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MiniReview

Multifaceted Pharmacist-led Interventions in the Hospital Setting: A Systematic Review

RUNNING TITLE: Multifaceted pharmacist-led interventions

Helene Skjøt-Arkil[1,2], Carina Lundby Olesen[3], Lene Juel Kjeldsen[4], Diana Mark Skovgårds[5], Anna Birna Almarsdóttir[6], Tue Kjølhede[7], Tina Hoff Duedahl [8], Anton Pottegård[3,9] and Trine Graabæk[3,10]

[1]*Emergency Department, Hospital of Southern Jutland, Aabenraa, Denmark*

[2]*Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark*

[3]*Hospital Pharmacy of Funen, Odense University Hospital, Odense, Denmark*

[4]*Amgros I/S, Copenhagen, Denmark*

[5]*Hospital Pharmacy, Lillebælt Hospital, Kolding, Denmark*

[6]*Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark*

[7]*Centre for Innovative Medical Technology, Odense University Hospital, Odense, Denmark*

[8]*Telepsychiatric Centre, The Mental Health Services, Region of Southern Denmark, Odense, Denmark*

[9]*Department of Public Health, University of Southern Denmark, Odense, Denmark*

[10]*Department of Quality, Hospital of South West Jutland, Esbjerg, Denmark*

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Author for correspondence: Helene Skjøt-Arkil, Emergency Department, Hospital of Southern Jutland, Kresten Philipsensvej 15, 6200 Aabenraa, Denmark (E-mail: Helene.Skjoet-Arkil@rsyd.dk).

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Abstract: Clinical pharmacy services often comprise complex interventions. In this MiniReview, we conducted a systematic review aiming to evaluate the impact of multifaceted pharmacist-led interventions in a hospital setting. We searched MEDLINE, Embase, Cochrane Library and CINAHL for peer-reviewed articles published from 2006 to 1 March 2018. Controlled trials concerning hospitalized patients in any setting receiving patient-related multifaceted pharmacist-led interventions were considered. All types of outcomes were accepted. Inclusion and data extraction was performed. Study characteristics were collected and risk of bias assessment was conducted utilising the Cochrane Risk of Bias tools. All stages were conducted by at least two independent reviewers. The review was registrered in PROSPERO (CRD42017075808).

A total of 11,986 publications were identified and 28 publications were included. Of these, 17 were conducted in Europe. Six of the included publications were multicentre studies and 16 were randomized trials. Usual care was the comparator. Significant results on quality of medication use were reported as positive in eleven studies (N=18; 61%) and negative in one (N=18, 6%). Hospital visits were reduced significantly in seven studies (N=16; 44%). Four studies (N=12; 33%) reported a positive significant effect on either length of stay or time to revisit, and one study reported a negative effect (N=12; 6%). All studies investigating mortality (N=6), patient-reported outcomes (N=7), and cost-effectiveness (N=1) showed no significant results.

This rMiniReview indicates that multifaceted pharmacist-led interventions in a hospital setting may improve the quality of medication use, reduce hospital visits and length of stay, while no effect was seen on mortality, patient-reported outcomes and cost-effectiveness.

Medication errors, inappropriate medication use and patient-experienced drug-related problems can lead to adverse drug events and result in increased morbidity, mortality and costs[1-6]. The risk of adverse drug events increases with insufficient pharmacological knowledge of health care professionals, documentation errors in patient records and limited pharmacy service in the clinic[3]. To mitigate this, clinical pharmacy services targeting different situations in the hospital setting have been developed and evaluated during the last decades[7-20].

The objective for most clinical pharmacy services is to ensure optimal and rational use of drugs for the benefit of patients and society by cooperation between pharmacist, other health professionals and the patient[21]. At the patient level, pharmacist-led interventions in hospitals have been summarised in recent systematic reviews and meta-analyses investigating the effect on clinical outcomes[7-11, 13-19], economic outcomes[10-12, 22] and patient-reported outcomes[8, 10, 11, 20]. Some of the reviews focused solely on medication reconcilliation[12, 17-19] and some on medication review[8, 9, 11, 13, 14]. Several of these reviews, however, failed to identify statistically or clinically relevant effect sizes, in particular those focusing on clinical outcomes[7, 9, 13, 14, 18]. One explanation might be that evaluation of clinical pharmacy services is particularly challenging, as it often aims at changing behaviour and comprise complex interventions which may act independently or interdependently[5, 7, 10, 15, 16, 23, 24]. These multifaceted interventions can consist of many single components, e.g. medication review, patient counselling and communication to primary care. The previous reviews have generally focused on a certain type of intervention and included both single and multifaceted interventions. To our knowledge, no previous systematic review has specifically focused on solely multifaceted pharmacist-led interventions.

We therefore aimed to evaluate the impact of multifaceted pharmacist-led interventions in a hospital setting by performing a systematic review. Specifically, the study objectives were how multifaceted pharmacist-led interventions are associated with I) various outcomes of care including

quality of medication use, mortality and health services use, II) patient-reported satisfaction and health-related quality of life, and III) cost savings and cost effectiveness.

MATERIALS AND METHODS

The study was conducted utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25]. The review was registered in PROSPERO (CRD42017075808).

Study eligibility criteria

In this MiniReview, we decided to define multifaceted intervention based on the number and type of component in the intervention, while not distinguishing time of intervention in relation to the patient treatment flow, since the latter information is difficult to collect and compare across studies. By studying the aim of the components in pharmacist-led interventions in hospital setting, four categories of type of components were described: I) medication history and reconciliation (identifying the most accurate list of medication a patient is taking), II) medication review and communication of relevant clinical recommandations to hospital care team (structured critical review of each drug taken by the patient with the objective of optimizing the impact of medicines and prevent adverse drug events), III) patient counselling and education (education on newly started medicines or counselling according to the needs of the patient), and IV) discharge report and communication to primary health care (structured medication report sent to the general practitioner, community pharmacy or municipal nurses at discharge with a description of current medication and any medicine adjustments made during hospitalization). Publications were included in the review if they included at least three of the four mentioned categories. This decision was based on the wish to include publications with as many interacting components as possible.

Publications were included if they:

- concerned hospitalized patients
- described a patient-related multifaceted intervention delivered by clinical pharmacist and/or pharmacy technician (including pharmaconomist). It was required that the patients' entire medication regimen was considered and that the intervention was conducted during the hospital stay. An intervention focusing on a specific disease area or drug type was included if the entire medication regimen was considered
- described original research
- were published in English, Danish, Norwegian or Swedish
- were controlled studies (randomized trials at patient-level, cluster-randomized trials and quasi-experimental trials).

Publications were excluded if they:

- described an intervention performed exclusively by pharmacy students
- concerned outpatients and patients seen in the emergency department but not admitted
- described interventions conducted after discharge
- were published as conference abstracts

All types of outcomes were accepted and divided into three categories: I) outcomes of care, e.g. quality of medication use, mortality and health services use, II) patient-reported outcomes, e.g. satisfaction and health-related quality of life (HRQL), and III) health economic outcomes, e.g. cost savings and cost effectiveness.

Search strategy

The literature search was performed by a medical librarian assisted by the authors. The electronic databases MEDLINE, Embase, Cochrane Library and CINAHL were searched for literature. The

databases were searched for literature from 1 January 2006 to 2 November 2016 to include only recent information. An additional search in MEDLINE and Embase was performed subsequently to include articles published from 2 November 2016 to 1 March 2018. The full search strategy is described in Appendix I. Additional literature was also searched by reviewing previous systematic reviews.

Data collection and analysis

A medical student and a nurse with a Master's degree in health science independently screened all titles and abstracts for potentially relevant articles under the supervision of a research pharmacist (HS). Afterwards, two research pharmacists (HS and CLO) independently screened the full text of all potential articles for inclusion. Disagreements between the two reviewers were discussed and consensus was achieved. The Covidence software (Veritas Health Innovation, Melbourne, Australia; www.covidence.org) was used as screening tool[26].

A research pharmacist (HS) and a nurse with a Master's degree in health science independently extracted data for all included articles. Two types of checklists were designed for those aspects: 1) characteristics of included studies and 2) risk of bias assessment. Information was sought in the method and result sections. If the study referred to a previously published article, data were extracted from this. Disagreements between the two reviewers were discussed and consensus was achieved. The following data were extracted: study characteristics (first author name, publication year, country, type of controlled study and setting), patient characteristics (type of included patients, number of included patients in intervention group and control group, distribution of sex and age at baseline), intervention characteristics (components of pharmacist-led intervention, time of intervention, profession, experience and number of providers of intervention) and outcomes characteristics (follow-up time, primary outcome and secondary outcomes as stated by the authors).

We used a tailored version of Cochrane Risk of Bias[27] and risk of bias criteria developed by Cochrane Effective Practice and Organisation of Care (EPOC)[28]. Scores of low, high, or unclear risk of bias were allocated to each included article according to the parameters: selection bias (random sequence generation, allocation concealment, representativeness and baseline imbalance), performance bias (blinding of patient and providers of intervention and usual care, time as potential modifier and contamination bias), detection bias (blinding of assessor of outcome and statician), attrition bias (power to detect a difference and incomplete outcome data) and reporting bias (selective outcome reporting). The score allocation is described in detail in Appendix II. A global risk of bias was calculated for each article according to the percentage of 'Low risk' score.

Results were summarized for each type of outcome. If a study used adjusted analysis, this measure was prioritized to be presented.

RESULTS

Study selection is presented in fig. 1. In total, 11,986 publications were imported, 544 full texts were read, and 28 publications[29-56] included in the analysis.

Characteristics

The characteristics of the included publications are presented in table 1. Some of the publications referred to the same study protocol: Alassaad 2014[30]and Gillespie 2013[40] referred to Gillespie 2009[41]; Scullin 2007[51] and Burnett 2009[36] referred to a study by McElnay *et al*.[57]; Farley 2014[38], Farris 2014[39] and Israel 2013[44] referred to a study protocol by Carter *et al.*[58], and Wallerstedt 2012[54] referred to Bladh 2011[35]. However, these studies are presented independently in Table 1 since outcomes and numbers of participants vary.

The included studies were conducted in eight countries in Europe, North America and Australasia; most frequently in Sweden with nine studies and USA with eight studies. A randomized, controlled design was applied for 16 of the studies and multicentre for six of the studies. The setting of the majority of the studies was internal medicine wards/units. For all 28 studies, usual care was the comparator. The number of included patients in either intervention or control groups ranged from 20 to 2,758 patients. The total amount of patients in the 28 studies were 18.113 patients. For four studies, the number of patients in the intervention and control group was purposefully dissimilar[43, 48-50]. All 28 studies included adults, and the mean age ranged from 58 to 85 years.

The interventions provided appeared similar but differed in number, type and time of components. The provider of the interventions was pharmacists in all studies, and for three studies a pharmacy technician delivered a part of the intervention[29, 36, 50]. There were limited details about the staff involved in the intervention as well as in the usual care.

The included studies used different outcome measures to evaluate the intervention. The most common measures were medication appropriateness, medication errors, hospital visits and length of stay. However, a large variety of measures within the categories were used and within these various tools, e.g. medication appropriateness assessed by the Medication Appropriateness Index (MAI), Beers criteria, Assessing Care of Vulnerable Elders (ACOVE) criteria, The Screening Tool of Older Persons' Prescription (STOPP) and Screening Tool to Alerts doctors to Right Treatment (START). A large part of the described outcomes were incomparable measures, e.g. quality indicators, assessment of adherence and complications (table 1). The follow-up time varied from three days to one year.

Methodological quality

In table 2, the risk of bias assessment is presented for each study.

All studies were at high risk of performance bias since the nature of the intervention meant that blinding of the patients and staff was not possible. Only one study did clarify blindness of

statistician[41]. For 14 of the studies, power calculations were performed[29, 32-35, 37, 41, 42, 46, 47, 52, 53, 55, 56].

Impact on various outcome of care

Outcomes of care has been divided into quality of medication use (table 3), hospital visits including readmissions, drug-related visits, and ED visits (table 4), length of stay (LOS) and time to revisits (table 5), and mortality (not shown).

We identified 18 studies/6,943 patients that compared the effect of a multifaceted pharmacist-led intervention with those of usual care on quality of medication use[29-40, 42, 44, 46, 52, 53, 56]. An overall significant positive effect was reported in eleven studies/3,041 patients (N=18, 61%)[31, 34, 36-38, 40, 42, 46, 52, 53, 56] - three on medication error[31, 37, 38], and seven on medication appropriateness[34, 36, 40, 42, 52, 53, 56]. One study/945 patients (N=18; 6%) reported a negative effect on medication appropriateness[39]. There was no apparent association between the observed effect and the type of study design.

Quality of medication use was the primary outcome in 14 studies (N=18)[29, 31, 33, 34, 36-40, 42, 44, 46, 52, 56], and relevant power calculation was performed in eight of these studies (N=18; 44%)[29, 33, 34, 37, 42, 46, 52, 56]().

Effect on hospital visits either as ED visits, readmissions or drug-related hospital visits were investigated in 16 studies/14,607 (table 4)[29, 39, 41-43, 45-53, 55, 56]. Of these, seven studies/4,866 patients (N=16; 44%) reported a significant positive difference[41, 45, 46, 49, 51, 55, 56]. The remaining nine studies/9,741 patients reported a non-significant result [29, 39, 42, 43, 47, 48, 50, 52, 53]. The follow-up time varied between three days and one year. There was no apparent association between the observed effect and observation time or type of study design.

A relevant power calculations was performed in two studies/2,191 patients (N=16; 13%)[53, 55]

LOS and time to revisit were investigated by 12 studies/11,519 patients (table 5)[29, 31, 35, 43, 45, 47-51, 53]. Of these, four studies/3,212 patients (N=12; 33%) reported a statistically significant positive effect[45, 48, 50, 51], and one study/199 patients (N=12; 8%)reported a negative result [47]. Considering only LOS of index admission, three studies/3,171 patients (N=12; 25%) showed a positive effect reducing LOS on average by 1.4 days[48, 50, 51]. One study/833 patients (N=2; 50%) reported a reduction on LOS of the first readmission within 12 months after index admission[50]. Two studies/803 patients (N=4; 50%) investigating the time from index admission to the first revisit showed a significant reduction[45, 51]. There was no apparent association between the observed effect and the type of study design.

LOS or time to visit were primary outcomes in five studies/7,344 patients (N=12; 42%)[43, 47, 48, 50, 51]. A relevant power calculation was performed in one of these studies/199 patients (N=12; 8%)[47].

Mortality in a follow-up period of 3-12 months was reported as secondary outcomes by six studies/6,929 patients [40, 43, 51, 52, 55, 56]. None of these studies found a significant effect, and the average mortality in both groups was 18%. Power calculations were not performed for mortality in any of the six studies.

Impact on patient-reported outcomes

The impact of multifaceted pharmacist-led interventions on patient-reported outcomes were investigated by seven studies/2,644 patients[29, 32, 35, 47, 52, 54, 56]. Two studies/385 patients investigated self-reported satisfaction and reported a positive experience with the intervention, however, the difference was not statistically significant[47, 52]. Five studies/2,259 patients reported HRQL by use of the questionnaires EQ-5D and SF-36[29, 32, 35, 54, 56]. None of these scores showed statistically significant differences between the groups. Two studies/1,526 patients likewise reported a non-significant difference in pain by use of the EQ-VAS score[29, 35]. One study/432

patients indicated a partial positive effect by reporting a significantly higher self-reported global health score in the intervention group but not in EQ-5D score[35]. One study/172 patients reported no significant difference in number of falls during hospital stay and up to three months follow-up[56].

Of the seven studies, two studies/648 patients performed a power calculation[32, 35]. These studies showed a non-significant result.

Impact on economic outcomes

Economic outcomes were investigated by four studies. Of these, three studies/2,806 patients reported a reduction in cost of hospital care by calculating the saved LOS of readmissions against the cost of pharmacy staff; however, they did not perform a statistical analysis [41, 49, 50].

The last study/345 patients performed a statistical analysis of cost between the groups and also performed a cost-effectiveness analysis[54]. Both analyses showed a non-significant difference.

DISCUSSION

Main study findings

This systematic MiniReview showed that numerous studies had investigated pharmacist-led interventions in the hospital setting of which many investigate different combinations of interventions. The 28 included publications from mainly Europe and North America described quite similar intervention elements but differed in number of intervention components, time of intervention, study design, observation time and type of outcome.

A positive significant impact on quality of medication use was reported in eleven studies/3,041 patients (N=18; 61%) and a significant negative result in one study/945 patients (N=18; 6%). The remaining 6 studies/2,957 patients (N=18; 33%) showed non-significant results. Hospital visits were reduced significantly in seven studies/4,866 patients (N=16; 44%) and the remaining nine studies/9,741 patients (N=16; 56%) reported non-significant results. Four studies/3,212 patients

(N=12; 33%) reported a positive significant result on either LOS or time to revisit, and one study/199 patients (N=12; 8%) reported a significantly negative result. The remaining seven studies reported non-significant results. Mortality was reported by six studies/6,929 patients and none of these found a statistically significant difference between groups. Patient-reported outcomes were investigated by seven studies/2,644 patients of which one study/432 (N=7; 14%) reported a partial significant effect which was positive. The remaining six studies reported non-significant results. Of the four studies/3,151 patients investigating economic outcomes, one study performed a statistical analysis showing a non-significant result.

Quality of evidence

The assessment of risk of bias was made difficult due to inadequate reporting, e.g. lack in reporting of blinding of involved project staff and power calculations. Of the included studies, 50% performed a power calculation. This is consistent with the finding of a recent literature review showing that the majority of clinical pharmacy intervention studies needs relevant power calculations if statistically significant differences are to be detected[59].

The deficiency in methodological quality is also due to the use of non-optimal study design, especially the high risk of educational bias in randomized trials, lack of adjusted analysis if imbalanced baseline exists, and lack of alternative methods to compensate for not blinding patients and project staff to the group allocation. In addition, many studies do not describe the intervention in enough detail, making the assessment difficult. In this MiniReview, more studies could have been eligible for inclusion had the intervention been described more clearly.

Outcomes in relation to existing systematic reviews

Recent reviews investigating pharmacist-led interventions have shown beneficial effects on quality of medication use, including medication discrepancies[19] and medication appropiateness[7]. This corresponds well to our findings.

Previous reviews reported no evidence that pharmacist-led interventions reduce mortality, hospital readmission of all causes or LOS[8, 9, 11, 13, 14]. However, one meta-analysis found a substantial reduction of all-cause readmission when investigating the effect of medication reconciliation[18]. Drug-related readmissions and ED contacts were also found to be reduced[8, 9, 11, 18]. In our review, only one study found a negative effect on LOS which could be due to confounding as stated by the authors[47].

In accordance with our review, medication review was reported as not having any effect on HRQL in two previous reviews[8, 11]. This could be due to the use of primarily generic tools for measuring HRQL where sensitivity to medication-related issues is small. In general, studies investigating the impact of multifaceted interventions on patient-reported outcomes were very few. As stated in a recent systematic review, there is a need for instruments measuring medicine-related experiences from the patients' perspective[60].

A systematic review investigating economic evaluations of clinical pharmacist interventions found an overall positive impact on hospital budgets, however, the quality of the included studies was limited[22]. The studies in this review mostly found a positive effect on cost using methods like reduced costs from readmissions[41, 49] and beddays[50] where the cost of the time for the pharmacist-led intervention was subtracted. Only one study performed a robust cost-effectiveness analysis which did not find a significant effect[54].

Various outcomes were measured in the included publications in this review, both generic and incomparable measures made specifically for each study. Combining this with the different time periods, elements of interventions, study designs and inclusion criteria makes comparison between the studies complicated. The results of this review confirm the need for more standardized outcome measures to quantify the effects of clinical pharmacy interventions[61]. Similarly, this is in

agreement with a recent systematic review summarizing all endpoints used in clinical pharmacy intervention studies[59]. Of the listed 135 endpoints, 107 (79%) were only used in one study, indicating a need for a more consistent planning of studies of pharmacist-led interventions.

Process evaluation

Evaluation of the process is important to keep in mind when measuring the effect of clinical pharmacy interventions. Most pharmacist-led interventions are heavily dependent on physicians to implement the interventions (medication change). This often makes the proportion of patients receiving the actual intervention smaller than the included patients in the intervention group. Hence, there are a number of problems with measuring the effects of multifaceted pharmacist-led interventions, such as standardizing the intervention, lower statistical power, and difficulty in isolating the intervention from other care activities. Futhermore, the intervention might be adapted during the study due to the nature of the intervention.

Multifaceted *versus* single intervention

This systematic review focused solely on multifaceted pharmacist-led interventions. Previous systematic reviews have not differentiated between studies investigating multifaceted components and single component, but included all studies investigating the intervention element relevant to their review. Therefore, several of the studies included in this review have also been included in systematic reviews focusing solely on e.g. medication reconciliation[12, 18, 19] or medication review[8, 9, 11, 13]. Before conducting this systematic review, we assumed there would be a greater effect when studies with a single or a few components were discarded. Our results showed more studies with significant positive effects on quality of medication use, hospital visits and LOS. However, it is not known which part of the components that is responsible. More research is required to definitively answer if multifaceted intervention is more effective than single-faceted intervention.

Limitations

The types of statistical analyses used in the included studies were not systematically collected which is important for interpretation of the results. Likewise, information on whether or not electronic health records and electronic records of current medication were available was not collected – and whether or not this information was shared with primary care. This could limit the comparability of the studies.

Some of the included studies referred to the same study protocol but investigated different outcomes. If this is taken into account, the 28 studies will be reduced to 22 studies. Futhermore, four of the included studies did not share study protocol but were both a part of the same main study at the same hospital. This will reduce the number of studies to 19. This over-representation of some of the studies might have inflated or over-represented some of the results.

It was decided to include both primary and secondary outcomes and not take into account whether a power calculation was performed. The question is whether the proportion of significant results would have been increased if only outcomes with relevant power calculations were collected? For studies measuring hospital visits, LOS/time to revisit, mortality, patient-reported outcomes and economic outcomes, there was a lack of power calculations and the question can not be answered. For studies measuring quality of medication use, the proportion of significant results did not change if only studies with relevant power calculations were taken into account.

Conclusion

This systematic review showed that multifaceted pharmacist-led interventions in a hospital setting may improve the quality of medication use and reduce hospital visits, length of stay and time to revisit. No statistically significant effects were observed on mortality, patient-reported outcomes and economic measures.

This review indicates that research of higher quality is needed, including relevant power calculation, more standardized outcome measures, targeted patient-reported outcome measures and process evaluation in order to better understand the effects of pharmacist-led interventions.

Authors' contributions: All authors conceptualised the trial and design. HS, CLO, DMS and TG participated in data collection, extraction, and analysis. HS contributed to manuscript development and all authors participated in the critical scrutiny and revision of the manuscript. All authors approved the final version.

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FIGURES

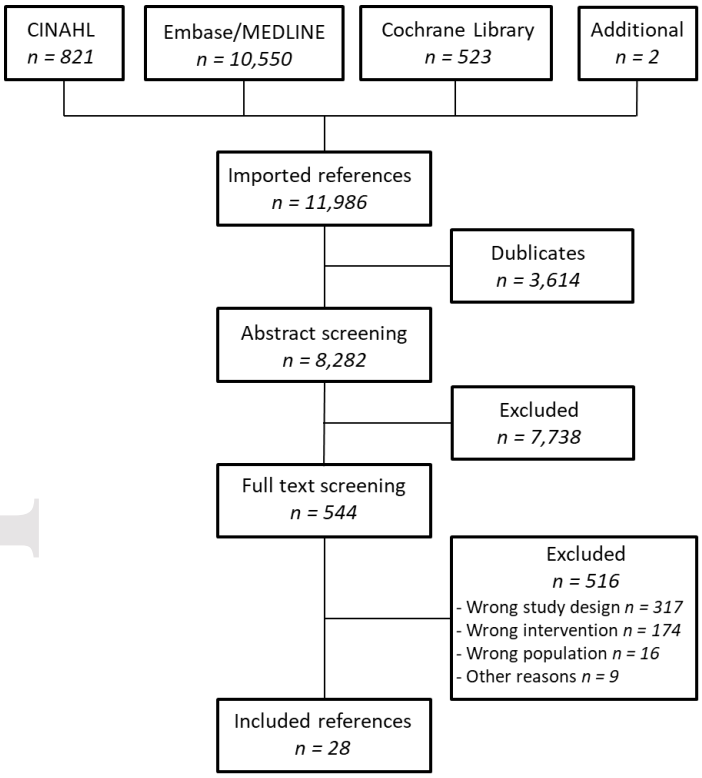

Figure 1 Flowchart of study selection

TABLES

Table 1 Characteristics of included studies

Study			Participants					Intervention		Outcomes		
Author year (ref), country	Type of controlled study	Setting - type of hospital/unit	Type of included patients	Number of patients in IG	Number of patients in CG	% males	Age at baseline - range - mean (±SD) - Median (IQR)	Components of pharmacist-led multifaceted intervention (time during hospital stay)	Provider of intervention - profession - experience - number	Follow-up time	Primary	Secondary
Alassaad 2014[30], Sweden	RCT - patient level	Singlecentre: Two acute internal medicine wards	Elderly (≥ 80)	182	186	41%	- NA - IG: 86,4(4.2), CG: 87,1(4.1) - NA	History and reconciliation (adm), review, communication to physician and education (inp), counselling, reconciliation and communicate of medication list to primary physician (dis), telephone counselling (after dis)	- Pharmacists - Experienced - 3	12m	ED visit	Quality of prescribing (STOPP, START)
Alex 2016[31], USA	QE (CG from non-pharmacist team)	Singlecentre: Two medical teams	Veterans	145	134	94%	- NA - IG: 66.7 (14.3), CG: 65.9 (12.6) - NA	History (adm), review and attended rounds (inp), reconciliation and counseling (dis)	- Pharmacist - NA - 1	NA	Medication error (adm vs dis)	NA
Basger 2015[32], Australia	RCT - patient level	Singlecentre: Private hospital	Elderly (> 65)	114	102	22%	- IG: 65-97, CG: 65-93 - IG: 82.7 (7.3), CG: 80.2 (6.7) - NA	Counseling, reconciliation, review and report to primary care (dis)	- Pharmacist - Experienced - 1	3m	HRQL (SF-36)	Medication appropriateness (criteria-set developed by authors) LOS
Bergkvist (a) 2009[34], Sweden	QE (historical CG from same units)	Singlecentre: Three internal medicine wards	Elderly (≥ 65)	28	25	38%	- NA - IG: 82 (6), CG: 84 (6) - NA	History and reconciliation and (adm), review, check of symptoms, care plan development, discussion with physician and education (inp), reconciliation and report to primary care (dis)	- Pharmacists - NA - NA	2w	Medication appropriateness (MAI)	NA
Bergkvist (b) 2009[33], Sweden	QE (historical CG from same units)	Singlecentre: Three internal medicine wards	Elderly (≥ 65)	52	63	35%	- NA - IG: 84 (6.2), CG: 84 (6.7) - NA	Reconciliation (adm), review, check of symptoms, care plan development, discussion with physician and education (inp) and reconciliation (dis)	- Pharmacists - NA - NA	NA	Medication error (dis vs primary care)	NA
Bladh 2011[35], Sweden	RCT - patient level	Singlecentre: Two internal medicine wards	Adults	ITT: 164 PP: 87	181	39%	- NA - 35-99 - NA	Review and discussion with physician (inp), counseling and report to primary care (dis)	- Pharmacist - Limited experience - 3	6m	HRQL (EQ5D (incl EQ-VAS), global health)	Medication appropriateness (quality indicators)

							- IG1: 81 (72-97), IG2: 84 (75-88), CG: 82 (75-86)					LOS
Burnett 2009[36], UK	RCT - patient level	Multicentre: Five medical units	Elderly (≥ 65)	59	58	ns	- NA - NA - NA	History and reconciliation (adm), review and counseling (inp), reconciliation and report to primary care (dis)	- Pharmacist and pharmacy technicians - Trained - 4 pairs	NA	Medication appropriateness (MAI) (adm vs dis)	NA
Eggink 2010[37], The Nederlands	RCT - patient level	Singlecentre: Department of cardiology	Heart failure adults	41	44	64%	- NA - IG: 74 (12), CG: 72 (10) - NA	Review, discussion with physician, counseling, reconciliation, report to primary care (dis)	- Pharmacist - NA - NA	6w	Medication error (dis vs follow-up)	Adherence
Farley 2014[38], USA	RCT - patient level	Singlecentre: General medicine, family medicine, cardiology and orthopaedics units	Adults	Minimal (IG1): 199, Enhanced (IG2): 195	198	49%	- NA - IG1: 59.8 (12.8), IG2: 61.1 (12.8), CG: 60.0 (12.7) - NA	Minimal: History (adm), reconciliation and education (inp) and counseling (dis) Enhanced: The same components as in 'Minimal IG' with addition of reconciliation and report to primary care (dis), and telephone counseling (after dis)	- Pharmacists - Experienced - 4	30d, 90d	Medication error (dis vs follow-up)	NA
Farris 2014[39], USA	RCT - patient level	Singlecentre: General medicine, family medicine, cardiology and orthopaedics units	Adults with cardiovascular diseases, COPD or asthma	Minimal (IG1): 315, Enhanced (IG2): 314	316	ns	- NA - 61.0 (12.2) - NA	Minimal: History (adm), reconciliation and education (inp), and counseling (dis). Enhanced: The same components as in 'Minimal IG' with addition of reconciliation and report to primary care (dis), and telephone counseling (after dis)	- Pharmacists - Experienced - >2	30d, 90d	Medication appropriateness (MAI)	Adverse events Hospital visits
Gillespie 2009[41], Sweden	RCT - patient level	Singlecentre: Two acute internal medicine wards	Elderly (≥ 80)	182	186	41%	- NA - IG: 86,4(4.2), CG: 87,1(4.1) - NA	History and reconciliation (adm), review, communication to physician and education (inp), counseling, reconciliation and communicate of medication list to primary physician (dis), telephone counseling (after dis)	- Pharmacists - Experienced - 3	12m	Hospital visits	Mortality Drug related readmissions ED visits Cost of hospital care
Gillespie 2013[40], Sweden	RCT - patient level	Singlecentre: Two acute internal medicine wards	Elderly (≥ 80)	182	186	41%	- NA - IG: 86,4(4.2), CG: 87,1(4.1) - NA	History and reconciliation (adm), review, communication to physician and education (inp), counseling, reconciliation and communicate of medication list to primary physician (dis), telephone counseling (after dis)	- Pharmacists - Experienced - 3	NA	Medication appropriateness (MAI, STOPP, START)	NA
Hellström 2011[42], Sweden	QE (historical CG from same units	Singlecentre: Three internal medicine units	Elderly (≥ 65)	109	101	47%	- NA - IG: 83.0 (7.0), CG: 81.8 (7.4)	History and reconciliation (adm), review and counseling (inp) and control of reconciliation (dis)	- Pharmacists - NA - NA	3m	Medication appropriateness (MAI) (adm vs dis)	Drug-related revisits

	but stepped-wedged design)						- NA					
Hellström 2012[43], Sweden	QE (historical CG from same units but stepped-wedged design)	Singlecentre: Three internal medicine units	Adults	1216	2758	45%	- NA - IG: 78.3 (NA), CG: 79.5 (NA) - NA	History and reconciliation (adm), review and counseling (inp)	- Pharmacist - NA - 1	6m	Time to ED visit	Hospital visits Mortality Primary care visits
Israel 2013[44], USA	RCT - patient level	Singlecentre: General medicine, family medicine, cardiology and orthopaedics units	Adults with cardiovascular diseases	Minimal: 245, Enhanced: 241	246	49%	- NA - NA - NA	Minimal: History (adm), reconciliation and education (inp) and counseling (dis) Enhanced: The same components as in 'Minimal IG' with addition of reconciliation and report to primary care (dis), and telephone counseling (after dis)	- Pharmacists - Experienced - 2	30d, 90d	Medication underutilization (according to guidelines)	NA
Koehler 2009[45], USA	RCT - patient level	Singlecentre: Medicine teams	Elderly (≥ 70)	20	21	27%	- NA - IG: 77.2 (5.3), CG: 79.8 (5.6) - NA	Reconciliation (adm), review and education (inp), reconciliation and counseling (dis), counseling (after dis)	- Pharmacists - Experienced - 4	30d, 60d	Hospital visits	ED visits LOS Time to revisit
Makowsky 2009[46], Canada	RCT - CR at unit level (cross-over design)	Multicentre: Four internal medicine and family medicine units	Adults with CAD, CAP, COPD, HF or T2DM	220	231	46%	- NA - IG: 74.9 (13.9), CG: 73.2 (14.7) - NA	History and reconciliation (adm), rounds and education (inp), reconciliation and report to primary care (dis)	- Pharmacists - Experienced - 2	3m, 6m	Adherence (at dis)	Readmission
Mortimer 2010[47], Australia	QE (naturalistic experiment where no intervention patients were CG)	Singlecentre: One emergency department	Elderly (≥ 65)	101	98	46%	- NA - IG: 77.0 (NA), CG: 77.6 (NA) - NA	Reconciliation, review and education (adm)	- Pharmacist - NA - 1	14d, 28d	LOS	Hospital visit Patient satisfaction (questionnaire)
Okere 2016[48], USA*	QE (CG from same unit)	Singlecentre: One medical unit	Adults	401	1175	52%	NA - Divided into age groups	History, review, communication with physician and education (NS)	- Pharmacists - NA - NA	30d, 60d, 90d	LOS	All-cause readmissions
Rafferty 2016[49], USA	QE (historical CG from same units)	Singlecentre: Pulmonary and medical-surgical unit	Adults	384	1221	45%	- 50-72 - IG:64 (NA), CG: 62 (NA) - NA	History and reconciliation (adm), reconciliation, education and communication to primary care (dis)	- Pharmacist - NA - 1	30d, 60d, 90d, 365d	Hospital visits (30d)	Hospital visit (60,90, 365d) LOS Cost savings

Ravn-Nielsen 2018[55], Denmark	RCT – at patient level	Multicentre: Four EDs	Adults	Basic: 493, Extended: 476	498	46%	- NA - NA IG-Basic: 72 (63-80), IG-Extended: 71 (63-79), CG: 73 (65-80)	Basic: review (adm). Extended: Basic component with addition of reconciliation, counseling (dis), and communication to primary care (dis), counseling by telephone (after dis)	- Pharmacists - Trained - 13	1w, 6m	Readmissions	Drug-related readmissions ED visits Mortality
Scullin 2007[51], UK	RCT - patient level	Multicentre: Five medical units	Elderly (≥ 65)	371	391	47%	- NA - IG: 70.3 (13.8), CG: 69.9 (14.8) - NA	History and reconciliation (adm), review and counseling (inp), reconciliation and report to primary care (dis)	- Pharmacist and pharmacy technicians - Trained - 4 pairs	12m	LOS	Readmission Mortality
Scullin 2012[50], UK	QE (naturalistic experiment where no intervention patients were CG)	Multicentre: Emergency admissions	Adults	749	84	49%	- NA - IG: 69.8 (12.6), CG: 71.7 (11.9) - NA	History and reconciliation (adm), review and education (inp), reconciliation and report to primary care (dis)	- Pharmacists - NA - NA	12m	LOS	Readmissions Cost savings
Spinewine 2007[52], Belgium	QE** (CG from same unit with addition of a historical CG)	Singlecentre: Geriatric department	Elderly (≥ 70)	96	90	31%	- NA - IG: 82.4 (6.9), CG: 81.9 (6.2) - NA	History (adm), review, rounds (inp), counseling and communication to GP (dis)	- Pharmacist - NA - 1	1m, 3m, 12m	Medication appropriateness (MAI, Beers, ACOVE)	Mortality Hospital visits Satisfaction (questionnaire)
Surepill study group 2015[29], The Nederlands	RCT - CR at ward level	Multicentre: Six surgical wards	Surgical patients	547	547	57%	- NA - IG: 61 (NA), CG: NA - NA	Reconciliation (adm), review and communication with physician (inp), reconciliation, counseling and report to primary care (dis)	- Pharmacists and specialized technicians - NA - NA	3m	Preventable ADE	LOS HRQL (EQ5D, EQ-VAS) Readmission Complications (questionnaire)
Van der Linden 2017[56], Belgium	QE (CG was one of the wards)	Singlecentre: Three acute geriatric wards	Elderly	91	81	48%	- NA - IG: 84.5 (4.7), CG: 84.5 (5.0) - NA	Reconciliation, review and communication to physician (adm), and letter to GP with recommendations (dis)	- Pharmacist - Trained - 5	1m, 3m	Discountinued admission drugs or reduction in dose (adm)	Discountinued drugs or reduction in dose (inp Readmission ED visits

												Mortality Falls Delirium HRQL (EQ5D) Medication appropriateness (RASP)
Walker 2009[53], USA	QE (CGs were randomly selected from non-pharmacist unit)	Singlecentre: General medicine unit	Adults	358	366	47%	- 19-97 - IG: 57.8 (NA), CG: 57.4 (NA) - NA	Attending rounds, patient interview, reconciliation, review, counseling, communication to primary care (dis) and telephone counseling (after dis)	- Pharmacist - NA - 1	3d, 14d, 30d	Readmission	ED visits Medication discrepancies LOS
Wallerstedt 2012[54], Sweden	RCT - patient level	Singlecentre: Two internal medicine wards	Adults	164	181	39%	- 35-99 - NA - IG: 81 (72-97), CG: 82 (75-86)	Review and discussion with physician (inp), counseling and report to primary care (dis)	- Pharmacist - NA - 3	6m	Cost	Cost-effectiveness ratio per QALY (EQ5D)

*It was chosen only to compare with usual care and not usual care including multidisciplinary rounds. ** We reclassified the study because the order of patient allocation was predictable.
Abbreviations: ACOVE: assessing care of vulnerable elders, ADE: adverse drug events, adm: admission, CAD: coronary artery disease, CAP: community acquired pneumonia, CG: control group, dis, discharge, COPD: obstructive pulmonary disease, CR: cluster-randomized, d: day, ED: emergency department, GP: General practitioner, HF: heart failure, HRQL: health related quality of life, IG: intervention group, inp: inpatient stay, ITT: intention-to-treat, LOS: length of stay, m: month, MAI: medication appropriateness index, NA: Not applicable, PP: per protocol, QALY: quality adjusted life years, QE: quasi-experimental, RASP: Rationalization of home medication by an adjusted STOPP list in older patients, SD: standard deviation, T2DM: type 2 diabetes, w: week.

Table 2 Risk of bias assessment

	Selection Bias				Performance bias			Detection bias			Attrition bias			Reporting bias
Author year (ref)	Random sequence generation	Allocation conceal-ment	Represen-tativeness	Baseline imbalance	Blinding of patients and staff	Time as a potential modifier	Contami-nation bias	Blinding of assessor of primary outcome	Blinding of assessor of secondary outcomes	Blinding of statician	Powered to detect difference	Incomplete primary outcome data	Incomplete secondary outcomes data	Selective outcome reporting
Alassaad 2014[30]	Low	Low	High	Low	High	Low	High	Unclear	NA	Unclear	Unclear	Low	NA	Low
Alex 2016[31]	High	High	High	High	High	Low	Unclear	Unclear	NA	Unclear	Unclear	Unclear	NA	Low
Basger 2015[32]	Low	Low	High	High	High	Low	High	Unclear	Unclear	Unclear	Low	Low	Low	Low
Bergkvist (a) 2009[34]	High	High	High	High	High	High	Low	Unclear	NA	Unclear	Low	Low	NA	Low
Bergkvist (b) 2009[33]	High	High	High	Low	High	High	Low	Unclear	NA	Unclear	Low	Low	NA	Low
Bladh 2011[35]	Low	Low	High	Low	High	Low	High	Low	Unclear	Unclear	High	High	Low	Low
Burnett 2009[36]	Low	Low	Low	High	High	Low	High	Unclear	NA	Unclear	Unclear	Low	NA	Low
Eggink 2010[37]	Low	Low	High	Low	High	Low	High	Unclear	Unclear	Unclear	Low	Low	Low	Low
Farley 2014[38]	Low	Low	High	Low	High	Low	High	Low	NA	Unclear	Unclear	Low	NA	Low
Farris 2014[39]	Low	Low	High	Low	High	Low	High	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Gillespie 2009[41]	Low	Low	High	High	High	Low	High	Low	Low	Low	Low	Low	Low	Low
Gillespie 2013[40]	Low	Unclear	High	Low	High	Low	High	Unclear	NA	Unclear	Unclear	Low	NA	Low
Hellström 2011[42]	High	High	High	Low	High	Low	Low	Low	Low	Unclear	Low	High	Low	Low
Hellström 2012[43]	High	High	High	High	High	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Low
Israel 2013[44]	Low	Low	High	Low	High	Low	High	Low	NA	Unclear	Unclear	Low	NA	Low
Koehler 2009[45]	Low	Low	High	Low	High	Low	High	Low	Low	Unclear	Unclear	Low	Low	Low
Makowsky 2009[46]	Low	Low	Low	Low	High	High	High	Low	Low	Unclear	High	Low	Low	Low
Mortimer 2010[47]	High	High	High	Low	High	Low	High	Low	Low	Unclear	Low	Low	Low*	Low
Okere 2016[48]	High	High	High	Low	High	High	Low	Low	Low	Unclear	Unclear	Low	Low	Low
Rafferty 2016[49]	High	High	High	Low	High	High	Low	Low	Low	Unclear	Unclear	Low	Low	Low
Ravn-Nielsen 2018[55]	Low	Low	Low	Low	High	Low	High	Low	Low	Unclear	Low	Low	Low	Low
Scullin 2007[51]	Low	Low	Low	Low	High	Low	High	Low	Low	Unclear	Unclear	Low	Low	Low
Scullin 2012[50]	High	High	Low	Low	High	Low	High	Low	Low	Unclear	Unclear	Low	Low	Low
Spinewine 2007[52]	High	Unclear	High	Low	High	Low	Low	Low	Low	Unclear	Low	Low	Low	High
Surepill 2015[29]	Low	Unclear	Low	Low	High	Low	Low	Low	Low	Unclear	Low	Low	High	Low
Van der Linden 2017[56]	High	High	High	Low	High	Low	High	Unclear	Unclear	Unclear	Low	Low	Low	Low
Walker 2009[53]	High	High	High	Low	High	Low	High	Low	High	Unclear	Low	Low	Low	Low
Wallerstedt 2012[54]	Low	Low	High	Low	High	Low	High	Low	Low	Unclear	Unclear	Low	Low	Low

Table 3 Impact on the quality of medication use

Author year (ref)	Outcome (time), unit	Results	Statistically significant*
Alassaad 2014[30]	- Change in medication appropriateness (dis), mean STOPP score (SD)	- IG: -0,5 (1,0), CG: 0,2 (0,7)	- ns
	- Change in medication appropriateness (dis), mean START score (SD)	- IG: -0,3 (0,6) CG: 0,04 (0,4)	- ns
Alex 2016[31]	- Medication error (NA), pts	- IG: 9/145 (6%), CG: 80/134 (60%)	- Positive
Basger 2015[32]	- Medication appropriateness for 41 criteria (3m), pts	- To many to be presented	- ns
Bergkvist (b) 2009[33]	- Medication error ≥1 (NA), pts	- IG: 14/52 (27%), CG: 23/63 (37%)	- ns
Bergkvist (a) 2009[34]	- Change in medication appropriateness (adm vs dis), mean MAI score (SD)	- Not stated	- ns
	- Inappropriate drugs (not stated), no. drugs	- Not stated	- Positive
Bladh 2011[35]	- Medication appropriateness (adm vs dis), mean score per pts(SD)	- IG-ITT: 0.34(0.7), IG-PP: 0.26(0.56), CG: 0.38(0.7)	- ns
Burnett 2009[36]	- Medication appropriateness difference adm vs dis (NA), mean score (SD)	- IG: -11.8 (14.6), CG: -3.2 (11.8)	- positive
Eggink 2010[37]	- Medication error with 1≤ discrepancies (6w), pts	- CG: 68% vs IG: 39%, RR: 0.6(95%CI 0.4-0.9)	- positive
	- Medications with error (6w), number	- CG: 15%, IG: 6%, RR 0.4 (95%CI 0.3-0.7)	- positive
	- Adherence (6w), pts	- CG: 80%, IG: 78%, RR: 1.1 (95%CI 0.5-2.5)	- ns
Farley 2014[38]	- High level error in physician record per pts (30d), mean	- IG2: 0.26, CG: 0.51	- positive
	- High level error in physician record per pts (90d), mean	- IG2: 0.4, CG: 0.5	- ns
Farris 2014[39]	- Medication appropriateness (dis), MAI score per pts(SD)	- IG1: 8.0(8.4), IG2: 7.1(7.0), CG: 6.1(6.6)	- negative
	- Medication appropriateness (30d), MAI score per pts(SD)	- IG2: 10.1(8.9), CG: 9.6(9.5)	- ns
	- Medication appropriateness (90d), MAI score per pts(SD)	- IG2: 11.6(10.5), CG: 11.1(11.3)	- ns
	- Adverse events (dis), pts	- IG2: 48/311 (16%), CG: 53/313 (17%)	- ns
Gillespie 2013[40]	- Change in medication appropriateness (adm vs dis), mean MAI score (SD)	- IG: -3.5(5.1), CG: 1.3(3.1)	- positive
	- Change in medication appropriateness (adm vs dis), mean STOPP score (SD)	- IG: -0.5(1.0), CG: 0.2(0.7)	- positive
	- Change in medication appropriateness (adm vs dis), mean START score (SD)	- IG: -0.3(0.6), CG: 0(0.4)	- positive
Hellström 2011[42]	- Medication appropriateness (3m), drugs with 1≤ inappropiate MAI rating	- IG-ITT: 51%(95%CI 43-58), CG: 39%(95%CI 30-48)	- positive
Israel 2013[44]	- Cardiovascular underutilization (dis), pts	- IG-enhanced: 67/241 (66%), CG: 62/246 (56%)	- ns
	- Cardiovascular underutilization (30d), pts	- IG-enhanced: 66/241 (65%), CG: 60/246 (56%)	- ns

	- Cardiovascular underutilization (90d), pts	- IG-enhanced: 61/241 (62%), CG: 56/246 (64%)	- ns
Makowsky 2009[46]	- Adherence to indicators (dis), mean score	- IG: 56%, CG: 45%; adjusted diff: 10.4 (95%CI: 5%-16%)	- positive
Spinewine 2007[52]	- Medication appropriateness (dis), MAI score OR (95%CI)	- 9.1 (4-22)	- positive
	- Medication appropriateness (dis), ACOVE score OR (95%CI)	- 6.1 (2-17)	- positive
	- Medication appropriateness (dis), Beers criteria OR (95%CI)	- 0.6 (0.3-1)	- ns
	- Unnessesary drug use (dis), pts	- IG: 38%, CG: 78%.	- not stated
Surepill 2015[29]	- Preventable ADE (dis), incidence RR	- 0.8 (95%CI: 0.4-1.7)	- ns
	- Complications ≥ 1 (dis), pts	- IG: 113/453 (25%), CG: 132/450 (29%)	- ns
Van der Linden[56]	- Discountinued admission drugs or dose reduction (adm), median (IRQ)	- IG: 5 (3-7), CG: 3 (2-5)	- positive
	- Ration of discontinued/started drugs (adm vs dis), median (IRQ)	- IG: 0.9 (0.7-1.1), CG: 0.9 (0.8-1.1)	- ns
	- Medication appropriateness (dis) according to RASP, median (IRQ)	- IG: 0.5 (0-1), CG: 2 (1-3)	- positive
Walker 2009[53]	- Medication discrepancies (12m), pts	- IG: 120/358 (34%), CG: 218/366 (60%)	- positive

Abbreviations: ADE: adverse drug event, adm: admission, CI: confidence interval, CG: control group, dis, discharge, d: day, ED: emergency department, IG: intervention group, inp: inpatient stay, ITT: intention-to-treat, m: month, MAI: medication appropriateness index, NA: Not applicable, ns: not significant, PP: per protocol, pts: patients, QE: quasi-experimental, RASP: Rationalization of home medication by an adjusted STOPP list in older patients, SD: standard deviation, w: week. * As stated by author

Table 4 Impact on hospital visits

Author year (ref)	Type of visits (time), unit	Result as n(5%)	Statistically significant*
Farris 2014[39]	- Hospital visit (30d), pts	- IG2: 81/311 (29%), CG: 87/313 (30%)	- ns
	- Hospital visit (90d), pts	- IG2: 97/311 (35%), CG: 88/313 (30%)	- ns
Gillespie 2009[41]	- Hospital visit (12m), pts	- IG: 107/182 (58%), CG: 110/186 (59%)	- ns
	- Drug-related hospital visit (12m), pts	- IG: 9/182 (5%), CG: 45/186 (24%)	- positive
	- ED visit (12m), pts	- IG: 49/182 (35%), CG: 93/186 (66%)	- ns
Hellström 2011[42]	- Drug-related visit (3m), pts	- IG: 6%, CG: 12%	- ns
Hellström 2012[43]	- ED visit (6m), adjusted hazard ratio(95%CI)	- 1.04(0.90-1.2)	- ns
	- Hospital visit incl death (6m), adjusted hazard ratio (95%CI)	- 1.03 (0.90-1.17)	- ns
	- Primary care visit (6m), pts	- IG: 908/1325 (69%), CG: 2084/2965 (70%)	- ns
Koehler 2009[45]	- Hospital visit (30d), pts	- IG: 2/20 (10%), CG: 8/21 (38%).	- positive
	- Hospital visit (60d), patients	- IG: 4/20 (30%), CG: 1/21 (43%)	- ns
Makowsky 2009[46]	- Readmission (3m), pts and OR	- IG: 80/221 (36%), CG: 105/231 (46%), adjusted OR: 0.63(95%CI 0.4-0.9)	- positive
	- Readmission (6m), pts and OR	- IG: 112/221 (51%), CG: 130/231 (56%), adjusted OR: 0,78 (95%CI 0.5-1)	- ns
Mortimer 2010[47]	- Hospital visit (14d), pts	- not stated	- ns
	- Hospital visit (28d), pts	- not stated	- ns
Okere 2016[48]	- Readmission (30d), mean adjusted (95%CI)	- IG: 9.5 (6.7-13.3), CG: 10.1 (7.6-13.2)	- ns
	- Readmission (60d), mean adjusted (95%CI)	- IG: 10.7 (7.5-15.2), CG: 11.8 (8.6-16.1)	- ns
	- Readmission (90d), mean adjusted (95%CI)	- 12.4 (8.8-17.2), 13.4 (10.0-17.7)	- ns
Rafferty 2016[49]	- Readmission (30d), pts	- IG: 43/384 (11%), CG: 274/1221 (23%)	- positive
	- ED-visit (30d), pts	- IG: 18/384 (5%), CG: 117/1221 (10%)	- positive
	- Readmission (60d), pts	- IG: 81/384 (21%), CG: 388/1221 (32%)	- positive
	- Readmission (90d), pts	- IG: 110/384 (29%), CG: 462/1221 (38%)	- positive
	- Readmission (365d), pts	- IG: 212/384 (55%), CG: 756/1221 (62%)	- positive
Ravn-Nielsen[55]	- Readmission (30d), pts; hazard ratio (95%CI)	- IG: 68/476 (14%), CG: 111/498 (22%); 0.62 (0.46-0.84)	- positive
	- Readmission (180d), pts; hazard ratio (95%CI)	- IG: 189/476 (40%), CG: 243/498 (49%); 0.75 (0.62-0.90)	- positive
	- ED visit (180d) , pts; hazard ratio (95%CI)	- IG: 15/476 (3%), CG: 21/498 (4%); 0.74 (0.38-1.44)	- ns
	- Drug-related readmission (30d) , pts; hazard ratio (95%CI)	- IG: 24/476 (5%), CG: 38/498 (8%); 0.65 (0.39-1.09)	- ns
	- Drug-related readmission (180d) , pts; hazard ratio (95%CI)	- IG: 75/476 (16%), CG: 96/498 (19%); 0.80 (0.59-1.08)	- ns
Scullin 2007[51]	- Readmission (12m), pts	- IG: 141/370 (38%), CG: 172/384 (45%)	- positive

Scullin 2012[50]	- Readmission (12m), mean no.	- IG: 2.51, CG: 2.70	- ns
Surepill 2015[29]	- Readmission (3m), pts	- IG: 84/362 (23%), CG: 64/362 (18%)	- ns
Spinewine 2007[52]	- ED visit (12m), pts	- IG: 7/89 (7.9%), CG: 19/83 (12.0%)	- ns
	- Readmission (12m), pts	- IG: 29/89 (32.6%), CG: 28/83 (33.7%)	- ns
van der Linden[56]	- Readmission (3m). pts	- IG: 30/87 (35%), CG: 31/79 (39%)	- ns
	- ED visit(3m), pts	- IG: 25/87 (29%), CG: 31/79 (39%)	- ns
	- ED visit without readmission(3m), pts	- IG: 1/87 (1%), CG: 7/79 (9%)	- positive
Walker 2009[53]	- Readmission (14d), pts	- IG: 45/358 (13%), CG: 42/366 (12%)	- ns
	- Readmission (30d), pts	- IG: 79/358 (22%), CG: 66/366 (18%)	- ns
	- ED visit (3d), pts	- IG: 10/358 (3%), CG: 8/366 (2%)	- ns
	- ED visit (14d), pts	- IG: 22/358 (6%), CG: 27/366 (7%)	- ns
	- ED visit (30d), pts	- IG: 34/358 (10%), CG: 45/366 (12%)	- ns

Abbreviations: CI: confidence interval, CG: control group, d: day, ED: emergency department, IG: intervention group, m: month, ns: not significant, OR: odds ratio, pts: patients, SD: standard deviation, w: week. * As stated by author

Table 5 Impact on length of stay and time to revisit

Author year (ref)	Type of variable(time), unit	Result in days	Statistically significant*
Alex 2016[31]	- LOS of index admission (NA), not stated	- IG: 5.4(4.8), CG: 5.7(5.6)	- ns
Basger 2015[32]	- LOS of index admission (NA), mean(SD)	- IG: 16.7(8.7), CG: 18.3(10.5)	- ns
Bladh 2011[35]	- LOS of index admission (NA), median(IQR)	- IG-ITT: 6(4-10), IG-PP: 8(5-10), CG: 6(4-11)	- ns
Hellström 2012[43]	- Time to ED visit(6m), HR(95%CI) - LOS of index admission (NA), median(IQR)	- 0.95(0.86-1.04) - IG: 6 (3-11), CG: 6 (3-11)	- ns - ns
Koehler 2009[45]	- LOS of index admission (NA), mean(SD) - Time to revisit (60d), mean	- IG: 6.2 (4.1), CG: 4.7 (3.7) - IG: 36.2, CG: 15.7	- insufficient power - positive
Mortimer 2010[47]	- LOS of index admission (NA), mean	- IG 0.5, CG 0.4	- negative
Okere 2016[48]	- LOS of index admission (NA), mean(SD) - LOS of index admission (NA), mean adjusted (95%CI)	- IG: 4.6 (2.1), CG: 5.3 (2.0) - IG: 4.7 (4.2-5.3), CG: 5.5 (5.0-6.0)	- positive - positive
Rafferty 2016[49]	- LOS of index admission (NA), mean	- IG: 4, CG: 4	- ns
Scullin 2007[51]	- LOS of index admisssion (NA), mean(SD) - LOS of readmissions (12m), mean(SD) - Time to readmission (12m), days	- IG: 7.8 (95%CI 7.1-8.6), CG: 9.8 (95%CI 8.8-10.9) - IG: 9.7 (24.3), CG: 13.1 (31.5) - IG: 262, CG: 242	- positive - ns - positive
Scullin 2012[50]	- LOS of index admission (NA), mean(SD) - LOS of first readmission (12m), mean(SD)	- IG: 8.1(4.8), CG: 9.5(5.5) - IG: 11.3 (14.9), CG: 17.2 (16.0)	- positive - positive
Surepill 2015[29]	- LOS of index admission (NA), median(95%CI)	- IG: 8(6-12), CG: 9(6-13)	- ns
Walker 2009[53]	- LOS of index admission (NA), median (range)	- IG: 4.0 (1-19), CG: 3.0 (1-18)	- ns

Abbreviations: CI: confidence interval, CG: control group, ED: emergency department, HR: hazard ratio, IG: intervention group, IQR: interquartile range, m: month, ns: not significant, NA: Not applicable, SD: standard deviation. * As stated by author