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Pharmacist-Led Medication Reviews: A Review of Clinical Utility and Cost-Effectiveness

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Abbreviations

ADE	Adverse drug event
ADR	Adverse drug reaction
BMI	Body mass index
CI	Confidence Interval
COI	Conflict of interest
CPS	Clinical pharmacy services
DBP	Diastolic blood pressure
DRP	Drug-related problems
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
LDL	Low density lipoprotein
MA	Meta-analysis
MAI	Medication Appropriateness Index
MRF	Medication review with follow-up
NCOM	Negative clinical outcomes related to medicines
NRS	Non-randomized studies
PICO	Population, intervention, comparator, outcome
PIM	Potentially inappropriate medicines
RCT	Randomized controlled trial
RoB	Risk of bias
SBP	Systolic blood pressure
SD	Standard deviation
SR	Systematic review

Context and Policy Issues

Adverse drug events refer to medication errors, adverse drug reactions, allergic reactions, and overdoses[1]and represent an important burden on the Canadian population and healthcare system. In 2010-11, an estimated 1 in 1,000 non-seniors, and 1 in 200 seniors aged 65 years and older were hospitalized due to adverse drug events in Canada.[2] More broadly, it has been estimated that between 1 and 25% of all hospital and emergency department visits are associated with adverse drug reactions; approximately 25% of which are admitted to hospital.[2]

Pharmacist-led medication reviews aim to improve patient outcomes by preventing adverse drug events and decreasing healthcare utilization.[3-5] Definitions of pharmacist-led medication reviews vary across jurisdictions and organizations. They can include services such as medication assessments, care plans, and follow-up evaluations.[6]

There is a substantial body of evidence describing the clinical effectiveness of these interventions. This body of evidence is diverse and varied in the populations, interventions, comparators, outcomes, and settings it covers. In 2017, Jokanovic et al.,[3] published an overview of systematic reviews that aimed to describe the body of evidence on pharmacist-led medication reviews in community settings.

Jokanovic et al.[3] conducted a comprehensive literature search for studies published between 1995 and December 2015. The review included 31 systematic reviews consisting of a total of 297 primary studies. Eighteen outcomes were reported across the body of evidence, with medication management, blood pressure control, healthcare utilization, diabetes control, improved cholesterol targets, and mortality the most commonly reported

clinical outcomes; and quality of life and adherence the most commonly reported humanistic outcomes. In considering the body of SR evidence, the authors concluded that medication reviews improved various clinical outcomes among patients with various medical conditions.

The aim of this report is to summarize the evidence regarding the clinical utility and cost-effectiveness of pharmacist-led medication reviews in the community setting, published since the Jokanovic et al. overview, in order to inform decision making around reimbursement.

Research Questions

1. What is the clinical utility of pharmacist-led medication reviews?
2. What is the cost-effectiveness of pharmacist-led medication reviews versus no medication reviews?

Key Findings

Evidence from four moderate- to high-quality systematic reviews suggests that pharmacist-led medicine reviews are associated with improvements in HbA1c and blood pressure control. However, the results may not be generalizable to the broader population.

One economic evaluation was identified that suggested there was a net benefit to the Spanish national health system when pharmacists carried out medication review with follow-up among patients 65 years or older taking 5 or more medications. Differences in the healthcare delivery models and unit costs between Spain and Canada should be considered when generalizing results for the Canadian context.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, Medline via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pharmacies and medication reviews. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, economic studies, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and August 8, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People of all ages, in a community setting, who are taking multiple medications
Intervention	Q1,2: Pharmacist-led medication reviews
Comparator	Q1,2: No medication review
Outcomes	Q1: Clinical utility (e.g., hospital admissions, deprescribing of medication(s), medication adherence, health markers or outcomes [e.g., blood pressure, HbA1c, LDL/HDL, INR, use of inhalers], and safety [e.g., death, adverse drug reactions]) Q2: Cost-effectiveness (e.g., cost per health benefit gained, cost per preventable adverse drug reaction, cost per disability adjusted life year avoided)
Study Designs	Q1, 2: Health Technology Assessments, Systematic Reviews, Meta-Analyses, Economic Evaluations

HbA1c = glycated haemoglobin; HDL = high density lipoprotein; LDL = low density lipoprotein; INR = international normalized ratio.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2016.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised by one reviewer using Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR II)[7] and the economic study was assessed using the Drummond checklist.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 587 citations were identified in the literature search. Following screening of titles and abstracts, 478 citations were excluded and 109 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 110 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. These comprised four systematic reviews and one economic evaluation. Appendix 1 presents the PRISMA[9] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The four SRs were published in 2019[10], 2018[11] and 2016.[12,13] Together, they included literature published between the inception of key databases and May 2015,[11] July 2015,[12] December 2015,[13] and June 2017.[10] Two studies[11,12] included RCTs, one study[10] included

RCTs and high quality cohort studies, and one study[13] included RCTs and an interrupted time series.

The number of included studies in each SR that met the selection criteria (Table 1) ranged from five[13] to 111.[10] There was some overlap in included studies across SRs. Between 40 and 50% of studies included in the narrow scope reviews – narrow in terms of population characteristics[12,13] or intervention[10] -- were included in the broad scope Cochrane review.[11] Additional details on the extent of this overlap are found in Appendix 5.

One economic evaluation was included.[14] which was a cost analysis and cost-benefit analysis. The time horizon was 6 months and the study was conducted from the Spanish national health system perspective. The clinical data were obtained from a cluster randomized trial that informed the analysis and the cost inputs were obtained from various health services within Spain, the Spanish General Council of Colleges of Pharmacists, and through pharmacist-completed surveys.

Country of Origin

The SRs were published in China[10], the United Kingdom[11], Brazil[12] and Ireland.[13] The economic analysis was published in Spain.[14]

Patient Population

Two SRs included studies with patient populations of any age, with or without underlying medical conditions.[10,11], whereas the remaining two were limited to studies that included adults with type 2 diabetes[12] or community-dwelling adults who were 65 years and older.[13] The economic evaluation focused on patients who were 65 years and older taking 5 or more medications for at least 6 months.[14]

Interventions and Comparators

The scope of practice included across the SRs and economic evaluation varied, but all included interventions applied in community settings. One study described the intervention as medication review, education, adherence assessment, health/ lifestyle advice, physical assessment, monitoring, and prescribing, adjusting and administering therapy.[10] A second described the intervention as medication review with feedback to the patient's physician.[13] The final two were more broad: any service delivered by pharmacists other than drug compounding or dispensing;[11] and activities in which a pharmacist performed clinical decision-making in order to improve patient outcomes.[12]

The intervention designed to inform the economic analysis consisted of a patient interview, comprehensive medication review, identification of negative clinical outcomes related to medicines (NCOMs) and drug-related problems (DRPs), and the development of an action plan.[14]

The comparators were standard pharmacy care, usual care, or no intervention,[10] no comparable service for the health problem or population,[11] usual care,[12] and usual care or other active (non-pharmacist) intervention.[13] The comparator for the economic analysis was usual care.[14] Descriptions of usual care for each SR was not provided.

Outcomes

Three SRs reported on glycated hemoglobin (HbA1c) as an outcome: two as the mean difference [10,12] and one as the percent outside targeted HbA1c.[11] Assessment of blood HbA1c provides an indicator of overall blood sugar levels over a period of weeks/months.[15]

It is often used as an indicator of diabetes control; the objective being to lower HbA1c.[16] Two SRs reported on blood pressure as an outcome: one as the mean difference in SBP and DBP[10] and one as the percentage outside the target blood pressure range.[11] In addition to percentage outside target blood pressure and HbA1c, one study reported on hospital attendance/admission, ADEs, SF-36 physical functioning (set of quality of life measures)[17] and mortality.[11] One study only included change in prescribing appropriateness as an outcome.[13] Inclusion of studies with this outcome required the use of a validated screening tool for the detection of potentially inappropriate prescribing.[13]

For the economic analysis, the cost per emergency department visit was €58.55, cost per hospital admission was €216.93 and the range in cost per QALY used was $USD 18,247 to 34,097.[14]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic reviews

The four included SRs were generally well conducted and reported. Common strengths across all SRs were: clear definition of the PICO elements in the inclusion/exclusion criteria; comprehensive and well-documented literature searches; duplicate study selection and data extraction (one SR was unclear in this domain),[13] the characteristics of included studies were provided, and no conflicts of interest were declared. Reporting and following the PICO framework establishes a transparent structure to the SR and enables study authors to answer a precise research question. Thorough literature searches ensure that SRs identify as many relevant studies as possible, in order to minimize bias and produce reliable effect estimates.[18] Duplicate selection and extraction ensures that the body of evidence summarized in the SR aligns with the research question, and that the data abstracted for further synthesis are accurate. In order to assess the extent to which the included studies align with the research question and PICO criteria, a table describing the characteristics of the included studies is important. This table also enables interpretation of heterogeneity of results. Transparency in terms of conflicts of interest is important because there is evidence that financial conflicts have been associated with positive study outcomes for that company's product.[19]

In terms of limitations, no SR provided a rationale for the type(s) of studies included. All but one SR[10,12,13] omitted information about the funding source(s) of the included studies. Publication bias was not assessed in two SRs.[10,13]

Statistical heterogeneity was observed in each SR. Due to the variation in interventions among included studies, this is not unexpected. The extent of heterogeneity across included studies in one SR was such that MA were not conducted. Instead, the evidence for clinical effectiveness across the five included studies was described narratively.[13] The statistical heterogeneity and high risk of bias in several studies in another SR led to downgrading the certainty of evidence of some outcomes, and less confidence in the overall effects.[11] The statistical heterogeneity in a third SR was substantial (I^2 = 50 to 90%) across two outcomes (SBP and DPB) and considerable (I^2 = 75 to 100%) across the remaining outcome (HbA1c).[10] This level of inconsistency in results limits the generalizability of the findings. And finally, substantial heterogeneity was observed in the MA of the sole outcome included in the fourth SR.[12] When significant statistical

heterogeneity is observed due to clinical heterogeneity, as was the case in this body of evidence, this results in inaccurate summary effects.[20]

Economic evaluation

The included economic evaluation was generally well designed. Other than not explicitly providing a rationale for the alternative, all checklist domains were met. The data collection was less comprehensive. While the source for the effect estimates, design details for the effect estimates, methods of synthesis, methods to value benefits, and quantities of resource use reported, the primary outcome was not clearly stated and all the details around productivity change were not included. It is important to report the primary outcome of the economic evaluation in order to determine whether the study is designed appropriately to measure it. By omitting costs associated with productivity, the cost-benefit results miss an important contributor to the overall economy.[21] There were also no details about discount rate(s), which may have resulted in inaccurate extrapolation of future cost savings (the value of costs and benefits change, and often decrease, over time, so discounting is important).[22] Finally, the analysis and interpretation domains performed well: details of the statistical tests, approach to sensitivity analysis, ranges of inputs, incremental analysis, and the outcomes were presented appropriately.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical utility of pharmacy-led medication reviews

HbA1c

Among the general population

HbA1c in the general population was assessed by two SRs[10,11] with mixed results. Both found a positive clinical benefit through significant decrease in mean difference of HbA1c among patients receiving the intervention compared to usual care. In addition, one of these studies measured as the percentage outside normal HbA1c range, and found no significant difference between intervention and control groups.[11] The considerable heterogeneity observed in the MA for both these SRs limits generalizability of these findings.

Among people with type 2 diabetes

One SR examined the effect of pharmacist intervention on HbA1c among people with type 2 diabetes and found that the intervention was significantly associated with improved glycemic control compared to usual care.[12] However, the generalizability of these findings is also a challenge due to substantial statistical heterogeneity.

Blood pressure

Blood pressure outcomes were assessed by two SRs[10,11] with consistent findings of a beneficial effect of the intervention. The mean difference in SBP and DBP was significantly reduced among the intervention group compared to the control group in one study.[10] However, the substantial heterogeneity limits generalizability. Participants receiving the intervention were significantly less likely to have blood pressure outside the target range in a second SR.[11] Thirty-seven percent of the statistical heterogeneity could not be explained by chance, therefore the confidence around these results and their applicability beyond this study is higher than the results reported.

Change in prescribing appropriateness

Change in prescribing appropriateness was assed narratively among adults aged 65 years and older, via the Medication Appropriateness Index (MAI).[13] Three of five studies included in the SR found that the appropriateness of prescribing was improved among the intervention group compared to the control group. However, the authors of two of these three studies suggest that the clinical significance in the extend of the change observed via the MAI is unclear.

Hospital admission, adverse drug events, mortality, and SF-36

Hospital admission, ADEs, mortality, and SF-36 were assessed in one SR.[11] There was no significant difference in hospital admission, ADE or mortality between the intervention and control groups. Physical functioning was significantly improved in the intervention group compared to control.

Cost effectiveness of pharmacy-led medication reviews

The results of the economic analysis suggest there was a net benefit to the Spanish national health system when pharmacists carried out medication review with follow-up among patients 65 years and older taking five or more medications. Over 6 months, the health system would experience a savings of 97€ per patient. Extrapolated over a one-year period and including a 22€ per patient-month fee-for-service, authors concluded that the (Spanish) health system would see a savings of 326€ per patient-year. The authors reported a net benefit of 3.3 to 6.2€ for every 1€ invested in medication review with follow-up (MRF). The willingness-to-pay per QALY ranged from $USD 18,247 to $34,097.

Limitations

By nature, the body of evidence for the clinical utility of pharmacist-led medication reviews is difficult to assess because it is highly varied. The intervention consists of a range of pharmacist-led clinical activities. Even among high quality SRs in the community setting, of which this report identified three,[11-13] the clinical heterogeneity (i.e. variability in participants [people of all ages vs. older adults with diabetes], variability in interventions [any service delivered by a pharmacist vs. a specific set of pharmacist-led interventions]) and statistical heterogeneity (level of variability across point estimates of studies included in a meta-analysis)[20] resulted in a lack of generalizability of study results and uncertainty in effect estimates around the majority of outcomes. Further, the variation in interventions among SRs (e.g. any services delivered by pharmacists other than drug compounding or dispensing[11], medication review with feedback to patient's physician[13]) makes it difficult to associate observed benefits with specific interventions.

Among the four SRs included in this report, two included participants from the general population (*i.e.,* people of any age, regardless of underlying medical condition).[10,11] The remaining two had limits on age (65 years and older)[13] or clinical history (patients with type 2 diabetes).[12] This decreased the amount of evidence available upon which to draw conclusions about clinical utility in the general population, which makes broad coverage decisions difficult.

There were gaps in the evidence. No Canadian economic analyses were identified. One Spanish economic analysis was included, which summarized the cost-benefit of a medication review with follow-up from the Spanish national health system perspective.[14]

Differences in the healthcare delivery models and unit costs between Spain and Canada should be considered when generalizing results for the Canadian context.

Conclusions and Implications for Decision or Policy Making

Four SRs[10-13] were identified addressing the clinical utility of pharmacy-led medication reviews. One economic analysis[14] was identified. No evidence on the cost utility or cost effectiveness specific to Indigenous Peoples was identified.

This review found that pharmacist-led medication reviews consistently had a positive effect on mean HbA1c [10-12] and blood pressure.[10,11] These findings are consistent with previous studies.[3] However, the extent of clinical and statistical heterogeneity among included studies limits the generalizability of these findings. This limitation was also observed in Jokanovic et al.[3] – the meta-analyses of HbA1c and blood pressure outcomes revealed moderate to high statistical heterogeneity due to differences in study design, intervention, and outcomes.

This review builds on an overview of SRs[3] which concluded that the body of moderate and high quality SR evidence (n = 31 SRs) suggested that pharmacist-led medication reviews were clinically effective across a range of outcomes.

Further SRs should be completed with focused objectives, particularly around reducing clinical heterogeneity of the intervention when designing the study protocol. This may help to reduce uncertainty around which aspects of pharmacist-led medication reviews are associated with positive clinical outcomes. Additionally, research including participants at risk of health inequities may also be warranted. Canadian cost-effectiveness studies with a focus on community-level interventions would be helpful in order to inform decisions in the Canadian context.

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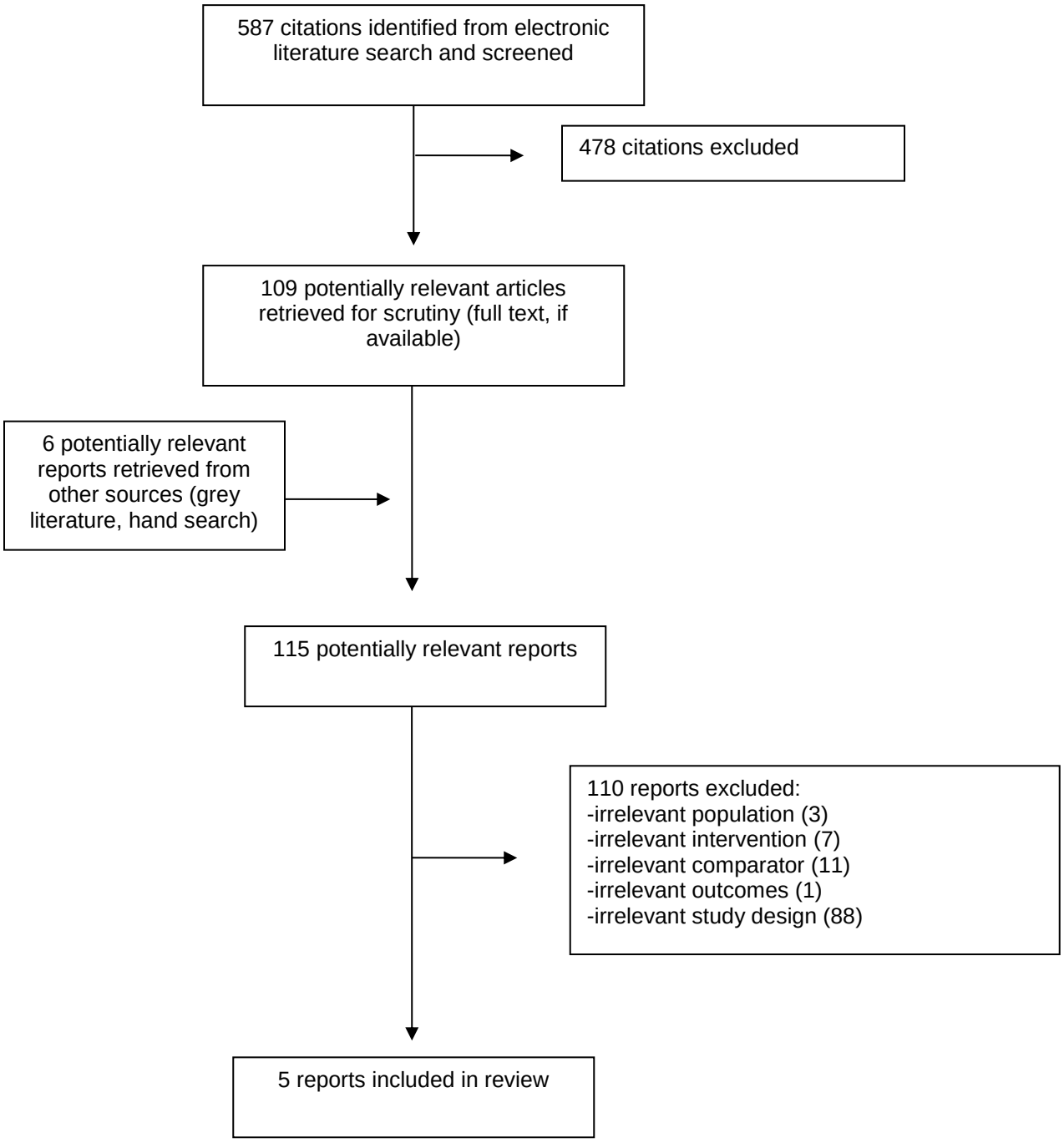
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2. Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Yuan, 2019, China	52 included studies (RCT and high quality cohort) Of these, 22 studies were included in the meta-analysis.	Patients of any age, with or without underlying medical conditions	**Intervention** **"**Community Pharmacy Services (CPS) … consisted of medication review, education, adherence assessment, health/lifestyle advice, physical assessment, monitoring, and prescribing, adjusting and administering therapy" (*pe568*). **Comparator** Standard pharmacy care, usual care or no intervention	Meta-analysis: mean difference in SBP, DBP and HbA1c
De Barra, 2018, United Kingdom	This Cochrane review included 116 RCTs. Of these, 111 compared the intervention to usual care. 73/111 trials had useable data for meta-analysis. Meta-analyses were performed on 15 outcomes across these 73 trials.	Patients receiving services from outpatient pharmacists. This included patients recruited in hospital or at discharge, but who received intervention in the community.	**Intervention** “Any services delivered by pharmacists other than drug compounding or dispensing.” (*p10*) Interventions were included “if they sought to improve patient health through the use of cessation of medications, …multidisciplinary interventions if multidisciplinary team was led by a pharmacist or most (<50%) of the intervention was delivered by pharmacists.” (*p10*) Interventions covered by other Cochrane/other SRs, health promotion interventions, and interventions aimed at medication adherence and automated care programs were excluded. **Comparator** No comparable service for the health problem or population	**Primary** Percentage outside target blood pressure range, percentage outside targeted glycated haemoglobin range, hospital attendance/admission, adverse drug effects, SF-36 physical functioning, mortality **Secondary** Other effects for HbA1c, continuous measures of blood pressure, lipids, respiratory function Average duration of intervention: 7.4 months (SD: 5.6).

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			Services delivered by other health professionals (other than pharmacists) for the health problem or population	
Aguiar, 2016, Brazil	30 RCTs (22 included in the meta-analysis; 7 of these were conducted in community settings)	Adults with type 2 diabetes	**Intervention** "Pharmacist interventions in clinical pharmacy services, defined as the activities in which the pharmacist performs a clinical decision-making process aimed at improving the patients' health outcomes" (*p3*). Specific components of the intervention ranged by study **Comparator** Usual care. Definitions varied among included studies, but generally referred to the care normally received from a general practitioner or other healthcare professional. Some studies' control groups included individuals who received access to educational programs or a free blood glucose monitor.	**Primary** Mean difference in HbA1c
Riordan, 2016, Ireland	5 included studies (four RCTs and one interrupted time series)	Community dwelling adults >= 65 years	**Intervention** Medication review with feedback to patient's physician (n=4 studies) and use of a computerized tool that "alerted pharmacists at the point of dispensing when older patients were newly prescribed PIMs" (*p3*) **Comparator** Usual care or other active interventions	**Primary** Change in prescribing appropriateness **Secondary** Any clinical or patient self-reported outcome

DBP = diastolic blood pressure; HbA1c = glycated hemoglobin; PIM = potentially inappropriate medicines; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation

Table 3. Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Malet-Larea, 2017, Spain	Type: Cost analysis and cost-benefit analysis Horizon: 6 months Perspective: national health system	To determine the economic impact of MRF on aged polypharmacy patients in community pharmacies compared to usual care	Patients ≥65 years taking 5 or more medications for at least 6 months. 1,474 patients enrolled in the study	**Intervention** MRF: Pharmacist conducts a patient interview to collect relevant information; performs comprehensive medication review; identifies NCOMs and DRPs; action plan developed if required. **Comparator** Usual care: dispensing medicines prescribed by physicians and minor ailments advice	Trial-based analysis Cluster randomized controlled trial in 178 pharmacies across 4 Spanish provinces.	**Clinical data** Number of ED visits, hospital admissions, QALY **Cost data** Medication costs, emergency department visits costs and hospital admission costs, costs of pharmacists' time, pharmacist training, investment of the pharmacy, and cost of the practice change facilitator	"A community pharmacy in Spain serves a mean of 2,500 patients; 16% of the population are aged patients using polypharmacy; 60% of these patients would accept the provision of service" (p. 1,072)

DRP = drug-related problems; MRF = medication review with follow-up; NCOM = negative clinical outcomes related to medicines.

Appendix 3: Critical Appraisal of Included Publications

Table 4. Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[7]

Strengths	Limitations
Yuan, 2019[10]	
• Inclusion/exclusion criteria included PICO components • Appropriate literature search • Rationale for inclusion of RCTs and cohort studies included • Duplicate selection • Duplicate data extraction • Cochrane RoB conducted • Applied appropriate statistical methods for MA • RoB results were considered in MA results • No COI declared	• No mention of a study protocol or guide • List of excluded studies not provided • Characteristics of included studies provided, but key information was missing (e.g., study design [RCT vs. cohort], number of study participants in each study) • Funding source of included studies not reported • Substantial heterogeneity across studies assessing SBP and DBP; considerable heterogeneity across studies assessing HbA1c. The impact of this heterogeneity on results was not interpreted by the authors. • Publication bias not assessed
De Barra, 2018[11]	
• Inclusion/exclusion criteria included PICO components • Appropriate literature search • Duplicate selection • Duplicate data extraction • List of excluded studies provided, including reasons for exclusion • Characteristics of included studies provided • Cochrane RoB conducted and results included • Funding source of included studies was provided • Applied appropriate statistical methods for MA • RoB results were considered in MA results • Evidence of publication bias was suggested for one outcome (percent outside blood pressure range) instances • No COI declared	• No justification provided for restriction to RCTs
Aguiar, 2016[12]	
• Inclusion/exclusion criteria included PICO components • Protocol registered on PROSPERO; a plan for assessing heterogeneity and for conducting MA was described • Appropriate literature search • Duplicate selection • Duplicate data extraction • List of excluded studies provided, including reasons for exclusion • Characteristics of included studies provided	• No justification provided for restriction to RCTs • Funding sources of included studies not reported • Heterogeneity across studies was significant and considerable; subgroup and meta-regression was conducted to explore this heterogeneity in more depth

Strengths	Limitations
• Cochrane RoB summary for included studies provided • Applied appropriate statistical methods for MA • RoB results were considered in MA results: conducted sensitivity analysis to explore the effect of high RoB studies on the results • No evidence of publication bias • No COI declared	
Riordan, 2016[13]	
• Inclusion/exclusion criteria included PICO components • Appropriate literature search • Duplicate selection • List of excluded studies provided, including reasons for exclusion • Characteristics of included studies provided • Cochrane RoB results provided and considered in narrative review results • No COI declared	• No mention of a study protocol or guide • No explanation for the selection of study designs • Duplicate data extraction unclear • Funding sources of included studies not reported • Publication bias not assessed • Due to the extent of the heterogeneity across included studies, an MA was not conducted

COI = conflict of interest; DBP = diastolic blood pressure; HbA1c = glycated haemoglobin; MA = meta-analysisPICO = population, intervention, comparator, outcome; RoB = risk of bias; SBP = systolic blood pressure

Table 5. Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

Strengths	Limitations
Malet-Larea, 2017[14]	
• Research question and the economic importance of the question were clearly stated • Viewpoint of the analysis was stated and justified • Alternative was clearly described • The type of economic analysis was stated • Source of effect estimates was stated • Design and results of the effect were provided • Methods for effect synthesis were provided • Methods to value benefits were stated • Quantities of resource use were reported separately from unit cost • Estimation methods for unit cost provided • Currency and price data provided • Time horizon of cost/benefits reported • Details of statistical tests were given • Approach to sensitivity analysis described, and variables provided • Ranges of inputs were justified • Incremental analysis was reported • Outcomes were disaggregated • An answer to the research question was given • Conclusions followed from the data • Conclusions included caveats	• Rationale for choosing the alternative for comparison was not provided • Justification for the type of economic evaluation conducted to answer the research question not provided • The primary outcome for the economic evaluation was not stated • Details of subjects of valuations not obtained • Productivity change not reported; nor was the relevance of productivity change discussed • No details on currency or price adjustment due to inflation • Discount rates, choice of discount rates, and explanation of costs/benefits not being discounted were not provided • Alternatives were not compared

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6. Summary of Findings for Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Yuan, 2019[10]	
The authors conducted meta-analyses of a subset of included studies reporting SBP, DBP and HbA1c: **SBP** (8 studies) MD: -5.28 (95% CI: -8.20 to -2.36), I^2=61%, p=0.012 **DBP** (7 studies) MD: -2.15 (95% CI: -3.65 to -0.64), I^2=55%, p=0.037 **HbA1c** (6 studies) MD: -0.56 (95% CI: -0.90 to -0.22), I^2=79%, p=0.000 Additional primary outcomes were reported in other studies, but the results were not pooled. Full study-level summaries of these outcomes are available in the paper's *Table 1. Characteristics of Included studies.* However, completeness of reporting in this table was poor: the statistical significance of study findings were reported in few studies. Those in which interpretation was possible are summarized here: • Two studies found a positive effect of CPS on medical adherence; • One study found a positive effect of CPS on mean asthma control; • One study found a positive effect of CPS on ADR; • One study found a positive effect of CPS on decreasing hospitalization rates.	"The review suggested that CPS has significantly positive effect in improving SBP, DBP and HbA1c." (*pe581*) "In most included studies, CPS had a positive effect on the primary clinical outcomes, such as HbA1c, triglycerides, BP, cholesterol, HDL, LDL, blood glucose, weight, BMI, peak expiratory rate and rates of ADRs (47/52 [included studies])" (*pe581*) "Positive effects were more often seen in the management of chronic conditions..." (*pe581*)
de Barra, 2018[11]	
Primary outcomes **Percentage outside blood pressure range** (18 RCTs) Patients in the intervention group were less likely to have blood pressure outside the target range (OR 0.40, 95% CI: 0.29 to 0.55, I^2=81%, P<0.00001). **Percentage outside HbA1c range** (5 RCTs) No significant difference between the intervention and control groups (OR 0.29, 95% CI 0.04 to 2.22, I^2=92%, P <00001) **Hospital attendance/admission** (14 RCTs) No significant difference between the intervention and control groups (OR 0.85, 95% CI: 0.65 to 1.11, I^2=44%, P =0.04) **ADE** (3 RCTs) No significant difference between the intervention and control groups (OR 1.65, 95% CI 0.84 to 3.24, I^2=52%, P =0.12)	"Compared with usual care, we are uncertain whether pharmacist services improved the percentage of patients outside the glycolated haemoglobin target range (very low-certainty evidence). Pharmacist services may make little or no difference to hospital attendance Pharmacist services for non-hospitalised patients or readmission (moderate-certainty evidence) or to adverse drug effects (low-certainty evidence). Pharmacist services may, however, reduce the percentage of patients whose blood pressure is outside the target range (low-certainty evidence) and may also slightly improve physical functioning (low-certainty evidence)." (*p16*) "As expected, we detected substantial heterogeneity in most of the meta-analyses undertaken, possibly due to variation in interventions tested and definitions used. Using GRADE, we downgraded all outcomes to moderate certainty due to high risks of bias, with some outcomes being further downgraded due to high levels of heterogeneity." (*p16*)

Main Study Findings	Authors' Conclusion
SF-36 physical functioning (7 RCTs) Patients in the intervention group had significantly improved physical functioning compared to the control group (MD: 5.84, 95% CI: 1.21 to 10.48, I^2=84%, *P* <00001) **Mortality** (9 trials) No significant difference between the intervention and control groups (OR 0.79, 95% CI: 0.56 to 1.12, I^2=13%, *P* =0.33) **Secondary outcomes** **Other effects for HbA1c** (15 RCTs) Mean HbA1c was lower among the intervention group compared to the control group (MD: -0.77, 95% CI: -0.97 to -0.58, I^2=77%, *P* <0.00001) **Continuous measures of blood pressure** (31 RCTs for DBP and 32 RCTs for SPB) DBP and SBP was reduced among intervention group compared to control (MD DBP: -3.50, 95% CI: -5.44 to -1.56, I^2=94%, *P* <0.00001, MD SBP: -5.96, 95% CI: -7.35 to -4.57, I^2=74%, *P* <0.00001) **Lipids** (7 RCTs) Patients in the intervention group had lower total cholesterol compared to patients in the control group (MD: -0.35, 95% CI: -0.56 to -0.13, I^2=77%, *P* =0.00017). No significant difference in LDL cholesterol between intervention and control groups (MD: -0.14, 95% CI: -0.30 to 0.02, I^2=56%, *P* =0.087) **Respiratory function** (3 RCTs for FEV1, 2 RCTs for peak flow, and 2 RCTs for dyspnoea) No significant difference in FEV1 (MD: 0.11, 95% CI: -0.01 to 0.23, I^2=0%, *P* =0.81), peak flow (MD: 3.36, 95% CI: -0.36 to 7.09, I^2=0%, *P* =0.54) or dyspnoea (OR 0.90, 95% CI: 0.68 to 1.20, I^2=0%, *P* =0.49) between the intervention and control groups.	"The pharmacist services were poorly described and thus limit the ability to replicate these interventions for future trials or for service delivery." (*p16*)
Aguiar, 2016{Aguiar 2016	
Pharmacist intervention was associated with improved glycemic control: **HbA1c** (7 RCTs) MD: -0.65 (95% CI: -0.88 to -0.41), I^2 36%, *P* =0.153	"…pharmacist interventions have positive effects on reducing HbA1c levels in outpatients with type 2 diabetic(sic)" (*p17*) "The included RCTs in this review presented high methodological and clinical heterogeneity, which produced substantial statistical heterogeneity in the effect estimate for HbA1c levels." (*p17*)
Riordan, 2016[13]	
A meta-analysis was not completed due to heterogeneity in interventions and outcomes.	"Three of the five studies reported an improvement in the MAI score in the intervention group compared to the control group." (p. 7), "…however, the effect sizes are small which highlights the need for further research to assess the impact of pharmacist-led interventions in primary care." (*p9*)

Main Study Findings	Authors' Conclusion
One study found a positive effect of community pharmacists undertaking clinical medication reviews on MAI scores (-2.0 versus -3.0, *P* <0.001).[23] The study also found a positive effect of the intervention on the change in number of medicines used (less in the intervention group) and dose reductions, as well as statistical improvements in SF-36 emotional role and social functioning among the control group. A second study found significant improvement in MAI score in the intervention group (sustained clinical pharmacist interventions for elderly outpatients with polypharmacy) compared to the control (-4.9 compared to -0.9, *P* <0.0001).[24] There was no significant difference between intervention and control for SF-36, medication compliance, medication knowledge, general healthcare satisfaction, or pharmacy-related healthcare satisfaction. A beneficial effect of the intervention on MAI was observed, but the authors note that the clinical significance of this change is unknown. A third study found no difference in appropriateness of prescribing among older patients in the intervention group (pharmaceutical care shared between community pharmacists and general practitioners) compared to the control group.[25] A fourth study found a positive effect of the intervention (medication review and educational meeting with physicians) on MAI.[26] However, no significant association between intervention and SF-36, but significant improvements in hospitalization and ED visits, blood pressure control, HbA1c control, LDL and INR, medication compliance and medication knowledge. A beneficial effect of the intervention on MAI was observed, but the authors note that the clinical significance of this change is unknown. And a fifth study found significant reductions in PIP among intervention (computerized tool that flagged potentially inappropriate medicines among patients ≥65 years) compared to control, and significant difference in dispensing rates of amitriptyline and diazepam.[27]	"…the methodological quality of the studies was poor overall, limiting the generalisability…" (*p9*)

ADR = adverse drug reactions; BMI = body mass index; CI = confidence interval; CPS = clinical pharmacy services; DBP = diastolic blood pressure; ED = emergency department; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; I^2 = heterogeneity; INR = international normalized ratio; LDL = low density lipoprotein; MAI = medication appropriateness index; MD = mean difference; PIP = potentially inappropriate prescribing; SBP = systolic blood pressure.

Table 7. Summary of Findings for Included Economic Evaluations.

Main Study Findings	Authors' Conclusion
Malet-Larea, 2017[14]	
The cost-benefit analysis suggests a net benefit for the intervention (benefit-cost ratio [B:C] between 3.33:1 and 6.22:1). The cost analysis suggested that by implementing MRF, the Spanish national health system would save 97€ per patient in 6 months. Cost savings were observed with inclusion of a 22€ per patient-month fee-for-service: extrapolated over a one-year period, the health system would see a savings of 326€ per patient-year. The willingness-to-pay per QALY ranged from $USD 18,247 to $34,097.	"The results of the present study show that MRF delivered in a community pharmacy setting targeted to aged polypharmacy patients has positive net benefits (between 420 € and 700 € per patient) and it saved 97 € per patient in 6 months. For every 1 € invested in MRF, the service returned a benefit from 3.3 € to 6.2 €." (*p6*)

MRF = medication review with follow-up; QALY = quality adjusted life year

Appendix 5: Overlap between Included Systematic Reviews

Table 8. Primary Study Overlap between Included Systematic Reviews.

Primary Study Citation	Systematic Review Citation			
	Yuan, 2019[10]	de Barra, 2018[11]	Aguiar, 2016[12]	Riordan, 2016[13]
Adibe 2013		X		
Adler 2004		X		
Albsoul-Younes 2011		X		
Ali 2012	X	X	X	
Amarilles 2012		X		
Andres 2007		X		
Armour 2007		X		
Barbanel 2003		X		
Bernsten 2001		X		
Blalock 2010		X		
Bogden 1998		X		
Bond 2000		X		
Bonnie	X			
Borenstein 2003a		X		
Borges	X			
Bosnic-Anticevich 2010		X		
Boyd 2013		X		
Brook 2003		X		
Bruhn 2013		X		
Bryant 2011		X		X
Capoccia 2004		X		
Cani 2015			X	
Carter 2008		X		
Castejon	X	X		

Primary Study Citation	Systematic Review Citation			
	Yuan, 2019[10]	de Barra, 2018[11]	Aguiar, 2016[12]	Riordan, 2016[13]
Chamoro 2011	X			
Chan 2012			X	
Charrois 2006		X		
Chisholm 2002		X		
Choe 2005		X	X	
Chrischilles 2014		X		
Chung 2014			X	
Clifford 2005		X	X	
Cody 1998		X		
Cohen 2011			X	
Cordina 2001		X		
De Castro 2006		X		
Di Donato 2014		X		
Doucete 2009		X	X	
Edwards 2014		X		
Farsaei 2011		X		
Faulkner 2000		X	X	
Fikri-Benbrahim 2012				X
Finley 2003		X	X	
Fornos 2006			X	
Garcao 2002		X	X	
Garcia-Cardenas 2013		X		
Gattis 1999		X		
Gonzalez-Martin 2003		X		
Goodyear 1995		X		
Green 2008		X		
Guirguis 2001			X	
Hammad 2011		X		

Primary Study Citation	Systematic Review Citation			
	Yuan, 2019[10]	de Barra, 2018[11]	Aguiar, 2016[12]	Riordan, 2016[13]
Hanlon 2009	X		X	
Hawes 2013		X		
Hawkins 1979		X		
Hay 2006		X		
Hendrie 2014		X		
Hirsch 2014		X		
Ho 2013		X		
Holland 2005		X		
Hunt 2008		X		
Jaber 1996	X	X		
Jackson 2004		X		
Jahangard-Rafsanjani 2015		X	X	
Jamenson 2010			X	
Jarab 2012	X	X		
Khdour 2009		X		
Krass 2007		X		X
Kritikos 2007		X		
Krska 2001		X		
Lai 2013		X		
Lee 2006		X		
Lee 2015				X
Lenaghan 2007		X		
Lenander 2014		X		
Li 2014		X		
Lopez 2006		X		
Losada-Camacho 2014		X		
Magrid 2013		X		

Primary Study Citation	Systematic Review Citation			
	Yuan, 2019[10]	de Barra, 2018[11]	Aguiar, 2016[12]	Riordan, 2016[13]
Mahwi 2013		X		
Malone 2001		X		
Marques 2013		X		
Marra 2012		X		
Mazroui 2009		X		
McAlister 2014		X		
Mehos 2000		X		
Mehuys 2011		X	X	
Milos 2013		X		
Mourao 2012	X			
Murray 2007		X		
Naunton 2003		X		
Obreli-Neto 2015		X		
Okamoto 2001		X		
Olesen 2014		X		
Park 1996		X		
Paulos 2005		X		
Peterson 2004		X		
Planas			X	
Raebel 2007	X			
Reid 2005		X		
Richmond 2010			X	
Rickles 2005		X		
Rothman 2005		X	X	
Rubio-Valera 2012		X		
Sadik 2005		X		
Salazar-Ospina		X		
Samtia 2013		X		

Primary Study Citation	Systematic Review Citation			
	Yuan, 2019[10]	de Barra, 2018[11]	Aguiar, 2016[12]	Riordan, 2016[13]
Sarkadi 2004		X		
Schneider 1982		X		
Schneiderhan 2014		X		
Sellors 2003		X		
Shen 2016				X
Sidel 1990		X		
Silveira 2014		X		
Simpson 2011		X		
Solomon 1998		X		
Sookaneknun 2004		X		
Stewart 2014		X		
Suppapitiporn 2005		X		
Tang 2014		X		
Tannenbaum 2014		X		
Taveira 2011		X		
Taveira 2014		X		
Taylor 2003		X		
Tommelein 2013		X		
Tsuyuki 2002		X		
Tsuyuki 2015		X		
Verret 2012		X		
Vivian 2002		X		
Volume 2001		X		
Wal 2013		X		
Weinberger 2002		X		
Wu 2006		X		
Zermansky 2001		X		