Multifaceted Pharmacist-led Interventions in the Hospital Setting

A Systematic Review

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**MiniReview**

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

**RUNNING TITLE:** Multifaceted pharmacist-led interventions

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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 registered 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 MiniReview 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 reconciliation[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 1) 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 recommendations 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 statistician), 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
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, 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 appropriateness[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. Furthermore, 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. Furthermore, 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**

![Flowchart of study selection](image-url)

*Figure 1 Flowchart of study selection*
### Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Study</th>
<th>Setting - type of hospital/unit</th>
<th>Type of included patients</th>
<th>Number of patients in IG</th>
<th>Number of patients in CG</th>
<th>Type of intervention</th>
<th>Provider of intervention</th>
<th>Follow-up time</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alassaad 2014[30], Sweden</td>
<td>RCT - patient level</td>
<td>Singlecentre: Two acute internal medicine wards</td>
<td>Elderly (≥ 60)</td>
<td>182</td>
<td>186</td>
<td>41%</td>
<td>- NA</td>
<td>- IG: 86.4 (4.2), CG: 87.1 (4.1)</td>
<td>12m</td>
<td>ED visit</td>
</tr>
<tr>
<td>Alex 2016[31], USA</td>
<td>QE (CG from non-pharmacist team)</td>
<td>Singlecentre: Two medical teams</td>
<td>Veterans</td>
<td>145</td>
<td>134</td>
<td>94%</td>
<td>- NA</td>
<td>- IG: 66.7 (14.3), CG: 65.9 (12.6)</td>
<td>3m</td>
<td>HRQL (SF-36)</td>
</tr>
<tr>
<td>Basger 2015[32], Australia</td>
<td>RCT - patient level</td>
<td>Singlecentre: Private hospital</td>
<td>Elderly (&gt; 65)</td>
<td>114</td>
<td>102</td>
<td>22%</td>
<td>- NA</td>
<td>- IG: 65-97, CG: 65-93</td>
<td>6m</td>
<td>HRQL EQ5D, global health</td>
</tr>
<tr>
<td>Bergkvist (a) 2009[34], Sweden</td>
<td>QE (historical CG from same units)</td>
<td>Singlecentre: Three internal medicine wards</td>
<td>Elderly (≥ 65)</td>
<td>28</td>
<td>25</td>
<td>38%</td>
<td>- NA</td>
<td>- IG: 82 (6), CG: 84 (6)</td>
<td>2w</td>
<td>Medication appropriateness (MAI)</td>
</tr>
<tr>
<td>Bergkvist (b) 2009[33], Sweden</td>
<td>QE (historical CG from same units)</td>
<td>Singlecentre: Three internal medicine wards</td>
<td>Elderly (≥ 65)</td>
<td>52</td>
<td>63</td>
<td>35%</td>
<td>- NA</td>
<td>- IG: 84 (6.2), CG: 84 (6.7)</td>
<td>NA</td>
<td>Medication error (dis vs primary care)</td>
</tr>
<tr>
<td>Bladh 2011[35], Sweden</td>
<td>RCT - patient level</td>
<td>Singlecentre: Two internal medicine wards</td>
<td>Adults</td>
<td>ITT: 164 PP: 87</td>
<td>181</td>
<td>39%</td>
<td>- NA</td>
<td>- IG: 35-99</td>
<td>6m</td>
<td>HRQL EQ5D (incl EQ-VAS), global health</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Setting</th>
<th>Participants</th>
<th>Follow-up</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Costs</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burnett 2009[36], UK</td>
<td>RCT - patient level</td>
<td>Multicentre: Five medical units</td>
<td>Elderly (≥ 65)</td>
<td>59 58 ns</td>
<td>History and reconciliation (adm), review and counseling (inp), reconciliation and report to primary care (dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Medication appropriateness (MAI) (adm vs dis)</td>
</tr>
<tr>
<td>Eggink 2010[37], The Netherlands</td>
<td>RCT - patient level</td>
<td>Singlecentre: Department of cardiology</td>
<td>Heart failure adults</td>
<td>41 44 64%</td>
<td>Review, discussion with physician, counseling, reconciliation, report to primary care (dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Medication error (dis vs follow-up)</td>
</tr>
<tr>
<td>Farley 2014[38], USA</td>
<td>RCT - patient level</td>
<td>Singlecentre: General medicine, family medicine, cardiology and orthopaedics units</td>
<td>Adults</td>
<td>198 49%</td>
<td>Minimal: History (adm), reconciliation and education (inp) and counseling (dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Medication error (dis vs follow-up)</td>
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<tr>
<td>Farris 2014[39], USA</td>
<td>RCT - patient level</td>
<td>Singlecentre: General medicine, family medicine, cardiology and orthopaedics units</td>
<td>Adults with cardiovascular diseases, COPD or asthma</td>
<td>316 ns</td>
<td>Minimal: History (adm), reconciliation and education (inp) and counseling (dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Medication appropriateness (MAI) (adm vs dis)</td>
</tr>
<tr>
<td>Gillespie 2009[41], Sweden</td>
<td>RCT - patient level</td>
<td>Singlecentre: Two acute internal medicine wards</td>
<td>Elderly (≥ 68)</td>
<td>182 186 41%</td>
<td>History and reconciliation (adm), review and communication to physician and education (inp), counseling, reconciliation and communicate of medication list to primary physician (dis), telephone counseling (after dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Hospital visits</td>
</tr>
<tr>
<td>Gillespie 2013[40], Sweden</td>
<td>RCT - patient level</td>
<td>Singlecentre: Two acute internal medicine wards</td>
<td>Elderly (≥ 68)</td>
<td>182 186 41%</td>
<td>History and reconciliation (adm), review and communication to physician and education (inp), counseling, reconciliation and communicate of medication list to primary physician (dis), telephone counseling (after dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Medication appropriateness (MAI, STOPP, START)</td>
</tr>
<tr>
<td>Hellström 2011[42], Sweden</td>
<td>QE (historical CG from same units)</td>
<td>Singlecentre: Three internal medicine units</td>
<td>Elderly (≥ 65)</td>
<td>109 101 47%</td>
<td>History and reconciliation (adm), review and counseling (inp) and control of reconciliation (dis)</td>
<td>- NA</td>
<td>- NA</td>
<td>Drug-related readmissions</td>
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</table>

This article is protected by copyright. All rights reserved.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Patient Population</th>
<th>Methods and Interventions</th>
<th>Intervention Details</th>
<th>Results</th>
<th>Time to ED Visit</th>
<th>Hospital visits</th>
<th>Mortality</th>
<th>Primary care visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellström 2012</td>
<td>QE (historical CG from same units)</td>
<td>Single centre: Three internal medicine units</td>
<td>Adults</td>
<td>- NA</td>
<td>History and reconciliation (admn), review and counseling (inp)</td>
<td>- NA</td>
<td>6m</td>
<td>Time to ED visit</td>
<td>Mortality</td>
<td>Primary care visits</td>
</tr>
<tr>
<td>Israel 2013</td>
<td>RCT - patient level</td>
<td>Single centre: General medicine, family medicine, cardiology and orthopaedics units</td>
<td>Adults with cardiovascular diseases</td>
<td>- NA</td>
<td>History and education (inp)</td>
<td>- NA</td>
<td>30d, 90d</td>
<td>Hospital visits</td>
<td>Primary care visits</td>
<td></td>
</tr>
<tr>
<td>Koehler 2009</td>
<td>RCT - patient level</td>
<td>Single centre: Medicine teams</td>
<td>Elderly (≥ 70)</td>
<td>- NA</td>
<td>Reconciliation (admn), review and education (inp), reconciliation and counseling (dis), counseling (after dis)</td>
<td>- NA</td>
<td>30d, 60d</td>
<td>Hospital visits</td>
<td>ED visits</td>
<td>LOS Time to revisit</td>
</tr>
<tr>
<td>Makowsky 2009</td>
<td>RCT - CR at unit level (cross-over design)</td>
<td>Multicentre: Four internal medicine and family medicine units</td>
<td>Adults with CAD, CAP, COPD, HF or T2DM</td>
<td>- NA</td>
<td>History and reconciliation (admn), rounds and education (inp), reconciliation and report to primary care (dis)</td>
<td>- NA</td>
<td>3m, 6m</td>
<td>Adherence (at dis)</td>
<td>Readmission</td>
<td></td>
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<tr>
<td>Mortimer 2010</td>
<td>QE (naturalistic experiment where no intervention patients were CG)</td>
<td>Single centre: One emergency department</td>
<td>Elderly (≥ 65)</td>
<td>- NA</td>
<td>Reconciliation, review and education (admn)</td>
<td>- NA</td>
<td>14d, 28d</td>
<td>LOS</td>
<td>Hospital visit Patient satisfaction (questionnaire)</td>
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<tr>
<td>Okere 2016</td>
<td>QE (historical CG from same unit)</td>
<td>Single centre: One medical unit</td>
<td>Adults</td>
<td>NA - Divided into age groups</td>
<td>History, review, communication with physician and education (NS)</td>
<td>- NA</td>
<td>30d, 60d, 90d, 365d</td>
<td>LOS</td>
<td>All-cause readmissions</td>
<td></td>
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<tr>
<td>Rafferty 2016</td>
<td>QE (historical CG from same units)</td>
<td>Single centre: Pulmonary and medical-surgical unit</td>
<td>Adults</td>
<td>50-72</td>
<td>History and reconciliation (admn), reconciliation, education and communication to primary care (dis)</td>
<td>- NA</td>
<td>30d, 60d, 90d, 365d</td>
<td>Hospital visits</td>
<td>Hospital visit (60,90, 365d)</td>
<td></td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Studies</th>
<th>Design</th>
<th>Setting</th>
<th>Participants</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravn-Nielsen 2018 [55], Denmark</td>
<td>RCT – at patient level</td>
<td>Multicentre: Four EDs</td>
<td>Adults</td>
<td>Basic: 493, Extended: 476</td>
<td>- NA</td>
<td>Basic: review (adm), Extended: Basic component with addition of reconciliation, counseling (dis), and communication to primary care (dis), counseling by telephone (after dis)</td>
</tr>
<tr>
<td>Scullin 2007 [51], UK</td>
<td>RCT - patient level</td>
<td>Multicentre: Five medical units</td>
<td>Elderly (≥ 65)</td>
<td>371</td>
<td>391</td>
<td>47%</td>
</tr>
<tr>
<td>Scullin 2012 [50], UK</td>
<td>QE (naturalistic experiment where no intervention patients were CG)</td>
<td>Multicentre: Geriatric department</td>
<td>Adults</td>
<td>749</td>
<td>84</td>
<td>49%</td>
</tr>
<tr>
<td>Spinewine 2007 [52], Belgium</td>
<td>QE** (CG from same unit with addition of a historical CG)</td>
<td>Singlecentre: Geriatric department</td>
<td>Elderly (≥ 70)</td>
<td>96</td>
<td>90</td>
<td>31%</td>
</tr>
<tr>
<td>Surepill study group 2015 [29], The Nederlands</td>
<td>RCT - CR at ward level</td>
<td>Multicentre: Surgical wards</td>
<td>Surgical patients</td>
<td>547</td>
<td>547</td>
<td>57%</td>
</tr>
<tr>
<td>Van der Linden 2017 [56], Belgium</td>
<td>QE (CG was one of the wards)</td>
<td>Singlecentre: Three acute geriatric wards</td>
<td>Elderly</td>
<td>91</td>
<td>81</td>
<td>48%</td>
</tr>
</tbody>
</table>

- Pharmacists | 1w, 6m | Readmission |
- Trained | - 13 | |
- Pharmacists and pharmacy technicians | - Trained | 4 pairs |
- Pharmacists | - NA | - NA |
- Pharmacists and specialized technicians | - NA | - NA |
- Pharmacists | - NA | - NA |
- Pharmacists | - NA | - NA |
- Pharmacists | - NA | - NA |
- Pharmacists | - NA | - NA |
- Pharmacists | - NA | - NA |
- Pharmacists | - NA | - NA |
- Pharmacists | - NA | - NA |

<table>
<thead>
<tr>
<th>Drug-related readmissions</th>
<th>ED visits</th>
<th>Mortality</th>
<th>Readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Participants</th>
<th>Results</th>
<th>Medication Appropriateness</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker 2009[53], USA</td>
<td>QE (CGs were randomly selected from non-pharmacist unit)</td>
<td>Single centre: General medicine unit</td>
<td>Adults</td>
<td>358</td>
<td>366</td>
<td>47%</td>
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<tr>
<td>Wallerstedt 2012[54], Sweden</td>
<td>RCT - patient level</td>
<td>Single centre: Two internal medicine wards</td>
<td>Adults</td>
<td>164</td>
<td>181</td>
<td>39%</td>
</tr>
</tbody>
</table>

*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.

## Table 2 Risk of bias assessment

<table>
<thead>
<tr>
<th>Author year (ref)</th>
<th>Random sequence generation</th>
<th>Allocation conceal-ment</th>
<th>Represen- tativeness</th>
<th>Baseline imbalance</th>
<th>Selection Bias</th>
<th>Performance bias</th>
<th>Detection bias</th>
<th>Attrition bias</th>
<th>Reporting bias</th>
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</thead>
<tbody>
<tr>
<td>Alex 2016[31]</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
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<td>Bergkvist (a) 2009[34]</td>
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<td>Low</td>
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<td>Gillespie 2009[41]</td>
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<td>Scullin 2007[51]</td>
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<table>
<thead>
<tr>
<th>Author year (ref)</th>
<th>Outcome (time), unit</th>
<th>Results</th>
<th>Statistically significant*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alassaad 2014[30]</td>
<td>- Change in medication appropriateness (dis), mean STOPP score (SD)</td>
<td>IG: -0.5 (1.0), CG: 0.2 (0.7)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>- Change in medication appropriateness (dis), mean START score (SD)</td>
<td>IG: -0.3 (0.6), CG: 0.04 (0.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Alex 2016[31]</td>
<td>- Medication error (NA), pts</td>
<td>IG: 9/145 (6%), CG: 80/134 (60%)</td>
<td>Positive</td>
</tr>
<tr>
<td>Basger 2015[32]</td>
<td>- Medication appropriateness for 41 criteria (3m), pts</td>
<td>To many to be presented</td>
<td>ns</td>
</tr>
<tr>
<td>Bergkvist (b) 2009[33]</td>
<td>- Medication error ≥1 (NA), pts</td>
<td>IG: 14/52 (27%), CG: 23/63 (37%)</td>
<td>ns</td>
</tr>
<tr>
<td>Bergkvist (a) 2009[34]</td>
<td>- Change in medication appropriateness (adm vs dis), mean MAI score (SD)</td>
<td>Not stated</td>
<td>ns</td>
</tr>
<tr>
<td>Bladh 2011[35]</td>
<td>- Medication appropriateness (adm vs dis), mean score per pts(SD)</td>
<td>IG: 0.34(0.7), IG-PP: 0.26(0.56), CG: 0.38(0.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Burnett 2009[36]</td>
<td>- Medication appropriateness difference adm vs dis (NA), mean score (SD)</td>
<td>IG: -11.8 (14.6), CG: -3.2 (11.8)</td>
<td>Positive</td>
</tr>
<tr>
<td>Eggink 2010[37]</td>
<td>- Medication error with 1≤ discrepancies (6w), pts</td>
<td>CG: 68% vs IG: 39%, RR: 0.6 (95%CI 0.4-0.9)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>- Medications with error (6w), number</td>
<td>CG: 15%, IG: 6%, RR 0.4 (95%CI 0.3-0.7)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>- Adherence (6w), pts</td>
<td>CG: 80%, IG: 78%, RR: 1.1 (95%CI 0.5-2.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Farley 2014[38]</td>
<td>- High level error in physician record per pts (30d), mean</td>
<td>IG2: 0.26, CG: 0.51</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>- High level error in physician record per pts (90d), mean</td>
<td>IG2: 0.4, CG: 0.5</td>
<td>ns</td>
</tr>
<tr>
<td>Farris 2014[39]</td>
<td>- Medication appropriateness (dis), MAI score per pts(SD)</td>
<td>IG1: 8.0(8.4), IG2: 7.1(7.0), CG: 6.1(6.6)</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>- Medication appropriateness (30d), MAI score per pts(SD)</td>
<td>IG2: 10.1(8.9), CG: 9.0(9.5)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>- Medication appropriateness (90d), MAI score per pts(SD)</td>
<td>IG2: 11.6(10.5), CG: 11.1(11.3)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>- Adverse events (dis), pts</td>
<td>IG2: 48/311 (16%), CG: 53/313 (17%)</td>
<td>ns</td>
</tr>
<tr>
<td>Gillespie 2013[40]</td>
<td>- Change in medication appropriateness (adm vs dis), mean MAI score (SD)</td>
<td>IG: -3.5(5.1), CG: 1.3(3.1)</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>- Change in medication appropriateness (adm vs dis), mean STOPP score (SD)</td>
<td>IG: -0.5(1.0), CG: 0.2(0.7)</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>- Change in medication appropriateness (adm vs dis), mean START score (SD)</td>
<td>IG: -0.3(0.6), CG: 0(0.4)</td>
<td>Positive</td>
</tr>
<tr>
<td>Hellström 2011[42]</td>
<td>- Medication appropriateness (3m), drugs with 1≤ inappropriate MAI rating</td>
<td>IG-ITT: 51%(95%CI 43-58), CG: 39%(95%CI 30-48)</td>
<td>Positive</td>
</tr>
<tr>
<td>Israel 2013[44]</td>
<td>- Cardiovascular underutilization (dis), pts</td>
<td>IG-enhanced: 67/241 (66%), CG: 62/246 (56%)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>- Cardiovascular underutilization (30d), pts</td>
<td>IG-enhanced: 66/241 (65%), CG: 60/246 (56%)</td>
<td>ns</td>
</tr>
<tr>
<td>Study</td>
<td>Outcome</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Makowsky 2009 [46]</td>
<td>Cardiovascular underutilization (90d), pts</td>
<td>IG-enhanced: 61/241 (62%), CG: 56/246 (64%)</td>
<td>- ns</td>
</tr>
<tr>
<td></td>
<td>Adherence to indicators (dis), mean score</td>
<td>IG: 56%, CG: 45%; adjusted diff: 10.4 (95%CI: 5%-16%)</td>
<td>- positive</td>
</tr>
<tr>
<td>Spinewine 2007 [52]</td>
<td>Medication appropriateness (dis), MAI score OR (95%CI)</td>
<td>IG: 9.1 (4-22)</td>
<td>- positive</td>
</tr>
<tr>
<td></td>
<td>Medication appropriateness (dis), ACOVE score OR (95%CI)</td>
<td>IG: 6.1 (2-17)</td>
<td>- positive</td>
</tr>
<tr>
<td></td>
<td>Medication appropriateness (dis), Beers criteria OR (95%CI)</td>
<td>IG: 0.6 (0.3-1)</td>
<td>- ns</td>
</tr>
<tr>
<td></td>
<td>Unnecesssary drug use (dis), pts</td>
<td>IG: 38%, CG: 78%</td>
<td>- not stated</td>
</tr>
<tr>
<td>Surepill 2015 [29]</td>
<td>Preventable ADE (dis), incidence RR</td>
<td>IG: 0.8 (95%CI: 0.4-1.7)</td>
<td>- ns</td>
</tr>
<tr>
<td></td>
<td>Complications ≥ 1 (dis), pts</td>
<td>IG: 113/453 (25%), CG: 132/450 (29%)</td>
<td>- ns</td>
</tr>
<tr>
<td>Van der Linden [56]</td>
<td>Discountinued admission drugs or dose reduction (adm), median (IRQ)</td>
<td>IG: 5 (3-7), CG: 3 (2-5)</td>
<td>- positive</td>
</tr>
<tr>
<td></td>
<td>Ratio of discontinued/started drugs (adm vs dis), median (IRQ)</td>
<td>IG: 0.9 (0.7-1.1), CG: 0.9 (0.8-1.1)</td>
<td>- ns</td>
</tr>
<tr>
<td></td>
<td>Medication appropriateness (dis) according to RASP, median (IRQ)</td>
<td>IG: 0.5 (0-1), CG: 2 (1-3)</td>
<td>- positive</td>
</tr>
<tr>
<td>Walker 2009 [53]</td>
<td>Medication discrepancies (12m), pts</td>
<td>IG: 120/358 (34%), CG: 218/366 (60%)</td>
<td>- positive</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Author year (ref)</th>
<th>Type of visits (time), unit</th>
<th>Result as n(5%)</th>
<th>Statistically significant*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farris 2014[39]</td>
<td>Hospital visit (30d), pts</td>
<td>IG2: 81/311 (29%), CG: 87/313 (30%)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Hospital visit (90d), pts</td>
<td>IG2: 97/311 (35%), CG: 88/313 (30%)</td>
<td>ns</td>
</tr>
<tr>
<td>Gillespie 2009[41]</td>
<td>Hospital visit (12m), pts</td>
<td>IG: 107/182 (58%), CG: 110/186 (59%)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Drug-related hospital visit (12m), pts</td>
<td>IG: 9/182 (5%), CG: 45/186 (24%)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>ED visit (12m), pts</td>
<td>IG: 49/182 (35%), CG: 93/186 (66%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hellström 2011[42]</td>
<td>Drug-related visit (3m), pts</td>
<td>IG: 6%, CG: 12%</td>
<td>ns</td>
</tr>
<tr>
<td>Hellström 2012[43]</td>
<td>ED visit (6m), adjusted hazard ratio (95%CI)</td>
<td>1.04 (0.90-1.12)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Hospital visit incl death (6m), adjusted hazard ratio (95%CI)</td>
<td>1.03 (0.90-1.17)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Primary care visit (6m), pts</td>
<td>IG: 908/1325 (69%), CG: 2084/2965 (70%)</td>
<td>ns</td>
</tr>
<tr>
<td>Koehler 2009[45]</td>
<td>Hospital visit (30d), pts</td>
<td>IG: 2/20 (10%), CG: 8/21 (38%)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Hospital visit (60d), patients</td>
<td>not stated</td>
<td>ns</td>
</tr>
<tr>
<td>Makowsky 2009[46]</td>
<td>Readmission (3m), pts and OR</td>
<td>IG: 80/221 (36%), CG: 105/231 (46%), adjusted OR: 0.63 (95%CI 0.4-0.9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Readmission (6m), pts and OR</td>
<td>IG: 112/221 (51%), CG: 130/231 (56%), adjusted OR: 0.78 (95%CI 0.5-1)</td>
<td>ns</td>
</tr>
<tr>
<td>Mortimer 2010[47]</td>
<td>Hospital visit (14d), pts</td>
<td>not stated</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Hospital visit (28d), pts</td>
<td>not stated</td>
<td>ns</td>
</tr>
<tr>
<td>Okere 2016[48]</td>
<td>Readmission (30d), mean adjusted (95%CI)</td>
<td>IG: 9.5 (6.7-13.3), CG: 10.1 (7.6-13.2)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Readmission (60d), mean adjusted (95%CI)</td>
<td>IG: 10.7 (7.5-15.2), CG: 11.8 (8.6-16.1)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Readmission (90d), mean adjusted (95%CI)</td>
<td>IG: 12.4 (8.8-17.2), 13.4 (10.0-17.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Rafferty 2016[49]</td>
<td>Readmission (30d), pts</td>
<td>IG: 43/384 (11%), CG: 274/1221 (23%)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>ED-visit (30d), pts</td>
<td>IG: 18/384 (5%), CG: 117/1221 (10%)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>Readmission (60d), pts</td>
<td>IG: 81/384 (21%), CG: 388/1221 (32%)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>Readmission (90d), pts</td>
<td>IG: 110/384 (29%), CG: 462/1221 (38%)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>Readmission (365d), pts</td>
<td>IG: 212/384 (55%), CG: 756/1221 (62%)</td>
<td>positive</td>
</tr>
<tr>
<td>Ravn-Nielsen[55]</td>
<td>Readmission (30d), pts; hazard ratio (95%CI)</td>
<td>IG: 68/476 (14%), CG: 111/498 (22%); 0.62 (0.46-0.84)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>Readmission (180d), pts; hazard ratio (95%CI)</td>
<td>IG: 189/476 (40%), CG: 243/498 (49%); 0.75 (0.62-0.90)</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>ED visit (180d), pts; hazard ratio (95%CI)</td>
<td>IG: 15/476 (3%), CG: 21/498 (4%); 0.74 (0.38-1.44)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Drug-related readmission (30d), pts; hazard ratio (95%CI)</td>
<td>IG: 24/476 (5%), CG: 38/498 (8%); 0.65 (0.39-1.09)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Drug-related readmission (180d), pts; hazard ratio (95%CI)</td>
<td>IG: 75/476 (16%), CG: 96/498 (19%); 0.80 (0.59-1.08)</td>
<td>ns</td>
</tr>
<tr>
<td>Scullin 2007[51]</td>
<td>Readmission (12m), pts</td>
<td>IG: 141/370 (38%), CG: 172/384 (45%)</td>
<td>positive</td>
</tr>
</tbody>
</table>

*Statistically significant values are marked with **positive** or **ns**.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Outcome/Time Frame</th>
<th>Intervention Group (IG)</th>
<th>Control Group (CG)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scullin 2012[50]</td>
<td>- Readmission (12m), mean no.</td>
<td>- IG: 2.51, CG: 2.70</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td>Surepill 2015[29]</td>
<td>- Readmission (3m), pts</td>
<td>- IG: 84/362 (23%), CG: 64/362 (18%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td>Spinewine 2007[52]</td>
<td>- ED visit (12m), pts</td>
<td>- IG: 7/89 (7.9%), CG: 19/83 (12.0%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td>van der Linden[56]</td>
<td>- Readmission (3m), pts</td>
<td>- IG: 30/87 (35%), CG: 31/79 (39%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ED visit (3m), pts</td>
<td>- IG: 25/87 (29%), CG: 31/79 (39%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ED visit without readmission (3m), pts</td>
<td>- IG: 1/87 (1%), CG: 7/79 (9%)</td>
<td>- positive</td>
<td></td>
</tr>
<tr>
<td>Walker 2009[53]</td>
<td>- Readmission (14d), pts</td>
<td>- IG: 45/358 (13%), CG: 42/366 (12%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Readmission (30d), pts</td>
<td>- IG: 79/358 (22%), CG: 66/366 (18%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ED visit (3d), pts</td>
<td>- IG: 10/358 (3%), CG: 8/366 (2%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ED visit (14d), pts</td>
<td>- IG: 22/358 (6%), CG: 27/366 (7%)</td>
<td>- ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- ED visit (30d), pts</td>
<td>- IG: 34/358 (10%), CG: 45/366 (12%)</td>
<td>- ns</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author year (ref)</th>
<th>Type of variable(time), unit</th>
<th>Result in days</th>
<th>Statistically significant*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alex 2016[31]</td>
<td>- LOS of index admission (NA), not stated</td>
<td>- IG: 5.4(4.8), CG: 5.7(5.6)</td>
<td>ns</td>
</tr>
<tr>
<td>Basger 2015[32]</td>
<td>- LOS of index admission (NA), mean(SD)</td>
<td>- IG: 16.7(8.7), CG: 18.3(10.5)</td>
<td>ns</td>
</tr>
<tr>
<td>Bladh 2011[35]</td>
<td>- LOS of index admission (NA), median(IQR)</td>
<td>- IG: 6(4-10), IG-PP: 8(5-10), CG: 6(4-11)</td>
<td>ns</td>
</tr>
<tr>
<td>Hellström 2012[43]</td>
<td>- Time to ED visit(6m), HR(95%CI)</td>
<td>- 0.95(0.86-1.04)</td>
<td>ns</td>
</tr>
<tr>
<td>Koehler 2009[45]</td>
<td>- LOS of index admission (NA), median(IQR)</td>
<td>- IG: 6.2 (4.1), CG: 4.7 (3.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Mortimer 2010[47]</td>
<td>- LOS of index admission (NA), mean</td>
<td>- IG 0.5, CG 0.4</td>
<td>negative</td>
</tr>
<tr>
<td>Okere 2016[48]</td>
<td>- LOS of index admission (NA), mean(SD)</td>
<td>- IG: 4.6 (2.1), CG: 5.3 (2.0)</td>
<td>positive</td>
</tr>
<tr>
<td>Rafferty 2016[49]</td>
<td>- LOS of index admission (NA), mean</td>
<td>- IG: 4, CG: 4</td>
<td>ns</td>
</tr>
<tr>
<td>Scullin 2007[51]</td>
<td>- LOS of index admission (NA), mean(SD)</td>
<td>- IG: 7.8 (95%CI 7.1-8.6), CG: 9.8 (95%CI 8.8-10.9)</td>
<td>positive</td>
</tr>
<tr>
<td>Scullin 2012[50]</td>
<td>- LOS of index admission (NA), mean(SD)</td>
<td>- IG: 11.3 (14.9), CG: 17.2 (16.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Surepill 2015[29]</td>
<td>- LOS of index admission (NA), median(IQR)</td>
<td>- IG: 8(6-12), CG: 7(6-13)</td>
<td>ns</td>
</tr>
<tr>
<td>Walker 2009[53]</td>
<td>- LOS of index admission (NA), median (range)</td>
<td>- IG: 4.0 (1-19), CG: 3.0 (1-18)</td>
<td>ns</td>
</tr>
</tbody>
</table>

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