Chapter title: Economic evidence for pharmacist-led medicines use review and medicines reconciliation

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Abstract

Pharmacist-led medicines use review (MUR) and medicines reconciliation (MedRec) aim to identify, resolve and prevent patient-related drug-related problems (DRP) and medication discrepancies in order to optimize medicines use and ensure the patient safety. As "diagnostic-resolution" interventions, the question of their economic impact and cost-effectiveness from healthcare systems perspective is crucial, and the level of their related evidence could support or challenge the dissemination and sustainability of these interventions in health systems. This chapter addresses two main questions: how is the economic impact and cost-effectiveness of these interventions modelling in the literature? And what is the economic evidence for these interventions? This content derives from the identification and selection of full economic evaluations of MUR and MedRec and systematic reviews or meta-analyses for which the main outcome was to assess their economic impact. Despite the demonstration of their effectiveness in identifying and resolving safety issues (patient-related DRP and medication discrepancies), studies have struggled to demonstrate their clinical and economic impact, probably due to the poor quality and heterogeneity of the studies, as well as the debatable accuracy of the outcomes. Future research and high-quality studies are needed to address these issues.

Keywords: medicines use review, medicines reconciliation, drug-related problems, medication discrepancies, cost-effectiveness, evidence

Introduction

Medicines use may imply potential medication errors and drug-related problems (DRP) which represent a global burden for the society. For instance, the global cost associated to medication errors was estimated to $42 billion annually or almost 1% of total global health expenditure [1]. Medication errors

are defined as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.” [2]

In order to optimize patient safety and medicines use in community and in hospital settings, the pharmacist plays a key role to identify, resolve, manage and prevent medication errors and patient-related DRP – defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” [3] -, as the medicine expert within the healthcare team. In this context, several structured approaches and interventions, as medicines use review (MUR) or medicines reconciliation (MedRec) at transition care points, are diffused and implemented worldwide with national-level specificities (e.g. dissemination, setting, remuneration, components, target population), but with a common goal: to optimise medicines use according to updated clinical and patient information, and to improve health outcomes (section 1).

MUR and MedRec are a combination of “diagnostic” and “resolution” interventions meaning that not every patient who receives them will have a DRP or patient-related medication discrepancy; and those identified can be clinically and/or economically inconsequential [4]. In economic terms, it is therefore expected that the additional cost of delivering one of these interventions (section 2) will either be covered by the costs avoided as a result of the detection and resolution of patient-related DRPs or medication discrepancies, or lost if there are no avoided costs. This chapter deals with the cost-effectiveness of pharmacist-led MUR and MedRec interventions from healthcare systems perspective, and is articulated around two main questions: how is the economic impact and cost-effectiveness of these interventions modelling (section 3)? What is the economic evidence for these interventions (section 4)? Several study designs can answer these questions from different perspectives. MUR and MedRec can be shown as cost-effective : i) if in a controlled study (ex: randomised controlled trial, RCT) the interventions costs are offset by the savings associated to intermediate (effectiveness, safety and humanistic) outcomes and avoided healthcare use, and the total healthcare costs in the intervention group are lower compared to the control group receiving usual care, ii) if a cost-effectiveness analysis shows an acceptable incremental cost-effectiveness ratio (ICER, i.e. the difference in cost between the intervention and control group divided by the difference in their effect, representing the incremental cost associated with one additional unit of the measure of effect) - according to the country-related threshold.

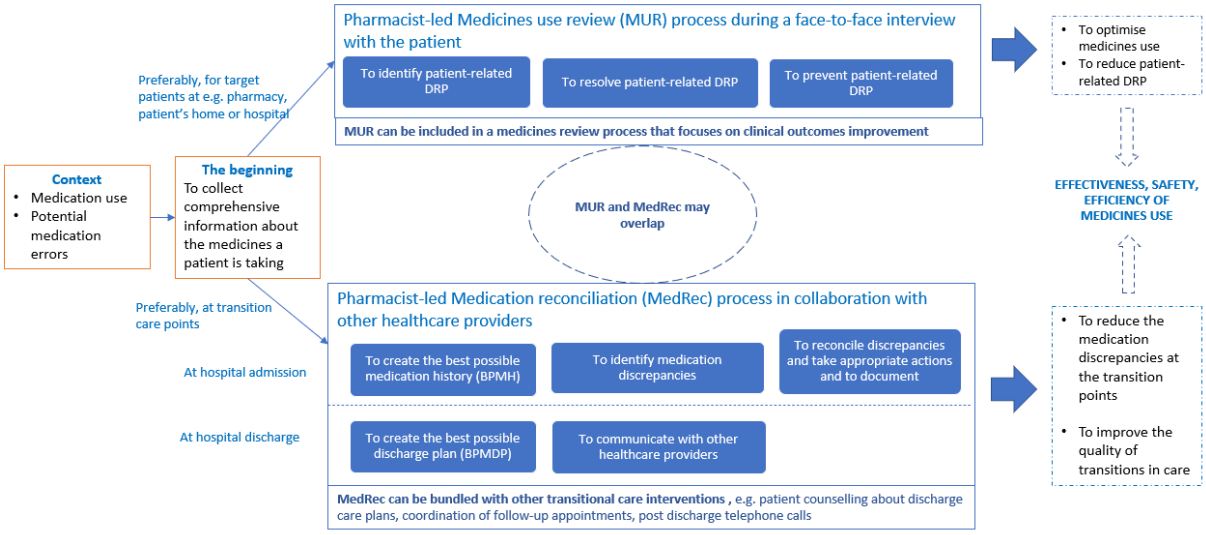
This chapter content derives from the identification and selection of cost-effectiveness analyses of MUR and MedRec (as defined in section 1), and systematic reviews or meta-analyses for which the main outcome was to assess their economic impact. First, we will define MUR and MedRec processes and aims, then expose their direct costs, discuss the modelling or their economic impact and cost-

effectiveness and finally expose their economic evidence. Findings will lead to recommendations for pharmacy practice research on this topic to turn into policy, action and change (section 5).

1. Definition of medicines use review (MUR) and medicines reconciliation (MedRec)

MUR and MedRec processes and aims as defined in this chapter are presented in Figure 1.

Figure 1: Medicines use review (MUR) and medicines reconciliation (MedRec) processes and aims



Legend: DRP: Drug-related problems

MUR is defined by the World Health Organization (WHO) and the International Pharmaceutical Federation (FIP) as a structured evaluation of patient's medicines with the aim of optimising medicines use and improving health outcomes; entails detecting DRPs and recommending interventions [5, 6]. MUR has been developed and implemented in different settings with national-level specificities (see FIP toolkit for a non-exhaustive table summarising the service in several countries and territories [6]). By adopting the vision of the advanced service implemented in the UK and commissioned by the National Health Services (NHS) until March 2021, MUR is a way to: (i) improve patients' understanding of their medicines; (ii) highlight problematic side effects and propose solutions where appropriate; (iii) improve adherence; and (iv) reduce medicines wastage, usually by encouraging the patient only to order the medicines they required. However, MUR is not considered as (i) a full clinical review; (ii) an agreement about changes to medicines; (iii) a discussion about the medical condition beyond that which was needed to achieve the above objectives; or (iv) a discussion on the effectiveness of treatment based on test results [7]. In this sense, MUR is mainly focused on the identification, resolution and prevention of DRP which are patient-related, i.e. whose cause is related to the patient and his/her intentional or

unintentional behaviour according to the classification of the Pharmaceutical Care Network Europe (PCNE) [3]. The patient-related DRPs are for instance: medication non-adherence, unregulated overuse or inappropriate drug storing or administration. MUR takes then the form of a structured review undertaken by a pharmacist, either at the pharmacy, at the patient's home or at the hospital, to help patients to manage their medicines more effectively. It involves the pharmacist reviewing the patients' use of their medication, ensuring they understood how their medicines should be used and why they have been prescribed, identifying and resolving any detected problems and then, where necessary, providing feedback to the prescriber. The NHS has defined targeting requirements to focus MUR delivery in patients who would benefit most, i.e. patients taking high-risk medicine (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, antiplatelet or diuretics), and patients recently discharged from hospital who had changes made to their medicines while they were in hospital [7].

MedRec is focused on critical moments in care pathways: i.e. transitions of care, such as hospital admission and discharge, which requires special attention to ensure good coordination between care sectors and avoid medication discrepancies. Medication discrepancies issued from care transitions can be classified as unintentional or intentional and lead to preventable medication errors and adverse drug events (ADE), representing potential significant clinical burden [8]. Healthcare professionals must collaborate with patients to ensure accurate and complete medication information transfer at interfaces of care. In this sense, MedRec is a formalized and standardized process that involves obtaining a patient's comprehensive current medication list and comparing it to any medication they request or are being delivered at any healthcare setting, in order to identify and resolve any discrepancies according to the standards of medication frequency, route, dose, combination and therapeutic purpose [8-10]. The process is centered on creating the most accurate list possible of all medications a patient is actually taking and comparing that list against the prescriber's orders. In addition, the patient's allergies, history of side effects from medications and medication aids are listed with the goal of providing correct medication to the patient at all transition points within the healthcare system.

Depending on the patients' needs or medication errors identified while these are performed, MUR and MedRec may potentially lead to other interventions, e.g. specific care protocols, or to no intervention at all. This "diagnostic" component of both interventions makes it difficult to evaluate MUR or MedRec alone. Therefore, their evaluation is usually included in the evaluation of other interventions. Moreover, MUR and MedRec interventions may overlap: e.g. you can do as a MedRec before MUR to list what needs to be discussed with the patient; or similarly, when the pharmacist presents the updated medication list to a patient, there is some components of a MUR, e.g. to include adherence supports.

2. Medicines use review (MUR) and medicines reconciliation (MedRec) cost

MUR and MedRec costs mainly include additional pharmacist time requirements to conduct and complete these interventions (see Table 1) ($1 = 1.03€ = £0.89, exchange rates as of 2022.11.03,www.xe.com). The mean time spent to deliver MUR and MedRec in the literature was estimated to 53 and 50 minutes per patient. A common way to limit costs induced by such interventions is to imply pharmacy technicians. A cost-benefit analysis of MedRec for reducing medication errors after hospital discharge compared to usual care was conducted from the hospital perspective in United-States [11]. In the sensitive analysis, the simulation model tested several allocation tasks to conduct MedRec and reduce intervention costs (pharmacists alone or a combination pharmacists-technicians) assuming that a medication history conducted by a pharmacy technician under a pharmacist's supervision as effective as that of one conducted by a pharmacist alone. Pharmacy technicians conducted 50% of MedRec-related tasks (e.g., taking medication histories) and pharmacists were assumed to supervise technicians and do some of the tasks, like patient counselling or order review themselves.

Table 1: Estimation of time and costs to perform medicines use review (MUR) and medicines reconciliation (MedRec)

MUR	• Spain [12]: Mean time employed by the pharmacists in the MUR was 52.80 ± 31.52 minutes including 27.34 ± 15.15 minutes in the interview and 25.39 ± 21.32 minutes for registering the MUR forms and reports. The total mean intervention cost was estimated to €17.27 ± 10.31 • Italy [13]: The cost for delivering the intervention was estimated to €40 for a group of asthma patients • UK [14]: Fee of £28 per MUR reimbursed by the NHS (regardless of the time spent)
MedRec	• In a literature review based on six studies [15], the pooled median (IQ) time spent per patient was estimated to 50 (14, 50) minutes to perform complete MedRec, i.e. upon admission through the hospital stay until discharge and with patient information being communicated accurately to the next health provider. • Sweden [16]: For drug review at hospital by a pharmacist = 39€ including 34€ at admission and 5€ at discharge • UK [17]: Mean additional time per patient receiving pharmacist-led MedRec at hospital admission = 22 min (95% CI 12-46 min), i.e. around £10 with an estimated hourly cost of £28 • US [11]: Mean pharmacist time per reconciliation at hospital discharge was estimated to 46.2 min (± 50% in the sensitive analysis) from a time-and-motion study [18]. Intervention cost was calculated with a mean annual salary of $120,850 for the pharmacist and $30,370 for the pharmacy technician and 25% overheads costs (including fringe and benefit) • Canada [18]: A time-and-motion study : geriatric reconciliations took the most time to complete at admission (mean: 92.2 min (SD=44,3)) and discharge (mean: 29.0 min (SD=23.8), followed by internal medicine (mean: 46.2 min (SD=21.2) and 19.4 (SD=11,7) and general surgery (mean: 9,9 min (SD=18,2).

($1 = 0.85€ = £0.73, exchange rates as of 2021.07.21, www.xe.com)

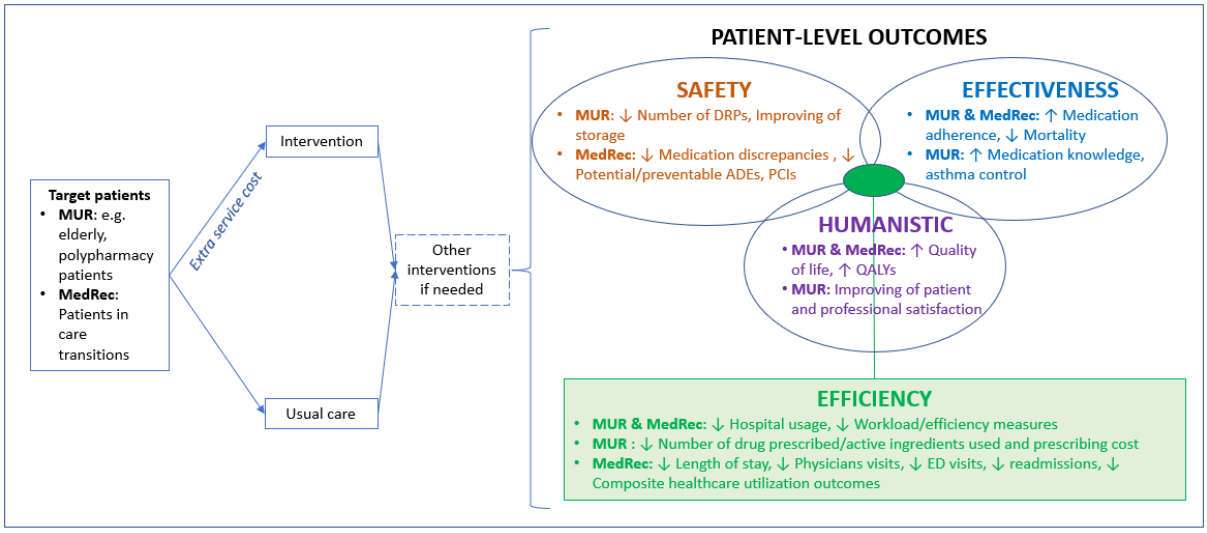
Implementation costs are often ignored in economic evaluations of MUR and MedRec, even though they help ensure the quality of interventions. In a UK simulation, the development and maintenance of the standardized form for MedRec interventions was estimated to the equivalent of one week's

work of a pharmacist (£1'050) each year, with the assigned development and maintenance cost as £0.06 per admission [17].

3. Modelling of the economic impact and cost-effectiveness of medicines use review (MUR) and medicines reconciliation (MedRec)

The Figure 2 synthetizes the research hypotheses and outcomes used in the identified literature reviews and economic evaluations to assess the economic impact and the cost-effectiveness of MUR and MedRec. The identification and the selection of the literature evaluating MUR and MedRec interventions is not an easy task. For MUR, the use of "medication review" as an umbrella term to describe a range of interventions, the lack of description of the interventions in some studies, as well as the different applications of MURs in different countries or in relation with specific diseases/medicines make it very difficult to identify and select appropriate restrictive studies evaluating this intervention. According to our definition (see section 1) excluding full medication review including clinical aspects or MUR bundled with other interventions, two systematic reviews [19, 20], one rapid review [21], and two full economic evaluations [22, 13] have been identified (see Table 2 and Table 3 for characteristics). For MedRec, six systematic reviews [23, 15, 24-27] – including five meta-analyses - and three full economic evaluations [11, 16, 17] (see Table 2 and Table 3 for characteristics) were identified from two reviews of systematic reviews [28, 29] and a FIP reference paper [8]. The reviews used different definitions of MedRec (see Table 2) and none of them defined strict selection criteria for the components of the interventions. This leads to a heterogeneity of interventions (e.g. primarily and supplemented MedRec, patient counselling, medication information, post-transition communication, medication review) that makes the interpretation of results difficult.

Figure 2: Hypotheses and outcomes used in the identified literature to assess the economic impact and the cost-effectiveness of MUR or MedRec interventions



Legend: ADE: Adverse-drug events, DRPs: Drug-related problems, ED: Emergency department, MedRec: Medicines reconciliation, MUR : Medicines use review, PCIs: Pharmaceutical care issues, QALYs: Quality-adjusted life years

The modelling of the economic impact and cost-effectiveness of MUR and MedRec is to evaluate is the extra cost associated to the interventions delivery are offset by the savings associated to intermediate outcomes and avoided healthcare use; generally comparing a group of patients receiving the intervention versus usual care. Several intermediate patient-level outcomes are used on the literature and can be classified into three categories: effectiveness, safety and humanistic outcomes (see Fig.2). The outcomes can be used alone or combined, assuming that their improvement will lead to cost-effectiveness.

Table 2 : Characteristics of systematic reviews and meta-analysis assessing the economic impact of medicines use review (MUR) and medication reconciliation (MedRec)

	Authors	Evaluated studies	Number of participants	Definition of intervention used	Setting	Healthcare utilization outcomes	Quality assessment
MUR	**Holland et al. 2008 [19]**	32 RCT	18'896	Structured evaluation of a patient's medicines, aimed at reaching agreement with the patient about drug therapy, optimizing the impact of medicines, and minimizing the number of DRP	Hospital, pharmacy, clinic/primary care setting, patient's home, nursing home	ED admissions, mortality, mean drug prescribed	10 criteria [1]
	Hasan et al. 2017 [20]	6 RCT, 4 pre-post, 1 prospective	25'861	A structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of DRPs and reducing waste	Residential aged care facilities	Drug cost savings	11 items related to design, bias and confounders
MedRec	**Cheema et al. 2018 [23]**	18 RCT	6'038	Institute for Healthcare Improvement [9] [4]	All care transitions in hospital	Drug-related ED visits	Cochrane Collaboration risk of bias tool [5]
	Hammad et al. 2017 [15]	3 RCT, 6 prospective, 3 pre-post, 1 observational	6'443	Complete MedRec (all MR five steps) distinguishing primarily and supplemented MedRec [2]	In hospital from admission till discharge	ED visits, readmission, length of stay	Cochrane Collaboration risk of bias tool [5], selected risk domains to assess
	Kwan et al. 2013 [24]	5 RCT, 4 pre-post, 9 post	39'465	Institute for Healthcare Improvement [9] [4]	All care transitions in hospital, home,	ED visits and readmission	Cochrane Collaboration risk of bias tool [5]
	McNab et al. 2018 [25]	5 RCT, 6 cohort, 3 pre–post	6'642 [3]	The reconciliation of preadmission and post admission lists of medication in the community	After hospital discharge	ED visits, readmissions primary and secondary care consultations	Critical Appraisal Skills Programme. Evidence
	Mekonnen et al. 2016 [26]	8 RCT, 6 pre-post, 3 nRCTs	21'342	Institute for Healthcare Improvement [9] [4]	All care transitions in hospital	ED visits, readmissions, hospital stay, ADEs readmission or hospital visit	EPOC risk of bias tool
	Redmond et al. 2018 [27]	25 RCT	6'995	Institute for Healthcare Improvement [9] [4]	All care transitions in hospital, community, Residential aged care facilities	Length of stay, mortality, ED visits, readmissions, hospitalizations	Cochrane Collaboration risk of bias tool [5]

DRP = Drug-related problems; ED= Emergency department; RCTs = Randomised controlled trials

[1] 3 trial quality criteria (adapted from Juni et al. (2001): concealment of allocation, use of intention-to-treat analysis and data checking; 4 criteria recommended by the York Centre for Reviews dissemination: explicit statement of inclusion criteria; baseline comparability between groups; a clearly defined primary outcome; and sample size calculation reported /NHS) and 2 criteria defined by the review team: length of follow-up (6 months was considered adequate), >80% of patients retained in the trial, and reporting the training or selection of pharmacists.

[2] "Primarily MedRec studies" = MedRec is the primary element of the intervention or "Supplemented MedRec studies" = MedRec is supplemented often with pharmacotherapy consultation or medication review, patient consultation and discharge planning

[3] not specified for one study

[4] The process of identifying the most accurate list of a patient's current medicines including the name, dosage, frequency and route—and comparing them to the current list in use, recognizing and documenting any discrepancies, thus resulting in a complete list of medications'

[5] random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias, sample size calculation

Table 3: Characteristics of cost-effectiveness analyses of medicines use review (MUR) and medicines reconciliation (MedRec)

	Authors Country	Interventions	Model	Cost item	Effectiveness outcomes	Perspective / Time horizon
MUR	**Pacini et al. 2007** **UK [22]**	(1) HOMER : Home-based medication review* in patients >80 years after hospital discharge Usual care	RCT-based CUA	• Intervention cost • Hospital, ambulance and general practice costs	QALYs	NHS / 6 months
	Manfrin et al. 2017 **Italy [13]**	(1) Community pharmacist-led MUR in asthma patients** Usual care	RCT-based CUA	• Intervention cost • Annual cost relating to ACT score (incl. healthcare visits, admission, ED visits) • Indirect costs (productivity loss, leisure time forgone)	QALYs	Public healthcare and societal / 3, 6 and 9 months
MedRec	**Najafzadeh et al. 2016** **US [11]**	At hospital discharge: (1) Non targeted pharmacist-led MedRec (for all patients) (2) Targeted pharmacist-led MedRec (only for patients at high-risk of ADEs (3) Usual care (no intervention)	CBA through a discrete-event simulation model	• pADEs-related ED visits and rehospitalizations and pADEs costs	Savings from avoiding health resource utilization due to preventable ADEs	Hospital / 30 days after hospital discharge
	Ghatnekar el al. 2013 **Sweden [16]**	(1) the LIMM model : a systematic MedRec and review process at initial hospital admission and during stay and a medication report for patients discharged from hospital to primary care (2) Usual care	CUA using a probabilistic decision tree model (LIMM)	• Drug-related readmissions and outpatients visits • Staff time	QALYs accounting dis-utilities due to medication errors	Health system / 3 months
	Karnon et al. 2009 **UK [17]**	(1) Pharmacist-led reconciliation (2) Standardized forms, pharmacy technicians, hospital policy (3) Nurses taking histories with standardized form (4) Computerized assessment and feedback by pharmacist (5) Current medication faxed from the GP practice (6) Baseline scenario	CUA using a simulation model based on (Karnon et al. 2007)	• Intervention • Detection • pADEs length of stay and cost according to severity	QALYs accounting loss by pADE severity	NHS / ?

* As a structured evaluation of a patient's medicines, aimed at reaching agreement with the patient about drug therapy, optimizing the impact of medicines, and minimizing the number of DRPs

** A systematic, structured interview, conducted in a private room within the pharmacy, which covered asthma symptoms, medicines used, attitudes towards medicines and adherence.

LIMM = Lund Integrated Medicines Management model, CUA = Cost-utility analysis, CBA = Cost-benefit analysis

4. Economic evidence of medicines use review (MUR) and medicines reconciliation (MedRec) interventions

a. What we know about medicines use review (MUR) ?

The studies that assess the economic impact and cost-effectiveness of MUR generally focus on patients ≥ 65 years: mean age of participants in the 32 included studies of Holland et al. (2008) [19] ranged from 61 and 85 years; with an only one study limited inclusion to specific diagnoses (either chronic obstructive pulmonary disease (COPD) or hypertension). In an implementation study of MUR in Spain, the target subjects were adults patients belonged to one of the following groups: (1) users of complex medicines, (2) users of high-risk medicines; (3) and polypharmacy patients; and the final sample of patients had an average age of 66 years [12]. Beyond age, in April 2015, the UK government redefined the targeted groups for MUR including : patient with prescribed high risk medicine(s) (NSAIDs, anticoagulants and diuretics), patients recently discharged from hospital who had changes made to their medicine(s) while they were in hospital, and patients with respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) at risk of or diagnosed with cardiovascular disease and regularly being prescribed at least four medicines [21].

The literature reviews show that there is some evidence that MUR interventions are effective to reduce the number of patient-related DRP and improve medication knowledge and adherence for the patients (see Table 4). Nevertheless, there are insufficient data, notably in quality of life, to evaluate the final economic impact of these interventions or their cost-effectiveness. The findings of the two full economic evaluations are conflicting. In UK, the HOMER intervention at home for older patients after hospital discharge [22] showed only 25% of probability that the intervention be cost-effective compared to usual care using an acceptable threshold for ICER of £30'000 per QALY gained. The findings seem to be more favorable in a cost-utility analysis in asthma patients in Italy [13] (see Table 5). The rapid literature review on the evidence of clinical pharmacy interventions in UK highlights the fact that the delivery of MUR interventions resulted in increasing in pharmacy staff workload [21].

Table 4 : Economic impact of medicines use review (MUR) and medicines reconciliation (MedRec) from identified literature reviews and meta-analysis

	Outcome		Qualitative synthesis findings	Meta-analyses findings
MUR	**Safety**	**Number of DRPs**	4/4 studies reported a significant positive effect [19]	No results
		Medication storage	2/3 studies reported a significant positive effect [19]	No results
	Effectiveness	**Medication adherence**	11/14 studies reported a significant (n=7) or non-significant (n=4) positive effect [19]	No results
		Medication knowledge	8/11 studies reported a significant (n=6) or non-significant (n=2) positive effect [19]	No results
		Mortality	No results	No effect on all-cause mortality : RR = 0.96, 95% CI 0.82 to 1.13 (n=22 studies, n=11'741 participants, I^2 = 0%, p=0.65) [19]
	Humanistic	**Quality of life**	• 4/12 studies reported a non-significant positive effect [19] • The quality of life has not been collected and consequently it is not possible to estimate the cost per QALY [21]	No results
		Patient satisfaction	3/12 studies reported a significant (n=2) or non-significant (n=1) positive effect [19]	No results
	Healthcare use/efficiency	**Hospital usage**	Conflicting results for all-cause admission probably due to the moderate heterogeneity [19]	No effect on all-cause admission : RR = 0.99, 95% CI 0.87 to 1.14 (n=17 studies, n=9'900 participants, I^2 = 50%, p=0.92) [19]
		Number of drug prescribed and prescribing cost	• 10/14 studies reported a significant (n=4) or non-significant (n=6) positive effect on prescribing cost [19] • 6/8 depicted significant cost savings in terms of decrement in total medication costs and associated cost savings [20]	May reduce number of drugs prescribed : weighted mean difference = -0.48, 95% CI -0.89 to -0.07 (n=15 studies, n=6'358 participants, I^2 =86%, p=0.02) [19]
		Workload	A resultant increase in pharmacy staff workload [21]	No results
MedRec	**Safety**	**Medication discrepancies**	Greater rates of identification and resolution on the intervention group (n=4 studies) [25]	• 55.9% of patients are at risk of having ≥ 1 medication discrepancies at transitions of care with standard health care (n= 20 studies, n= 2'355 participants), respectively : 72.8% at hospital admission (n= 4 studies, n= 567 participants), 63.2% at discharge (n=5 studies, 370 participants) [27] • Effect of MedRec to reduce medication discrepancies when MedRec was performed at any time point : RR = 0.53, 95% CI 0.42 to 0.67 (n=20 studies, n=4'629 participants, I^2 = 91%, p<0.0001); at admission: RR = 0.43, 95% CI 0.27 to 0.68 (n=4 studies, n=1'167 participants, I^2 = 90%, p=0); and at discharge : RR = 0.71, 95% CI 0.50 to 1.02 (n=5 studies, n=649 participants, I^2 = 73%, p=0.06) [27] • An important reduction due to MedRec including all care transition within the hospital : RR = 0.58 , 95% CI 0.49 to 0.67 (n= 4 RCTs, n=1'136 participants, I^2 = 28%, p=0.00001) [23] • A significant reduction in patients with medication discrepancies when MedRec performed at single transitions (either admission or discharge) : RR=0.34, 95% CI 0.23-0.50 (n= 13 studies; n=5'568 participants, I^2 =96%, p=<0.00001, very-low quality evidence); but not at multiple transitions : RR= 0.88, 95% IC 0.77 to 1.02 (n=5 studies, n=1'246 participants, I^2 = 0%, p=0.09) [30]
		Adverse drug events (ADE)	Potential for fewer ADE after pharmacists had completed MedRec (n= 2 studies) [25]	• Little or no effect on preventable ADEs due to the very low certainty of the available evidence: RR=0.37; 95% CI 0.09 to 1.57 (n= studies; n=1'253 participants) [27] • A small reduction in potential ADEs : RR=0.90, 95% CI 0.78 to 1.03 (n= 4 RCTs, n=2'163 participants, I^2= 0%, p=0.12) [23] • A small reduction in preventable ADEs : RR=0.73, 95% CI 0.22 to 2.40) (n= 4 RCTs, n=2'263 participants, I^2= 50%, p=0.60) [23]

	Effectiveness	**Medication adherence**	No results	No statistically significant differences in non-adherent with at least one medications : RR = 0.76, 95% CI 0.41 to 1.42 (n= 2 studies, n=379 participants, I^2= 74%, p=0.4) [27]
		Mortality	• No statistically significant differences between MR and standard care : RR = 0.75, 95% CI 0.27 to 2.08 [29] (n=1 study, n= 190 participants) • At 12 months, none identified a significant impact (n=3 studies) [15]	All-cause mortality: RR = 1.05, 95% CI 0.95 to 1.16 without heterogeneity (n=8 studies, n= 7'362 participants, I^2 = 0%, p=0.30) [26]
	Healthcare use/efficiency	**Length of stay**	Significant shorter hospital stays in residential aged care facilities (p=0.026) (n=1 study) [31]	• Mean difference : 0.48 (95% CI -1.04 to 1.99) with some evidence of heterogeneity between the studies (n=2 studies, n= 475 participants, I^2 = 52%; p=0.15); very low-certainty evidence [27]
		Hospital usage	Mixed effect with a pooled median (IQ) increase of 8.4 (0,16) hours for the intervention and contradictory findings [15]	• Uncertain effect on a composite measure (hospitalisation, ED, rehospitalisation) : RR 0.78, 95% CI 0.50 to 1.22 (n= 4 studies, n= 597 participants, I^2 = 48%; very low-certainty evidence [27] • A substantial reduction of in ADE-related hospital revisits : RR = 0.33; 95% CI 0.20 to 0.53 (n= 3 studies, n= 9'343 participants, I^2=0%, p<0.00001) [26]
		Physician visits	• No significant trend (n=1 prospective controlled study) [31] • Conflicting results with a significant increase in GP visits of 43% (p=0.002) in the MedRec group in 1 RCT while and no significant difference at 6 months in another 1 RCT [25]	No results
		ED visits	• No statistically significant differences within 72 hours, 14 days or 30 days after discharge (n=1 before-and-after study) [31] • Conflicting results with no difference observed between the groups in 2 non-RCTs whereas a large reduction in a small RCT [25]	• Reduced rates within 30 days after discharge : RR= 0.07, 95% IC 0.00 to 1.07 (n= 1 study, n=61 participants) [27] • All-cause ED visits: RR = 0.72, 95% CI 0.57 to 0.92 with high heterogeneity (n=9 studies, n= 18'998 participants, I^2 = 81%, p=0.009) However, there was no heterogeneity without affecting the significance difference after the exclusion of one study: RR = 0.89 95% IC 0.79 to 0.99, I^2 = 22%, p=0.25 [26]
		Readmissions	• Decreased at 7 (p=0.01) and 14 days (p=0.04) but not at 30 days (p=0,29) after discharge [31] • Conflicting results with a statistically reduction in readmission rate (n= 3 studies) and an increase (n=1 study) [25]	• Probably little or no difference : RR = 0.72, 95% CI 0.44 to 1.18 with some evidence of heterogeneity (n=5 studies with follow up from 5 to 30 days; n=1206 participants, I^2 = 45%, p=0,12); moderate-certainty evidence [27] • No clear effect : RR=0.91, 95% CI 0.66 to 1.25 with high heterogeneity (n=7 studies with follow-up from 30 days to 6 months; n= 2'336 participants; I^2 = 71%, p=0.002) [25] • All-cause readmission RR = 0.81, 95% CI 0.70 to 0.95 with high heterogeneity (n=15 studies, n= 21'969 participants, I^2 = 79%, p=0.008) [26]
		Composite healthcare utilization outcomes	• Supplemented MedRec studies appeared to report more often a positive impact, particularly on readmission rate and length of hospital stay, compared to primarily MedRec studies [15] • Pooled median (range) reduction in readmission and ED visits = 4% (1%-5.9%) (n=4 studies). At 3 months, the reduction in readmission and ED visits ranged from 6.4% (p=0.045) to 9.3% (p=0.047) but the effect is not significant at 6 months after discharge (n=1 study) [15]	• No significant reduction in healthcare utilization post-hospital discharge: RR = 0.78, 95% CI 0.61 to 1.00 (n= 4 RCT; n= 1'087 participants; I^2 = 0%; p=0.05) [23] • A statistically significant reduction : RR=0.77, 95% CI 0.63 to 0.95 (n=3 RCT, no heterogeneity assessment) [24]
		Workload	• Pharmacist completing MedRec had the potential to free up clinical time for other healthcare team members in one	No results

			pre-post intervention: 2 hours of pharmacist time freed 3 hours of nursing time and 1 hour of physician time [25]	

Table 5: Cost-effectiveness findings of medicines use review (MUR) and medicines reconciliation (MedRec)

	Authors Country	Main findings
MUR	**Pacini et al. 2007 UK [22]**	• The intervention did not reduce hospital admissions and the average cost per intervention group patient was £1'695 compared with £1'424 for control patients. • The intervention group patients lived 3.4 years of life gained (p=0.14), with a mean difference in survival of 0.007 years. Average EQ-5D scores differed slightly at baseline between the groups and decreased over the 6 months for both but not significantly. The mean difference in QALY was 0.0075. • The incremental cost per QALY gained in the intervention was £54'454. • Sensitivity analysis suggested a 25% probability that HOMER is cost effective using a threshold of £30 000 per QALY.
	Manfrin et al. 2017 Italy [13]	• 60%, 83% and 98% of plots were into the south-east quadrant, i.e. dominant strategy with 72%, 93% and 100% of probability that intervention be cost-effective with a threshold of €30'000 per QALY gained respectively at 3, 6 and 9 months. • These favorable findings are mainly explained by the fact that the key factor influencing asthma control was adherence and the resultant improvements were sustained during the follow-up period.
MedRec	**Najafzadeh et al. 2016 US [11]**	• Under the base-case assumption that MedRec could reduce medication discrepancies by 52%, the cost of preventable ADEs could be reduced to $266 (95% CI, $150-$423), resulting in a net benefit of $206 (95% CI, $73-$373) per patient, after accounting for intervention costs. • A MedRec intervention that reduces medication discrepancies by at least 10% could cover the initial cost of intervention. • Targeting MedRec to high-risk individuals would achieve a higher net benefit than a non-targeted intervention only if the sensitivity and specificity of a screening tool were at least 90% and 70%, respectively.
	Ghatnekar el al. 2013 Sweden [16]	• The total cost for the LIMM model was €290 compared to €630 for standard care, in spite of a €39 intervention cost. The main cost offset arose from avoided drug-related readmissions in the Admission part (€262) whereas only €66 was offset in the discharge part as a result of fewer outpatient visits and correction time. • The reduced disutility was estimated to 0.005 QALYs, indicating that LIMM was a dominant alternative. • The probability of being cost-effective was estimated to 98% by a QALY value of €0.
	Karnon et al. 2009 UK [17]	• All five interventions are estimated to be extremely cost-effective when compared with the baseline scenario. • Pharmacist-led reconciliation intervention has the highest expected net benefits and is a dominant strategy. • The probability of being cost-effective of over 60% by a QALY value of £10 000. • Strong evidence that some form of intervention to improve medicines reconciliation is a cost-effective use of NHS resources.

($1 = 0.85€ = £0.73, exchange rates as of 2021.07.21, www.xe.com)
LIMM = Lund Integrated Medicines Management model,

Quality of original studies included in the literature reviews identified for MUR was checked according 10 or 11 criteria (see Table 2). In Holland et al. (2001) [19]: only 5/32 (16%) of RCT satisfied all three trial quality components together adapted from Juni et al (2001)[32] (concealment of allocation, intention-to-treat analysis, data checking). When trials were considered against all ten quality criteria: the majority (17/32) met at least six. Quality issues often lacking were reporting a sample size calculation and defining a primary outcome; and poorer quality studies seemed to yield greater effect than higher quality studies. The lack of quality in the original studies, indicating that some of them may have been susceptible to bias, lead to take caution in the interpretation of these findings.

Finally, Holland et al (2001) discuss the fact to take the hard outcome "all-cause emergency hospital admission" as economic impact outcome as hospital admissions may not relate specifically to the interventions delivered, or particular patient's needs; but that the other outcomes are not consistently reported in the trials limiting the ability to draw any robust conclusions [19].

b. *What we know about MedRec ?*

The studies assessing the economic impact and cost-effectiveness of MedRec focus on patients experiencing a transition in care (e.g. hospital admission, discharge, in-transfer), which represent a high-risk situations for medication discrepancies, and then for potential harm for the patients. The six identified systematic reviews conclude that MedRec interventions are effective to reduce the medication discrepancies [25, 23]. However, some uncertainty remains when MedRec was performed at multiple transitions [30] (see Table 4). Nevertheless, the economic impact due to this reduction of medication discrepancies is not clear due to contradictory results for the other intermediate outcomes, i.e. in terms of potential and preventable ADE (safety outcome), medication adherence and mortality (effectiveness outcomes). By consequent, there is an uncertain effect on avoided healthcare utilization.

In the three full economic evaluations identified, the cost-effectiveness of MedRec at hospital admission and/or discharge is modelled through its impact on the identification and resolution of medication discrepancies compared to usual care. In these evaluations, medication discrepancies can be associated to observed harm ("preventable ADE") or to no harm observed ("potential ADE"); in addition both types of ADE can be classified according to their severity (e.g life-threatening, serious, significant) [33]. These criterions are used to evaluate the savings associated to avoided health resource utilisation (e.g. emergency department (ED) visits and hospitalisations) according to ADE severity (see Table 5). From a healthcare system perspective, two studies showed promising findings: 1) in UK, pharmacist-led MedRec intervention had the highest expected net benefits of the five other assessed interventions aiming to prevent medication error at hospital admission, and was a dominant strategy (i.e. more effective and less costly) compared to usual care with a probability of being cost-effective of over 60% by a QALY value of £10 000 [17]; 2) in Sweden, the LIMM model (Lund Integrated Medicines

Management model) including a systematic MedRec and review process at initial hospital admission and during stay and a medication report for patients discharged from hospital to primary care generated cost savings (mainly arose from avoided drug-related readmissions) and higher QALY to the patients (i.e. dominant strategy) with a high probability of cost-effectiveness [16]. From a US hospital perspective, the net benefit associated to MedRec intervention at hospital discharge was estimated to $206 (95% CI, $73-$373) per patient compared to usual care, after accounting for intervention costs and within 30 days after hospital discharge. The net benefit depended of the percentage of reduction in medication discrepancies (estimated by at least 10% to cover the initial cost of intervention) and targeting the intervention to high-risk individuals for ADEs (i.e., patients most likely to have a postdischarge ADE due to a medication discrepancy) achieved a higher net benefit than a non-targeted intervention only if the sensitivity and specificity of a screening were at least 90% and 70%, respectively. [11]

Beyond the observed poor quality of the systematic reviews themselves [29], all identified systematic reviews acknowledge moderate or high risk of bias for the majority of included studies [23, 25, 15]. Potential bias for RCT design are related to randomisation, allocation concealment and potential contamination bias [27, 15], or details on missing data or power calculations [23]. Moreover, the inclusion of non-controlled studies might affect the quality of evidence as seen by the high risk of bias in these groups of studies [26].

The authors acknowledge that one of the challenges to make some evidence about the clinical and economic impacts of MedRec is the variety of potential confounding factors. For instance, the different intervention components, duration and intensity make it difficult to conclude on the impact. In [15], “supplemented MedRec studies” (i.e. MedRec supplemented with pharmacotherapy consultation or medication review, patient consultation or discharge planning) appeared to report more often a positive impact, particularly on readmission rate and length of hospital stay, compared to “primarily MedRec studies” (i.e. MedRec as the primary element of the intervention) [15]. Moreover, the heterogeneity in the study designs, population or settings should lead to caution in the findings synthesis, notably for meta-analyses that often mixed interventions and settings.

5. Recommandations

The literature show that MUR and MedRec interventions are effective to reduce their main safety outcome, i.e. patient-related DRP and medication discrepancies respectively. Nevertheless, there is no clear evidence and some uncertainty about the impact on effectiveness (e.g. mortality, medication adherence) and humanistic outcomes; which leads to an uncertain economic impact and cost-effectiveness of these interventions: 1) MUR do not reduce hospital admissions [22, 19] and findings of full economic evaluations were contradictory. A UK study showed a low probability of cost-

effectiveness due to a no significant gain in quality of life without reduction in hospital admissions [22] versus more favorable findings in Italian asthma patients due to sustained improvements in adherence and disease control [13]; 2) MedRec have an uncertain effect on healthcare utilization but the two full economic evaluations from the healthcare system perspective showing high probability of being cost-effective estimated to 98% in Sweden [16] and 60% in UK [17] by a QALY value of €0 and £10 000 respectively.

As "diagnostic" interventions with a probability for some patients of no possible return on investment for the intervention delivery cost in case of no DRP or medication discrepancies detected, to target high-risk patients could favor the cost-effectiveness of these interventions. The cost-effectiveness of MUR in residential aged care facilities seems to be more favorable [20]. Nevertheless, focusing on high-risk patients did not consistently increase the effect of MedRec in the literature review of Kwan et al (2013) [24] but achieved a higher net benefit than a non-targeted intervention under certain conditions in a cost-effectiveness from hospital perspective [16]. Although target group were required for MUR in UK, there is no data in this work to discuss the impact of that for this intervention.

The lack of economic evidence of MUR and MedRec could be due to several factors notably related to the study designs and confounding factors. Firstly, original studies included were susceptible to bias with moderate quality, and meta-analyses are confronted with the heterogeneity of the studies and include pharmacist interventions from a mix of clinical settings; leading to some issues for adequate pooling of data. This heterogeneity is correlated to differences in terminology and components of MUR and MedRec intervention configurations across countries and could be improve with a standardization of processes. The FIP proposes crucial steps for MUR [6] and MedRec in this sense [8]. Moreover, the PaCIR tool has been created to improve the quality of reporting of pharmacist patient care intervention with a checklist of nine elements [34] and could lead to better understand intervention components in the studies.

The question of appropriate outcomes used to assess the economic impact of MUR and MedRec is crucial as "hard outcomes" (e.g hospital admissions or mortality) could be not appropriate but with a lack of data for other outcomes [19]. Because evidence of the impact of MUR and MedRec focuses on safety outcomes (DRP and medication discrepancies respectively), it may also be appropriate to better assess direct clinical and economic impacts, rather than using indicators of healthcare use. For example, a Swiss study identified, characterized and categorized medication discrepancies occurring in adult community pharmacy customers with long-term polypharmacy use for any transition in the healthcare system using two classification systems [4]. Potential direct or indirect clinical impact of each medication discrepancy on the patient's medical conditions was evaluated using three different severity classes: "unlikely", "moderate" or "potentially severe" adapted from Cornish et al. (2005) [35]. Then potential economic impact was defined as immediate impact of medication discrepancies on the

medication costs (levels: increase, null, decrease) from a healthcare system's perspective by comparing the medication of the BPML and the latest medication prescription; evaluated with the economic dimension of the tool CLEOde tool [36]. Finally, the potential cost savings from the perspective of the patients, or including indirect costs, should be more investigated as they assume more and more the responsibility over their healthcare.

Conclusion

MUR and MedRec interventions are the core business of the pharmacist to ensure patient safety and optimization of drug use. Despite the demonstration of their effectiveness in identifying and resolving safety issues (patient-related DRP and medication discrepancies), studies have struggled to demonstrate their clinical and economic impact. The poor quality and heterogeneity the studies, as well as the debatable accuracy of the outcomes are probably the cause of this issue. Future research and high-quality studies are needed to address these issues.

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