physician, resident physician, or nurse practitioner visits without pharmacy support (no standardized	Medication reconciliation, developing a problem-based assessment and plan Pharmacist reviews all recommendations with clinician during the visit	Hospital clinic pharmacist	Face-to-face	Outpatient clinic within medical centre, USA	Single interaction Not clear when interaction was meant to occur (79% occurred ≤14 days)

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
			criteria to refer patients to one service over the other)					
Stafford et al. 2011[53]	Non-RCT C: 139 I: 129	Prescribed warfarin and an indication of needing it for at least ≥ 3 months	Received management according to normal procedures on managing warfarin (no formal post-discharge outreach program)	At discharge: all primary care providers received a summary of patient's inpatient warfarin therapy Visit 1: Medication review, point-of-care INR monitoring, warfarin counselling. Results of INR and any issues communicated to PCP. Visit 2 and 3: point-of-care INR monitoring, further warfarin education, resolution of any drug-related problems.	Pharmacist who had been trained in the intervention and accredited to deliver home medication reviews	Face-to-face	Patient's home; Australia	Two to three interactions (depending on risk) Visit 1: 2 – 3 days after discharge Visit 2: optional, 4 – 6 days after discharge Visit 3: Level 1, 7 – 8 days after discharge; Level 2, 8 – 10 days after discharge.
Stewart et al. 1998[54]	RCT C: 381 I: 381	Admitted to a medical or surgical unit and prescribed a medication regimen for a chronic condition	Appointments with their PCP or hospital outpatient clinic within 2 weeks (usual care)	Pharmacist and nurse aimed to 'optimise home-medication management, detect otherwise hidden problems, increase patient vigilance for impending crisis, improve liaison with community-based services'. Pharmacist assessed medication compliance, offered counselling,	Study pharmacist Nurse	Face-to-face	Patient's home; Australia	Single interaction 1 week after discharge

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				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
				compliance aids, monitoring and medication information. Nurse conducted a physical assessment and review of symptoms. Those requiring medical review referred to PCP. PCPs contacted (via nurse) after home visit to discuss the visit and need for further action.				
Stranges et al. 2015[40]	Non-RCT C: 572 I: 572	≥60 years	Comprehensive discharge planning, medication reconciliation and education (usual care)	Pharmacist call to provide a preliminary medical assessment, medication review and reconciliation, assess symptoms and self-monitoring. Findings, recommendations and up-to-date medication list given to team prior to clinic visit via electronic medical record. Clinic visit consists of social worker and medical provider/ PCP	Patient-centred medical home pharmacist, social worker and medical provider/PCP	Telephone Face-to-face	Telephone Patient-centred medical home USA	Two interactions Call 2 – 4 days after discharge Clinic visit ≤ 1 week after discharge
Tedesco et al. 2016[16]	Non-RCT C: 45 I: 34	≥ 65 years, Medicare as primary insurance provider	Usual care at a similar primary care clinic which did not involve a pharmacist but	Call: Medication review and reconciliation, reinforced hospital's instructions with regard to discharge counselling. Appointment prior to PCP appointment: targeted medication	Primary care clinic pharmacist	Telephone Face-to-face	Telephone Primary care clinic USA	Two interactions Call ≤ 3 business days after hospital discharge Clinic visit within 7 – 14 days after discharge

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
			had a transition of care program.	therapy management session (more in depth medication reconciliation, reinforced medication adherence and addressed any medication-related problems). Any recommendations were conveyed to PCP prior to the PCP appointment				
Tuttle et al. 2018[17]	RCT C:75 I: 84	Patients with chronic kidney disease stages 3 – 5 not treated by dialysis who were hospitalised for an acute illness	Receiving an electronic medical record, clinical education from nursing staff, and were told the importance of follow-up and giving their medication list to their PCP (usual care)	Medication review and reconciliation, medication action plan, personal medication list. PCP were contacted via telephone or email to discuss medication problems.	Study pharmacists were specifically trained in the intervention	Face-to-face	Patient's home; USA	Single interaction ≤ 7 days after discharge
Westberg et al. 2014[41]	Non-RCT C: 270 I: 135	≥65 years being admitted for heart failure, dysrhythmias, genitourinary conditions, ischemic heart disease or digestive disorders. Primary care provider was affiliated with hospital and no	Matched patients retrospectively who received usual care	'Medication management': medication review, development of a care plan. Pharmacist worked with the primary care team to resolve all identified drug therapy problems (not clear how it was reported) Follow-up if patients had ≥ 3 drug problems identified (not clear on content)	Primary care clinic pharmacist	Face-to-face Follow-up via telephone for low risk, face-to-face for high risk	Primary care clinic; USA	Two interactions ≤ 2 weeks after discharge, prior to follow-up appointments with PCP Follow-up 4 weeks after initial visit

STUDY	DESIGN, N	INCLUSION CRITERIA	CONTROL GROUP	INTERVENTION CHARACTERISTICS				
				WHAT *Describe each activity/process in the intervention*	**WHO PROVIDED** *Who provided and any specific training*	**HOW** *Mode of delivery*	**WHERE** *Type of location where the intervention occurred*	**WHEN and HOW MUCH** *Time period conducted over and number of times delivered*
		prior visit with pharmacist						
Wright et al. 2019[42]	Non-RCT C: 3075 I: 615	Had an active diagnosis for heart failure, acute myocardial infarction, COPD, pneumonia or diabetes; and (intervention group only) attended a participating pharmacy	Did not attend participating pharmacy. Usual care involved receiving discharge summary with no communication between hospital and community pharmacy. Nurse phone call to check well-being and encourage adherence. Appointment with PCP was scheduled ≤7 days after discharge.	In hospital: Medication reconciliation and pass notes on to community pharmacist After discharge: reinforcing discharge medication instructions, reviewing new medications, assessing and managing adherence, providing a time-of-day–sensitive medication list to the patient, and assessing medication therapy and immunization status. Notes of encounter with patient faxed to PCP Follow-up consultations to assess health status and review medication use, including adherence. Fax recommendations to PCP	Hospital Pharmacist (in hospital) Community Pharmacist (after discharge)	Face-to-face (if patients did not arrive at pharmacy, they were called) Follow-up via telephone	Community pharmacy USA	At least two interactions 1st time patient arrived at pharmacy (around time of discharge) 3-7 days after discharge and up to another 2 follow-ups if required

C, control; COPD, chronic obstructive pulmonary disease; CTP, care transition program; CVD, cardiovascular disease; ED, emergency department; HF, heart failure; HIV, human immunodeficiency virus; I, intervention; INR, international normalised ratio; MI, myocardial infarct; MEMS, Medication Event Monitoring Systems; Non-RCT, non-randomised controlled trial; PCP, primary care provider; RCT, randomised controlled trial; UK, United Kingdom; USA, Unites States of America

[a] Score is based on a multifactorial, validated tool used to determine a patient's likelihood of hospital readmission or death (no further information)

[b] High medication risk patients defined as those with polypharmacy (9 or more medications), medication nonadherence, low medication literacy, high risk medications (including insulin, anticoagulants, and antiplatelet medications), high risk admission diagnoses (including acute MI, heart failure, pneumonia, COPD, coronary artery bypass grafting (CABG), total hip or total knee arthroplasty, and uncontrolled diabetes), and/or with specific clinical scenarios at the discretion of the nurse.

[c]Newly diagnosed chronic disease (diabetes mellitus, heart failure, COPD, MI) AND 5+ regular medications OR hospital admission or ED visit within last 6 months AND 10+ regular medications OR use of high risk medication (rifaximin, lactulose, oral chemotherapy) OR documented medication nonadherence.

[d] Tool authors: Crane SJ, Tung EE, Hanson GJ, et al. Use of an electronic administrative database to identify older community dwelling adults at high-risk for hospitalization or emergency department visits: the elders risk assessment index. BMC Health Serv Res 2010;10:338.

[e] CTP consisted of a home visit by a nurse practitioner within 3 days of discharge who reviewed medications and made changes or discussed with patient's physician. Follow-up telephone calls were made based on patient needs.

[f] Concerns regarding the patient or carer's abilities to manage medications plus one other risk factor (e.g. history of non-adherence, recent changes to medication, use of high risk medication, ≥4 medications).

[g] No clear method, but based on following factors: (1) whether current hospitalization was a readmission, (2) whether patients had complex care plans, (3) primary diagnosis of chronic disease, (4) important medication changes during hospital stay, and (5) concerns of patients' ability to self-manage.

[h] High risk category: ≥ 7 medications or used at ≥ 5 medications and had ≥ 1of the following conditions: congestive heart failure, chronic obstructive pulmonary disease, asthma, pneumonia, diabetes, end-stage renal disease, schizophrenia or bipolar disorder, dizziness, and a history of falls. Moderate-to-high risk category: 5 or 6 medications and had none of the conditions described above or used 3-4 medications and had ≥ 1 of the described conditions.

[i] Matched based on following matching order: location of hospitalisation, age, hospital length, admitting service and category of admitting diagnosis.

Risk of bias in individual studies

The risk of bias for RCTs (n=16) and non-RCTs (n=29) are presented in Figure 2a and 2b, respectively. The nature of the interventions meant it was not possible to blind participants, thus conferring a high risk of performance bias in all studies. Non-RCTs had an inherent high risk of selection bias. Most studies (n=34, 76%) had low ascertainment bias as readmission outcomes were objectively recorded by hospital coders who would not have known whether patients were receiving intervention or usual care.

Risk of publication bias across studies

The funnel plot for the primary analysis demonstrated asymmetry (Figure 1in on-line supplement), with Eggers test formally confirming a significant degree of publication bias towards studies with positive effects (t=-3.56, p=0.001).

Quality of evidence

Details of how the GRADE system was applied to studies included in meta-analyses are outlined in table 1 in the on-line supplement. The quality of evidence, and hence certainty of effect estimates, were rated low for the 15 RCTs and very low for the 22 non-RCTs.

Primary outcome meta-analysis

The analysis of pooled data from all 37 studies combined showed a statistically significant reduction in the proportion of patients readmitted at least once during the stated follow-up period in the intervention group (n=6720) compared to controls (n=9997), RR=0.87, CI: 0.79–0.97, p=0.01 (low to very low certainty of evidence). Statistically significant heterogeneity was present (Q=80.47, p=<0.001) and of moderate degree (I^2 =55.3%, CI: 35.2–69.1).

Separate meta-analyses of the primary outcome reported at different follow-up periods showed attenuation in intervention effect over time (figure 2 in on-line supplement). The proportion of patients readmitted in the intervention group was significantly reduced versus control at 30 days (RR=0.78, CI: 0.67–0.92), but not at 90 days (RR=0.90, CI: 0.78–1.05) or 6 months (RR=0.94, CI: 0.83–1.07). Tests for interaction between follow-up periods were not statistically significant (p=0.21).

In estimating the absolute reduction in the proportion of patients readmitted that would result from a relative risk reduction of 13%, as derived from the all-study meta-analysis, the proportion of patients readmitted in the control group (n=3075) of the largest study[42] was

used to calculate an absolute risk reduction of 2.0%. This equates to a number of patients needed to treat to prevent at least one readmission of 50.

In regard to the eight studies that did not report findings in a format that allowed pooling of data for the primary meta-analysis,[13, 15, 26, 27, 33-35, 51] three reported the proportion of patients readmitted at 30 days[27, 34, 35] and one at six months.[35] Of these, one study showed a significant reduction in readmissions at 30 days (odds ratio[OR]=0.72, CI: 0.53–0.99) and 6 months (OR=0.68, CI: 0.51–0.91)[35] and another study reported a 9.8% absolute reduction in the proportion of patients being readmitted the intervention group, but did not test for significance.[27] The remaining study showed no significant effects.[34]

Incidence rates of readmission

Five studies examined the incidence rate of all readmissions at 30 days,[13, 15, 26, 33, 55] two studies at 60 days,[15, 26] three studies at 90,[15, 55, 61] one study120 days,[15] seven studies reported incidence rates at 6 months[14, 15, 54-56, 61, 62] and three studies reported incidence rates at 12 months.[51, 55, 61]

Of these eleven studies, only four reported person-time at risk and were able to be included in the secondary meta-analysis.[14, 33, 55, 56] The analysis of pooled data from these four studies found no statistically significant difference in the incidence of readmissions in the intervention compared to control group (incidence rate ratio[IRR]=0.84, CI: 0.54–1.28, p=0.41), although there was statistically significant heterogeneity (Q=24.1, p=<0.001) of a substantial degree (I^2 =87.6.0%, CI: 70.4–94.8).

In the other seven studies that did not report data suitable for meta-analysis, five reported a significant reduction in the incidence of readmissions in the intervention group compared to control, at 30 days (in one study 8.9% absolute rate reduction [ARR], p=0.01:[13] in another study 4.2% ARR, p<0.001[26]), in a third study 26% relative rate reduction at 6 months (IRR=0.74, CI: 0.59–0.92),[62] and in a fourth study reduction in readmissions per person of 0.12 (154 readmission in 381 intervention participants vs 197 readmissions in 381 control participants, p=0.022).[54] The fifth study reported a significantly greater rate of admissions among control compared to intervention patients at 90 days (IRR=2.79, p=0.016), 180 days (IRR=2.42, p=0.024) and 12 months (IRR=1.78, p=0.044).[61]

Subgroup analyses

Separate analyses did not demonstrate any significant differences between control and intervention patients within subgroups based on tests of interaction (Table 2)... However, those interventions featuring multiple components showed a 14% reduction in readmissions (RR=0.86, CI: 0.77 – 0.96), while interventions that reported direct communication between the pharmacist and PCP, such as via the telephone or face-to-face showed a 34% reduction in patients readmitted (RR=0.66, CI: 0.47 – 0.93).

Interventions involving single components, the number of interactions involved (whether it was one or more interactions), indirect communication and the reason for PCP contact (both proactive and reactive communication) showed no significant effects.

Table 2: Subgroup analysis according to intervention characteristics (RR, mean effect size risk ratio; CI, confidence intervals for effect size)

Variable	Subgroups	No. of studies	No. of participants	RR	CI	p-value for interaction*
Number of interactions between pharmacist and patient	*Single interaction*	16	5684	0.84	0.70 – 1.01	0.54
	≥ 2 interactions	21	1s1,033	0.90	0.79 – 1.02	
Components of Intervention	*Single component only (e.g. adherence only)*	5	1687	0.96	0.68 – 1.36	0.55
	Multiple components (e.g. comprehensive medication review)	32	15,539	0.86	0.77 – 0.96	
PCP contact⁺	*Direct*	8	3573	0.66	0.47 – 0.93	0.14
	Indirect	14	7807	0.89	0.75 – 1.05	
Reason for PCP contact⁺	*Proactive (contacted regardless of whether issues identified)*	16	10,941	0.86	0.73 – 1.01	0.87
	Reactive (only contacted if had issues or recommendations)	17	4582	0.85	0.70 – 1.02	

*P-value based on test for interaction between subgroup differences using random-effects model.

[+] Studies that were unclear on the type of physician contact and the reason for the contact were excluded from the subgroup analyses.

Sensitivity analyses

Interventions were associated with a statistically significant reduction in the proportion of patients readmitted when data were pooled from the 22 non-RCTs (RR=0.82, CI: 070–0.96) but not when pooled from the 15 RCTs (RR=0.92, CI: 0.80–1.06), with the test for subgroup interaction being insignificant (p for interaction=0.30) (Figure 3).

When RCTs were pooled according to follow-up time-points, there was no statistically significant intervention effect at any time-point (Table 2, Figure 3 and 4 in on-line supplement). For non-RCTs, intervention effects were only significant at 30 days after discharge (RR=0.80, CI: 0.67–0.96).

In the five studies reporting results of both PP and ITT results, the relative reduction in admissions in meta-analyses was similar for both (RR for PP=0.80, CI: 0.71–0. 89, p<0.001 vs RR for ITT=0.87, CI: 0.79 –0.97, p=0.01).

DISCUSSION

This systematic review explored whether pharmacist-led interventions with PCP communication were effective at reducing all-cause readmission to hospital. Meta-analysis of all studies combined showed an overall 13% reduction in readmissions following hospital discharge, although significantly reduced risk of readmission was confined to 30 days at discharge in meta-analysis of pooled data from non-RCTs, and was not seen at any time-point after discharge in meta-analysis of RCTs.

Previous reviews have reported varying effects on readmissions, depending on the type of interventions included or type of pharmacist conducting the intervention. Pharmacist-led medication reconciliation interventions at transitions of care were found to be effective at reducing readmissions (RR=0.81);[6] however, in-hospital pharmacist-led medication reviews (assessed in RCTs only)[63] or community pharmacist-led interventions did not show any effect on readmissions.[9] In an effort to synthesise the totality of evidence, the present review intentionally included all types of pharmacist-led interventions and all study designs, both RCTs and non-RCTs. RCTs of complex interventions can be difficult to conduct and may have limited generalisability because of selected populations and fixed protocols. Observational studies provide insights into real-world clinical interactions, allow contingent and contextual flexibility in how interventions are implemented, and provide a test of feasibility.

Most of the interventions in this review involved a pharmacist undertaking a medication review to reconcile any differences between the discharge medication lists and current medication use, identifying and rectifying any medication-related problems, and addressing patient concerns. This usually occurred within 14 days of discharge. Subgroup analysis suggested no significant difference in readmissions in response to more than one interaction (i.e. follow-up phone call) compared with a single interaction only. This contrasts with a previous review of pharmacists working within primary care clinics which suggested more positive effects on clinical markers (e.g. blood pressure, cholesterol) with additional follow-up of patients over time periods which included three to six months.[64] In contrast, most of the studies included in the present review examined readmission at 30 days within which a second interaction may have been deemed unnecessary. Only studies with longer outcome follow-ups (e.g. 90 days, 6 months) may require multiple interactions. It is also unclear in many studies whether all intervention patients received the follow-up interaction with the pharmacist, and most studies did not describe the nature of the follow-up interaction.

The effects of pharmacist-led interventions appear to attenuate over time, as measured by the binary outcome of whether or not patients had been readmitted, regardless of the number of readmissions per patient. However, intervention effects over longer periods of follow-up may have been significant if the reported outcome measure was total number of readmissions after discharge. As an example, Stewart et al. found their multi-faceted intervention significantly reduced the total number of unplanned readmissions but not the number of patients who experienced a readmission.[54] Of the four studies in this review that could be included in a meta-analysis of incidence rates of readmissions, there was no significant difference between intervention and usual care groups. However; five out of seven studies that were unable to be included (due to unavailable data) reported positive results.[13, 26, 54, 61, 62] The small number of studies examining incidence rates of readmissions yielded mixed results and more studies are required, as are studies measuring readmissions at different time-points as both binary and rate outcomes.

Studies with no direct contact with the PCP (e.g. only faxing recommendations) showed less favourable outcomes.[29, 31, 53, 57] These two intervention characteristics (reason for contact and mode of communication) appear interrelated, and it is possible that direct communication between the PCP and pharmacist provides more opportunity for discussion beyond solely the reason for contact, leading to a more effective collaboration.[65, 66]

In terms of patient characteristics that may have influenced outcomes, researchers used their own *ad hoc* criteria to characterise patients as being at high risk of readmission. Age, number of regular medications and number of medical conditions were the most common characteristics used to recruit patients, with cut-offs for each variable varying widely, which precluded comparisons of effects across patient subgroups.

The strengths of this review comprise a comprehensive literature search, precise quantification, using meta-analysis, of intervention effects as measured by the hard end-point of all-cause readmissions, and subgroup and sensitivity analyses that identified effect modifiers. The review also has limitations. The majority of included studies were small non-RCTs conducted within single institutions. Statistically significant results were only seen in analyses of non-RCTs, and the quality of evidence and level of certainty in effect estimates were rated as low for RCTs and very low for non-RCTs. Usual care groups varied markedly between studies and intervention components, as assessed by the TIDieR checklist, were often poorly described. Several control groups received an established transition of care service,[12, 16, 17, 31, 43, 48, 54] while others did not indicate any post-discharge healthcare input. The effect of an intervention may vary greatly depending on the features of the already established model of usual care. All these factors makes it difficult to compare studies, and more high quality studies are needed that minimise risk of bias and adequately describe all the care that both intervention and usual care groups receive.

CONCLUSION

This review suggests that pharmacist-led interventions which include direct pharmacist-PCP communication at transition of care, may be effective in reducing readmissions to hospital at 30 days. However; the absence of a significant effect in randomised studies limits the level of certainty of these results. Future studies need to adopt more rigorous study designs, apply well defined patient eligibility criteria, adequately describe the actual care provided to both intervention and control groups, and include longer follow-up periods. Such efforts may allow effective interventions to be identified that improve medication-related care during transitions from hospital back into primary care and reduce the risk of avoidable readmission to hospital.

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FIGURE LEGENDS

Figure 1: PRISMA flow diagram of eligible studies

Figure 2a: Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials. Studies are categorised as 'Low risk' of bias (+), 'High risk' of bias (-) or 'Unclear risk' of bias (?).

Figure 2b: ROBINS-I tool for assessing risk of bias for non-randomised controlled trials.

Figure 3: Forest plot of effect of intervention compared to control on readmission to hospital by study design for studies with available data (n=37) (RCT, randomised controlled trial; RR, mean effect size risk ratio; CI, confidence intervals for effect size).

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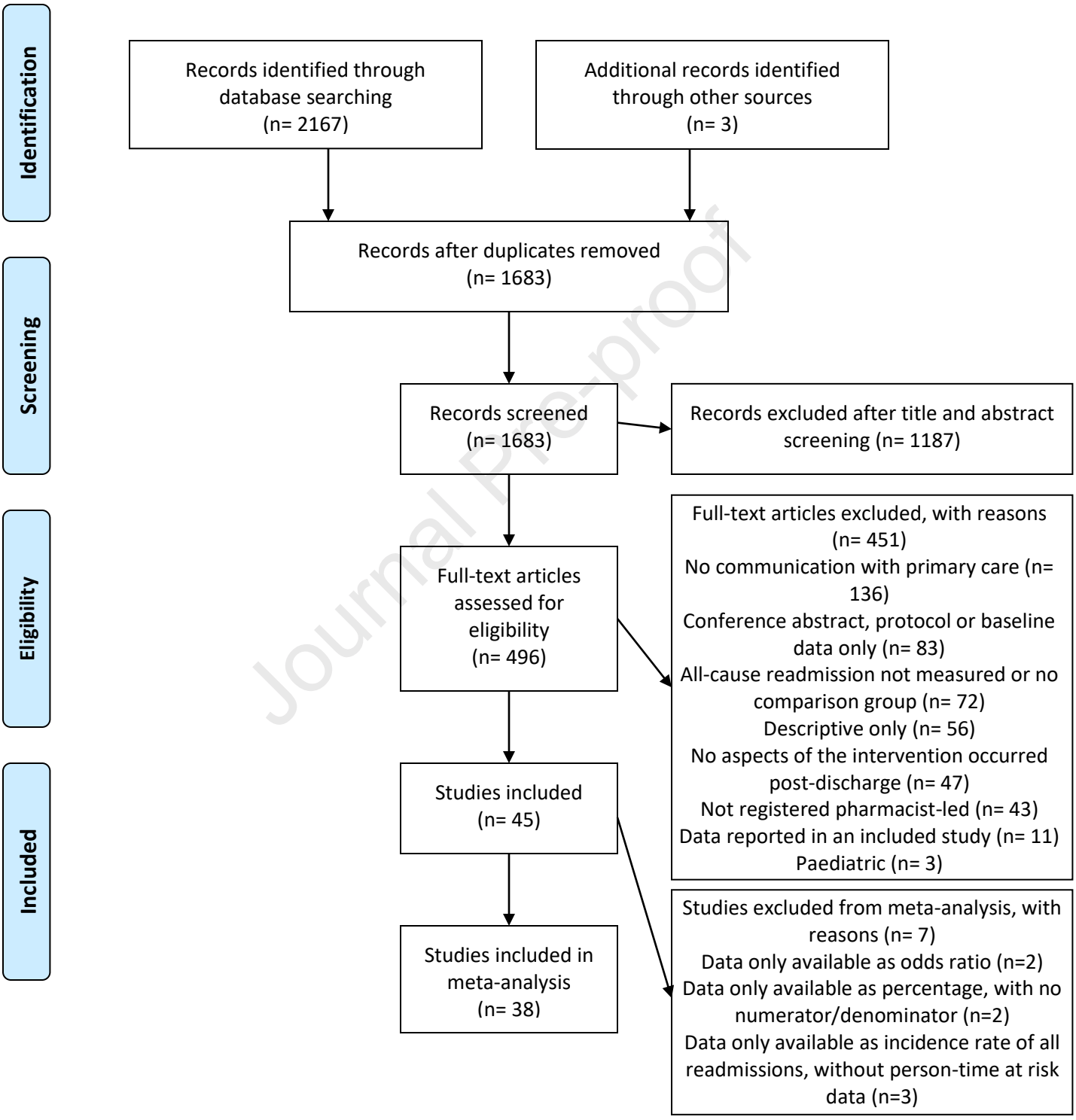
PRISMA 2009 Flow Diagram



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