Annals of Pharmacy Practice and Pharmacotherapy
ISSN: 3062-4436
2023, Volume 3, Issue 2, Page No: 136-151

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Which Components of Pharmacist-Led Medication Optimization Change Hard Clinical Outcomes? A Mechanism-Sensitive Systematic Review of Comparator Fidelity and Outcome Proximity, 2017–2024

Laura Fitzgerald[1]*, Thomas Andersen[2], Aisha Bello[3], Kenji Nakamura[4]

[1]Department of Clinical Pharmacy and Evidence Synthesis, School of Pharmacy, University College Dublin, Dublin, Ireland.
[2]Department of Clinical Pharmacy and Health Services Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.
[3]Department of Pharmacy Practice and Outcome Evaluation, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria.
[4]Department of Clinical Pharmacy and Systematic Review Methods, Faculty of Pharmacy, Keio University, Tokyo, Japan.

***E-mail** ✉ laura.fitzgerald@ucd.ie
Received: 16 September 2023; **Revised:** 09 December 2023; **Accepted:** 15 December 2023

ABSTRACT

Pharmacist-led medication optimization encompasses interventions that differ in review intensity, patient involvement, prescriber collaboration, follow-up, and continuity across care settings. Improvements in prescribing processes are frequently reported, but effects on medication-related harm, unscheduled healthcare use, readmission, and mortality are less consistent. Interpretation is further complicated when control groups receive overlapping medication-management activities and when successful recommendations do not lead to actual treatment modification. To determine which components of pharmacist-led medication optimization are associated with hard clinical outcomes and to examine how comparator fidelity, achieved treatment modification, and outcome proximity alter interpretation of apparently positive or null intervention effects. A systematic review of controlled intervention studies published from 2017 through 2024 was conducted using bibliographic, journal/publisher, and citation-chain searches. Eligible direct-synthesis studies evaluated pharmacist-led or pharmacist-co-led medication optimization and reported at least one patient-important clinical endpoint; co-reported intervention processes, implemented treatment changes, and intermediate medication outcomes were extracted to examine the pathway to those endpoints. Intervention components, actual comparator content, treatment modification, and outcome proximity were extracted separately. Risk-of-bias judgments were assigned only when the reported methodological information supported them. Heterogeneous evidence was synthesized without statistical pooling. Seventy-six records were identified, 15 duplicate or alternate records were removed, and 61 unique records were screened. Twenty-eight records were excluded at title/abstract screening; 33 reports were retrieved and underwent full-text assessment. Nineteen full-text reports were excluded, leaving 14 unique controlled studies in the qualitative synthesis. Interventions ranged from medication reconciliation or one-time medication review to longitudinal, multicomponent programmes spanning discharge and follow-up. Hard-outcome benefit was not consistently related to the presence of medication review itself. Positive findings occurred in some high-contrast integrated interventions, whereas several intensive programmes were null despite medication changes or reductions in inappropriate prescribing. Comparator groups varied from routine care with little explicit medication optimization to active medication reconciliation, pharmacist input, or medication education. Pharmacist-led medication optimization cannot be interpreted as a uniform exposure. The evidence supports a conditional interpretation in which component composition, the incremental contrast over actual comparator care, successful implementation of medication changes, and distance to the measured clinical endpoint jointly influence observed outcomes. Available multicomponent studies rarely permit causal attribution to individual pharmacist activities.

Keywords: Clinical pharmacy, Medication optimization, Medication review, Medication-related harm, Hospital readmission, Care transitions

How to Cite This Article: Fitzgerald L, Andersen T, Bello A, Nakamura K. Which Components of Pharmacist-Led Medication Optimization Change Hard Clinical Outcomes? A Mechanism-Sensitive Systematic Review of Comparator Fidelity and Outcome Proximity, 2017–2024. Ann Pharm Pract Pharmacother. 2023;3(2):136-51. https://doi.org/10.51847/kTImvhT0Jn

Introduction

Pharmacist-led medication review has accumulated a large intervention literature, but the label obscures substantial differences in what patients actually receive. Reviews may incorporate reconciliation, identification of drug-related problems, adherence assessment, deprescribing, dose adjustment, prescriber communication, patient education, monitoring, and postdischarge follow-up in different combinations. Recent systematic analyses demonstrate pronounced variation in patient selection, intervention components, accompanying activities, and outcome measurement across trials[1–3]. Consequently, treating medication review as a single exposure can conceal the mechanisms through which a pharmacist could plausibly influence a patient-important outcome.

This heterogeneity becomes particularly consequential when effectiveness is judged using readmission, emergency healthcare use, medication-related injury, or survival. Syntheses of hospitalized older patients generally find clearer effects on medication appropriateness than on mortality or emergency utilization, with any reduction in readmission tending to be small or uncertain[4, 5]. Such findings do not establish that medication optimization is clinically irrelevant. They instead expose a long causal distance between identifying a medication problem and preventing a future event that may have multiple medication-related and non-medication-related causes.

Service context further changes that distance. Pharmacist–physician collaboration, transition-of-care pharmacy programmes, and community medication reviews have each produced encouraging findings, but intervention design and study design materially influence estimated effects[6–8]. A pharmacist working within a longitudinal multidisciplinary service may have greater opportunity to translate a recommendation into a changed regimen than a pharmacist delivering a single review shortly before discharge.

Transfer-of-care evidence illustrates this distinction. Medication review and reconciliation are prominent pharmacist activities when responsibility moves from secondary to primary care, yet the rigor and outcome focus of that evidence remain variable[9]. Similarly, pharmacist-led primary-care initiatives have more consistently demonstrated changes in prescribing or overprescribing than improvements in patient-level clinical outcomes[10]. These observations make the intermediate steps between pharmacist activity and patient benefit scientifically important rather than incidental.

Medication reconciliation provides a particularly clear example. Its immediate purpose is to identify and resolve discrepancies between medication lists[11]. Interventions that extend beyond hospitalization can add counselling, communication and follow-up, thereby increasing opportunities for medication problems to be acted upon after discharge[12]. A reduction in discrepancies, however, is not equivalent to a reduction in readmission. For reconciliation to alter a hard endpoint, an identified discrepancy must be clinically meaningful, corrected, maintained across subsequent care and sufficiently important to influence an event that would otherwise occur.

Hard endpoints also require careful definition. Drug-related readmissions remain a measurable burden among older adults[13]. Earlier evidence indicates that a meaningful proportion of such readmissions may be preventable, although estimates depend strongly on definitions and adjudication methods[14]. Postdischarge medication-related harm likewise varies widely across studies and includes events ranging from adverse drug reactions to medication errors requiring additional healthcare[15]. Prospective work shows that medication-related harm requiring healthcare use can be explicitly adjudicated as a patient-important safety outcome, although risk prediction remains imperfect[16]. The relevance of particular pathways also depends on population and treatment; for example, hypoglycaemia and harms related to insulin or sulfonylureas are prominent contributors to medication-related hospital and emergency care among older adults with diabetes[17].

The resulting problem is not adequately addressed by counting pharmacist contacts or asking whether a study contained a medication review. Interpretation requires four separable questions: what components were actually delivered; how much medication-management activity was already present in the comparator; whether recommendations produced an implemented change in treatment; and how far the reported endpoint lay from that change. This review therefore examines controlled studies through those distinctions while preserving null and context-dependent results rather than averaging structurally different pharmacist services into one exposure.

Aim

The primary objective was to determine which components of pharmacist-led medication optimization were associated with hard clinical outcomes in controlled studies published from 2017 through 2024. Secondary objectives were to determine whether apparent intervention effects changed with the fidelity and activity of the comparator, whether recommendations translated into actual treatment modification, and whether outcome patterns differed according to the proximity of the measured endpoint to the medication intervention. Component causality was considered identifiable only where the study design itself permitted that inference.

Materials and Methods

Eligibility and review-unit definition

The review unit was a unique controlled intervention study. Eligible studies enrolled adult clinical populations and evaluated a pharmacist-led or explicitly pharmacist-co-led medication-optimization intervention against a concurrent comparison condition. Medication optimization included structured medication review, medication reconciliation when linked to optimization activity, deprescribing or appropriateness review, pharmacist–prescriber medication modification, or multicomponent programmes in which these activities were central.

To enter the direct efficacy synthesis, a controlled study had to report at least one patient-important hard clinical endpoint (P3), including medication-related harm or adverse events, emergency or unscheduled healthcare use, hospital admission or readmission, or mortality. Intervention-process (P0), implemented treatment-change (P1), and intermediate medication or clinical outcomes (P2) were extracted when co-reported because they informed the mechanism linking pharmacist activity to hard outcomes. Controlled pharmacist-led studies reporting only P0-P2 outcomes were retained as contextual mechanism evidence rather than counted as direct efficacy units. Process-only and implementation studies could also inform mechanism but were not counted as controlled efficacy units. Multiple reports from the same study were linked to the parent study to prevent double counting. Journal quartile was not an eligibility criterion for individual studies.

Search and evidence identification

The evidence-development search covered publications from 1 January 2017 through 31 December 2024. Searches combined pharmacist-related terms with medication review, medication reconciliation, medicines or medication optimization, deprescribing, intervention, randomized or controlled study, readmission, hospitalization, emergency care, adverse drug events, medication-related harm, and mortality. PubMed/MEDLINE-indexed literature was supplemented by targeted journal and publisher searches and backward and forward citation-chain examination of eligible trials and recent systematic reviews. Identification and reporting followed PRISMA 2020 principles[18].

Evidence searches were deliberately broader than the final controlled-study eligibility criteria so that prior syntheses, endpoint epidemiology, methodological sources, and implementation analyses could inform interpretation. Such contextual references were retained in the reference list without being reclassified as included controlled studies.

Screening, study linkage, and data extraction

Screening proceeded in two sequential stages: title/abstract screening followed by full-text eligibility assessment against the controlled-study criteria. Full-text exclusion reasons were classified by clinical/outcome eligibility, pharmacist role or intervention centrality, study design, duplicate or secondary-report status, and population/date/intervention criteria. Reports were linked where they represented secondary analyses or additional publications from the same intervention programme.

Extraction separated information that is frequently collapsed in medication-review literature. For each included study, the extracted fields included study design and setting, population, intervention components, duration and continuity of pharmacist involvement, other professionals involved, comparator content, outcome definitions, follow-up interval, whether pharmacist recommendations were accepted, whether medication changes were actually implemented, and the direction of proximal and hard clinical outcomes. Missing implementation information was retained as not reported rather than inferred.

Comparator fidelity, treatment modification, and outcome-proximity coding

Comparator fidelity referred to the degree to which the report allowed the actual medication-management content of the comparison condition to be recovered. The comparator was therefore coded from reported care rather than from labels such as "usual care." Overlap was recorded when control participants received medication reconciliation, pharmacist services, structured medication education, deprescribing activity, or another intervention capable of acting on the same medication pathway.

Achieved treatment modification required evidence that prescribing or medication use was actually changed. Identification of a drug-related problem, generation of a recommendation, or clinician acceptance was not treated as equivalent to an implemented medication change.

Outcomes were organized into four proximity levels. P0 represented intervention processes, including discrepancies detected or recommendations generated or accepted. P1 represented implemented treatment modification. P2 represented intermediate medication or clinical states, including medication count, potentially inappropriate medication exposure, discrepancy burden, or disease-control measures. P3 comprised patient-important hard outcomes, including medication-related harm, emergency or unscheduled healthcare use, admission or readmission, and mortality. The categories were used as an interpretive structure for this review and not as a validated causal scale.

Risk-of-bias appraisal and mechanism-sensitive synthesis

Risk-of-bias judgments were assigned only when the reported methodological information was sufficient. Randomized and cluster-randomized studies were considered against RoB 2 domains, including the randomization process, deviations from assigned intervention, missing outcome data, outcome measurement, and selective reporting. Nonrandomized controlled studies were considered against ROBINS-I domains, with particular attention to confounding, participant selection, intervention classification, and deviations from intended exposure. No overall rating was inferred from a study-design label alone.

Clinical and methodological heterogeneity precluded a single pooled treatment estimate. Intervention composition, comparator activity, implementation, outcome definition and follow-up varied to an extent that a pooled "pharmacist effect" would obscure the contrast being tested. Synthesis therefore followed SWiM principles for transparent synthesis without meta-analysis[19]. Findings were grouped by component delivery, comparator contrast, achieved treatment modification and outcome proximity. Within-study comparisons were given greater interpretive weight than cross-study comparisons when they provided different intervention intensities against a common comparator.

Results and Discussion

Search yield and included-study profile

The search identified 76 records. Fifteen duplicate or alternate records were removed before screening, leaving 61 unique records. Twenty-eight records were excluded at title/abstract screening. Thirty-three reports were sought for retrieval; all 33 were available and underwent full-text assessment (reports not retrieved, n = 0). Nineteen full-text reports were excluded: seven lacked an eligible patient-important clinical endpoint or sufficient outcome-proximity information, four did not evaluate a pharmacist-led or pharmacist-co-led medication-optimization intervention, four were uncontrolled or process-only designs, two were secondary or duplicate reports without a separate eligible study unit, and two failed another population, date, or intervention criterion. Fourteen unique controlled studies were included in the qualitative synthesis.

The 14-study count refers only to direct efficacy units; contextual, implementation, secondary, and methodological references were not counted as included studies **(Figure 1)**.

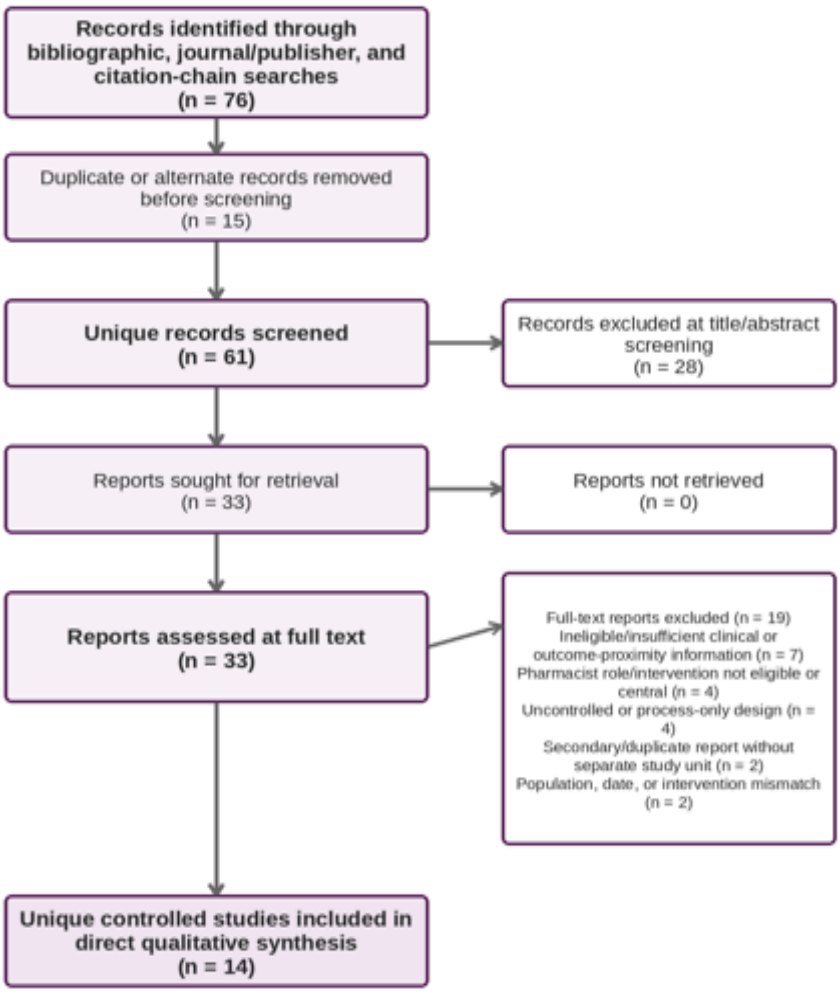

Figure 1. Selection of controlled studies for the mechanism-sensitive synthesis

Study-selection ledger and risk-of-bias appraisal

Included direct efficacy studies (n = 14) were Ravn-Nielsen *et al*. (OPTIMIST) [20], Kempen *et al*. (MedBridge) [21], Johansen *et al*. (IMMENSE) [22], Grischott *et al*. [23], Nymoen *et al*. [24], Martínez *et al*. [25], El Hajj *et al*. [26], Gurwitz *et al*. [27], Ceschi *et al*. [28], Santolaya-Perrín *et al*. [29], Lexow *et al*. [30], Vasilevskis *et al*. (Shed-MEDS) [31], Ie *et al*. [32], and Blum *et al*. (OPERAM) [33]. Named studies retained as contextual mechanism evidence rather than direct efficacy units were Peled *et al*. [34], Martin *et al*. (D-PRESCRIBE) [35], O'Mahony *et al*. (SENATOR) [36], Schnipper *et al*. (MARQUIS2) [37], and the MARQUIS2 on-treatment/site analysis [38]. D-PRESCRIBE was consistently classified as contextual because its principal outcome in this review was discontinuation of targeted inappropriate medication (P1), rather than a P3 hard clinical endpoint.

For the study with sufficient nonrandomized-design information to support a formal judgment, El Hajj *et al*. [26] was judged at least moderate risk of bias under ROBINS-I, driven primarily by nonrandomized quasi-experimental allocation and the associated confounding concern; the reported attenuation of some effects after adjustment was consistent with this judgment. No additional overall study-level rating was assigned without sufficient domain information.

Intervention content, delivery, and achieved treatment modification

The clearest within-study demonstration that intervention intensity mattered came from OPTIMIST. Patients received usual care, a basic medication-review intervention, or an extended intervention adding patient interview and continuing follow-up across the sector transition. Hard-outcome improvement was concentrated in the extended intervention, which reduced 30- and 180-day readmission and the composite of readmission or emergency attendance; the design did not isolate which added component generated that difference[20].

Greater intensity nevertheless did not consistently produce benefit. In the MedBridge cluster trial, hospital comprehensive medication review alone and comprehensive review plus postdischarge follow-up failed to reduce unplanned hospital visits relative to usual care, and the extended arm was associated with more emergency-department visits over 12 months[21]. IMMENSE similarly combined several medication-safety steps across secondary and primary care but did not reduce emergency visits, readmissions or mortality[22]. A Swiss cluster trial combining checklist-guided medication review with enhanced information transfer at discharge did not delay readmission[23]. Systematic emergency-department medication review in Norway also failed to reduce unplanned hospital contact during 12 months[24].

Other studies produced more favorable patterns. Integration of a clinical pharmacist into a Chilean emergency-department team for medication selection, evaluation and discharge education reduced 30-day revisits compared with standard care[25]. In patients discharged after acute coronary syndrome, an intervention combining reconciliation, counselling and postdischarge pharmacist follow-up showed a favorable cardiac-readmission signal, although the prospective quasi-experimental allocation and attenuation of some effects after adjustment limited causal certainty[26]. Conversely, a US intervention for patients receiving high-risk medications—home pharmacist assessment, education, primary-care communication and telephone follow-up—did not reduce adverse drug-related incidents or clinically important medication errors compared with mailed education[27].

More proximal interventions further separated successful delivery from patient-important benefit. Admission medication reconciliation in a large Swiss randomized trial corrected the medication-information pathway but did not reduce 30-day unplanned hospital visits[28]. A Spanish emergency-department programme based on pharmacist STOPP/START review and communication of treatment recommendations had no significant overall effect on emergency visits and hospitalization, although more favorable centre-specific findings occurred where recommendation acceptance was higher[29]. In long-term care, a one-time pharmacist medication review generated more medication changes and resolved some drug-related problems without reducing hospital admissions, falls or deaths[30].

Recommendation uptake therefore represented an important intermediate state. Implementation evidence outside the 14 direct efficacy units showed that acceptance of pharmacist recommendations can change substantially as pharmacists become integrated into clinical services[34]. D-PRESCRIBE was retained as contextual mechanism evidence because medication discontinuation was its principal endpoint in this review (P1), rather than a P3 hard clinical outcome. It nevertheless demonstrated that pharmacist-linked education could generate a large difference in discontinuation of targeted inappropriate medications, establishing that treatment modification is achievable[35]. Shed-MEDS, which did contribute to the direct synthesis because adverse events were also reported, reduced medication burden and potentially inappropriate exposure during the transition to postacute care while adverse-event rates remained similar[31].

Two larger optimization trials made the same distinction especially visible. A multidisciplinary STOPP/START-based intervention in older Japanese inpatients reduced potentially inappropriate medication exposure through 12 months but did not reduce the composite of death, unscheduled hospital visits and rehospitalization[32]. In OPERAM, doctor–pharmacist pharmacotherapy optimization generated multiple recommendations and at least one recommendation was implemented in a substantial proportion of intervention patients, yet drug-related hospital admission was not significantly reduced[33]. The recurring separation between medication change and hard clinical benefit argues against using recommendation counts or prescribing improvement as a surrogate for patient-important outcomes.

The intervention configurations and settings underlying these comparisons are summarized in **Table 1**.

Table 1. Controlled studies contributing to the direct mechanism-sensitive synthesis

Study	Setting and population	Design / analysed population	Pharmacist-led or pharmacist-inclusive intervention	Principal clinical endpoint domain
Ravn-Nielsen *et al.*, 2018	Danish acute hospitals; adults using ≥5 medicines	Three-arm randomized trial; 1467	Medication review; extended arm added patient interview and cross-sector follow-up	Readmission and emergency use
Kempen *et al.*, 2021	Four Swedish hospitals; older inpatients	Cluster randomized crossover; 2637	Comprehensive medication review with or without postdischarge follow-up	Unplanned hospital visits

Johansen *et al*., 2022	Hospital-to-primary-care transition; adults ≥70 years	Randomized trial; 480	Five-step interdisciplinary pharmacist medication-safety programme	Emergency visits, readmission, mortality
Grischott *et al*., 2023	21 Swiss hospitals; age ≥60 with polypharmacy	Cluster randomized trial; 609	Checklist medication review plus enhanced discharge information transfer	Time to readmission
Nymoen *et al*., 2022	Norwegian emergency department	Randomized trial; 789 in primary analysis	Systematic pharmacist medication reconciliation and review	Unplanned hospital contact
Martínez *et al*., 2024	Chilean university emergency department	Pragmatic randomized trial; 1001	Pharmacist integrated into medication selection, evaluation and discharge education	30-day emergency revisits
El Hajj *et al*., 2023	Qatar; patients discharged after acute coronary syndrome	Prospective controlled quasi-experiment; 373	Reconciliation, counselling and pharmacist follow-up at 4 and 8 weeks	Hospitalization and cardiac readmission
Gurwitz *et al*., 2021	US posthospital care; high-risk medications	Randomized trial; 361	Home pharmacist assessment, education, primary-care communication and follow-up	Medication-related incidents/errors
Ceschi *et al*., 2021	Two Swiss hospitals; very old/high-polypharmacy patients	Randomized trial; 1702	Best possible medication history and pharmacist-led admission reconciliation	30-day unplanned hospital visits
Santolaya-Perrín *et al*., 2019	Four Spanish emergency departments; adults >65 years	Multicentre randomized trial	STOPP/START review, discussion with emergency physician and recommendation to primary care	Emergency visits and hospital admissions
Lexow *et al*., 2022	Three German long-term-care facilities	Prospective controlled study; 211	One-time medication review and recommendations to physicians/nurses/pharmacists	Hospital admission, falls, death
Vasilevskis *et al*., 2023	Hospital-to-postacute-care transition	Randomized trial; 284 intention-to-treat	Comprehensive review and patient-approved deprescribing continued through postacute care	Medication burden and adverse events
Ie *et al*., 2024	Japanese inpatient wards; age ≥65 with ≥5 medicines	Randomized trial; 442	Multidisciplinary STOPP/START review, optimization proposal and discharge transfer	Death, unscheduled visits, rehospitalization
Blum *et al*., 2021	Hospitals in four European countries; age ≥70 with multimorbidity/polypharmacy	Cluster randomized trial; 2008	Doctor–pharmacist optimization supported by decision software	Drug-related hospital admission

Comparator fidelity and contrast actually tested

Control conditions were not interchangeable. In several trials the comparator approximated routine care without the structured pharmacist package, producing a comparatively wide incremental contrast. In OPTIMIST, the three-arm design was particularly informative because it distinguished usual care from basic medication review and from a substantially extended pharmacist intervention[20]. The randomized three-arm structure permits a more informative comparison of intervention intensity than unrelated cross-trial labels; a difference between significance patterns alone, however, does not establish an effect difference between arms.

In other studies, the comparator already contained parts of the medication-management pathway. MedBridge compared additional structured comprehensive medication review with existing hospital care[21]. The Swiss reconciliation trial compared pharmacist-led reconciliation against physician-acquired medication history rather

than absence of medication assessment[28]. The Japanese optimization trial explicitly described usual care as including medication reconciliation[32]. These comparisons tested the incremental value of an added optimization layer, not the value of medication management versus no medication management.

Comparator overlap was even more explicit in the high-risk-medication trial, where control participants received mailed educational material[27]. In the acute-coronary-syndrome study, three groups represented structured pharmacist follow-up, usual discharge care involving clinical pharmacists, and discharge outside pharmacists' working periods, creating materially different treatment contrasts within the same study[26]. A null estimate against an active medication-oriented comparator therefore cannot be interpreted in the same way as a null estimate against routine care with little overlapping intervention activity.

Comparator specification also interacted with implementation. The Spanish emergency-department study compared structured STOPP/START review and communicated recommendations with standard care, but centre-specific benefit was observed where recommendation acceptance was higher[29]. The long-term-care study documented that only part of the drug-related-problem pathway progressed from identification to forwarded recommendation, acceptance or clarification, and final resolution[30]. Accordingly, the nominal randomized or controlled assignment represents intervention opportunity; it does not guarantee that the medication regimen experienced by the patient was materially different.

Table 2 separates the comparator described in each controlled study from the incremental contrast that can defensibly be attributed to the experimental condition.

Table 2. Comparator content and the medication-optimization contrast actually tested

Study	Comparator as reported	Overlap or co-intervention relevant to interpretation	Incremental contrast actually tested
Ravn-Nielsen *et al.*, 2018	Usual care; separate basic-review arm	Basic arm already received pharmacist medication review	Added patient interaction and continuing cross-sector pharmacist involvement versus basic review/usual care
Kempen *et al.*, 2021	Usual hospital care	Existing multiprofessional hospital care; intervention arms differed by follow-up	Structured CMR, and separately CMR plus postdischarge follow-up
Johansen *et al.*, 2022	Standard care	Routine secondary/primary-care activities continued	Added five-step interdisciplinary pharmacist medication-safety programme
Grischott *et al.*, 2023	Usual discharge routines	Normal discharge communication remained available	Checklist-guided review plus deliberately enhanced information transfer
Nymoen *et al.*, 2022	Standard ED physician/nurse care	Routine medication management by treating clinicians	Added pharmacist reconciliation and systematic medication review during ED stay
Martínez *et al.*, 2024	Standard ED care	Same clinical service without integrated clinical pharmacist	Pharmacist participation in medication selection/evaluation plus discharge education
El Hajj *et al.*, 2023	Usual clinical-pharmacist discharge care and a no-pharmacist-hours control	One comparator already contained pharmacist care	Structured reconciliation/counselling plus repeated follow-up beyond routine pharmacist exposure
Gurwitz *et al.*, 2021	Mailed educational material	Medication-safety education present in control	Home pharmacist assessment, individualized interaction, primary-care communication and telephone follow-up
Ceschi *et al.*, 2021	Standard physician-acquired medication history	Medication history already performed	Added best possible medication history and pharmacist-led discrepancy reconciliation/adaptation

Santolaya-Perrín *et al*., 2019	Standard emergency care	Treating emergency and primary-care clinicians continued routine management	Added STOPP/START pharmacist review, case discussion and communicated modification recommendation
Lexow *et al*., 2022	Usual long-term-care practice	Existing physician, nursing and community-pharmacy care	Added one-time structured medication review with explicit drug-related-problem recommendations
Vasilevskis *et al*., 2023	Usual hospital and postacute care	Standard medication management throughout transition	Added comprehensive review, patient-approved deprescribing and continuation through postacute care
Ie *et al*., 2024	Usual care including medication reconciliation	Reconciliation already present	Added multidisciplinary STOPP/START optimization proposal and continuity information
Blum *et al*., 2021	Usual hospital care	Standard prescribing review remained available	Added structured doctor–pharmacist optimization supported by decision software

This comparator analysis changes the interpretation of both positive and null findings. A large observed effect where the experimental arm adds multiple activities to minimally overlapping routine care may reflect the package as a whole. A small or null effect where the control group already receives reconciliation, medication education or clinical-pharmacy input may reflect either genuine lack of additional benefit or a reduced incremental contrast. The included designs generally cannot separate those explanations quantitatively. Comparator fidelity must therefore accompany, rather than replace, conventional risk-of-bias assessment when interpreting pharmacist-led medication-optimization trials.

Outcome proximity and hard clinical outcome patterns

The included studies showed a recurrent separation between intervention activity, treatment modification, intermediate medication outcomes, and patient-important clinical events. This separation was most visible when trials achieved a measurable medication change but failed to alter hospitalization or other hard outcomes. Medication modification therefore cannot be assumed to function as a validated surrogate for downstream benefit. As contextual mechanism evidence at the proximal end of the pathway, D-PRESCRIBE demonstrated that a pharmacist-linked educational intervention could substantially increase discontinuation of targeted potentially inappropriate medications[35]. Shed-MEDS reduced medication burden and potentially inappropriate medication exposure during hospitalization and postacute care while also reporting similar adverse-event rates[31]. The Japanese medication-optimization trial produced sustained reductions in potentially inappropriate medication use[32]. OPERAM achieved implementation of pharmacotherapy recommendations in many intervention participants[33]. These studies demonstrated that prescribing behavior or medication exposure could be changed, but treatment modification alone was not sufficient evidence of a corresponding reduction in major healthcare utilization or mortality.

This proximal–distal discordance was also evident in trials focused on medication reconciliation. Admission reconciliation did not reduce 30-day returns to hospital despite directly targeting medication discrepancies[28]. Emergency-department medication review similarly failed to decrease subsequent unplanned hospital contact[24]. These results are compatible with several explanations: the medication problems corrected may not have been sufficiently consequential to determine later utilization; some recommendations may not have been implemented or sustained; subsequent clinical events may have arisen from non-medication causes; or active comparator care may already have addressed part of the medication-related risk. The trials do not permit those mechanisms to be ranked definitively.

Hard-outcome benefit was nevertheless observed in selected configurations. The extended OPTIMIST intervention reduced readmission and the composite of readmission or emergency attendance, whereas the basic medication-review arm did not show an equivalent pattern[20]. The Chilean emergency-department trial also reported fewer 30-day revisits after integration of a clinical pharmacist into medication selection, evaluation and

discharge education[25]. The post-acute-coronary-syndrome intervention produced a favorable cardiac-readmission signal under a structured reconciliation, counselling and follow-up model[26]. These positive studies differed in setting and design, but all represented more than the mere identification of medication problems.

Several equally intensive programmes remained null. MedBridge did not reduce its primary healthcare-use outcome despite comprehensive medication review and postdischarge follow-up[21]. IMMENSE did not reduce emergency visits, readmissions or mortality despite its multistep cross-setting design[22]. The Swiss discharge trial combining medication review and enhanced information transfer did not delay readmission.[23] Gurwitz and colleagues found no reduction in adverse drug-related incidents or clinically important medication errors after a home-based, multifaceted pharmacist intervention compared with mailed medication education[27]. Intervention complexity alone therefore did not discriminate effective from ineffective programmes.

Table 3 separates the outcome classes represented across the evidence and the inference that each class can support.

Table 3. Outcome proximity in pharmacist-led medication-optimization studies

Outcome-proximity level	Observable study event	Typical manifestations in the included evidence	What success at this level establishes	What it does not establish
P0 — Intervention process	Medication problem identified or recommendation generated/accepted	Discrepancy identification, recommendation generation, clinician acceptance, medication-review completion	The service reached and acted on a medication-management opportunity	That treatment changed or patient risk was reduced
P1 — Achieved treatment modification	Medication regimen actually altered	Drug initiation or discontinuation, dose/regimen change, deprescribing	A recommendation propagated into treatment	That the modification improved an intermediate or hard outcome
P2 — Intermediate medication or clinical state	Medication exposure or a proximal clinical measure changed	Lower medication burden, fewer potentially inappropriate medicines, fewer discrepancies	Medication use or an intermediate state changed in the intended direction	That hospitalization, harm or mortality was prevented
P3 — Patient-important hard outcome	Clinically consequential event altered	Medication-related harm, emergency or unscheduled healthcare use, hospitalization/readmission, mortality	The intervention was associated with a consequence directly important to patients or healthcare use	Which individual component produced the effect in a multicomponent intervention

The pattern across these levels was asymmetric. Positive findings were more common and mechanistically interpretable for P0–P2 endpoints, whereas P3 outcomes were more inconsistent. This should not be interpreted as a quantitative dose-response gradient because the studies differed in population, intervention composition, follow-up, comparator care and statistical power. It instead indicates that the evidentiary burden increases as the endpoint moves farther from the pharmacist's immediate action.

When the hypothesized route to a P3 outcome is medication modification, several steps must remain intact: a clinically meaningful problem must be identified; an appropriate change must be recommended; that change must be accepted and implemented; the altered regimen must persist long enough to affect risk; and the preventable event must remain medication-sensitive. Failure at any step can attenuate the observed clinical effect without showing that every preceding step was ineffective. Conversely, an observed reduction in readmission does not identify which component within a multicomponent programme produced the benefit.

Mechanism-sensitive integration and evidentiary limits

The evidence does not support ranking medication review, reconciliation, patient education, prescriber communication or follow-up as independently effective components for hard outcomes. Most included interventions were bundled, and the same component appeared in both positive and null studies. Component presence is therefore an insufficient discriminator.

Implementation evidence helps explain why. Recommendation generation is only one stage in the medication-optimization pathway. Acceptance and implementation can vary with clinical integration, communication and organizational context[34]. A service may consequently demonstrate substantial pharmacist activity while producing little difference in actual treatment exposure. Conversely, high recommendation acceptance remains an intermediate implementation outcome rather than proof of reduced medication-related harm.

The SENATOR trial provides an additional boundary condition. Computer-supported medication recommendations did not reduce adverse drug reactions when recommendation uptake and implementation were constrained[36]. Because the intervention was not specifically a pharmacist-led service, it is not part of the 14-study direct efficacy synthesis. Its relevance is methodological: identifying medication improvements does not alter clinical outcomes when recommendations fail to become effective treatment changes.

Evidence from medication-reconciliation implementation provides a parallel example. MARQUIS2 showed that a structured toolkit and mentored implementation could reduce medication discrepancies across participating hospitals[37]. Subsequent on-treatment analyses associated several system-level and patient-level reconciliation components with fewer discrepancies[38]. These findings help identify plausible active implementation processes, but component exposure was not independently randomized and the endpoint remained a proximal discrepancy measure. They cannot be converted into claims that those individual components prevent readmission or mortality.

Taken together, four variables provide the most defensible interpretation of the controlled evidence. First, component composition determines what opportunities exist for intervention. Second, comparator content determines the incremental medication-management contrast, while comparator fidelity indicates how reliably that content can be recovered from the report. Third, achieved treatment modification indicates whether the intervention propagated into the patient's regimen. Fourth, outcome proximity determines how many additional clinical steps must occur before an effect can appear in the measured endpoint.

These variables are related but not interchangeable. A multicomponent intervention may have high nominal intensity but low achieved modification. A trial may implement medication changes successfully while testing them against an active comparator, leaving little between-group contrast. A large contrast may still fail to change readmission when the corrected medication problems account for only a small fraction of subsequent events. The same nominal pharmacist intervention can therefore produce different observed effects without requiring the assumption that one trial is "correct" and another is "wrong."

Table 4 integrates these distinctions while retaining the central evidentiary limitation: most individual component effects remain non-identifiable.

Table 4. Mechanism-sensitive interpretation of observed pharmacist-intervention patterns

Evidence configuration	Component exposure	Comparator contrast	Achieved medication change	Observed endpoint pattern	Defensible interpretation	Component identifiability
Extended longitudinal package with patient interaction and cross-setting follow-up	High and multicomponent	Wider than basic review	Present but incompletely component-specific	Favorable hard-outcome signal	The package may improve outcomes under this service configuration	**Not identifiable individually**
Comprehensive review plus postdischarge follow-up	High	Context-dependent	Variable	Null hard-outcome pattern	Greater intervention intensity alone is insufficient	**Not identifiable individually**
Integrated emergency-department pharmacist service	Multicomponent and embedded in team	Relatively distinct from standard care	Treatment influence plausible	Favorable short-term revisit pattern	A high-contrast integrated service can alter utilization	**Bundle only**

Reconciliation against an existing medication-history process	Narrow/proximal	Modest because comparator already manages medication information	Discrepancy correction possible	Null hospital-return pattern	A proximal process improvement may not propagate to utilization	**No isolated hard-outcome component**
Deprescribing/appropriateness intervention	Targeted treatment modification	Variable	Clearly demonstrated	Improved medication exposure with null or similar hard outcomes	Treatment modification is achievable but not a validated surrogate for hard benefit	**Treatment-change effect identifiable; hard-outcome mechanism not**
Pharmacotherapy optimization with substantial recommendation implementation	Multicomponent	Moderate	Demonstrated	Null drug-related admission outcome	Implementation is necessary but may be insufficient when competing risks and endpoint distance are large	**Individual components not identifiable**
Recommendation or reconciliation implementation study	Process-focused	No conventional efficacy comparator	Acceptance/discrepancy improvement demonstrated	Proximal endpoint only	Useful for mechanism specification, not hard-outcome efficacy	**Associative only**

The synthesis therefore supports a conditional proposition rather than a universal effectiveness claim. Hard-outcome benefit becomes more plausible when an intervention creates a meaningful contrast over comparator care, produces implemented medication changes and acts on medication problems sufficiently consequential to influence the endpoint within the observation period. The available evidence does not establish that satisfying these conditions guarantees benefit.

A converse proposition is equally important. When an apparently intensive pharmacist intervention produces a null P3 result, the trial should be interrogated for comparator overlap, incomplete implementation, weak medication-event linkage and endpoint distance before concluding that its individual components are ineffective. These explanations remain competing hypotheses unless the study directly measures the intermediate pathway.

The four-variable relationship is summarized in **Figure 2**. It distinguishes observed intervention content, experimental contrast, achieved treatment modification and endpoint distance. It does not depict an unverified causal chain from pharmacist activity to clinical benefit.

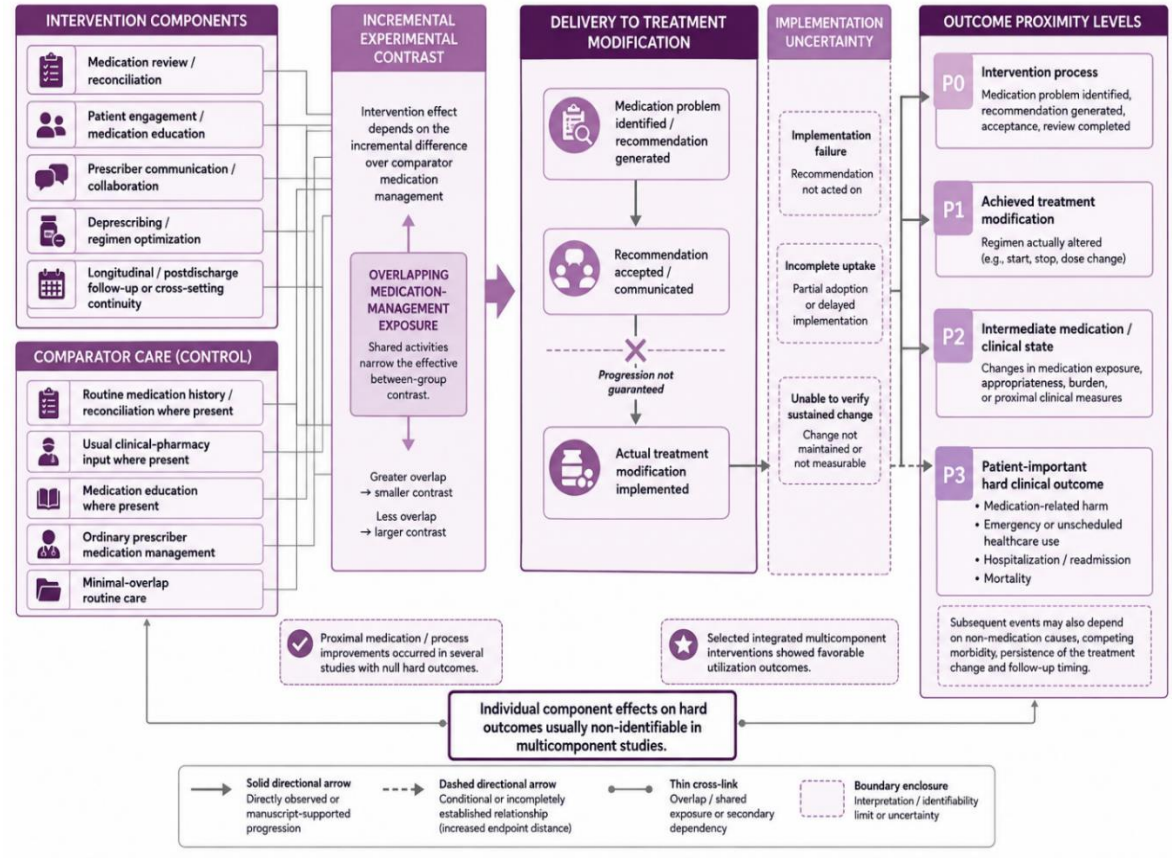

Figure 2. Conditions governing interpretation of pharmacist-led medication-optimization effects

Conclusion

Pharmacist-led medication optimization is not a single reproducible clinical exposure, and the available controlled evidence does not identify one universally effective component for preventing hospitalization, medication-related harm or death. Medication review, reconciliation, patient engagement, prescriber communication, deprescribing and follow-up appear in both positive and null programmes.

The most defensible answer to the review question is conditional. Interpretation improves when the content of the intervention is separated from the medication-management activity already present in comparator care, when implemented treatment modification is distinguished from recommendations or acceptance, and when the distance between medication change and the measured clinical endpoint is made explicit. Several trials demonstrate meaningful medication changes without corresponding improvement in hard outcomes, while selected integrated interventions demonstrate favorable utilization effects without revealing which individual component generated them.

Future controlled studies should therefore report comparator care with the same precision as the experimental intervention, measure whether recommendations become sustained medication changes, and connect proximal medication effects with prospectively defined patient-important endpoints. Dismantling, factorial or otherwise mechanism-identifying designs are required before individual pharmacist activities can be assigned causal responsibility for hard clinical outcomes.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Craske ME, Hardeman W, Steel N, Twigg MJ. Components of pharmacist-led medication reviews and their relationship to outcomes: A systematic review and narrative synthesis. BMJ Qual Saf. 2024;33(12):808-22. doi:10.1136/bmjqs-2024-017283
2. Craske M, Hardeman W, Steel N, Twigg MJ. Pharmacist-led medication reviews: A scoping review of systematic reviews. PLoS One. 2024;19(9). doi:10.1371/journal.pone.0309729
3. Vogt CJ, Moecker R, Jacke CO, Haefeli WE, Seidling HM. Exploring the heterogeneity in community pharmacist-led medication review studies - a systematic review. Res Social Adm Pharm. 2024;20(8):679-88. doi:10.1016/j.sapharm.2024.03.012
4. Bülow C, Clausen SS, Lundh A, Christensen M. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2023;1(1). doi:10.1002/14651858.CD008986.pub4
5. Carollo M, Crisafulli S, Vitturi G, Besco M, Hinek D, Sartorio A, et al. Clinical impact of medication review and deprescribing in older inpatients: A systematic review and meta-analysis. J Am Geriatr Soc. 2024;72(10):3219-38. doi:10.1111/jgs.19035
6. Foot H, Scott I, Sturman N, Whitty JA, Rixon K, Connelly L, et al. Impact of pharmacist and physician collaborations in primary care on reducing readmission to hospital: A systematic review and meta-analysis. Res Social Adm Pharm. 2022;18(6):2922-43. doi:10.1016/j.sapharm.2021.07.015
7. Harris M, Moore V, Barnes M, Persha H, Reed J, Zillich A. Effect of pharmacy-led interventions during care transitions on patient hospital readmission: A systematic review. J Am Pharm Assoc (2003). 2022;62(5):1477-98.e8. doi:10.1016/j.japh.2022.05.017
8. Al-Babtain B, Cheema E, Hadi MA. Impact of community-pharmacist-led medication review programmes on patient outcomes: A systematic review and meta-analysis of randomised controlled trials. Res Social Adm Pharm. 2022;18(4):2559-68. doi:10.1016/j.sapharm.2021.04.022
9. Yahya F, Nazar H, Huckerby C, Hadi MA. Facilitating the transfer of care from secondary to primary care: A scoping review to understand the role of pharmacists in general practice. Int J Clin Pharm. 2023;45(3):587-603. doi:10.1007/s11096-023-01547-3
10. Chambers D, Preston L, Clowes M, Cantrell AJ, Goyder EC. Pharmacist-led primary care interventions to promote medicines optimisation and reduce overprescribing: A systematic review of UK studies and initiatives. BMJ Open. 2024;14(8). doi:10.1136/bmjopen-2023-081934
11. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. Cochrane Database Syst Rev. 2018;8(8). doi:10.1002/14651858.CD010791.pub2
12. Daliri S, Boujarfi S, El Mokaddam A, Scholte Op Reimer WJM, Ter Riet G, den Haan C, et al. Medication-related interventions delivered both in hospital and following discharge: A systematic review and meta-analysis. BMJ Qual Saf. 2021;30(2):146-56. doi:10.1136/bmjqs-2020-010927
13. Prasad N, Lau ECY, Wojt I, Penm J, Dai Z, Tan ECK. Prevalence of and risk factors for drug-related readmissions in older adults: A systematic review and meta-analysis. Drugs Aging. 2024;41(1):1-11. doi:10.1007/s40266-023-01076-8
14. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt PMLA, Janssen MJA, Karapinar-Çarkit F. Prevalence and preventability of drug-related hospital readmissions: A systematic review. J Am Geriatr Soc. 2018;66(3):602-8. doi:10.1111/jgs.15244
15. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of medication-related harm in older adults after hospital discharge: A systematic review. J Am Geriatr Soc. 2018;66(9):1812-22. doi:10.1111/jgs.15419
16. Parekh N, Ali K, Davies JG, Stevenson JM, Banya W, Nyangoma S, et al. Medication-related harm in older adults following hospital discharge: Development and validation of a prediction tool. BMJ Qual Saf. 2020;29(2):142-53. doi:10.1136/bmjqs-2019-009587
17. Vonna A, Salahudeen MS, Peterson GM. Medication-related hospital admissions and emergency department visits in older people with diabetes: A systematic review. J Clin Med. 2024;13(2):530. doi:10.3390/jcm13020530
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372. doi:10.1136/bmj.n71

19. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. BMJ. 2020;368. doi:10.1136/bmj.l6890
20. Ravn-Nielsen LV, Duckert ML, Lund ML, Henriksen JP, Nielsen ML, Eriksen CS, et al. Effect of an in-hospital multifaceted clinical pharmacist intervention on the risk of readmission: A randomized clinical trial. JAMA Intern Med. 2018;178(3):375-82. doi:10.1001/jamainternmed.2017.8274
21. Kempen TGH, Bertilsson M, Hadziosmanovic N, Lindner KJ, Melhus H, Nielsen EI, et al. Effects of hospital-based comprehensive medication reviews including postdischarge follow-up on older patients' use of health care: A cluster randomized clinical trial. JAMA Netw Open. 2021;4(4). doi:10.1001/jamanetworkopen.2021.6303
22. Johansen JS, Halvorsen KH, Svendsen K, Havnes K, Robinson EG, Wetting HL, et al. Interdisciplinary collaboration across secondary and primary care to improve medication safety in the elderly (the IMMENSE study) - a randomized controlled trial. BMC Health Serv Res. 2022;22(1):1290. doi:10.1186/s12913-022-08648-1
23. Grischott T, Rachamin Y, Senn O, Hug P, Rosemann T, Neuner-Jehle S. Medication review and enhanced information transfer at discharge of older patients with polypharmacy: A cluster-randomized controlled trial in Swiss hospitals. J Gen Intern Med. 2023;38(3):610-8. doi:10.1007/s11606-022-07728-6
24. Nymoen LD, Flatebø TE, Moger TA, Øie E, Molden E, Viktil KK. Impact of systematic medication review in emergency department on patients' post-discharge outcomes-A randomized controlled clinical trial. PLoS One. 2022;17(9). doi:10.1371/journal.pone.0274907
25. Martínez MF, Herrada L, Gutiérrez-Cáceres C, Espinoza-Muñoz S, Palma D, Jirón M. Effect of a clinical pharmacist on 30-day revisits following discharge from an emergency department: A randomized controlled clinical trial. Emergencias. 2024;36(1):33-40. doi:10.55633/s3me/02.2023
26. El Hajj MS, Kaddoura R, Abu Yousef SEA, Orabi B, Awaisu A, AlYafei S, et al. Effectiveness of a structured pharmacist-delivered intervention for patients post-acute coronary syndromes on all-cause hospitalizations and cardiac-related hospital readmissions: A prospective quasi-experimental study. Int J Clin Pharm. 2023;45(3):630-40. doi:10.1007/s11096-023-01538-4
27. Gurwitz JH, Kapoor A, Garber L, Mazor KM, Wagner J, Cutrona SL, et al. Effect of a multifaceted clinical pharmacist intervention on medication safety after hospitalization in persons prescribed high-risk medications: A randomized clinical trial. JAMA Intern Med. 2021;181(5):610-8. doi:10.1001/jamainternmed.2020.9285
28. Ceschi A, Noseda R, Pironi M, Lazzeri N, Eberhardt-Gianella O, Imelli S, et al. Effect of medication reconciliation at hospital admission on 30-day returns to hospital: A randomized clinical trial. JAMA Netw Open. 2021;4(9). doi:10.1001/jamanetworkopen.2021.24672
29. Santolaya-Perrín R, Calderón-Hernanz B, Jiménez-Díaz G, Galán-Ramos N, Moreno-Carvajal MT, Rodríguez-Camacho JM, et al. The efficacy of a medication review programme conducted in an emergency department. Int J Clin Pharm. 2019;41(3):757-66. doi:10.1007/s11096-019-00836-0
30. Lexow M, Wernecke K, Sultzer R, Bertsche T, Schiek S. Determine the impact of a structured pharmacist-led medication review - a controlled intervention study to optimise medication safety for residents in long-term care facilities. BMC Geriatr. 2022;22(1):307. doi:10.1186/s12877-022-03025-3
31. Vasilevskis EE, Shah AS, Hollingsworth EK, Shotwell MS, Kripalani S, Mixon AS, et al. Deprescribing medications among older adults from end of hospitalization through postacute care: A Shed-MEDS randomized clinical trial. JAMA Intern Med. 2023;183(3):223-31. doi:10.1001/jamainternmed.2022.6545
32. Ie K, Hirose M, Sakai T, Motohashi I, Aihara M, Otsuki T, et al. Medication optimization protocol efficacy for geriatric inpatients: A randomized clinical trial. JAMA Netw Open. 2024;7(7). doi:10.1001/jamanetworkopen.2024.23544
33. Blum MR, Sallevelt BTGM, Spinewine A, O'Mahony D, Moutzouri E, Feller M, et al. Optimizing therapy to prevent avoidable hospital admissions in multimorbid older adults (OPERAM): Cluster randomised controlled trial. BMJ. 2021;374. doi:10.1136/bmj.n1585
34. Peled O, Vitzrabin Y, Beit Ner E, Lazaryan M, Berlin M, Barchel D, et al. Acceptance rate of clinical pharmacists' recommendations-an ongoing journey for integration. Front Pharmacol. 2023;14:1253990. doi:10.3389/fphar.2023.1253990

35. Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: The D-PRESCRIBE randomized clinical trial. JAMA. 2018;320(18):1889-98. doi:10.1001/jama.2018.16131
36. O'Mahony D, Gudmundsson A, Soiza RL, Petrovic M, Cruz-Jentoft AJ, Cherubini A, et al. Prevention of adverse drug reactions in hospitalized older patients with multi-morbidity and polypharmacy: The SENATOR randomized controlled clinical trial. Age Ageing. 2020;49(4):605-14. doi:10.1093/ageing/afaa072
37. Schnipper JL, Reyes Nieva H, Mallouk M, Mixon AS, Rennke S, Chu ES, et al. Effects of a refined evidence-based toolkit and mentored implementation on medication reconciliation at 18 hospitals: Results of the MARQUIS2 study. BMJ Qual Saf. 2022;31(4):278-86. doi:10.1136/bmjqs-2020-012709
38. Schnipper JL, Reyes Nieva H, Yoon C, Mallouk M, Mixon AS, Rennke S, et al. What works in medication reconciliation: An on-treatment and site analysis of the MARQUIS2 study. BMJ Qual Saf. 2023;32(8):457-69. doi:10.1136/bmjqs-2022-014806