Evaluation of the potential impact of pharmacist interventions : development and validation of the CLEO multidimensional tool

Thi Ha Vo

UNIVERSITÉ GRENOBLE ALPES

THESE

Pour obtenir le grade de

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Présentée par

Thi Ha VO

Thèse dirigée par **Pierrick BEDOUCH** et
codirigée par **Benoît ALLENET**

préparée au sein du **Laboratoire TIMC-IMAG**
dans **l'École Doctorale Ingénierie pour la santé la Cognition et l'Environnement**

Évaluation de l'impact potentiel des interventions pharmaceutiques : développement et validation de l'outil multidimensionnel CLEO

Thèse soutenue publiquement le **16 décembre 2015**,
devant le jury composé de :

Monsieur le Professeur Benoît ALLENET
Co-directeur, Université Grenoble Alpes, France
Monsieur le Docteur Pierrick BEDOUCH
Directeur, Université Grenoble Alpes, France
Monsieur le Docteur Johnny BENEY
Rapporteur, Université de Genève, Suisse
Monsieur le Professeur Jean-Luc BOSSON
Président, Université Grenoble Aples, France
Madame le Professeur Anne SPINEWINE
Rapporteur, Université catholique de Louvain, Belgique
Madame le Docteur Thi Lien Huong NGUYEN
Examinateur, Université de Pharmacie de Hanoi, Vietnam

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Doctor Pierrick BEDOUCH
Director, University of Grenoble Alpes, France
Doctor Johnny BENEY
Reviewer, University of Geneva, Switzerland
Professor Jean-Luc BOSSON
President, University of Grenoble Alpes, France
Professor Anne SPINEWINE
Reviewer, Catholic University of Louvain, Belgium
Doctor Thi Lien Huong NGUYEN
Member, Hanoi University of Pharmacy, Vietnam

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Publications/Communications

1. Publications/communications related to the thesis's topic

Articles

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Conferences

- Vo TH, Bardet JD, Bosson JL, Allenet B, Bedouch P. ***Methods assessing the significance of a pharmacist intervention: literature review.*** 42nd European Society of Clinical Pharmacy 2013 International Workshop. Edinburgh, Scotland 30 – 31 May 2013, (Poster).
- Vo TH, Bardet JD, Bosson JL, Allenet B, Bedouch P. ***Development and validation of a multidimensional scale for evaluating potential significance of a pharmacist intervention.*** 13th Asian Conference in Clinical Pharmacy. Haiphong, Vietnam 13 -15 September 2013 (Oral communication).
- Vo TH, Charpiat B, Juste M, Catoire C, Roubille R, Rose FX, Bosson J-L, Conort O, Allenet B, Bedouch P. ***[Development and validation of a multidimensional for evaluating the significance of a pharmacist intervention.]*** *Développement et validation d'une échelle multidimensionnelle pour évaluer la pertinence d'une intervention pharmaceutique.* SFPC Conference. Grenoble, France 5-7 February 2014 (Oral Communication).
- T.-H. Vo, C. Catoine, B. Charpiat, M. Juste, R. Roubille, F.-X. Rose, J.-L. Bosson, O. Conort, B. Allenet, P. Bedouch. ***Development and Validation of a multidimensional scale "CLEO" for evaluating potential significance of a pharmacist intervention.*** 2014 American College of Clinical Pharmacy Annual Meeting. Austin, Texas, USA 12-15 October 2014 (Poster).
- Thi-Ha Vo, Bruno Charpiat, Michel Juste, Renaud Roubille, François-Xavier Rose, Jean-Luc Bosson, Ornella Conort, Benoit Allenet, Pierrick Bedouch. ***Development of a multidimensional scale "CLEO" for evaluation of clinical, economic, and organizational impacts of a pharmacist intervention.*** 43rd ESCP 2014 Symposium. Copenhagen, Denmark 22-24 October 2014 (Oral communication).
- T.-H. Vo, C. Zecchini, I. Federspiel, S. Chanoine, B. Allenet, P. Bedouch. ***Validation of the CLEO tool for evaluating potential significance of pharmacist interventions in a centralized chemotherapy preparation unit.*** 44th ESCP 2015 Symposium. Lisbon, Portugal 28-30 October 2015 (Oral Poster Discussion).
- C. Zecchini, T.-H. Vo, S. Chanoine, B. Allenet, I. Federspiel, P. Bedouch. ***Clinical, economic and organizational impact of pharmacist interventions during***

pharmaceutical analysis of injectable antineoplastics. 44th ESCP 2015 Symposium. Lisbon, Portugal 28-30 October 2015 (Oral Communication).

- Vo T.H., Zecchini C., Federspiel I., Charpiat B., Juste M. , Roubille R., Rose F.X., Bosson J.-L., Conort O., Allenet B., Bedouch P. ***[Validation of the CLEO tool for evaluating potential significance of pharmacist interventions in a centralized chemotherapy preparation unit.]*** *Validation de l'échelle CLEO pour évaluer les impacts potentiels des interventions pharmaceutiques dans une unité de reconstitution centralisée des cytotoxiques.* SFPC Conference. Montpellier, 3-5 February 2015, France. (Oral communication). Accepted.

2. Publications/communications not related to the thesis's topic but conducted during the period of study.

Articles

- Vo T.-H., Bedouch P., Nguyen T.-L.-H., Hoang T.-K.-H., Calop J., Allenet B. ***Pharmacy Education in Vietnam***. American Journal of Pharmacy Education. August 12, 2013.
- Bardet JD, Vo TH, Bedouch P, Allenet B. ***Physicians and community pharmacists collaboration in primary care: A review of specific models.*** Res Social Adm Pharm. 2015 Sep-Oct;11(5):602-22.

Conferences

- Bardet, Vo TH, Bosson JL, Bedouch P, Allenet B. ***General Practitioner – Community Pharmacist Collaboration Models: a systematic review.*** The European Society of Clinical Pharmacy International Workshop. Edinburgh, 30 -31 may 2013, Scotland (oral communication).
- Bardet JD, Vo TH, Bosson JL, Bedouch P, Allenet B. ***Community Pharmacists' perspective in General Practitioner – Community Pharmacist collaboration initiation in France : a qualitative study.*** 13th Asian Conference on Clinical Pharmacy. Haiphong, 13-15 September 2013 (Oral communication).

3. Participation to article peer-review

- Teeraporn Chanakit et al. ***Hospital pharmacists' perceptions of the suitability of doctor of pharmacy graduates in hospital settings in Thailand.*** BMC Medical Education. 2015, 15:181

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TABLE

Abbreviations list

ADE: Adverse drug event
ADR: Adverse drug reaction
CBA: Cost-benefit analysis
CEA: Cost-effectiveness analysis
CMA: Cost-minimization analysis
CPS: Clinical pharmacy service
CUA: Cost-utility analysis
DRM: Drug-related morbidity
DRP: Drug-related problem
GP: General practitioner
HCP: Health care providers
IRA: evaluating interrater agreement
IRR: interrater reliability
k: kappa score, kw: weighted kappa
LOS: Length of stay
ME: Medication error
MR: Medication review
PI: Pharmacist intervention
QALY = Quality-adjusted life years
SFPC: Société Française de Pharmacie Clinique (French Society of Clinical Pharmacy)
SHPA: Society of Hospital Pharmacists of Australia
SIG: the Special Interest Group ‘‘Standardizing and demonstrating the value of clinical pharmacy activities’’ belonging to the SFPC
CPU: Centralized Preparation of cytotoxic drugs Unit
USA: United States of America

Definitions list

Pharmacist intervention: any action by a clinical pharmacist that directly results in a change in patient management or therapy

Medication review: a structured, critical examination of a patient's medications with the objectives of reaching an agreement with the patient about their treatment and optimizing the impact of medications on patient's health outcomes.

Drug-related problem: an event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care.

Medication error: the failure of a planned action to be completed as intended or use of a wrong plan to achieve an aim.

"Actual" or "potential" impact/consequence/significance: Term "actual" is understood as meaning the entity that has appeared in the patient, while the term "potential" referred to the situation in which the possibility that the entity could appear in the patient existed.

A tool for assessing the impacts of a pharmacist intervention: an explicit description of a method for rating the impacts of a pharmacist intervention.

Quality: quality can have two meanings: 1. the characteristics of a product or service that bear on its ability to satisfy stated or implied needs; 2. a product or service free of deficiencies. (ISO 9000)

Structure of care: context in which care is delivered, including hospital buildings, staff, financing, and equipment...

Process of care: transactions between patients and providers throughout the delivery of healthcare

Costs: Costs can be thought of as "inputs" or resources required to provide the service. In the case of clinical pharmacy services, inputs are primarily comprised of the labor costs associated with the personnel who provide the care or services.

Outcomes: outcomes can be thought of as "outputs" of the service or program. Outcomes can be in the form of clinical outcomes, humanistic outcomes, or economic outcomes.

Clinical outcome: medical events occur as a result of disease or treatment.

Humanistic outcome: consequences of disease or treatment on patient functional status, or quality of life.

Economic outcome: direct, indirect, and intangible costs, compared with the consequences of medical treatment alternatives.

Cost savings of a PI: The difference between the cost of the original therapy and the new therapy gives the cost savings (or the increase in the cost of therapy).

Cost avoidance of a PI: Cost avoidance refers to the prevention of additional health resources which are required to treat drug adverse events if a pharmacist has not intervened such as a hospitalization or a medical visit.

Cost of implementation of a PI: cost refers to the expenses of providing the PI such as cost of pharmacist's time, phone calls.

INTRODUCTION

Prescription medication use is widespread, complex, and increasingly risky. For example, clinicians have access to more than 10,000 prescription medications, and nearly one-third of adults take 5 or more medications in the United States of America (USA) (1). Advances in pharmaceutical treatments have undoubtedly resulted in major improvements in health for patients with many diseases, but these treatments have also been accompanied by increased risks.

Drug-related problems (DRPs) are one of the significant causes of morbidity and mortality in developed countries (2). The rate of drug-related admission have ranged from 2.3% (3) to 27.3% (4) in different studies in USA. In France, the serious adverse drug events are responsible for 1.5% of the hospital admissions (5). The cost of adverse drug events admitted to urgent care services was estimated at 636 million EUR in France in 2002 (6). In both USA and France, approximately 50% of these drug-related hospital admission were potentially preventable (5, 7).

A major report by the Institute of Medicine in USA on medication errors suggests that, despite all the progress in patient safety, medication errors remain extremely common, and the health care system can do much more to prevent them. The report emphasizes actions that health care systems, providers, funders, and regulators can take to improve medication safety (7).

Clinical pharmacists are experts in the therapeutic use of medications and, thus, are an essential part of promotion of the patient safety and optimization of patient outcomes (8). The nature and extent of clinical pharmacy services (CPSs) provided appear to be highly variable. Of which, medication review (MR) is one of the major contribution of pharmacists, defined as "as a structured, critical examination of a patient's medications with the objectives of reaching an agreement with the patient about their treatment and optimizing the impact of medications on patient's health outcomes (9)."

One of the major outputs of MR is the generation of pharmacist interventions (PIs) described as "any action by a clinical pharmacist that directly results in a change in patient management or therapy" (10). Within the system of health care, pharmacists routinely provide medication therapy evaluations and recommendations to patients and health care professionals (8).

While the pharmaceutical care has undergone dramatic changes since 30 years, pharmacists still need to demonstrate the benefits or added value of services. Clinical pharmacy services in general and PIs in particular add quality and value to health care outcomes, but the magnitude and value of these effects have not been adequately established. Anecdotal reports of CPSs' impact on outcomes are more common than empirical evidence. In times of limited resources allocation, it is necessary for pharmacists to justify the added value of CPSs and PIs (11).

Methods and tools assessing the significance of PIs are diverse and their valid, reliable, comprehensive and practical properties are questionable. The only literature review of tools of rating of pharmacist interventions was reported in 1999 by Overhage and Lakes (12). The paper noted that among 51 identified articles, only 10 included an explicit description of the rating tool used. Thus, the authors developed a two-dimensional tool that could characterize the severity of the DRP inspired from the tool of Folli et al. (13) and the value of that intervention inspired from the tool of Hatoum et al. (14). A broad adoption of this validated tool has been used for characterizing clinical activities in different settings. This tool was demonstrated to be valid, comprehensive and practical in the original study. However, others adopted this tool and many found *poor* agreement of ratings. There were some risks of bias which were likely to explain high agreement in the study of Overhage and Lakes but not repeatable in other studies. To our knowledge, there is no other up-to-date literature review of existing tool for assessing potential impacts of PIs. Furthermore, since then, with economic constraints growing, aging, burden of chronic disease, patient's lack of compliance, the assessment of quality of PIs is shifting from only clinical to economic and humanistic impacts (e.g., patient's quality of life, compliance, and satisfaction). This trend requires new properties of tools. Therefore, the purpose of this thesis work is to research on methodologies of evaluation of value of PIs as well as development and validation of a new tool for assessing potential impacts of PIs in hospitals.

The **Part 1** presents the global picture of MR with three main sub-parties: (i) context in which medication review locates, (ii) characteristics of practice of MR, and (iii) methodologies of evaluation of impacts of MR/PIs.

In the **Part 2**, we review tools for assessing potential significance of PIs in literature and present some important tools in detail.

The **Part 3** presents the process of development and validation of a new tool - CLEO for assessing potential impacts of PIs in hospital.

Then in the **Part 4**, we discuss on findings of the work and perspectives from results of the studies.

PART 1.

MEDICATION REVIEW: CONTEXT, PRACTICE AND EVALUATION OF IMPACTS

*In this **Part 1,** firstly, we present why drug safety has become a major problem of health care system and how clinical pharmacy services can contribute to resolve this problem. MR is considered as a core and integrated practice of other CPSs, therefore, practice of MR in literature is described in detail. We finish this part by review of methodologies of evaluation of impacts of MR, which is useful to development a new tool for assessing PIs in the **Part 2**.*

1. Context: drug safety and clinical pharmacy services

1.1. Drug safety

Although there is a growing interest in drug safety, there remains much confusion about the terminology used to describe the problem. The inconsistencies in the definitions of commonly used terms may have an adverse impact on the accuracy of event rates, the establishment of medication safety priorities and on the validity of cross-study comparisons. It is imperative that standardized terminology be adopted and used consistently (15).

1.1.1. Types of problems associated with drug use

Ackroyd-Stolarz et al. (15) performed a review of the drug safety literature. The differences between the main types of problems associated with medication use are substantial: some are preventable events and some are not, some result in injury and some do not. A description of commonly used terms is provided.

First, the terminology will be defined broadly to include drug-related (therapy) problems (DRPs). Subsets of DRPs include drug-related morbidity (DRM) and medication misadventures. The latter term includes medication errors, adverse drug reactions (ADRs), and adverse drug events (ADEs). ***Figure 1*** provides a visual depiction of the relationships between these terms. The authors have classified events into those that result in injury and those that do not.

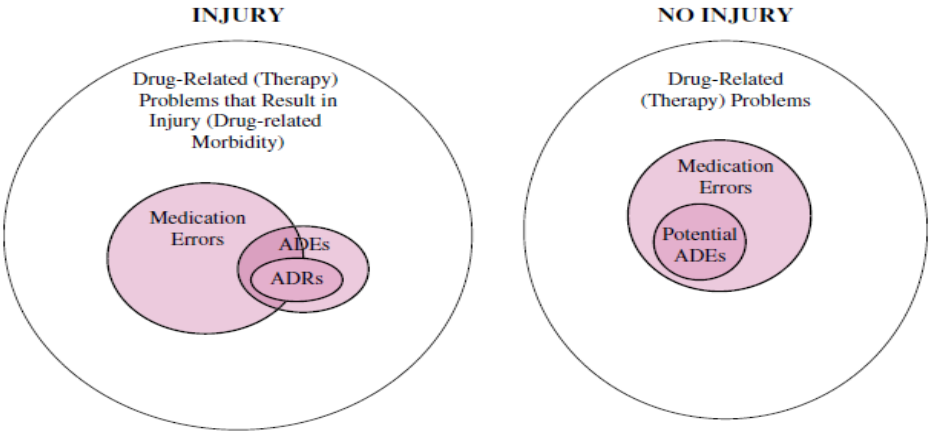

Figure 1. Relationships between the different types of problems associated with medication use

ADE: adverse drug event. ADR: adverse drug reaction

Source: Duplicated from Ackroyd-Stolarz S, Hartnell N, Mackinnon NJ. Demystifying medication safety: making sense of the terminology. Res Social Adm Pharm. 2006 Jun;2(2):280-9.

1.1.1.1. Drug-related problems

A DRP can be defined as "an event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care" by Hepler and Strand (16).

1.1.1.2. Drug-related morbidity

Drug-related morbidity (DRM) is defined as "the failure of a therapeutic agent to produce the intended therapeutic outcome, or the clinical or biosocial manifestation of unresolved DRPs" (16). In helping to distinguish between DRPs and DRMs, Hepler (17) states that the patient injury that occurs as part of a DRM is a ‘‘severe, dangerous, injurious, or disabling clinical outcome that was not correctable or required significant additional medical care to correct, e.g., emergency treatment or hospitalization.’’ Thus, all DRMs result in injury whereas only a small percentage of DRPs result in injury, and those injuries would not be serious.

It is estimated that approximately 50% of DRMs are preventable (18). To claim that a particular DRM is preventable, Hepler and Strand state that the following 4 characteristics must be met: a preexisting DRP must have been recognizable: the adverse outcome or treatment failure must have been foreseeable; the causes of the DRP and the outcome must have been both identifiable and controllable (16).

1.1.1.3. Medication misadventures

Another ‘‘broad’’ term that captures several different types of adverse outcomes from pharmaceuticals is medication misadventure. According to the American Society of Health-System Pharmacists, medication misadventures consist of the sum of (1) medication errors, (2) ADRs, and (3) ADEs. Medication misadventures encompass more events than DRM in that DRM only includes events that result in serious injury while a medication misadventure does not necessitate a serious injury to the patient (e.g., may result in discomfort only) (19).

1.1.1.4. Adverse drug events

An ADE is any injury that is caused by a medication (or lack of an intended medicine) (20). A subset of ADEs can happen despite proper use of the medication by the patient, and these would be considered ADRs. Not all ADEs are caused by error. But, most of the ADEs that are caused by errors are usually predictable and preventable (e.g., excessive dose) (15).

1.1.1.5. Medication errors

Medication error (ME) is defined as "the failure of a planned action to be completed as intended or use of a wrong plan to achieve an aim" (7). Medication errors are preventable. Events that can occur at any stage in the medication use process that lead to patient harm or inappropriate medication use. Only a very small percentage of medication errors actually result in injury. All of those that do result in an injury would also be classified as ADEs. However, not all ADEs are classified as medication errors, such as ADRs that do not occur as a result of error (15). According to James Reason, errors depend in two kinds of failures:

either the correct action does not proceed as intended (an error of execution) or the original action is not correct (an error of planning) (21).

1.1.1.6. Adverse drug reactions

The World Health Organization has defined an ADR as a "response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease, or for modification of physiologic function." This definition does not include therapeutic failures, drug abuse, errors in drug administration, noncompliance with directions for drug use, or intentional and accidental poisonings. Some ADRs do result from medication errors (also known as preventable ADRs). ADRs can also be thought as a subset of ADEs. All ADRs result in injury, although the injury can be temporary or permanent (15).

1.1.2. Epidemiology of drug safety

1.1.2.1. Incidence

The Harvard Medical Practice Study (22) is probably the most well-known retrospective study of ADEs, suggested that ADEs occurred in 0.7% of inpatients. A more recent US study suggested a similar figure of 0.6% (23). From Australian and UK studies, it can be estimated that preventable medication-related harm (harm due to MEs) occurred in 0.8% of admissions (24). In France, a frequency of ADEs was of 6.7-10.4% of inpatients (6).

ME rates reported in the literature vary widely. Studies suggest that MEs occur in 0.3–9.1% of medication orders written for hospital inpatients (24). Not all errors have equal propensity for harm; one study estimated that only 0.9% of errors resulted in harm (20). Medication errors can happen in all stages in the drug use process, most frequently at the prescribing and administration stages:
- prescription (37%(25); 56%(26))
- transcription of prescription (18%(25); 6%(26))
- dispensing (22%(25); 4%(26))
- administration (23%(25); 34%(26)).

The incidence of DRPs will be presented in **2.2. Epidemiology of medication review**.

1.1.2.2. Morbidity/Mortality

ADEs are one of the significant causes of morbidity and mortality in developed countries (2). Incidence estimates suggest that more than 1.5 million preventable ADEs occur each year in the United States, responsible for approximately 3-16% of the hospital admissions. In 1983, 2876 people died from ME in USA. ME deaths increased 2.57-fold between 1983 and 1993 (27). It caused a significant impact on their health care system, estimated at $76 and $177 billions in the years 1995 and 2000, respectively (28).

In France, the serious adverse drug events were responsible for 1.5% of the hospital admissions (5) and the cost of ADEs admitted to urgent care services was estimated at 636 million EUR (6). In both the USA and France, approximately 50% of these drug-related hospital admission are potentially preventable (5, 7).

1.2. Management of medication errors

1.2.1. System Approach of management of medication errors

The problem of ME can be viewed in 2 ways: the person approach and the system approach. Each has its model of error causation, and each model gives rise to different philosophies of error management which are described in ***Table 1***(29).

Table 1. Approach of management of medication errors

	Person approach	**System approach**
Philosophy	It focuses on the unsafe acts—errors and procedural violations—of people on the front line: nurses, physicians, surgeons, anesthetists, pharmacists, and the like.	Errors are seen as consequences rather than causes, having their origins not so much in the perversity of human nature as in "upstream" systemic factors.
Causes	Errors of individuals include forgetfulness, inattention, or moral weakness.	Defenses, barriers and safeguards failed to prevent errors.
Corrective strategies	Reducing unwanted variability in human behavior (campaigns that appeal to people's fear, writing another procedure, disciplinary measures, threat of litigation, retraining, naming, blaming, and shaming	We can change the conditions under which humans work = system defenses

Source: Adapted from Reason J. Human error: models and management. BMJ. 2000 Mar 18;320(7237):768-70.

The person approach has serious shortcomings and is ill-suited to management of ME. Indeed, continued adherence to this approach is likely to prevent the development of safer health care institutions. Preventing errors means designing the health care system at all levels to make it safer by using the system approach (7).

The "Swiss Cheese"model of system accidents

According to the "Swiss Cheese" model of system accidents, defenses, barriers, and safeguards occupy a key position in the system approach (29). Their function is to protect potential victims and assets from local hazards. They are more like slices of Swiss cheese, having many holes—although, unlike in the cheese, these holes are continually opening, shutting, and shifting their location. The presence of holes in any one "slice" does not normally cause a bad outcome. Usually this can happen only when the holes in many layers momentarily line up to permit a trajectory of accident opportunity—bringing hazards into

damaging contact with victims (***Figure 2***). The holes in the defenses arise for 2 reasons: active failures and latent conditions.

- Active failures: are the unsafe acts committed by people who are in direct contact with the patient or system. They take a variety of forms: slips, lapses, fumbles, mistakes, and procedural violations.
- Latent conditions: are the inevitable "resident pathogens" within a system. They arise from decisions made by designers, builders, procedure writers, and top-level management.

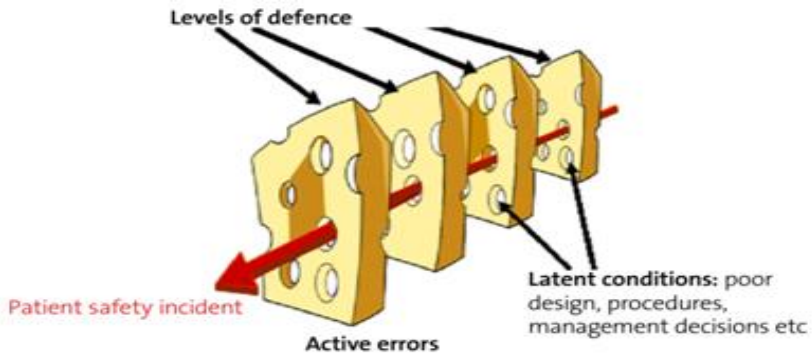

Figure 2. The Swiss cheese model of how defenses, barriers, and safeguards may be penetrated by a patient safety incident

Source: Duplicated from Reason J. Human error: models and management. BMJ. 2000 Mar 18;320(7237):768-70.

Latent conditions—as the term suggests—may lie dormant within the system for many years before they combine with active failures and local triggers to create an accident opportunity. Unlike active failures, whose specific forms are often hard to foresee, latent conditions can be identified and remedied before an adverse event occurs. Understanding this leads to proactive rather than reactive risk management (29).

For example, Leape et al. have taken the analysis of ADEs (30). They defined a system as "an interdependent group of items, people or processes with a common purpose" and recognized that a medicines use system would involve external systems, e.g., professional education and information dissemination, and would include subsystems of various complexities. They first classified errors into 15 types and cross-tabulated them by the stage in order processing where they had occurred. Then they searched for proximal causes, defined as the apparent reason the error was made. They found 13 proximal causes and 16 system failures. The usefulness of the system view was demonstrated powerfully by the fact that there was not a one-to-one relationship between proximal causes and errors. Some proximal causes contributed to many error types. Likewise, an error could result from more than one proximal cause. The identification of system failures led the investigators to recommend four specific system changes: computerized order entry, adding a clinical pharmacist to the patient care team, providing electronic drug information, and standardizing doses and administration times.

1.2.2. Strategies for improvement of drug safety

In a study, physician raters identified three strategies that might be most effective in preventing errors: computerized physician order entry with clinical decision support systems (76%); ward-based clinical pharmacists (81%); and improved communication among physicians, nurses, and pharmacists (86%) (31).

Single methods of optimizing medication outcomes have not been shown to be as effective as multifaceted approaches (32). Recent analyses have shown that there is a higher likelihood of achieving improved outcomes of care when three or more of the following aspects of healthcare are impacted: patient self-management, clinical information availability, redesign of the way care is delivered, decision support strategies, the healthcare system, and the provider organization. In a review of interventions designed to improve the care of patients with chronic illnesses, process variables were improved when one or two of the aspects were improved. Outcome variables were improved when three or four of the aspects were impacted (32).

A comprehensive approach to improving patient safety is needed. Consistent with recommendations from the Institute of Medicine in USA this will mean (7):

1. Creation of leadership and research to enhance the knowledge base about safety (eg, tools for identifying and analyzing errors and evaluate approaches taken; tools and methods for educating consumers about patient safety; standardizing and simplifying equipment, supplies, and processes).
2. Identifying and learning from errors through immediate and strong mandatory reporting efforts, as well as the encouragement of voluntary efforts.
3. Raising standards and expectations for improvements in safety (such as licensing, certification, and accreditation) through the actions of organizations, group purchasers, and professional groups
4. Improvement of provider-patient and inter-provider communications
5. Development of effective multidisciplinary teams with good cooperation among patients, physicians, and pharmacists
6. Establish interdisciplinary team training programs for providers that incorporate proven methods of team training, such as simulation.
7. Information technology in planning care and in evaluating quality: e.g., computerized prescription order entry and computerized decision support systems, bar coding and smart intravenous (IV) pumps.
8. Coordination of care across patient conditions, and type and location of service
9. Development of clinical pharmacy services (e.g., patient education, medication review, pharmacist participation on hospital rounds).

1.3. Clinical pharmacy and clinical pharmacy services

1.3.1. Clinical pharmacy: definition and history

Clinical pharmacy is a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention (8). The

practice of clinical pharmacy embraces the philosophy of pharmaceutical care as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (16). Within the system of health care, clinical pharmacists are experts in the therapeutic use of medications. They routinely provide medication therapy evaluations and recommendations to patients and health care professionals. Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications(8).

The strategic framework for optimizing drug therapy outcomes has evolved over time (***Table 1***). Since 2000, the focus shifted to population-based approaches of reducing cost and maintaining quality care for patients with chronic illnesses and disease prevention (32).

Table 2. Evolution of strategic framework for optimizing drug therapy outcomes

Period	Strategy	Features
1980-1990	Drug focus	Choices of medications within drug classes; drugs blamed for poor outcome
1990-2000	Disease focus	High-cost, prevalent diseases; drug classes involved in disease treatment; disease or physician blamed for poor outcome
1995-present	Patient focus	High-cost, complex-care patients; patient or physician blamed for poor outcome
2000-present	Chronic care focus; disease prevention	System of providing care; blameless culture

Source: Czubak R, Tucker J, Zarowitz BJ. Optimizing drug prescribing in managed care populations - Improving clinical and economic outcomes. Dis Manage Health Outcomes 2004;12(3):147-67.

1.3.2. Clinical pharmacy services

For optimizing drug therapy outcomes, there are various types of clinical pharmacy services (CPSs) which pharmacists participate actively in patient care. Bond et al. (33) gave a definition of 15 CPSs in hospitals which were divided into 2 groups: central and patient-specific CPSs (***Table 3***) while Harrison et al. (34) described 7 types of CPSs in ambulatory settings (***Table 4***).

Table 3. Definitions of Clinical Pharmacy Services in hospitals

Service	Definition
Central Clinical Services	
1. Drug-Use evaluation	check if at minimum, drug-use patterns are analyzed and results are reported to a hospital committee.
2. In-service education	pharmacist presents continuing education to fellow employees (physicians, nurses, pharmacists, etc.) on a scheduled basis at least 4 times/year.
3. Drug	provided only if a formal drug information service with specifically

information	assigned pharmacist is available for questions. Does not required a physical location called drug information center.
4. Poison information	provided only if a pharmacist is available to answer toxicity and overdose questions on a routine basis with appropriate resources.
5. Clinical research	performed by pharmacist either as a principal investigator or coinvestigator. Pharmacist is likely to be (co-) author on a published paper. Do not check if activity is limited to investigational drug distribution or record keeping.
6. Drug safety officer	pharmacist(s) has specific time set aside each week to work on improving drug safety in the hospital.
Patient-Specific Clinical Pharmacy Services	
7. ADR management	pharmacist evaluates potential ADR while the patient is hospitalized and appropriately follows through with physicians.
8. Pharmacokinetic consultation	provided only if at a minimum, the drug regimen, serum level, and patient's medical record is reviewed, and verbal or written follow-up is provided when necessary.
9. Drug therapy monitoring	provided only if a patient's medical record is reviewed, and verbal or written follow-up is provided when needed. Monitoring is ongoing and repeated, often on a daily basis. Do not check if drug orders are reviewed. Does not include pharmacokinetic consults, total parenteral nutrition (TPN) team, rounds, ADR management, or drug therapy protocol management.
10. Drug protocol management	pharmacist, under the order of a prescriber, requests laboratory tests if needed and initiates or adjusts drug dosage to obtain the desired therapeutic outcome (e.g., aminoglycoside or heparin dosing per pharmacy).
11. TPN team participation	pharmacist, at a minimum, reviews patient's medical records and/or provides written or verbal follow-up if needed.
12. Drug counseling	pharmacist provides counseling on drugs either during hospitalization or at time of discharge. Do not check if counseling involves solely review of label direction.
13. Cardiopulmonary resuscitation team participation	pharmacist is an active member of the CPR team attending most cardiac arrests when the pharmacist is present in the hospital.
14. Medical rounds participation	pharmacist rounds with a medical team at least 3 days/week, actively providing specific input.
15. Admission drug histories	pharmacist provides admission histories.

ADR: adverse drug reaction. TPN: total parenteral nutrition. CRP: Cardiopulmonary resuscitation team

Source: Bond CA, Raehl CL, Franke T. Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. Pharmacotherapy. 2002 Feb;22(2):134-47.

Table 4. Types of clinical pharmacy services in ambulatory settings

Service	Description
1. Primary pharmaceutical care intervention	Comprehensive patient assessment with review of drug therapy regimen for indication, efficacy and safety Identification of actual and potential drug therapy problems, preparation of care plans and therapeutic recommendations
2. Patient teaching	Medication teaching and review of drug therapy regimens Providing updated medication schedule to patient
3. Medication reconciliation	Performing a comprehensive medication history including all prescription, non-prescription and complementary and alternative medication use Documentation of full medication history in outpatient electronic chart Communicating medication changes to patients, other health care providers and community pharmacies
4. Referral of issue for team follow-up	Re-directing and communicating patient care issues as appropriate to other members of the inter-professional team; may involve verbal and/or written communication
5. Optimizing medication adherence	Optimizing medication schedules to promote patient adherence taking into account cultural/lifestyle factors and medication-taking behavior Developing and implementing patient-specific adherence strategies and tools
6. Medical/drug information and advice	Responding to drug information queries from patients and the inter-professional team Providing medical advice where appropriate, in collaboration with the inter-professional team
7. Other	Assisting with drug coverage and reimbursement issues Assisting with preparation of prescriptions Updating community pharmacies with changes to drug therapy regimens Collaborating with community pharmacist to manage adherence issues (e.g., blister packing)

Source: Harrison JJ, Wang J, Cervenko J, Jackson L, Munyal D, Hamandi B, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clin Transplant. 2012;26(2):E149-57.

The provision of CPSs to individual patients consists of a range of overlapping CPSs, many which are performed concurrently. These CPSs contribute to the patient's medication view with the goal of optimizing the drug use (10). Medication review will be introduced in detail in the Section **"Practice of medication review"**.

1.3.3. Impacts of clinical pharmacy services

1.3.3.1. Clinical impacts

Clinical pharmacists provide a unique set of knowledge and skills to the health care team by assuming the role of drug therapy expert to proactively advance rational drug therapy (1). There is a growing body of literature demonstrating the beneficial effects of clinical

pharmacist care on important outcomes for both hospitalized (35, 36) and ambulatory patients (37, 38).

A recent systematic review of 36 controlled trials (35) found that "interacting with the health care team on patient rounds, interviewing patients, reconciling medications, and providing patient discharge teaching and follow-up" led to reductions in MEs, ADEs, ADRs, and length of hospital stay (LOS), with no evidence of harm. A retrospective analysis of data from nearly 3 million patients in 885 US hospitals (36) showed that CPSs were associated with improvements in mortality and LOS. Favorable results were also found in hemoglobin A1c, LDL cholesterol, blood pressure, and adverse drug events with pharmacists' direct patient care over comparative services (39).

Where it may be appropriate to anticipate that pharmacists can positively impact in deaths or hospital admissions, given the types of PIs make, the outcome achieved are likely to be more limited. For example, hospital admissions that are related to drug therapy and are preventable occur at a rate of 4.5% of all admissions. However, only approximately 13% of patients who receive pharmaceutical care will be admitted to hospital; hence, the proportion in whom a PI could prevent an admission is likely to be around 0.6%. Using admissions as primary outcome measure would thus seem to be limited in its sensitivity to PIs, requiring large patient numbers to detect benefit (40). Many studies have involved patient groups at high risk of drug-related hospital admissions, yet researchers often fail to detect a benefit (41). In heart failure, for example, meta-analysis, has shown that there may be benefits, but only if pharmacists are part of a multi-disciplinary team (42). In addition, there are occasions when hospital admission is a beneficial outcome of a PI (40).

1.3.3.2. Economic impacts

A study of 1016 hospitals in USA found that CPSs were associated with lower total cost of care (43). Another review of economic evaluations of CPSs found that a positive economic benefit associated with CPSs was noted in 69% of studies and the pooled median value was 4.81:1- meaning that for every $1 invested in CPS, $4.81 was achieved in reduced costs or other economic benefits (44). Another systematic review found 16% of studies indicated positive economic benefits as a result of CPSs.

1.3.3.3. Humanistic impacts

Humanistic impacts, also called as patient-related outcome measures are increasingly recognized as important. Results for humanistic outcomes varied across studies. A meta-analyses found that medication adherence, patient knowledge, and quality of life-general health were favorable with pharmacists' direct patient care (35, 39). In contrary, many studies assessing the potential benefits of PIs have measured quality of life, using generic measures, such as *the 36-Item Short Form Health Survey (SF-36)* or *the EG-5D* (a standardized measure of health status), which generally have shown no impact. Studies using disease-specific quality-of-life measure have been more successful (45).

In conclusion, drug safety is a major problem of public health because of its morbidity and mortality. System approach rather than personal approach is effective to manage drug safety and quality improvement. In fact, combination and cooperation of many strategies at different levels is necessary to deal with this problem. Of that, clinical pharmacy and pharmaceutical care in a form of many different clinical pharmacy services were proved as promising solutions to improve rational drug use and improve patient outcomes.

2. Practice of medication review

The provision of CPSs to individual patients consists of a range of overlapping CPSs, many which are performed concurrently. These CPSs contribute to the patient's medication view with the goal of optimizing the drug use (10). Medication review is one of the major contributions of pharmacists to detect, resolve and prevent DRPs for patients. In this section, we will describe how MR is practiced in literature.

2.1. Process of Medication Review

2.1.1. Definitions

2.1.1.1. Medication review

Medication review is one of daily main activities of pharmacists in clinical settings. "Medication review can be defined as a structured, critical examination of a patient's medications with the objectives of reaching an agreement with the patient about their treatment and optimizing the impact of medications on patient's health outcomes (9)."

Medication review is available in many countries in different names and characteristics such as Medicines Use Review in UK (46), Medication Therapy Management in United States of America (47), Home Medication Review in Australia (48), MedsCheck in Canada (49) and Medicines Use Review in New Zealand (50) and Pharmaceutical Analysis in France (51).

2.1.1.2. Pharmacist Interventions

One of the major outputs of medication review is the generation of PIs. Within the system of health care, pharmacists routinely provide MR and recommendations to patients and health care professionals (8). Definitions of pharmacist interventions vary across studies. Some typical definitions are summarized in ***Table 5.*** Among them, a PI is commonly defined as "any action by a pharmacist that directly resulted in a change in patient management or therapy" by the Society of Hospital Pharmacists of Australia (52). In this thesis, we used this definition of a PI.

Table 5. Definitions of pharmacist intervention

Terms	Definition	Author(s), published year
Pharmacist intervention	"discrete activities by pharmacists related to patient care"	Rothschild et al., 2010 (53)
Pharmacists' Clinical Intervention	"any reactive (in response to an erroneous medication order) activity undertaken to suggest changes in one medication order that might involve contacting medical staff"	Abdel-Qader et al., 2010 (54)
Clinical Pharmacy Intervention	"any action by a pharmacist that directly resulted in a change in patient management or therapy"	Society of Hospital Pharmacists of Australia, 2005 (55)

2.1.2. Process of medication review

Medication review by pharmacists is a systematic process of collecting patient-specific information, assessing drug therapy to identify medication related problems, prioritizing such problems, and creating a care plan to resolve them (16). The Review Process consists of 4 steps (46):

1. Identify patients
2. Carry out the review
3. Record review outcomes/Feedback results
4. Audit/Quality assurance

2.1.2.1. Identifying patients

Patients with a potential need for MR can be identified by the pharmacist, the physician or other healthcare professionals, or the patients themselves when DRPs are suspected (47). Starting to carry out MRs can be quite daunting particularly where there are large numbers of patients involved. Therefore, MR initially needs to be prioritized to patients who are at risk of DRPs. Some screening tools for the patient at risk were developed. For example, according to "A Guide to Patient Medication Review" of the Northern Health and Social Services Board in UK (46), these risk groups fall into 5 main categories that often overlap as shown in ***Table 6***.

Table 6. High risk group of drug-related problems

High Risk Group	**Examples of reasons for high risk**
Elderly (>75 years)	• Complex medication regimen • Polypharmacy • Multiple pathologies • Compliance issues • Physical problems (e.g., swallowing, arthritis) • Resident in care home • Mental states (e.g., confusion, dementia, depression, anxiety)
Chronic diseases	• Polypharmacy • Recent discharge from hospital • Medicines from more than one source • Adverse effects/drug interactions • Taking drugs requiring special monitoring • Current management plan is outdated due to the availability of new evidence
Specialist drugs**	Drugs with narrow therapeutic range (e.g., digoxin, warfarin) • Drugs on red/amber lists • Drugs which require special monitoring (e.g., lithium)
Nursing/ Residential Homes	• • Use of commercial sip feeds as an ‘easy’ alternative to liquidized or pureed foods • Polypharmacy • Poor utilization of "Home Remedies"

	• Reordering systems can be time-consuming • Overuse of antipsychotics/sedatives
Polypharmacy	• Taking four or more regular medicines daily • Complex regimes • Compliance problems • Adverse effects or drug interactions • Current management plan is outdated due to the availability of new evidence

Source: Clyne W, Blenkinsopp A, Seal R. A Guide to Medication Review. 2008. Available at http://www.npc.nhs.uk/review_medicines/intro/resources/agtmr_web1.pdf (last accessed November 2011). 2008.

The descriptions of other screening tools are summarized in ***Table 7***.

Table 7. Screening Tools for patients at risk of DRPs

Tools	Description
Indicators for the selection of ambulatory patients (56)	An eight-member panel of ambulatory-care pharmacists choose and tested 6 prognostic indicators: (1) five or more medications in present drug regimen, (2) 12 or more medication doses per day, (3) medication regimen changed four or more times during the past 12 months, (4) more than three concurrent disease states present, (5) history of noncompliance, and (6) presence of drugs that require therapeutic drug monitoring
A computer-based program to identify patients at high risk for DRPs (57)	The program used 6 criteria regarding medication use: (1) five or more medications, (2) > or = 12 doses per day, (3) four or more changes to the medication regimen, (4) three or more chronic diseases, (5) history of noncompliance, and (6) presence of a drug requiring therapeutic drug monitoring
A self-administered medication-risk questionnaire in an elderly population (58)	10-item self-administered questionnaire for use by elderly patients to identify who is at increased risk of potentially experiencing a DRP
A screening tool for the identification of patients experiencing DRPs (59)	A semi-structured tool
Using the costs of drug therapy (60)	Using the cost of drug therapy (threshold = 2000 Swiss francs [CHF], 1440 USD, 1360 EUR) as a screening criterion for identifying patients who may benefit from community pharmacy-based MR.
Considerations for identification of patients who	Providing 12 factors needed to take into account for prioritizing who may benefit most from Medication Therapy Management: experienced a transition of care, receiving care from more than one prescriber, has

may benefit from Medication Therapy Management Services (47)	at least one chronic disease or chronic health condition...
Medication Regimen Complexity Index (61)	A 65–item Medication Regimen Complexity Index was developed, including the number of drugs, dosage frequency, administration instructions, and the prescribed dosage forms.
Electronic screening of medical records to detect inpatients at risk of DRPs (62)	A screening tool consists of electronic queries: patients receiving drugs such as cytochrome P450 inducers, inhibitors or high-risk medications, those with renal impairment, those on digoxin with low serum potassium, those with intravenous anti-infectives or intravenous acetaminophen for more than 3 days, and elderly patients with poly-medication (>or=80 years and >10 drugs).
A new set of explicit medication assessment criteria and prioritization of topics for improvement (63)	Fifty-two final "quality" assessment criteria target patients with unmet indications, sub-optimal selection or intensity of beneficial drug treatments. A total of 124 "safety" assessment criteria target patients with unmet needs for risk-mitigating agents, high-risk drug selection, excessive dose or duration, inconsistent monitoring or dosing instructions.
A method of targeting CPSs at high-risk patients through the use of an electronic prescribing system (64)	A scoring system assigned patients into a low, medium or high risk category. The results were then emailed to all members of the clinical pharmacy team automatically for use and evaluation.
An electronic patient prioritization tool for clinical pharmacist interventions (65)	Developed the Assessment of Risk Tool (ART), an application for monitoring pre-specified clinical "flags" for high-risk medication use and other ADE risk factors. The ART permits ADE risk assessment in virtual real time (e.g., medication-use data and other clinical information are updated multiple times daily). Each of the 38 flags captured by the ART is assigned a weighted score; the item scores are summed to provide a total ART score indicating low, medium, or high ADE risk, and patients are prioritized by the ART score for PIs such as clinical review and discharge coordination.

DRP: drug-related problem. MR: medication review. ART: assessment of risk tool. ADE: adverse drug event. PI: pharmacist intervention

2.1.2.2. Carrying out the review

Depending on its scope, the MR may include the following (47):
- Gather all relevant clinical information of the patient, including demographic information, general health and activity status, medical history, medication history, immunization history, and patients' thoughts or feelings about their conditions and medication use
- Assessing the patient's physical and overall health status, including current and previous diseases or conditions
- Assessing the patient's values, preferences, quality of life, and goals of therapy
- Assessing cultural issues, education level, language barriers, literacy level, and other characteristics of the patient's communication abilities that could affect outcomes
- Evaluating the patient to detect symptoms that could be attributed to adverse events caused by any of his or her current medications
- Interpreting, monitoring, and assessing patient's laboratory results
- Assessing, identifying, and prioritizing DRPs related to:
    - ✓ The clinical appropriateness of each medication being taken by the patient, including benefit versus risk
    - ✓ The appropriateness of the dose and dosing regimen of each medication, including consideration of indications, contraindications, potential adverse effects, and potential problems with concomitant medications
    - ✓ Therapeutic duplication or other unnecessary medications
    - ✓ Adherence to the therapy
    - ✓ Untreated diseases or conditions
    - ✓ Medication cost considerations
    - ✓ Healthcare/medication access considerations
- Developing a plan for resolving each DRP identified
- Providing education and training on the appropriate use of medications and monitoring devices and the importance of medication adherence and understanding treatment goals
- Coaching patients to be empowered to manage their medications
- Monitoring and evaluating the patient's response to therapy, including safety and effectiveness
- Communicating appropriate information to the physician or other healthcare professionals

The useful of systematic procedure to conduct MR has been demonstrated, comparing them to traditional procedures (66). Many methods have been suggested for standardization of process of MR and enhancement of DRP detection.

The simplest tool is perhaps a checklist which could be used as a prompt to verify that all critical checks have been performed and to ensure that optional check items are not forgotten. For example, a checklist developed by Meyler et al. (67) contained items related to order urgency, verification of patients' identity, therapeutic review (for safety and efficacy), and actionable items, and was designed for general purpose use on all wards for all types of patients. The French Society of Clinical Pharmacy (SFPC) developed also a comprehensive checklist as recommendations for a good practice of MR (51).

Different methods of MR in community pharmacy in France were introduced. Of them, Calop proposed a step-by-step process through an algorithm (68); Dupin-Spriet presented the ALAC pocket card (69) of 4 simple steps "Accueillir, Lire, Analyser, Commenter" (means "welcome, read, analyze, comment"); and the ADAPCO association (70) developed 6 specific evaluation grids to facilitate and standardize MR in community pharmacy. Kassam et al. in Canada (1999) (71) developed also tools used to help community pharmacists implement comprehensive pharmaceutical care.

In other study, Rovers et al. (66) developed the guided interview tool (a paper form) for pharmacy students in a hospital to gather a medication history, perform a review of general medication safety, and determine the need for additional therapy. The Northern Health and Social Services Board in UK (72) provided "A Guide to Patient Medication Review" with examples of forms and prompts that may be used during the review.

Many methods of documentation of MR also assisted pharmacists in completing the MR. Many acronyms have been coined that suggest the proper steps to follow when writing-up a patient (73). For example, the well-known SOAP (subjective, objective, analysis, plan) (74), an expanded-SOAP (adds goals, monitoring and education) (75), HOAP (replaces subjective and objective with history and observations) (76), FARM (findings, assessment, resolution, monitoring) (77), PWDT (pharmacist's workup of drug therapy) (78), PMDRP (Pharmacist's Management of Drug- Related Problems) (79), or SMPC (Standardized Method for Pharmaceutical Care) (80), PH-MD-ROME (Patient Introduction, Health Problems, Medications, Pharmaceutical Diagnoses, Recommended Orders, Desired Outcomes, Monitoring, Patient Counseling and Education) (73).

These various approaches all contain important elements of MR, but they all have advantages and disadvantages. The checklists, pocket card are simple but they are not complete and maybe difficult for initial stages of learning/practicing. The original SOAP concentrates on development of a medical diagnosis rather than DRPs or pharmacotherapeutic assessment. The expanded SOAP and FARM emphasize therapeutic problems, but continue to be organized around medical diagnoses (73). The PWDT, PMDRP, SMPC and PH-MD-ROME provided a structure which explicitly guided pharmacists through the pharmaceutical care process, assist pharmacists and students in the initial stages of learning and they can modify it into various shorter specialized tools according to practice requirement (79). In conclusion, during the initial training of pharmacy students, very detailed methods such as the PMDRP, PMDRP, SMPC can help inexperienced students more fully internalize aspects of the pharmaceutical care process. However, as students progress and develop a basic knowledge of therapeutic principles, these methods become cumbersome and checklists, post cards, algorithms are more efficient.

Coding instruments for recoding of PIs (16, 81-83) also assisted pharmacists in completing the MR. Other explicit/implicit tools have been developed to guide healthcare professionals in reviewing the medication patterns of general patients (84, 85), elderly patients (86, 87) or patients with chronic kidney disease (88).

Although MR and the needs of individual patients may vary, the use of consistent and standardized tools for MR, as described above, will enhance their efficient delivery and effective quality measurement (34).

2.1.3.3. Documentation and Follow-up

- **Documentation**

Documentation of MR and PIs has recognized as essential for demonstrating the added value of pharmacists to the healthcare system and justification for obtaining additional resources in clinical pharmacy practice. This assessment is also used as indicators of pharmacist's performance and the continuing quality improvement, research and education (89). There are many guidelines for the documentation of pharmacist-provided care (90), (91). Documentation elements for the patient record may include, but are not limited to, the following (47):

Table 8. Documentation elements for the patient record

Documentation category	Examples
Patient demographics	Basic information: address, phone, e-mail, gender, age, ethnicity, education status, patient's special needs, health plan benefit/insurance coverage
Subjective observations	Pertinent patient-reported information: previous medical history, family history, social history, chief complaints, allergies, previous adverse drug reactions
Objective observations	Known allergies, diseases, conditions, laboratory results, vital signs, diagnostic signs, physical exam results, review of systems
Assessment	Problem list, assessment of DRPs
Plan	A care plan is the healthcare professional's course of action for helping a patient achieve specific health goals
Education	Goal setting and instruction provided to the patient with verification of understanding
Collaboration	Communication with other healthcare professionals: recommendations, referrals, and correspondence with other professionals (cover letter, SOAP note)
Personal Medication Record	A record of all medications, including prescription and nonprescription medications, herbal products, and other dietary supplements
Medication-related action plan	Patient-centric document containing a list of actions to use in tracking progress for self-management
Follow-up	Transition plan or scheduling of next follow-up visit
Billing	Amount of time spent on patient care, level of complexity, amount charged

DRP: drug-related problem. SOAP note: an acronym for Subjective, Objective, Assessment, and Plan which is a method of documentation.
Source: American Pharmacist Association and National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model. 2008.

MR documentation includes creating and maintaining an ongoing patient-specific record that contains, in chronological order, a record of all provided care in an established standard. Ideally, documentation will be completed electronically or alternatively on paper (47).

A variety of coding instruments has been reported for recoding of intervention. For example, Classification of Helper and Strand (16), a comprehensive classification tool for treatment-related problems (92), PCNE Classification for DRPs (81), PI-Doc (82), APS-Doc (93), CPR taxonomy (94), systems developed by Westerlund (95), DOCUMENT system (96), Act-IP (97).

A computerized system for documenting PIs compared favorably with a manual system in terms of ease of use, accessibility, time efficiency, and acceptability (98) and facilitate integration with other clinicians, payer records, and healthcare systems (99).

Under-reporting of PIs is a known phenomenon that has been observed. Boardman et al. (100) found that under one-third (31%) of PIs were actually documented. The interventions that were documented tended to be those of highest clinical importance and those that were time-consuming to the pharmacist, interventions accepted by the attending physician. This high patient burden may contribute to under-reporting of PIs, as there is often not adequate time during clinic to document each PI. A survey of documentation practices was conducted in 106 community pharmacists in North Carolina in 2003(101) found that pharmacists spent an average of 14.9 hours per week providing patient care, with an average of 3.9 of these hours (approximately one fourth of patient care time) devoted to documentation. If recorded PIs continue to be used the main source of evidence of outputs of CPS, a better way of capturing this data needs to be developed (100).

- **Follow-up**

When a patient's care setting changes (e.g., hospital admission, hospital to home, hospital to long-term care facility, home to long-term care facility), the pharmacist transitions the patient to another pharmacist in the patient's new care setting. In these situations, the initial pharmacist participates cooperatively with the patient's new pharmacist to facilitate the coordinated transition of the patient, including the transfer of relevant medication and other health-related information.

If the patient will be remaining in the same care setting, the pharmacist should arrange for consistent follow-up in accordance with the patient's unique medication-related needs. All follow-up evaluations and interactions with the patient and his or her other healthcare professional(s) should be documented (47).

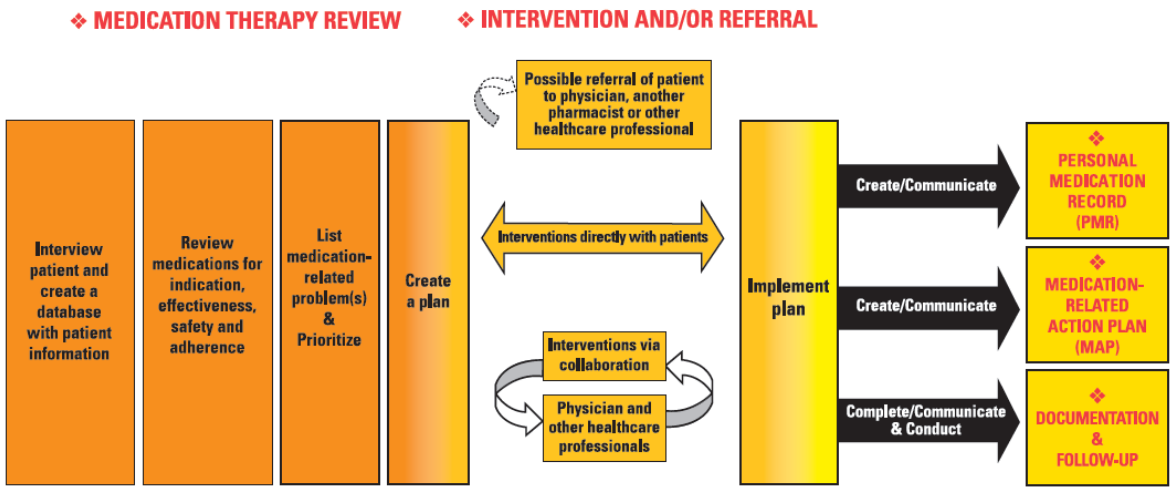

Figure 3. Flow Chart of a Medication Therapy Management Service Model

Source: American Pharmacist Association and National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model. Version 2.0. 2008.

2.1.3.4. Quality Assurance/Audit

Pharmacists have a responsibility to develop and participate in a continuous quality improvement program. Quality assurance and audit should be part of the continuous quality improvement program of MR process (72).

❖ **Quality Assurance**

One method of assessing the quality of the review system is by evaluating the feedback from patients or their careers who have participated in the MR process. This might include an evaluation of their experience of the review and the level of satisfaction with its outcome.

❖ **Audit**

Medication review is an integral part of the repeat prescribing process and many practices undertake regular audits of their repeat prescribing system.

❖ **Measuring Progress**

It is important to identify the baseline before audit is undertaken. The practice should agree an achievable target for increasing their MR rate. Regular feedback is essential to enable evaluation of the progress being made and to ensure that the practice is on target to achieve their objectives.

The utilization of documentation system of PIs to quantify the pharmacy productivity has been conducted in many settings. Some pharmacy productivity models have been developed (102-105). A survey found that 79% of hospitals identified the inability to account for CPSs as the single biggest limitation of productivity monitoring (106). In order to solve this problem, Pawloski et al.(104) developed an automated tool to quantify decentralized clinical pharmacists' productivity by extracting these data from the electronic medical record. Decentralized pharmacists were asked to weigh each activity relative to other activities on the basis of the average time and cognitive skill required to complete a specific intervention. Reports were generated and extracted into a database for data analysis, data graphing, and

final report generation. This report assists in the determination of staffing levels and assignment constructs and identifies pharmacists who need additional training in a particular assignment area.

2.1.3. Types of medication review

2.1.3.1. Comprehensive and target medication review

In a *comprehensive MR*, ideally the patient presents all current medications to the pharmacist, including all prescription and nonprescription medications, herbal products, and other dietary supplements. The pharmacist then assesses the patient's medications for the presence of any DRPs, including adherence, and works with the patient, the physician, or other healthcare professionals to determine appropriate options for resolving identified problems. In addition, the pharmacist supplies the patient with education and information to improve the patient's self-management of his or her medications.

Targeted MRs are used to address an specific DRP. Ideally, targeted MRs are performed for patients who have received a comprehensive MR. Whether for a new problem or subsequent monitoring, the pharmacist assesses the specific DRP in the context of the patient's complete medical and medication history. Following assessment, the pharmacist intervenes and provides education and information to the patient, the physician or other healthcare professionals, or both, as appropriate (47).

2.1.3.2. Levels of medication review

Medication review can be classified differently according to authors/associations. "Room for Review" in 2002 in UK (46) described 4 levels of MR depending on whether a patient is presented and whether access to the patient's clinical record is possible.

Table 9. Levels of medication review in UK

Level	Definitions
Level 0	Ad hoc: *an unstructured opportunistic review*
Level 1	*Prescription review*: a technical review of a list of patient's medicines (paper-based)
Level 2	*Treatment review*: a review of medicines with patient's full notes (not necessarily with the patient present)
Level 3	*Clinical medication review*: face-to-face review of medicines and condition with the patient

Source: Clyne W, Blenkinsopp A, Seal R. A Guide to Medication Review. 2008.

The French Society of Clinical Pharmacy(107) groups MR into 3 levels: (1) *prescription review*, (2) *therapeutic review*, (3) *pharmaceutical care review*, depending on context, content, and required elements of MR (***Table 10***). The SFPC recommends medication review level 3 for all patients. Levels 1 and 2 may be required for patients already known, not justifying more comprehensive review.

A new classification of MR (46) focuses on the purpose of MR rather than a hierarchy of MR. MR can be classified into three types: *prescription review*, *adherence support review*, and *clinical MR*. In some countries, an extension of type 3 exists and includes the authority for prescribing. Therefore, Hatah et al. (9), added the fourth type of MR - *clinical MR with prescribing* (as in type 3 but pharmacist had the ability to prescribe or adjust the medication dose, either in a supplementary or fully independent role). A subgroup meta-analysis of 36 studies found that *clinical MR* but not *adherence support review* reduced hospitalization (9).

Table 10. Levels of medication review according to the SFPC

Type	Context	Content	Required elements
Level 1: Prescription review	Patient known, without new clinical information	- Choice and availability of health products, dosages, contraindications, and major interactions	All prescriptions, basic patient information
Level 2: Therapeutic review	Patient known, with evolving situation	- Choice and availability of health products, dosages, contraindications, and major interactions. - Dose adjustments in relationship with biological results, markers of effect	All prescriptions, basic patient information, biological data
Level 3: Pharmaceutical care review	New admission of a patient, current evolution and issues not established	- Choice and availability of health products, dosages, contraindications, and major interactions - Dose adjustments in relationship with biological results, markers of effect - Compliance with therapeutic goals, therapeutic drug monitoring, compliance. Links to conciliation, patient counseling and patient education	All prescriptions, basic patient information, biological data, drug history, therapeutic goals

Source: Société français de pharmacie clinique. Recommandation de Bonne Pratique de Pharmacie Clinique - Niveaux Analyse Pharmaceutique. 2012.

2.1.4. The factor affecting the quality of medication review

There are many factors which affect the quality of MR such as quality of patient information (exact, sufficient, updated), relevance and validity), involvement of patient in decision, collaboration between health care providers, and competence and training of pharmacists.

2.1.5.1. Quality of patient information

Collection of patient information should be as much as possible from prescriptions, clinical records, interview with the patient (e.g., medication history). To perform the most comprehensive assessment of a patient, personal interaction with direct contact between a healthcare professional and a patient is optimal (47). A face-to-face interaction optimizes the pharmacist's ability to observe signs of and visual cues to the patient's health problems (e.g., ADRs to medications) and can enhance the patient–pharmacist relationship. It is useful to construct a guide on interview with patients (66). It is recognized, however, that alternative methods of patient contact and interaction such as telephonic may be necessary for those patients for whom a face-to-face interaction is not possible or not desired (e.g., patients at home) or in pharmacy practice settings in which the pharmacist serves in a consultative role on the healthcare team (47). Pharmacists have been shown to obtain accurate and efficient medication related information from patients rather than other health care professionals (108, 109).

A study of Kwint et al. (110) found that 27% of all DRPs were identified during patient interviews and 74% from medication and clinical records. Compared to DRPs identified from medication and clinical records, DRPs identified during patient interviews were more frequently assigned a higher clinical relevance. Of all the interventions performed in a study on pharmacotherapy consultations in ambulatory care patients receiving polypharmacy, 73% of the original problems were recognized only through a patient interview, suggesting that an interpersonal relationship remains critical to the provision of pharmaceutical care (111). Another study evaluated the activities and interventions provided by ambulatory care clinical pharmacists in US found that more drug-related problems were addressed and resolved when visits were 15 minutes or longer ($p=0.001$) and when the contact was in person ($p=0.001$) rather than telephone contact (112).

2.1.5.2. Involvement of patient in decision

PI is only implemented by "reaching an agreement with the patient". Therefore, PIs should be based on not only evidence from clinical and pharmacological research, also evidence about the medicines that the patient is actually taking, about the patient's capacity and motivation to take the medicines, and about the patient's priorities and beliefs about medicine taking (patient compliance) (113).

Motivational interviewing with patients has been shown to improve treatment adherence and outcomes, promote behavior change, and improve patient satisfaction with care. Therefore, pharmacists should use behavioral interventions such as "a coaching approach to improving concordance". A coaching approach focuses the four elements in concordant consultations:

- ✓ Explore what the patient wants to know and follow their agenda (patient engagement: they'll stay interested).
- ✓ Educate them on what they want to know (patient education: benefits, concerns).
- ✓ Empower patients to take responsibility for medicines taking (patient motivation: they take responsibility).

- ✓ Enable behavioral change for patients to achieve their aims (patient action: identify and implement their way) (114).

2.1.5.3. Collaboration

Knez et al. found that pharmacists were more likely to independently solve problems of minor significance, whereas they worked with clinicians and nurses to implement interventions of higher significance (115).

A systematic review of Kwint et al. 2013(116) found that the more intense collaboration between the general practitioners (CP) and pharmacists in MR leaded to a higher rate of implementation of recommendations arising from medication review. The following key elements reflecting collaborative aspects between a general practitioner and a pharmacist were assessed:

- ✓ "pharmacist with clinical experience" means that the pharmacist had adequate clinical training and expertise to perform MRs
- ✓ "own pharmacist involved" means that the pharmacist is the patient's regular pharmacist who has a longer lasting therapeutic relationship with his or her patient
- ✓ "sharing of medical records" describes full access for the care provider performing the medication review to GP data on diseases of the patient and clinical values
- ✓ "patient interview by pharmacist" means a face-to-face consultation between a pharmacist and a patient—this pharmacist must have a relationship with the GP
- ✓ "invitation of the patients by GP" means that the patient is invited to the study or referred for MR by the GP
- ✓ "case conference GP and pharmacist" indicates a face-to-face meeting between at least the GP and the pharmacist to discuss the DRPs and recommendations for specific patients
- ✓ "action plan" means that the study investigators reported that the agreed recommendations were formulated as an action plan and that there were designated persons responsible for implementation of this plan
- ✓ "follow-up" has taken place to assess whether the actions have been implemented, and to assess the patient's experience with these actions.

2.1.5.4. Competence and training of Pharmacists

A study of Currie et al.(117) showed that the training program proved to be an effective way to increase the number of DRPs identified and addressed by pharmacists. A 40-hour pharmaceutical care training program was developed and presented to pharmacists who provide pharmaceutical care in a community pharmacy; and 1 078 patients were randomly assigned to receive either (1) traditional pharmacy services or (2) pharmaceutical care. Patients receiving pharmaceutical care were more than seven times as likely to have any problems identified, more than eight times as likely to have an intervention performed. Another study suggested also that community pharmacists with limited experience in MR may need more intensive post-graduate training (118).

2.1.5. Remuneration

Several countries such as the UK, the US, Denmark, Germany, the Netherlands, Chile, Belgium, Canada, Australia, New Zealand pay pharmacists for providing MRs for patients(9). These can be termed "fee-for-service" MRs because pharmacists are remunerated by the government or a health provider for each item of service; or under capitation models.

2.2. Epidemiology of medication review

2.2.1. Place where medication review were conducted

MR are currently being delivered in both the public and private sectors (47). MR can be conducted in clinical departments or central pharmacy department at hospitals, community pharmacies, medical centers in community, patients' home, nursing home care, acute care, long-term care, home care (9, 46, 47). A study (119) found that 2 of the 23 DRP domains differed significantly when comparing MRs conducted in the patient's home to those conducted in the medical centre.

2.2.2. Who should carry out medication review

Pharmacists who are considered as experts on pharmacotherapy should be play a key role in MR. Many studies showed that types of health care professionals influence performance of MR. A study of Rovers at al. (66) found that clinical pharmacists reported a higher median number of DRPs (3; range 0-6 versus 2; range 0-5) compared to student pharmacists. Compared to the clinical pharmacists, student pharmacists were more likely to report wrong drug, adverse drug reaction, and inappropriate compliance. Clinical pharmacists were more likely than the student pharmacists to report unnecessary drug therapy, dosage too low, dosage too high, and the need for additional therapy. Similarly, another study (120) showed that PIs done by faculty clinical pharmacists, and student pharmacists were very different than those performed by the hospital staff pharmacists. The authors concluded that the different interventions performed by the three groups may suggest a multi-interdisciplinary approach to patient care where different types of PIs may result in improved outcomes.

2.2.3. Number/rate of DRPs and PIs and time spent on PIs

The rate of PIs (number of PIs/number of prescription reviewed) ranged from 1 to 37% (121, 122). Analysis of the time spent on interventions can be used for quality improvement initiatives and can be used to estimate clinical pharmacist workload. The mean time spent on an intervention was 7.0-9.6 minutes (52, 123, 124).

2.2.4. Which medications most involved

A high-risk medication was defined as a medication that, if involved in an erroneous medication order, carried a greater risk of significant harm or death. Although errors involving these drugs are not more frequent than with other products, the consequences can be devastating for patients. For this reason, high-risk drugs must be handled differently from others, whether at the time of packaging, storage, prescription or administration. In 2014, the

Institute for Safe Medication Practices Canada suggested two lists of "High Alert Medications" - one in ambulatory care (125) and one in intensive care (126). In the US, the campaign 5 Million Lives, launched in December 2006 by the Institute for Healthcare Improvement chose to target four drug groups with higher risks: anticoagulants, narcotics and opiates, insulins and sedatives (127). A review in 2003 found that five drug groups which were most frequently associated with preventable ADEs were cardiovascular drugs, psychoactive and other central nervous system drugs, analgesic drugs, anticoagulants, and anti-infectives. In an another systematic review in 2007, Howard et al.(128) found that four groups of drugs accounted for more than 50% of the drug groups associated with preventable drug-related hospital admissions. These were anti-platelets, diuretics, non-steroidal anti-inflammatory drugs and anticoagulants.

2.2.5. Which DRPs detected and PIs proposed

In a prospective study of PIs (129) conducted in 6 French hospitals, the most commonly identified DRPs were nonconformity to guidelines or contraindication (21.3%), followed by improper administration (20.6%), supra-therapeutic dose (19.2%), and drug interaction (12.6%). Another study of Bedouch et al. (130) reviewed PIs documented into Act-IP© - a French database of PIs over a 30-month period. A total of 34 522 PIs were registered by 201 pharmacists working in 59 hospitals. The most common type of DRP identified was similar to the former study, including "supra-therapeutic dosage" (20.6%), followed by "improper administration" (20.1%) and "non-conformity to guidelines/contra-indication" (17.6%). PIs were mainly proposals for "dose adjustment" (24.5%), followed by "drug discontinuation" (20.0%) and "drug switch" (19.0%).

2.2.6. Acceptance and Implementation of pharmacist interventions

In order for the pharmacist to impact upon the quality of patient care or drug costs, the prescriber must accept the suggestions. A review of 23 studies conducted in 1990 (131) found that the average rate of acceptance was 85.5%. Factors affecting acceptance included time, communication, solicited versus unsolicited recommendations, type of prescriber, and type of pharmacist. Factors leading to non-acceptance included lack of physician awareness of pharmacokinetic parameters, quality of suggestions, prescribers' exercise of caution with respect to patient safety and well-being, and negative attitude toward clinical pharmacy.

The factors that affected the rate of physician-accepted PIs in acute care hospitals in the United Kingdom found that ward type, pharmacist grade, and total time spent on the ward by the pharmacist were significant predictors of the intervention rate (132, 133). A higher acceptance rate was achieved if the recommendations from the pharmacist were communicated directly to the prescriber. Barber et al. (132) also found that on pediatric wards, the number of physician-accepted interventions was 1.7 times greater than on other types of wards.

Anderegg et al.(134) found that recommendations to reconcile medications or address actual drug allergies or medication errors were frequently accepted. Physicians were less likely to accept recommendations related to drug indications ($p<0.001$), drug efficacy ($p=0.041$), and

therapeutic drug and disease state monitoring (p=0.011) than the "other" category which were typically more procedural such as clarify duration, provide dietician consultation, or restart a drug when at home. Recommendations made for patients with a relatively greater number of drugs were also less likely to be accepted (p=0.003). The study also determined whether recommendations made by pharmacists and accepted by hospital physicians resulted in fewer post-discharge readmissions and urgent care visits compared with recommendations that were not implemented. Data on readmissions, emergency department use, urgent care visits, and death of 192 patients were collected for 90 days after discharge. The acceptance rate was lower for those who had an urgent care visit compared with all other patients (33.6% vs 52.2%, p=0.033). No significant association was noted between recommendation acceptance rates and readmission, emergency department visit, or death. Because only 48% of all recommendations were accepted by inpatient physicians, and there was no impact on health care use 90 days after discharge. This study suggests that recommendations by pharmacy case managers were underused, and the low acceptance rate may have reduced the potential to avoid readmissions. Other studies of PIs to hospitalized patients reported positive clinical and economic outcomes associated with acceptance rate of IPs over 90% (135-137).

The medical literature also supports the notion that valid PIs are not always accepted. The well-established theory of psychological reactance might at least partially explain instances when physicians do not act upon such recommendations. Reactance theory suggests that when recommended to take a certain action, a motivational state compels us to react in a way that affirms our freedom to choose. Often we choose to do the opposite of what the recommendation is proposing that we do or we just become entrenched in our initial position. Making recommendations regarding clinical care, including pharmacotherapy, may carry with it implied threats, as it can be perceived as an attempt to restrict one's freedom of choice potentially generating reactance and efforts to avoid them. By identifying and taking into account factors likely to promote reactance, physician-oriented interventions could become more effective (138).

2.2.7. Risk factors of medication errors

Due to the variability between health care facilities, so the trans-validity of predictors of DRPs is not always valid. Therefore, hospitals could use an epidemiological framework to identify their own error predlictors in order to target interventions. For example, a retrospective case-control study of Fijn et al. (139), comparing prescriptions with and without MEs, found that only prescriber and drug characteristics were associated with errors. Prescriber characteristics were medical specialty (e.g. orthopaedics) and prescriber status (e.g. verbal orders transcribed by nursing staff). Drug characteristics were dosage form (e.g. inhalation devices), therapeutic area (e.g. gastrointestinal tract) and continuation of preadmission treatment (Yes). In a retrospective cross-sectional study conducted at an acute-care hospital in Singapore, Koh et al. (140) found that age and gender were less important than the number of drugs prescribed as predictors for experiencing a DRP for patients with polypharmacy. Errors were much more likely to be intercepted if the error occurred in the earlier process (26).

Some studies showed that medical residents (141), doctors of having less years of experience (54), or with less training(13, 142) were also more likely to make MEs; specialists prescribed fewer abnormalities than generalists (22% against 41%). The best performances seem to see by physicians with between 15 and 30 years of practice (143). However, another study in the Netherlands where it was shown that specialists had a higher rate of errors than the GP (144) and the frequency of prescribing errors in prescriptions from hospital physicians is higher than on prescriptions from GPs (145). It has been shown that prescribers with a high rate of trivial prescribing errors also make more serious errors (146).

2.2.8. Factors influencing pharmacist interventions

According to a study performed in a pediatric intensive care setting, a full-time unit-based clinical pharmacist substantially decreased the serious medication error rate, but a part-time pharmacist was not as effective (147). In another study, the total cost avoidance to the institution over a 4.5-month period with the ICU pharmacist would have been $209,000–$280,000. The majority of interventions were initiated during chart review (40%) and patient care rounds (39%) (148). Most of the costs avoided were generated from interventions made during patient care rounds and chart-review activities, each of which ranged from approximately $80,000 to $110,000. These results suggest that systems changes (e.g., CPOE, technician support for routine order entry) that minimize the time spent verifying orders and maximize the time spent on these activities are most likely to improve patient outcomes.

There is considerable evidence that clinical pharmacists providing medication reviews can decrease the occurrence of DRPs. Successful interventions require that clinical pharmacists work in close liaison with the prescriber, and have access to the full clinical record of the patient (149). Several studies that did not meet these conditions reported only weak impact or even detrimental effects (150, 151).

In conclusion, practice of medication review varies across individuals, settings and countries. There is a variety of factors that influence quality and impacts of medication review. Research on relationships between the characteristics of practice of MR and its impacts is necessary to optimize its outcomes. Standardization and continuous quality improvement are also the two key strategies to improve impacts of MR.

3. Evaluation of impacts of medication review/pharmacist interventions

In this section, we will present some models or conceptual frameworks that can be applied to assess impacts of MR/PIs. Then, we combined these existing models into an integrated model for assessment of MR/PIs.

3.1. Quality of medical care - The Structure-Process-Outcome model of Donabedian

The Donabedian's Model (152, 153) is a conceptual model that provides a framework for evaluating quality of medical care. According to the model, information about quality of care can be drawn from three categories abbreviated SPO: ***S****tructure* (context in which care is delivered, including hospital buildings, staff, financing, and equipment...), ***P****rocess* (transactions between patients and providers throughout the delivery of healthcare), and ***O****utcomes* (effects of healthcare on the health status of patients and populations).

The outcome has been frequently used as an indicator of the quality of medical care. Examples are studies of death, event (hospitalization, medical consultation), and quality of life (52, 154). To be complete, outcome assessment should include all factors that contribute to the outcomes such as functional status; symptomatology; and psychologic, economic, social factors, and quality of life (155). Its advantages includes a validity and a fairly concrete and precise measurement in many situations (153). However, the use of outcomes as measures of quality is associated with some main difficulties: criteria/technology of follow-up, time, determination of causal relationships between medical care and outcomes (136, 156-158). Furthermore, sometimes a particular outcome may be irrelevant, as when survival is chosen as a criterion of success in a situation which is not fatal but is likely to produce suboptimal health. Some outcomes, not so clearly defined, can be difficult to measure, for example patient attitudes and satisfactions, social restoration and physical disability and rehabilitation. However, outcomes remain the ultimate validators of the effectiveness and quality of medical care (153).

Another approach to assessment is to examine the process of care itself rather than its outcomes. Par example, a number and type of DRPs, consistence of PIs to practice standards, acceptance by physicians and health care providers in case of MR. Process evaluation are often preferred by providers because they are generally simple to understand and interpret and they related directly to practice. However, process measures may be of little value if standard practice cannot be agreed upon or if process and outcome are not causally related (155). They may, however, be more relevant to the question at hand: whether pharmacists is properly practiced (153). Process criteria of quality assessment usually are categorized as either technical or interpersonal. Technical care in pharmacy represents the procedures/knowledge/skills pharmacists employ to provide the optimal drug therapy. The interpersonal component of process addresses the characteristics of the interaction between

patients and pharmacists such as concerned, polite, respectful, friendly, and honest (or their opposites).

A third approach to assessment is to study not the process of care itself, but the settings in which it takes place (structure). It is concerned with such things as the adequacy of facilities and equipment; the qualifications of pharmacy staff; the administrative structure and operations of programs. This approach offers the advantage of dealing, at least in part, with fairly concrete and accessible information. It has the major limitation that assessment of the relationship between structure and process or structure and outcome, is often not well established (153). Structure represents the stable, physical structure and capacities of a healthcare setting. Therefore, an individual PI rarely has impacts on structure outcomes.

According to the Donabedian's Model, measures of structure, process, and outcome (SPO framework) are all useful for assessing health care quality. For example, a SPO framework for quality assessment of pharmaceutical care in a community pharmacy was described in ***Figure 4***. Each element of quality is dependent on the other, like links in a chain. However, as one moves down the chain from structure to process to outcome, measures become harder to capture and more subject to questions of validity and reliability(11).

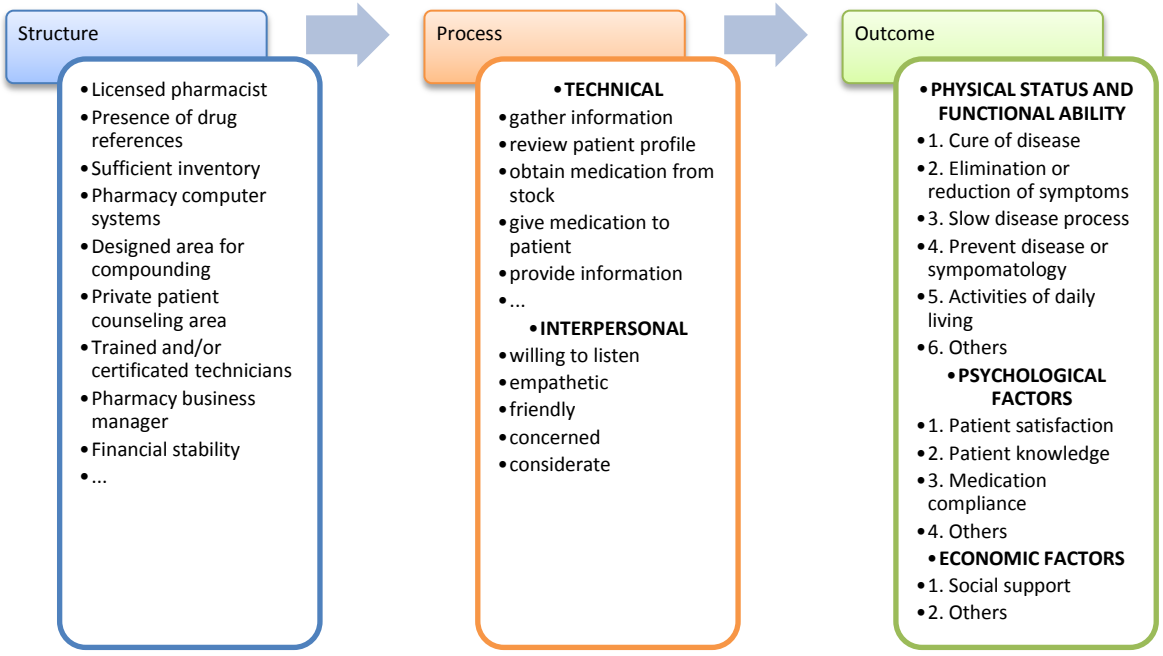

Figure 4. Structure-process-outcome: a framework for quality assessment of pharmaceutical care in community pharmacies

Source: Adapted from the figure in an article by Farris KB, Kirking DM. Assessing the quality of pharmaceutical care. II. Application of concepts of quality assessment from medical care. Ann Pharmacother. 1993;27(2):215-23.

3.2. The Model of Systems Engineering Initiative for Patient Safety

The Systems Engineering Initiative for Patient Safety (SEIPS) model was adopted to study pharmacy work systems (***Figure 5***). According to the SEIPS model, a *person* (the person

could be a care provider, another employee of a healthcare institution such as a biomedical engineer, a unit clerk, or the patient) performs a range of *tasks* using various *tools and technologies*. The performance of these tasks occurs within a certain *physical environment* and under specific *organizational conditions*. The five components of the work system (*person, tasks, tools and technologies, physical environment, organizational conditions*) interact with each other and influence each other. Overall, the *work system* in which care is provided affects both the work and clinical *processes*, which in turn influence the patient, employee, and organizational *outcomes* of care (159).

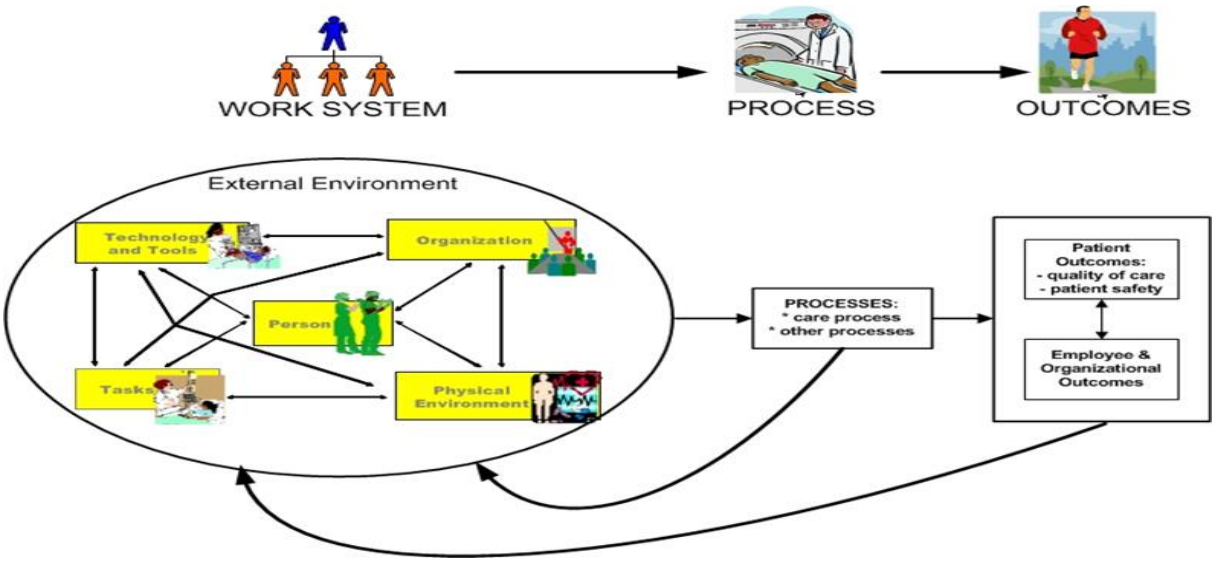

Figure 5. The SEIPS model of work system and patient safety

Source: Duplicated from Carayon P, Schoofs Hundt A, Karsh BT, Gurses AP, Alvarado CJ, Smith M, et al. Work system design for patient safety: the SEIPS model. Qual Saf Health Care. 2006 Dec;15 Suppl 1:i50-8.

The model was used to study how the relationship between the structural components of the work system interact to influence the various working system processes and ultimately influence the outcomes of the work system. The model SEIPS could offer an improvement over the Donabedian's SPO model, which tends to focus only on components, while the SEIPS model focuses on the different components of a working system and the interactions between the components and how the components can influence the process and outcomes of care (159, 160). ***Table 11*** displays elements of the various SEIPS model components.

Table 11. Components and elements of the SEIPS model

	Components	Elements (examples)
Work system or structure	Person	Education, skill and knowledge Motivation and needs Physical characteristics Psychological characteristics
	Organization	Teamwork Coordination, collaboration and communication Organizational culture and patient safety culture Work schedules Social relationships Supervisory and management style Performance evaluation, rewards and incentives
	Technologies and tools	Various information technologies: electronic health record, computerized provider order entry and bar coding medication administration Medical devices Other technologies and tools Human factors characteristics of technologies and tools (e.g., usability)
	Tasks	Variety of tasks Job content, challenge and utilization of skills Autonomy, job control and participation Job demands (e.g., workload, time pressure, cognitive load, need for attention)
	Environment	Layout Noise Lighting Temperature, humidity and air quality Work station design
Process	Care processes and other processes	Care processes Other processes: information flow, purchasing, maintenance, cleaning Process improvement activities
Outcomes	Employee and or organizational outcomes	Job satisfaction and other attitudes Job stress and burnout Turnover Organizational health (e.g. profitability)
	Patient outcomes	Patient safety Quality of care

Source: Carayon P, Schoofs Hundt A, Karsh BT, Gurses AP, Alvarado CJ, Smith M, et al. Work system design for patient safety: the SEIPS model. Qual Saf Health Care. 2006 Dec;15 Suppl 1:i50-8.

3.3. Quality of medication review - The model of Martini

The first time in literature, Martini M. (161) suggested a definition of the quality of medication review. The author stated that the quality of MR in a given case depends on (1) the *accuracy* (*trueness* and *precision*) of MR, (2) the *acceptance* and *implementation* by health care providers and the patient, and (3) the *benefits* on the patient (clinical, economic

and humanistic impacts) and the society (economic impacts) (see *Figure* ***6***). Medication review consists of two main steps: detection of DRPs and proposition of PIs to solve DRPs. Therefore, the *trueness* of MR includes detection of right DRPs (*consistency to a reference*) and a right number of DRPs (*exhaustiveness*) and proposition of right PIs (*trueness*) and relevant PIs (*pertinence*) by a pharmacist. The *precision* of MR is the concordance between results of MR conducted by different pharmacists. And the expected MR is the one that has all above characteristics.

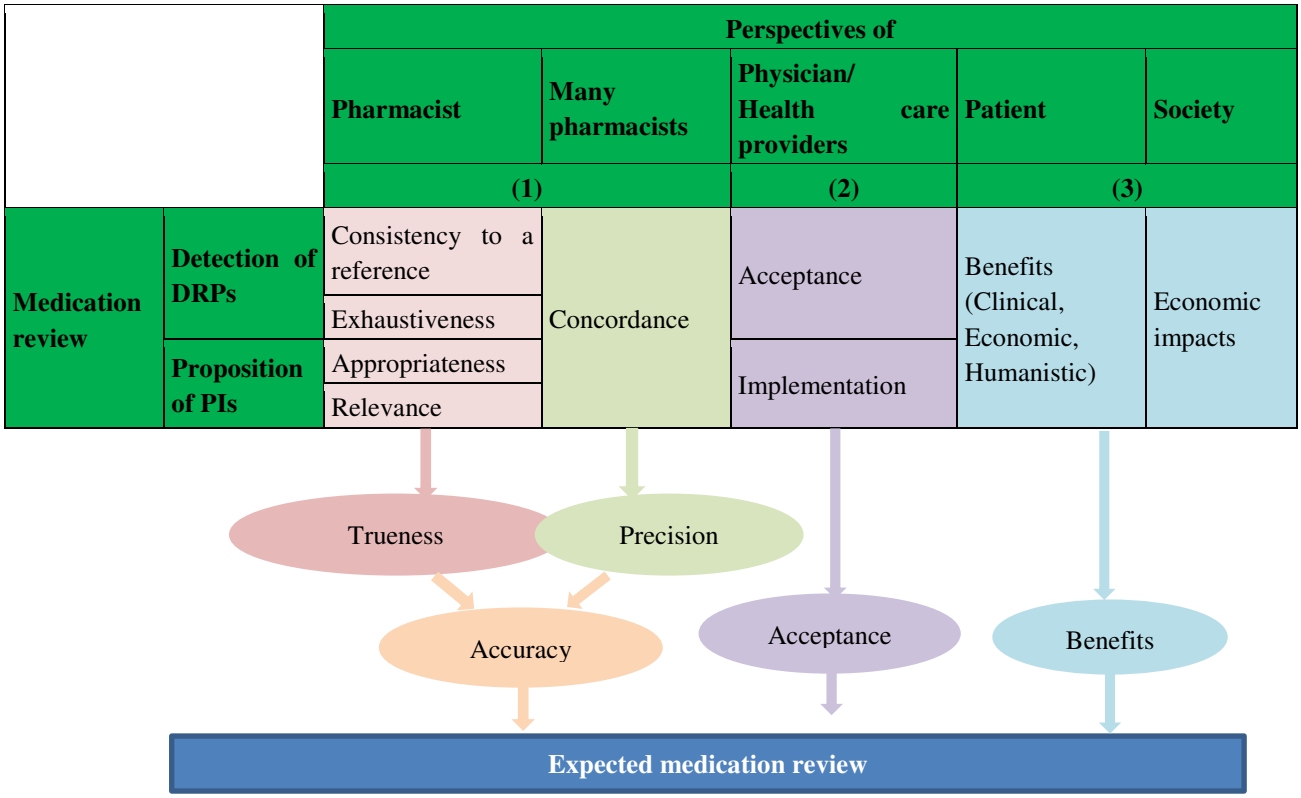

Figure 6. Quality of medication review

DRP: drug-related problem. PI: pharmacist intervention. Source: Adapted from a figure in a thesis by Martini M. La qualité de l'analyse pharmaceutique des traitements médicamenteux au centre hospitalier de Luneville Nancy: Université Henri Poincare - Nancy 1; 2010.

3.4. The Economic-Clinical-Humanistic Outcome Model

The model provided by Kozma et al. (162) describes the proposed relationships of causality between the disease, medical interventions (e.g., drug treatment or CPSs) and outcomes (*Figure* ***7***). The authors argued that the evaluation of outcomes related CPSs should include an assessment of ***E****conomic,* ***C****linical,* and ***H****umanistic* ***O****utcomes* (ECHO model).

Clinical outcomes are defined as medical event that occur as a result of disease or medical intervention. *Economic outcomes* are defined as direct, indirect, and intangible costs, compared with the consequences of intervention alternatives. *Humanistic outcomes* are defined as the consequences of disease or treatment on patient functional status, or quality of life.

Many variables exist within each type of outcomes. Some of these variables are intermediate outcomes, or *intermediaries*. For example:

- ✓ A patient's physical and biomedical status are intermediaries of clinical outcomes.
- ✓ Humanistic outcomes have other humanistic intermediaries, such as the patients' willingness or ability to pay, patient compliance, patient knowledge, patient satisfaction.
- ✓ The economic outcomes have intermediaries introduced from both the clinical and humanistic outcomes. The clinical outcomes have intermediaries introduced from the direct costs of medical care, including direct medical costs (the cost of laboratory testing, emergency department visit and hospitalization, and costs of retreatment from product failures) and direct nonmedical costs (costs for transportation to the hospital or physician's office). Humanistic outcomes have intermediaries, including indirect costs such as time lost from work (163).

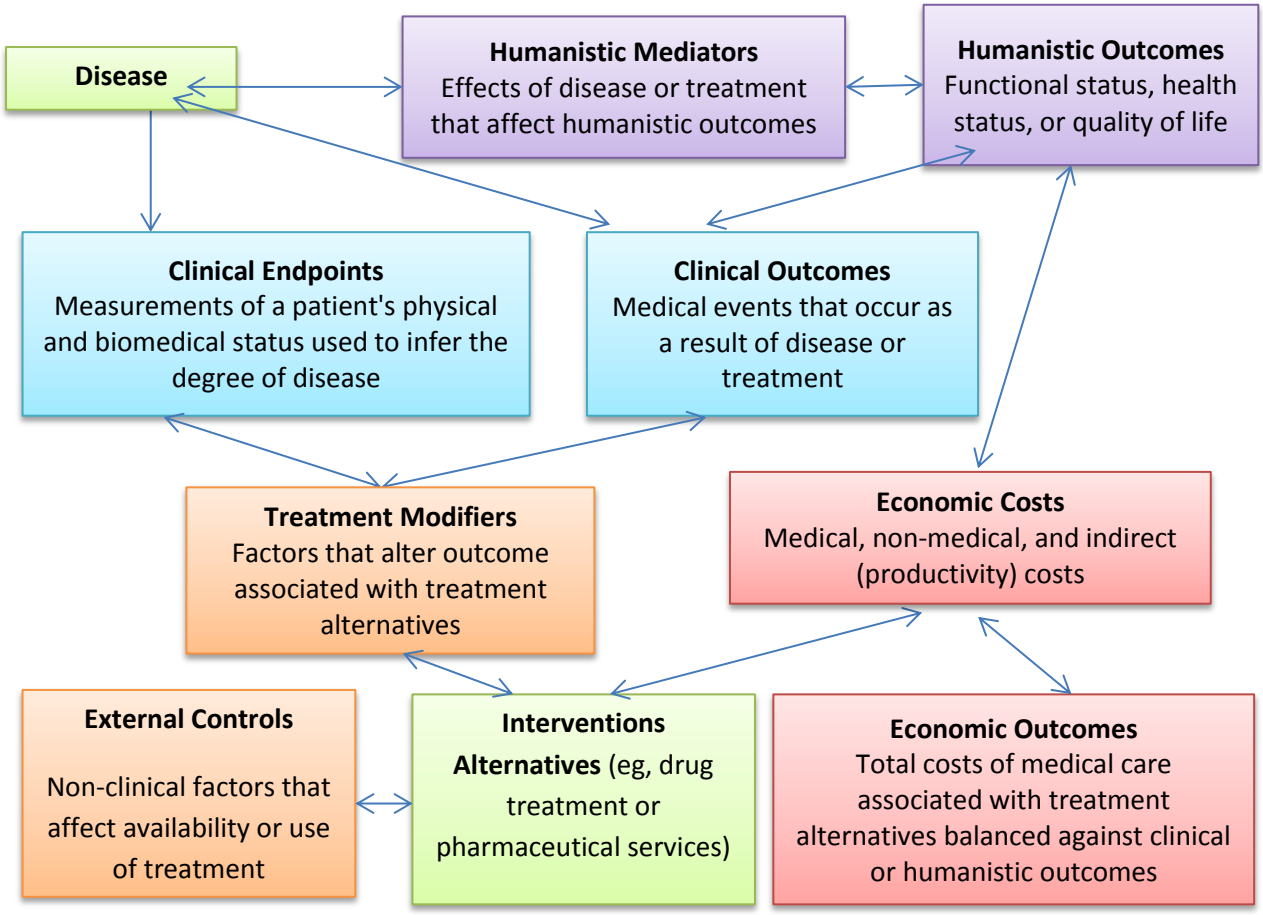

Figure 7. The conceptual model: Economic, Clinical, and Humanistic Outcomes (ECHO) Model

Source: Adaption of a figure in an article by Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. Clin Ther. 1993;15(6):1121-32.

Kozma et al. also suggest that pharmacists generally influence the outcomes of treatment alternatives through the use of *external controls* and *treatment modifiers*.

- ✓ *External controls* are defined as non-clinical factors, par example, formulary and clinical guidelines, that affect the availability or use of alternative treatment.
- ✓ *Treatment modifiers* are defined as factors that affect the outcomes associated with treatment alternatives, for example, pharmacists affect patient compliance or act of prescription by the physician (162).

Medication review is one of CPSs and a pharmacist intervention is an action by a pharmacist to change patient management or therapy. Therefore, the ECHO model can be applied for each individual PI to evaluate value of a PI. That means that the value of the PI consists of the total of value of economic, clinical, humanistic outcomes, compared to the case in absence of the PI.

Measures used to evaluate the impacts of CPSs were grouped according to the models of Donabedian and Kozma et al. as shown in Table 12 (11).

Table 12. Measures used to assess the impact of clinical pharmacy services

Outcomes	*Clinical outcomes* (the end physiologic result of antecedent health care): events (emergency room visits, hospitalizations) or cases prevented, improvement or resolution of disease, days hospitalized after start of medication, length of stay, mortality, morbidity, complications, decrease in disease symptoms, adverse drug reactions, absence of disease, readmission rates, drug resistance
	Economic outcomes (ratios of cost to some desirable outcome): cost-effectiveness, cost minimization
	Humanistic outcomes (measures of non-physiologic patient outcomes): patient satisfaction, compliance with medication, quality of life
Intermediaries	*Clinical intermediaries* (risk and effectiveness markers) • *Risk markers*: wheezing, exercise tolerance, forced expiratory volume, blood cholesterol, white blood cell count, temperature • *Effectiveness markers:* drug concentration, mean daily dosage required for effect, drug interactions
	Cost intermediaries (financial measures of impact): increased revenues, costs, charges, wastage, inventory level, expenditures, cost avoidance
	Process intermediaries (processes associated with patient outcomes): communication, documentation errors, number of interventions, accepted recommendations, prescribing changes, decreased use of targeted drugs, adherence to guidelines, prescribing within accepted limits, improved record keeping, improved narcotic control, relative use of drugs)

Source: Adaption from Holdford DA, Smith S. Improving the quality of outcomes research involving pharmaceutical services. Am J Health Syst Pharm. 1997;54(12):1434-42.

3.5. Matrix of evaluation of risk

According to matrix of risk assessment (164), *risks* are analyzed by combining *severity* of consequences and their *probabilities* in the context of existing situation. A risk matrix is used predominantly in safety risk management such as National Patient Safety Risk Matrix in UK

(164), Safety Assessment Code Matrix in USA (165), Standard for risk management in Australia (10). Below is the National Patient Safety Risk Matrix (164), assessing a broad range of risks including clinical, financial risks, risk related to reputation, business process, and system, etc.

❖ **Model matrix of the National Patient Safety**

Instructions for use

- ✓ Define the risk(s) explicitly in terms of the adverse consequence(s) that might arise from the risk.
- ✓ Use *table 1* to determine the consequence score(s) (C) for the potential adverse outcome(s) relevant to the risk being evaluated.
- ✓ Use *table 2* to determine the likelihood score(s) (L) for those adverse outcomes.
- ✓ Calculate the risk score by multiplying the consequence by the likelihood:

C (consequence) x L (likelihood) = R (risk score)

- ✓ Identify the level at which the risk will be managed in the organization, assign priorities for remedial action, and determine whether risks are to be accepted on the basis of the color bandings and risk ratings, and the organization's risk management system.

Table 1. Consequence scores

Choose the most appropriate domain for the identified risk from the left hand side of the table Then work along the columns in same row to assess the severity of the risk on the scale of 1 to 5 to determine the consequence score, which is the number given at the top of the column.

	Consequence score (severity levels) and examples of descriptors				
	1	**2**	**3**	**4**	**5**
Domains	**Negligible**	**Minor**	**Moderate**	**Major**	**Catastrophic**
Impact on the safety of patients, staff or public (physical/psychological harm)	- Minimal injury requiring no/minimal intervention or treatment. - No time off work	- Minor injury or illness, requiring minor intervention - Requiring time off work for >3 days - Increase in length of hospital stay by 1-3 days	- Moderate injury requiring professional intervention - Requiring time off work for 4-14 days - Increase in length of hospital stay by 4-15 days - RIDDOR/agency reportable incident - An event which impacts on a small number of patients	- Major injury leading to long-term incapacity/disability - Requiring time off work for >14 days - Increase in length of hospital stay by >15 days - Mismanagement of patient care with long-term effects	- Incident leading to death - Multiple permanent injuries or irreversible health effects - An event which impacts on a large number of patients

Quality/complaints /audit	Peripheral element of treatment or service suboptimal Informal complaint/inquiry	- Overall treatment or service suboptimal - Formal complaint (stage 1) - Local resolution - Single failure to meet internal standards - Minor implications for patient safety if unresolved - Reduced performance rating if unresolved	- Treatment or service has significantly reduced effectiveness - Formal complaint (stage 2) complaint - Local resolution (with potential to go to independent review) - Repeated failure to meet internal standards - Major patient safety implications if findings are not acted on	- Non-compliance with national standards with significant risk to patients if unresolved - Multiple complaints/ independent review - Low performance rating - Critical report	- Totally unacceptable level or quality of treatment/service - Gross failure of patient safety if findings not acted on - Inquest/ombudsman inquiry - Gross failure to meet national standards
Human resources/ organisational development/staffing/ competence	Short-term low staffing level that temporarily reduces service quality (< 1 day)	- Low staffing level that reduces the service quality	- Late delivery of key objective/ service due to lack of staff - Unsafe staffing level or competence (>1 day) - Low staff morale - Poor staff attendance for mandatory/key training	- Uncertain delivery of key objective/service due to lack of staff - Unsafe staffing level or competence (>5 days) - Loss of key staff - Very low staff morale - No staff attending mandatory/ key training	- Non-delivery of key objective/service due to lack of staff - Ongoing unsafe staffing levels or competence - Loss of several key staff - No staff attending mandatory training /key training on an ongoing basis
Statutory duty/ inspections	No or minimal impact or breech of guidance/ statutory duty	- Breech of statutory legislation - Reduced performance rating if unresolved	- Single breech in statutory duty - Challenging external recommendations/ improvement notice	- Enforcement action - Multiple breeches in statutory duty - Improvement notices - Low performance rating - Critical report	- Multiple breeches in statutory duty - Prosecution - Complete systems change required - Zero performance rating - Severely critical report
Adverse publicity/ reputation	Rumours Potential for public concern	- Local media coverage – short-term reduction in public confidence - Elements of public expectation not being met	Local media coverage – long-term reduction in public confidence	National media coverage with <3 days service well below reasonable public expectation	- National media coverage with >3 days service well below reasonable public expectation. MP concerned (questions in the House) - Total loss of public confidence
Business objectives/ projects	Insignificant cost increase/ schedule slippage	- <5 per cent over project budget - Schedule slippage	- 5–10 per cent over project budget - Schedule slippage	- Non-compliance with national 10–25 per cent over project budget - Schedule slippage - Key objectives not met	- Incident leading >25 per cent over project budget - Schedule slippage - Key objectives not met
Finance including claims	Small loss Risk of claim remote	- Loss of 0.1–0.25 per cent of budget - Claim less than £10,000	- Loss of 0.25–0.5 per cent of budget - Claim(s) between £10,000 and £100,000	- Uncertain delivery of key objective/Loss of 0.5–1.0 per cent of budget - Claim(s) between £100,000 and £1 million - Purchasers failing to pay on time	- Non-delivery of key objective/ Loss of >1 per cent of budget - Failure to meet specification/ slippage - Loss of contract / payment by results - Claim(s) >£1 million
Service/business interruption Environmental impact	- Loss/interruption of >1 hour - Minimal or no impact on the environment	- Loss/interruption of >8 hours - Minor impact on environment	- Loss/interruption of >1 day - Moderate impact on environment	- Loss/interruption of >1 week - Major impact on environment	- Permanent loss of service or facility - Catastrophic impact on environment

Source: National Patient Safety Agency. A risk matrix for risk managers. London; 2008.

Table 2. Likelihood score (L)

What is the likelihood of the consequence occurring?

The frequency-based score is appropriate in most circumstances and is easier to identify. It should be used whenever it is possible to identify a frequency.

Likelihood score	**1**	**2**	**3**	**4**	**5**
Descriptor	**Rare**	**Unlikely**	**Possible**	**Likely**	**Almost certain**
Frequency How often might it/does it happen	This will probably never happen/recur	Do not expect it to happen/recur but it is possible it may do so	Might happen or recur occasionally	Will probably happen/recur but it is not a persisting issue	Will undoubtedly happen/recur, possibly frequently

Source: National Patient Safety Agency. A risk matrix for risk managers. London; 2008.

Table 3. Risk scoring = consequence x likelihood (C x L)

	Likelihood				
Likelihood score	**1**	**2**	**3**	**4**	**5**
	Rare	**Unlikely**	**Possible**	**Likely**	**Almost certain**
5-Catastrophic	5	10	15	20	25
4-Major	4	8	12	16	20
3-Moderate	3	6	9	12	15
2-Minor	2	4	6	8	10
1-Negligible	1	2	3	4	5

Source: National Patient Safety Agency. A risk matrix for risk managers. London; 2008.

For grading risk, the scores obtained from the risk matrix are assigned grades as follows:

1 - 3	Low risk
4 - 6	Moderate risk
8 - 12	High risk
15 - 25	Extreme risk

3.6. The model of pharmacoeconomic analysis

Theory about the model of pharmacoeconomic analysis is so useful to evaluate the value of PIs. Firstly, we will introduce about pharmacoeconomics as a method of analysis of value of drugs or pharmaceutical services in general. Then, we will demonstrate how this model can be applied to evaluate the value of PIs from typical examples of studies in literature.

3.6.1. Pharmacoeconomics

Pharmacoeconomics typically is defined as the description and analysis of the costs and consequences of drugs or pharmaceutical services, and its impact in individuals, health care systems, and society (163).

The basic model of an economic evaluation includes measurement of both costs and consequences (outcomes) of a service and of an alternative for comparison (166). Costs can be thought of as "inputs" or resources required to provide the service. In the case of CPSs, inputs are primarily comprised of the labor costs associated with the personnel who provide the care or services. Outcomes can be thought of as "outputs" of the service or program. Outcomes can be in the form of clinical outcomes, humanistic outcomes, or economic outcomes. The key element of this model is the inclusion of a comparison or alternative to the service in question. An alternative might be, for example, the absence of service (control) (166).

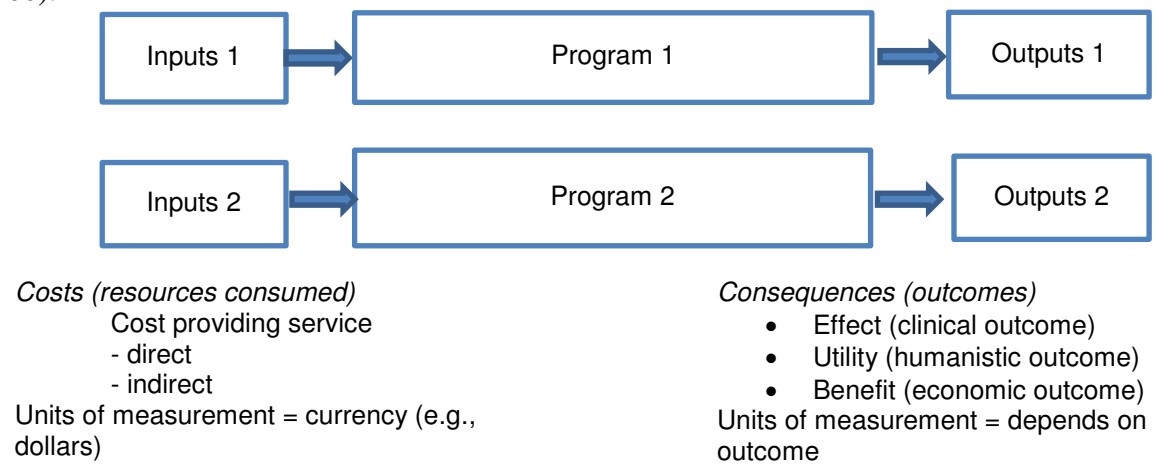

Figure 8. Model of pharmacoeconomic analysis

Source: Schumock GT. Methods to assess the economic outcomes of clinical pharmacy services. Pharmacotherapy. 2000;20(10 Pt 2):243S-52S.

3.6.1.1. Costs

Cost categories that need to be considered included direct, indirect, and intangible costs (***Figure 9***).

- Direct costs: Direct costs are the resources consumed in the prevention, detection, or treatment of a disease or illness. These costs can be divided into direct medical costs (eg, costs associated directly with health care interventions include hospitalizations, drugs, laboratory testing, and physician visits) and direct nonmedical costs (resource expenditure

born by patients in seeking care, for example, transportation to and from health settings, family care expenses, special diets or clothes).

- Indirect cost: Indirect costs are those costs that result from morbidity and mortality. These costs are related to changes in production capacities that result from disease or health care interventions. To estimate indirect costs, two techniques typically used are the human capital method, and the "willingness-to-pay" method. Each method attempts to estimate different types of costs. The human capital approach attempts to value morbidity and mortality losses based on an individual's earning capacity. In the willingness-to-pay approach, patients are explicitly asked how much money they would be willing to spend to reduce the likelihood of illness. While the willing-to-pay approach incorporates indirect and intangible costs, the human capacity approach considers only changes in work loss and productivity due to morbidity and mortality.

- Intangible costs: Intangible costs are probably the most difficult costs to measure. Intangible costs are those costs incurred that represent nonfinancial outcomes of disease and medical care, and which are not properly expressed in monetary terms. Examples of intangible costs include pain, suffering, inconvenience and grief. These costs can either be presented as a caveat in the discussion of the result of an economic evaluation or converted into a common unit - a quality-adjusted life-year.

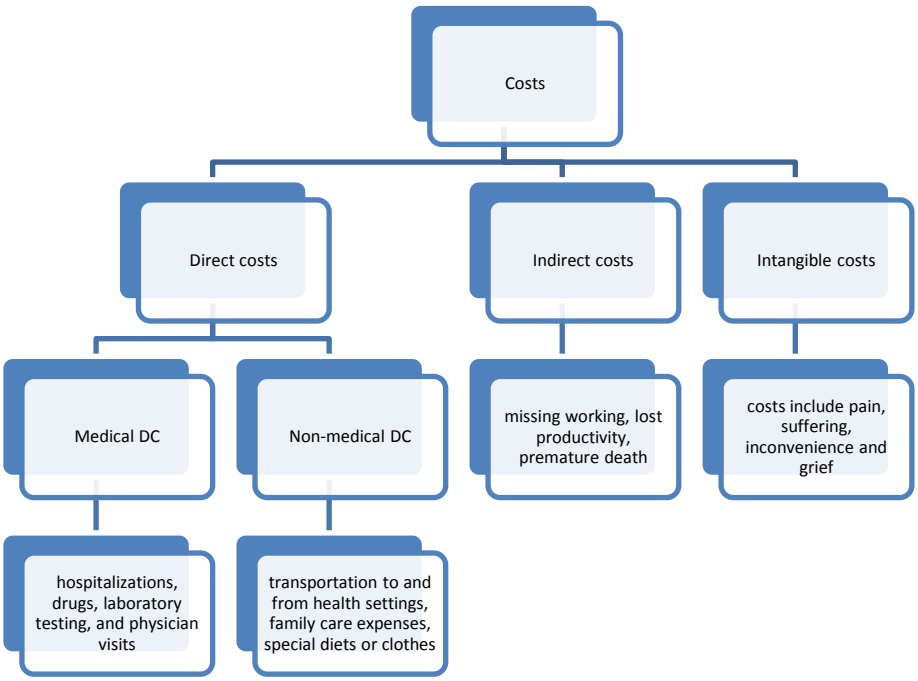

Figure 9. Types of costs in pharmacoeconomic analysis

DC: direct cost

3.6.1.2. Outcomes

Outcomes include clinical, economic and humanistic outcomes. How to consider both costs and outcomes to evaluate economic value of a service was described in the ECHO model (162) and in the next section "Types of pharmacoeconomic evaluation".

There are two considerations concerning the choice of consequences to evaluate:

- Positive versus negative outcomes: A comprehensive assessment of benefits of drug therapy will address both positive and negative effects of competing alternatives. Positive consequences may translate into life-years gained, improved functional status and well-being. Negative consequences can include harmful effects, drug toxicity, or even death.
- Intermediate versus final outcomes: Intermediate consequences are commonly used in clinical trials to demonstrate clinical efficacy of drug therapy because of cost and time savings, practicality (167). For example, a decrease in low-density lipoprotein cholesterol levels serves as an intermediate outcome for more relevant final outcomes, expressed as a decrease in myocardial infarction rate and an increase in lives saved. But the challenges lies in finding intermediate outcome indicators that can reliably predict long-term effects.

3.6.1.3. Perspectives

Perspective refers to the point of view from which the economic is performed. These perspectives will influence the costs and consequences identified and measured. An economic evaluation can be conducted from a single perspective, or multiple perspectives. Common perspectives include those of the patient, provider, payer, and society (163).
- Patient perspective: Costs from the perspective of patients are essentially what they pay for a product or service, that is, the portion not covered by insurance.
- Provider perspective: Costs from the provider's perspective are the true expense of providing a product or service, regardless of the charge. Charge data may be more readily available, but are usually not reflective of the true costs of health care. Providers can be hospitals, health care organization, or private physicians.
- Payer perspective: Payers include insurance companies, the government, or employers. The costs to the payer are those charges for health care products and services allowed, or reimbursed, by the payer.
- Societal perspective: This perspective is the broadest of all perspectives because it is the only one that considers the benefit to society as a whole. In general, all direct and indirect costs are included in an economic evaluation performed from a societal perspective(163).

The perspective of most of the study was unclear. It was obvious in many studies that the payer was the primary focus, because cost savings were a common measure of outcome. However, it was unclear whether the payer was the institution, the insurer or the patient (11). Because of differences in the healthcare systems of each country, the payer varied between studies. Hence, the differing health-care systems lake it unfeasible to compare the studies (168).

3.6.1.4. Types of pharmacoeconomic evaluation

There are several types of pharmacoeconomic analysis. Based on the elements of the model that are incorporated into an evaluation, analyses of CPSs can be characterized as shown in Table 13 (169).

Table 13. Types of pharmacoeconomic evaluation

		Were both cost and outcomes considered?	
		No	**Yes**
Were two or more alternatives considered?	**No**	Cost description or outcome description	Cost and outcome description
	Yes	Cost analysis or outcome analysis	True clinical economic analysis *Cost-minimization analysis (CMA)* *Cost-benefit analysis (CBA)* *Cost-effectiveness analysis (CEA)* *Cost-utility analysis (CUA)*

Source: Drummond M, Stoddart G, Torrance G, editors. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford Medical Publications; 1997.

The four most commonly used analysis methods (CMA, CBA, CEA, CUA) are shown in Table 14. For all four types, costs are measured in currency (e.g., dollars). The unit of measure of the consequences differentiates each type of analysis, and each analysis serves a different purpose.

Table 14. Comparison of types of pharmacoeconomic analysis

Method	**Unit of measure of costs**	**Unit of measure of consequences**	**Use**
Cost-minimization analysis	Currency (e.g., dollars)	None, assumed equivalent	Compare efficiency of alternatives
Cost-effectiveness analysis	Currency (e.g., dollars)	Natural units (e.g., lives saved)	Least costly way to achieve clinical objective
Cost-utility analysis	Currency (e.g., dollars)	Natural units adjusted for quality Least costly way to achieve quality of life (e.g. QALYs gained)	Least costly way to achieve quality of life
Cost-benefit analysis	Currency (e.g., dollars)	Currency (e.g., dollars)	Best investment

QALYs: Quality-adjusted life years. *Source:* Drummond M, Stoddart G, Torrance G, editors. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford Medical Publications; 1997.

3.6.1.5. Strategies of pharmacoeconomic evaluation

As a practical approach to documenting the value of, and gaining approval for, CPS, three methodological strategies can be considered: literature generalization, modeling, and local assessment (166).

- **Literature generalization:** Literature generalization is the application of data from published studies of services or practice sites similar to one's own environment. For example, a pharmacy department in a community hospital proposed and gained approval for implementation of CPS as a cost savings measure (170). Published articles that described

CPSs in community hospitals were reviewed to identify those that described patient mix, drug utilization patterns, and types of services similar to those proposed. Drug cost savings or cost avoided, and the number of clinical pharmacists man-hours associated with those costs were abstracted from each article. By combining the results of applicable articles, the authors estimated that implementing CPS would require 3.5 full-time equivalents in clinical pharmacists and would save about $500,000 (gross) in drug expenses in their hospital. Costs were determined based on the average pharmacist salary. Net benefits were projected to exceed $250,000 with a B:C ratio of > 2:1.

- Economic modeling: Economic modeling may also use previously published literature and/or may use locally collected data, and more effectively defines costs and consequences by use of a decision analysis model. For example, a study (171) compared outcomes of patients who received consultant pharmacist services versus those who did not. Probabilities for each outcome were determined by an expert panel. The cost to provide the service, based on pharmacist time, was estimated to be $10 per encounter. The authors determined that for each optimal outcome achieved with a consultant pharmacist, $1,034 was saved by prevention of costly DRPs. The B:C ratio for this service based on the data provided was approximately 12:1.

- Local evaluation: The last strategy is to measure and analyze the actual costs and consequences of existing CPS in one's own local practice site. In a recent article, Lai evaluated CPS provided in an ambulatory practice site (172). The implemented CPS provided intensive monitoring and intervention on DRPs for Medicaid patients at an ambulatory clinic. The goal was to determine the ability of the CPS to reduce health care utilization and associated expenses by comparing outcomes with a control group that did not receive the monitoring. The costs to provide the service for 1 year were $84,363 and primarily represented personnel costs. Overall health utilization was reduced by $173,651 in the intervention group. The B:C ratio was just over 2:1.

3.6.2. Economic studies of pharmacist interventions

3.6.2.1. Key methodological issues

The intervention process begins with the detection and recognition of a DRP by the pharmacist, followed by a recommendation for the resolution of the problem. In considering the value of the intervention process, a number of issues raised at each step of the process (see *Figure 1*), including:

- ✓ Three scenarios may occur when a DRP is present:
  - The DRP is not identified by the pharmacist nor anyone else involved in managing the patient.
  - The DRP is not identified by the pharmacist but is identified and addressed by another person involved in managing the patient
  - The DRP is identified and addressed by the pharmacist.
- ✓ Multiple consequences are possible for each situation. However, most previous studies have asked experts to predict only *the most likely* consequence of the PI.
- ✓ Each consequence may have a different probability of occurring.

- ✓ The value of a PI depends on both probability and severity of consequences without and with a PI.
- ✓ The value cannot be attributed to the pharmacist if someone else carries out the intervention.
- ✓ Compliance with the recommendation by the physician and/or the patient will affect actual but not potential value of the intervention.
- ✓ To gain more confidence in the robustness of the estimate, it is prudent to use uncertainty analysis.
- ✓ Consider utilizing actual economic costs where possible, rather than charges or government-established fees.
- ✓ Develop a common framework for resource costs, as recommended by Schulman et al. (173) that will facilitate cost comparisons across healthcare systems and countries.
- ✓ The generalizability of economic evaluations to other countries is questionable because of unique national data collection systems and disparities between different healthcare systems.
- ✓ Develop an instrument to promote standardized economic data collection in pharmaceutical care research.

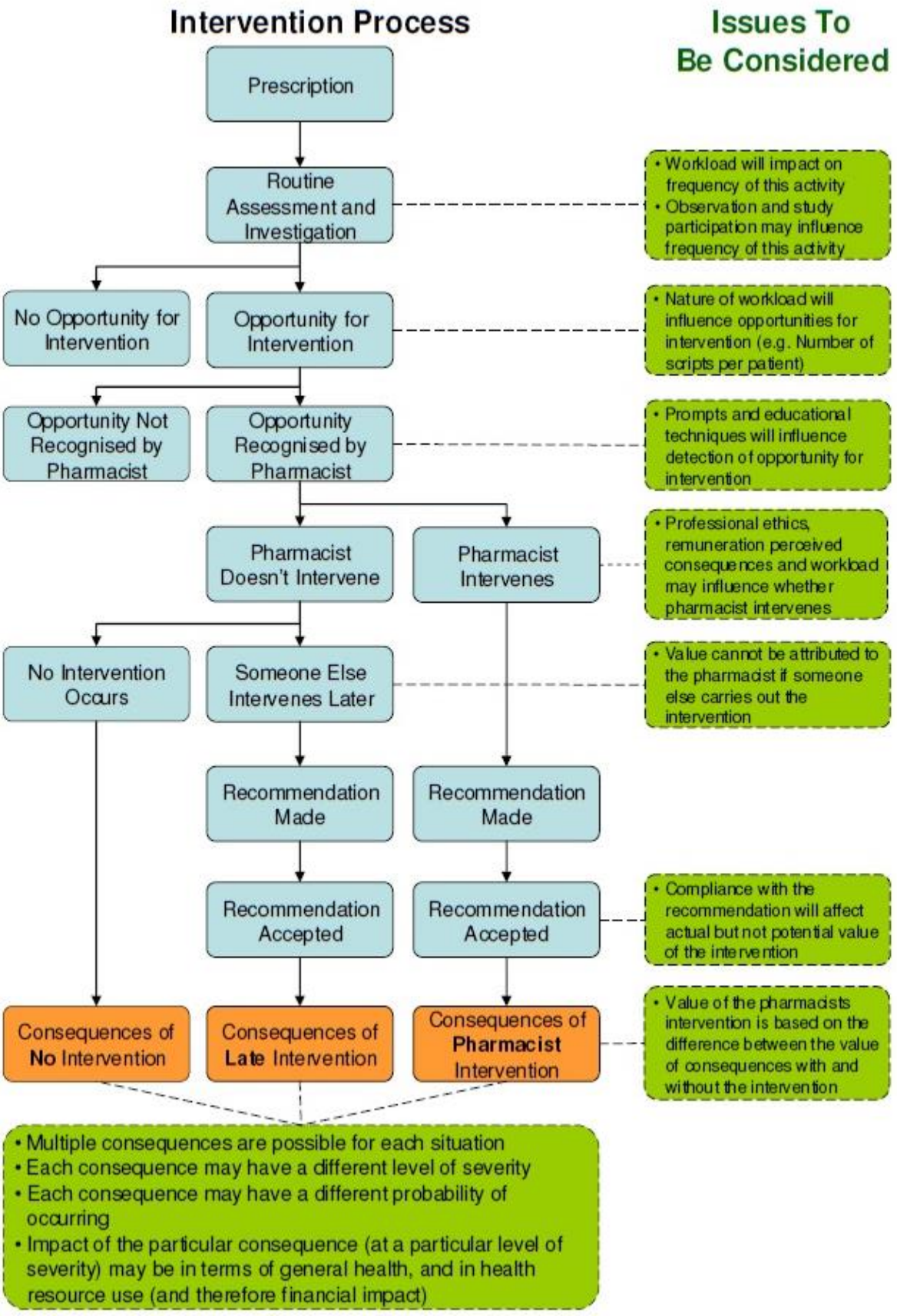

Figure 10. Issues to be considered in determining value of the intervention process

Source: Peterson G et al. PROMISe Intervention Study - Final report to the Pharmacy Guild of Australia. 2003. Available from: http://goo.gl/hUI1Mi.

3.6.2.2. Economic model for estimation of the value of a pharmacist Intervention

Applying the basic model of pharmacoeconomic analysis to evaluate the value of each PI, the value of a PI is the sum of the savings of inputs and the added outputs of the recommended drug therapy (with a PI) compared to the original drug therapy (without a PI) (see *Formula 1* in *Figure **11***).

In most studies (38, 44, 174-178), the economic value of a PI is estimated through cost savings ***plus*** cost avoidance ***less*** cost of implementation of a PI (*Formula 2*). The difference between the cost of the original therapy and the new therapy gives the cost savings (or the increase in the cost of therapy). Cost avoidance refers to the prevention of additional health resources which are required to treat drug adverse events if a pharmacist has not intervened such as a hospitalization or a medical visit. Cost of implementation of a PI refers to the expenses of providing the PI such as cost of pharmacist's time, phone calls. These value estimations made were limited to the *medical direct costs*, and did not include the *non-medical direct costs*, the *indirect* (lost productivity) and *intangible costs* (quality of life). Overall, the indirect costs exceed the direct costs(168). Therefore, these value estimations will underestimate the value of PIs.

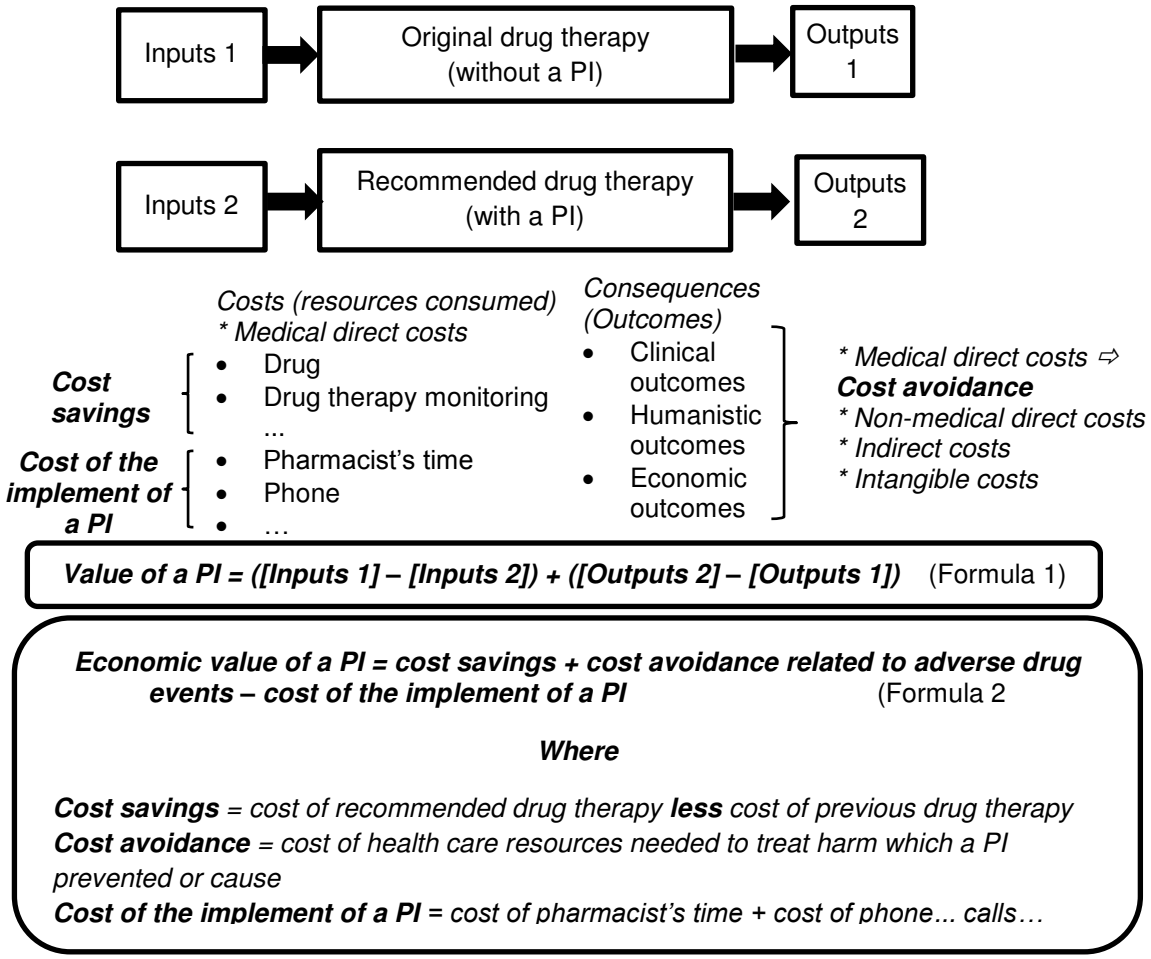

Figure 11. Economic model for estimation of the value of a PI

3.6.2.3. Methods for estimation of cost of implementation of pharmacist interventions

It is difficult to estimate the cost of implementation of each PI. Clinical activities of pharmacists included professional communication, medication chart review, medication history interview, clinical review, providing information to patients/caregivers, ascertaining discharge drugs required, and obtaining drug information, etc. (179). A PI is often a result of complex multi-activities. Therefore, attribution of time that a pharmacist spent to propose a PI was not clear. Costs for training and mentoring pharmacists should be considered also(175).

Most studies include the cost of the intervention, based on the time required to propose the IP and labor costs (salaries plus benefits of the pharmacists) (175, 180). Working time spent on this activity is variable depending on the study. The mean time spent on an intervention was 7.0-9.6 minutes (52, 123, 124). Nerich et al. found that one minute was sufficient for prescription without IP against 8.7 to 14.7 minutes for a prescription with IP (181). In France, the same activity would take between 1 and 5 minutes (182). On this basis, Rose et al. estimated 5 minutes as time spent on each PI related to IV/PO change (183).

Some authors considered the total time spent in prescription analysis and not only one dedicated to the realization of a single PI (52, 184, 185). Finally, in some studies, the time spent by pharmacists in health care services (participation in medical rounds) was also recorded in the cost involved (184, 186). Other costs of implementation of PIs included the cost of the equipment used to record PIs (175), expert panel's time for assessment (185), phone call (178) or materials necessary to provide PIs (176).

Development of an instrument to promote standardized economic collection is useful. In the IMPROVE study - a multicenter randomized pharmaceutical care study of patients at high risk for DRPs, cost of clinical PIs was based on standard costs assigned by the decision support system that accounted for time and intensity of intervention (low, medium or high) (187).

3.6.2.4. Methods for estimation of cost savings related to pharmacist interventions

The difference between the cost of the original therapy and the new therapy recommended by a PI gives the *cost savings* (or the *increase in the cost of therapy*). For example, in the case of conversion from IV to oral dosage forms, drug discontinuation, the IP gives the cost savings while the PI as indication of additional drugs, switch to more expensive drugs increase the cost of therapy.

Methods for estimation of cost savings related to the PI varied across studies (180). However, a common major component contributed to cost savings in all studies was *drug cost.* In some studies (184, 188), other components were taken into consideration such as *cost savings on medical devices and working time of nurses* for preparation and administration of drug prescribed. Indeed, in the case of an injectable treatment, some solutions or medical devices must be used (e.g., catheter, syringe, needle) for reconstitution, dilution and administration. All these steps require additional work to the nurse, which has a cost.

Cost savings can be also calculated relative to a more cost-effective method for *drug therapy monitoring*, e.g., use of appropriate monitoring variables, cancellation of unnecessary laboratory orders, and identification of therapeutic agents requiring fewer monitoring and/or fewer costly laboratory tests (14, 189).

The formula of cost saving is as follows:

[cost saving] = [cost of the previous drug therapy] - [cost of the recommended drug therapy] = [daily cost saving] X [number of days of modified treatment]

Methods used to determine the number days affected by the PI differ across studies, including the whole rest of hospitalization length (175), the number of anticipated treatment (136, 175), a mean estimated by an expert panel (with a minimum and maximum)(190), or a fixed number of days (for example, 1.5 days (175) or 2 days (191) for witch IV/PO). Rose et al. used many hypotheses: the first one was the PI affects only 1 day, the second was the half of a rest of hospital stay and the final was the whole rest of hospital stay (192). Lee at al. also provided guidelines for determining duration of therapy when calculating cost of original and recommended therapy (136).

3.6.2.5. Methods for estimation of cost avoidance related to pharmacist interventions

Cost avoidance refers to the prevention of additional health resources which are required to treat ADEs if a pharmacist has not intervened such as a hospitalization or a medical visit. These methods are similar to the conceptual model for estimation of the cost-of-illness of drug-related morbidity (168, 193). In contrary, harm could have resulted from the PI if the PI was not appropriate, and in these cases, the PI could induce costs (136).

Many methods for estimation of cost avoidance were available. For example, cost avoidance focused on:

- ✓ only avoided LOS in the study of Bayliff et al. (194);
- ✓ avoided primary care visit and avoided LOS in the study of Westerlund et al. (195),
- ✓ probability of an ADE in the study of Nesbit et al. (175)
- ✓ both probability of ADEs prevented and different levels of care avoided in the study of Rupp et al. (196) and in the study of Lee et al. (136)
- ✓ probability of change in readmission and LOS with and without the PI in the study of Dooley et al. (52)
- ✓ difference in probability of different consequences before and after the PI and attribution the PI to the pharmacist in the study of Stafford et al. (154) and Peterson et al. (178)

Economic methodologies for estimation of the value of PIs were summarized in Table 15. Some studies estimated partly either cost savings, cost avoidance, or cost of implementation of PIs while others considered all. However, overall, the value of the PI considered only medical direct costs and did not consider non-medical direct, indirect and intangible costs which were difficult to estimate.

Table 15. Economic methodologies for estimation of the value of PIs

A. Only cost avoidance

2. Bayliff (1990) (194) - Hospital

a. The objective of the study was: to assess the impact of PIs by physicians.

b. Value of PI:

[Cost avoidance] = [number of days of hospitalization avoided] x [cost per day]

c. The result was expressed as:

- The number of PIs judged to have a prolonged hospital stay
- The mean days of hospitalization avoided per intervention
- The total cost avoidance

2. Rupp (1992) (196) - Community pharmacy

a. The objective of the study was: to estimate the impact on patient health status of the PIs.

b. Value of PI:

[Expected medical cost avoidance] = [Probability of the most likely harmful outcome would have occurred] x [cost of medical care associate with that outcome]

- Probability: 0 (zero), 0.1 (very unlikely), 0.3 (somewhat unlikely), 0.5 (neither likely nor unlikely), 0.7 (somewhat likely), 0.9 (very likely) or 1.0
- Medical care: emergency medical attention with hospitalization ($2001), emergency medical attention without hospitalization ($110), unscheduled physician contact ($60), scheduled physician contact ($40), or self-care ($0).

c. The result was expressed as:

- % PIs where was a potential for harm, had the pharmacist not intervened.
- % PIs prevented different medical care
- The expected medical cost avoidance per intervention

B. Cost avoidance and cost of implementation

5. Westerlund (2005) (195) - Community pharmacy

a. The objective of the study: to assess the clinical and economic outcomes of community pharmacy interventions in patient DRPs.

b. Value of PI:

Ratio **= [**cost avoidance]/[cost of implementation]

- [Cost avoidance] = [cost of avoided primary care visit] OR [number of avoided hospitalization days] x [cost per day]
- Cost of implementation of PIs = personal cost (salaries of pharmacists)

c. The result was expressed as:

- The total cost avoidance
- The total cost implementation
- The ratio between the total cost avoidance and the cost of implementation of PIs

C. Studies estimated both cost savings and cost avoidance

5. Dooley 2003 (52) - Hospital

a. The objective of the study was: to determine the financial value of pharmacist initiated changes to hospitalized patients' drug therapy at hospitals

b. Value of PI:

[Financial value] = [cost avoidance of readmission] + [cost avoidance of LOS] + [cost

savings of medical procedures or laboratory monitoring] + [cost savings of drug therapy]

- [Cost avoidance of readmission] = ([Probability of readmission without the PI] - [Probability of readmission with the PI]) x [cost per relevant Diagnostic-Related Group]
- [Cost avoidance of LOS] = [Probability of change in LOS] x ([LOS without the PI] - [LOS with the PI]) x [cost per day]
- [Cost savings of medical procedures or laboratory monitoring] = [Probability of change in medical procedures or laboratory monitoring] x [local costs of that procedure or laboratory test]
- [Cost savings of drug therapy] = [cost of previous drug therapy] - [cost of recommended drug therapy]

c. The result was expressed as:

- The value by type of PIs
- The annual value

D. Studies estimated cost savings, cost avoidance and cost of implementation of a PI

1. Hatoum (1988) (14) - Hospital

a. The objective of the study was: to evaluate value of PIs in a hospital

b. **Value of PI:**

$V = D + M + U + L - C$

In this formula, it is possible for any one the four variables to be positive, negative, or zero.

- V: [Value]
- D: [Cost saving of drug therapy]: e.g., use of less expensive drugs, discontinuance of a drug, conversion to a less expensive drugs (including change of dose, dose interval, route, duration, or form of medication).
- M: [Cost savings of drug therapy monitoring]: e.g., use of appropriate monitoring variables, cancellation of unnecessary laboratory orders, and identification of therapeutic agents requiring fewer monitoring and/or fewer costly laboratory tests.
- U: [Cost avoidance of complications of drug therapy]: e.g., costs related to the detection and management of such untoward effects as toxic side effects, adverse drug reactions, and therapeutic failures.
- L: [Cost avoidance related to LOS]: e.g., more effective drug therapy resulting in improved therapy and more efficient management of patient care, thus reducing the length of stay and/or avoiding predictable complications that might increase the hospital stay (e.g.;, preventing an allergic reaction in a patient for whom a known allergy is documented).
- C: [Cost of CPSs] = [personnel cost (salaries)] + [indirect personnel cost (fringe and other employer-paid benefits)].

c. The result was expressed as:

- the average value for interventions implemented
- the average value for interventions not implemented
- the annual realized value for intervention implemented
- the annual potential value for interventions not implemented

3. Lee (2002) (136) - Hospital

a. The objective of the study was:

To estimate the level of benefit or harm that would have occurred with and without PIs, as well as the economic and clinical consequences.

b. Value of PI:

[Value] = [cost savings] + [cost avoidance]

- [Cost savings] = [cost of the original therapy] - [cost of recommended therapy]
  - [Cost of original therapy] = [daily drug acquisition cost] x [duration of therapy] + [labor cost for filling and processing order by pharmacist]
  - [Cost of the recommended therapy] = [drug acquisition cost] x [duration of therapy] + [labor cost] + [average cost of making recommendation]
- [Cost avoidance] = [probability of harm which a PI prevented or caused] x [cost of care]
  - [Probability of harm]: estimated by a scale from 0 to 1.0
  - Type of health care resources need to treat the harmful event: included medication, laboratory and diagnostic procedures, clinical visits, telephone care, emergency-room visits, self-care and hospitalization
    - If hospitalization, [Cost of care] = [number of hospital days] x [International Classification of Disease-specific bed-cost per day]
    - If other, [Cost of care] = [local cost]

c. The result was expressed as:

- The average probability of harm prevented or caused
- The mean cost savings per recommendation
- The minimum, maximum and mean cost avoidance per recommendation
- The total minimum, maximum and mean cost avoidance

* [Cost of implementation of the PI] was integrated into [the cost of the recommended therapy]

4. Nesbit (2001) (175) - Hospital

a. The objective of the study was: to estimate the value of the CSP practice model to the institution.

b. Value of PI:

[Net economic value] = [cost savings] + [cost avoidance related to averted ADEs] - [the costs of the CSP model]

- [Cost savings] = [cost of the previous drug therapy] - [cost of the recommended drug therapy]
- [Cost avoidance] = [Probability of an ADE in absence of intervention] x [Average cost of an ADE]
  - [Probability of an ADE]: 0 (zero), 0.01 (very low), 0.1 (low), 0.4 (medium) or 0.6 (high)
  - [Average cost of an ADE] = $5,006
- [Costs of the CSP model] = [personnel cost (salaries + benefits of pharmacists)] + [equipment used to record PIs]

c. The result was expressed as:

- Cost avoidance, cost savings per intervention, per intervention type per 12 months
- Net economic value to institution

5. Stafford (2011)

a. The objective of the study was:

To develop a methodological framework for estimating health resource savings and quality of life effects resulting from PIs by community pharmacists

b. Value of PI:

Value of PI attributed to the pharmacist = [value] x [% attribution to the pharmacist]

- Value = [difference in probability of *Severe consequence A*] x [parameters describing *Severe consequence A*] + [difference in probability of *Moderate consequence A*] x [parameters describing *Moderate consequence A*] + [difference in probability of *Mild consequence A*] x [parameters describing *Mild consequence A*] +...[difference in probability of *Severe, Moderate & Mild consequence B, C, D etc.*] x [parameters describing *Severe, Moderate & Mild consequence B, C, D etc.*]
  - [Difference in probability of *Severe Consequence A]* = [Probability of *Severe consequence A before PI]* - [Probability of *Severe consequence A after PI]*
  - [Difference in probability of Moderate *Consequence A]* = [Probability of Moderate *consequence A before PI]* - [Probability of Moderate *consequence A after PI]*
  - [Difference in probability of *Mild Consequence A]* = [Probability of *Mild consequence A before PI]* - [Probability of *Mild consequence A after PI]*
  - ...
- [% Attribution to the pharmacist] = 1 - [likelihood of someone other than the pharmacist performing the PI]

* Consequences: such as hospitalization admission, emergency department visits, ambulance/patient transport costs, general practitioner or specialist consultations, allied health professional consultations, medications commenced and ceased, and pathology/laboratory investigation.

PI: pharmacist intervention. DRP: drug-related problem. LOS: length of stay. CPS: clinical pharmacy service. ADE: adverse drug event

3.7. The integrated model for evaluation of impacts of PIs

We synthetized five models: *the SPO model*, *the ECHO model*, *the SEIPS model*, *the model of Martini*, *the economic model*, and *the risk assessment matrix* into an integrated model for evaluation of impacts of PIs, named *the SP(ECH)O-P* (

Figure 12).

According to *the SP(ECH)O-P model*, the PI can have impacts on structure, process of care and outcomes on the patient (similar to *the SPO model*). The outcomes can include economic, clinical, and humanistic outcomes (similar to *the ECHO model*). Not all impacts of the PI is obvious and certain but a potential to occur (probability). Therefore, it should combine probability of each impact and severity/importance of each impact into risk matrix (similar to

the risk matrix). The value of each PI is the sum of differences of value of the scenario with and without the PI (similar to *the economic model*).

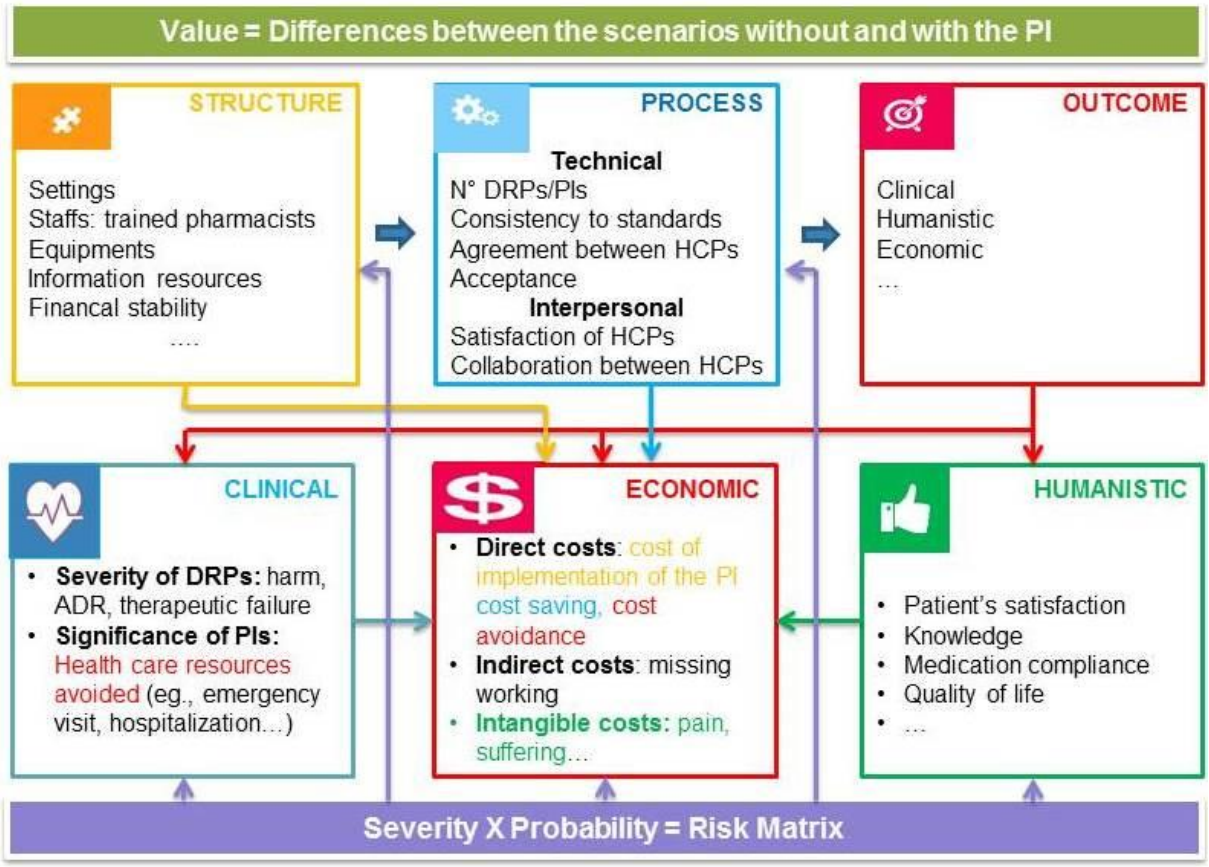

Figure 12. The SP(ECH)O-P integrated model for evaluation of impacts of PIs

IT: information techonolgy. DRP: drug-related problem. PI: pharmacist intervention. CMA: cost-minimization analysis. CBA: cost-benefit analysis. CEA: cost-effectiveness analysis. CUA: cost-utility analysis

In conclusion, understanding of theoretical models or conceptual frameworks that can be applied to assess impacts of MR/PIs helps pharmacists and researchers to have a broad picture of possible impacts of MR. Firstly, the Structure-Process-Outcome model emphasizes that the quality of health care interventions depends on structure, process and outcomes-related indicators. The model of Martini evaluates specifically the quality of MR based on quality of detection of DRPs and proposition of PIs; and from perspectives of intervening pharmacists, other pharmacists, the physician, the patient and society. Meanwhile, the Systems Engineering Initiative for Patient Safety (SEIPS) model considers MR as "pharmacy work systems" with the various components (five components of the work system: person, tasks, tools and technologies, physical environment, organizational conditions; process and outcomes) and their interactions. Next, the ECHO model described in detail three type outcomes (economic, clinical and humanistic outcomes) and their relationships while the risk assessment matrix considers probability of impacts into risk classification. Then, the pharmacoeconomic model is applied to estimate exactly the economic value of a pharmacist intervention. Finally, we tried to summarize the five models into an integrated model, named

SP(ECH)O-P which requires to consider impacts of PIs on indicators related to Structure, Process, Economic, Clinical, and Humanistic Outcomes and Probabilities of their impacts.

PART 2.

SYSTEMATIC REVIEW OF TOOLS FOR ASSESSMENT OF POTENTIAL SIGNIFICANCE OF PHARMACIST INTERVENTION

*In this **Part 2**, we will present a systematic review of tools for assessing potential significance of PIs. Then, some important tools will be introduced more in details.*

1. A systematic review of tools for assessing potential significance of pharmacist interventions

Assessment of potential significance of PIs are common in literature by using various methods and tools. However, few information on summarization and discussion of these tools has been found. The only literature review of tools of rating of pharmacist interventions was reported in 1999 by Overhage et al. (12). The paper noted that among 51 identified articles, only 10 included an explicit description of the rating tool used. However, to our knowledge, there is no other up-to-date literature review on this topic. Recently, a systematic review of tools for measuring the severity of prescribing errors was reported in 2013 by Garfield et al. (197). Forty tools were identified that assessed severity, only two of which had acceptable reliability and validity. Tools for measuring errors may be used to evaluate the effectiveness of interventions designed to reduce them. However, in general, tools for assessing potential impacts of PIs have specific properties. Furthermore, since then, with economic constraints growing, aging, burden of chronic disease, patient's lack of compliance, the assessment of quality of PIs is shifting from only clinical to economic and humanistic impacts (e.g., patient's quality of life, compliance, and satisfaction)(11). Therefore, the purpose of this systematic review is to update available tools for assessment of potential significance of a PI and to propose the pragmatic, psychometric and theoretical properties of ideal tools.

We searched English and French-language publications (from 1986 to 2013) were conducted in PubMed, PsycINFO, PASCAL, and CINAHL. Of 873 citations screened, 82 distinct tools were identified from 133 studies. While clinical aspect was often defined quite clearly, terminology of humanistic and economic, and process-related aspects of PIs was often omitted, incomplete or ambiguous in most tools. Few tools measured simultaneously economic, clinical, humanistic, and process-related variables. Of 133 identified studies, there was limited evidence for the validity (8/133, 6.0%), inter-rater reliability (49/133, 36.8%), and intra-rater reliability (2/133, 1.5%).

Currently, there are no formal guidelines or any standardization of methodology concerning methods of assessment of the potential significance of PIs. Researchers and clinicians may have different needs in relation to a tool for assessing the potential significance of PIs. However, in general, an ideal tool should be specific to PIs' potential significance, relatively easy and not too time consuming to use, reliable, and validated in different healthcare systems. Taking into account the results of this review, we suggest some desirable pragmatic, psychometric and theoretical properties of idea tools for assessing of potential significance of PIs. Furthermore, due to the wide range of tools used in the literature, this review article is useful for researchers who want compare tools to assist in comparing findings across studies or to develop a new tools for local use.

Article 1.

Tools for assessing potential significance of pharmacist interventions: A systematic review

Thi-Ha VO, Bruno CHARPIAT, Claire CATOIRE, Michel JUSTE, Renaud ROUBILLE, François-Xavier ROSE, Sébastien CHANOINE, Jean-Luc BOSSON, Ornella CONORT, Benoît ALLENET, Pierrick BEDOUCH

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Article 1. Tools for assessing potential significance of pharmacist interventions: A systematic review

Short running title: Tools for assessing potential significance of pharmacist interventions

Authors: Thi-Ha VO[1,2], Bruno CHARPIAT[1,2,3], Claire CATOIRE[1,2,4], Michel JUSTE[5], Renaud ROUBILLE[6], François-Xavier ROSE[7], Sébastien CHANOINE[1,4], Jean-Luc BOSSON[1,2], Ornella CONORT[8], Benoît ALLENET[1,2,4], Pierrick BEDOUCH[1,2,4]

1. Univ. Grenoble Alpes, TIMC-IMAG, F-38000 Grenoble, France.
2. CNRS, TIMC-IMAG, F-38000 Grenoble, France.
3. Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Pharmacie, F-69000 Lyon, France.
4. CHU Grenoble, Pôle Pharmacie, F-38000 Grenoble, France.
5. Centre Hospitalier Auban-Moët, Pharmacie, F-51200 Epernay, France.
6. Centre Hospitalier Lucien Hussel, Pharmacie, F-26000 Vienne, France.
7. EPSM-Morbihan, Pharmacie, F-56890 Saint-Avé, France.
8. Assistance Publique des Hôpitaux de Paris, Hôpital Cochin, Pharmacie, F-75000 Paris, France.

on behalf of the Working group "Standardizing and demonstrating the value of clinical pharmacy activities" of the French Society for Clinical Pharmacy

Abstract

Introduction

Assessment of significance of pharmacist interventions (PIs) is essential to demonstrate added value of pharmacists. Methods and tools assessing potential significance of PIs are diverse and their properties are questionable.

Objectives

We aimed to review systematically on tools for assessing potential significance of PIs.

Methods

Systematic searches for English and French-language publications (from 1986 to 2013) were conducted in PubMed, PsycINFO, PASCAL, and CINAHL. Studies were screened by two independent reviewers based on inclusion/exclusion criteria and were abstracted for content, structure of tools and validation process.

Results

Of 873 citations screened, 82 distinct tools were identified from 133 studies. While clinical aspect was often defined quite clearly, terminology of humanistic and economic, and process-related aspects of PIs was often omitted, incomplete or ambiguous in most tools. Probabilities of consequences of PIs/drug-related problems were evaluated in 20/82 tools. Few tools measured simultaneously economic, clinical, humanistic, and process-related variables. Tools' structure varied from an implicit, mono-dimension tool to an explicit, multi-dimensional algorithm. Validation processes were diverse in term of quantification and number of raters, rating method, and psychometric parameters. Of 133 identified studies, there was limited evidence for the validity (8/133, 6.0%), inter-rater reliability (49/133, 36.8%), and intra-rater reliability (2/133, 1.5%).

Conclusions

The majority of tools focused primarily on assessing clinical aspect and failed to detect comprehensive impacts. Heterogeneity of tools and assessment process hindered our ability to synthetize the results of evaluations. Limited results for their validity and reliability questioned credibility of this methodology for justification of value of PIs. Recommendations for development of tools with optimal theoretical, pragmatic and psychometric properties are proposed.

Key messages

- The role of pharmacists should be to determine the value of PIs and target PIs which have most value.

- The majority of tools for assessing potential significance of PIs were used in literature. However, an optimal tool has not found.

- Recommendations for development of new tools with optimal theoretical, pragmatic and psychometric properties are proposed.

1. INTRODUCTION

Adverse drug events (ADEs) are one of the major problems relating to patient safety. They are associated with increased morbidity and mortality, prolonged hospitalizations, and higher costs of care [1, 2]. The ADEs are considered preventable in nearly half of the cases [1]. Therefore, detection, resolution and prevention of actual or potential drug-related problems (DRPs) through pharmacist interventions (PIs) are considered as a key strategy to reduce ADEs [1]. In this article, a DRP is commonly defined as "an event or circumstance involving drug treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care" [2], and PIs as "discrete activities by pharmacists related to patient care" [3].

Assessment of significance of a PI is now recognized as essential for demonstrating the added value of pharmacists to the healthcare system and justification for obtaining additional resources in clinical pharmacy practice. This assessment is also used as indicators of pharmacist's performance and the continuing quality improvement, research and education [1].

Through studies in the literature, it is possible to classify the approaches of assessing the significance of an individual PI into 3 main types: *Approach 1* **-** the evaluation of *actual* consequences of DRPs (e.g., actual severity of harm); *Approach 2* - the evaluation of *actual* consequences after performing a PI and following-up the patient (e.g., actual clinical outcomes); or *Approach 3* - the estimation of *potential* significance of a PI (**Fig.1**). Term "*actual"* is understood as meaning the entity that has appeared in the patient, while the term "*potential"* referred to the situation in which the possibility that the entity could appear in the patient existed [4].

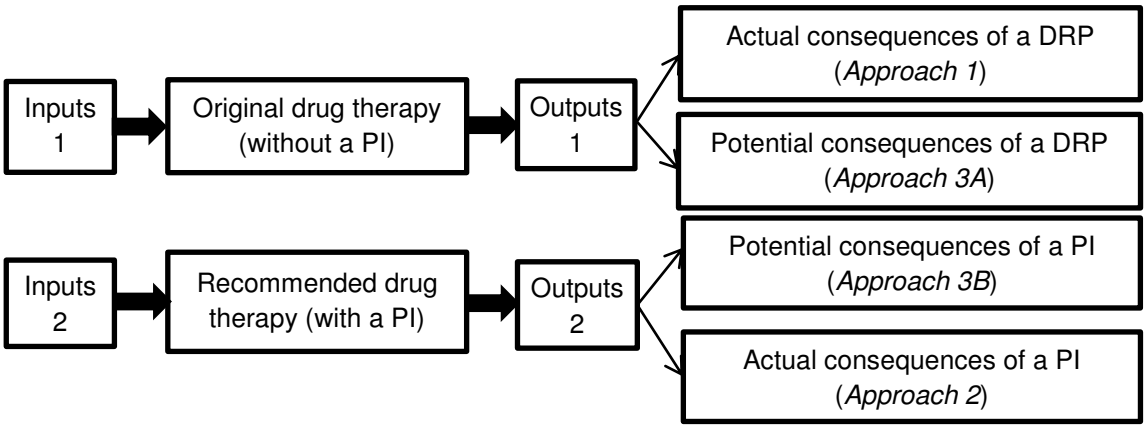

Fig.1 Different approaches to evaluate the significance of a pharmacist intervention.

DRP: drug-related problem. PI: pharmacist intervention

According to the *approach 1***,** the earlier the pharmacist intervenes to prevent harm to the patient, the more significant a PI is likely to be. In fact, harm due to DRPs in the patient rarely occurs. For example, Vessal et al. found that about 90% of the prescription errors resulted in no harm in patients because a great majority of errors were corrected early by pharmacists [5]. Two limitations of this approach are to offer little guidance for improving quality of a PI in

the future and reflect the quality of the whole system of patient care rather than the only contribution of a PI [6].

According to the *approach 2***,** the assessment of *actual* consequences*,* commonly clinical outcomes, in the patient after performing a PI and following-up the patient is the only valid indicators of the quality of a PI. It is helpful to assist in decision making on a daily basis for physicians and pharmacists [1]. However, the assessment of *actual clinical outcome* in the patient is associated with some main difficulties: criteria/technology of follow-up, timeframe, determination of causal relationships between PIs and health outcomes [7-10].

According to the *approach 3***,** the assessment of *potential* significance of PIs may be done through two sub-types: *approach 3A* – prediction of the *potential* consequences of DRPs in absence of a PI; *approach 3B* **-** prediction of the *potential* consequences of an implemented PI [11, 12]. The assessment of the *potential* significance of a PI is associated with metrological problems such as subjectivity, validity and reliability of predictions. However, this method is frequently used as a means of commenting in the significance and quality of a PI because of its practicability when the lack of data of evaluation of actual consequences, its usefulness in guidance for improving quality of a PI (e.g., hierarchy of potential significance of a PI and target the most potential significant PIs). Therefore, the review in this article only synthetized the tools for assessment of *potential significance of PIs – Approach 3*.

Methods and tools assessing the significance of PIs are diverse and their pragmatic, psychometric and theoretical properties are questionable. The only literature review of tools of rating of pharmacist interventions was reported in 1999 by Overhage et al. [12]. The paper noted that among 51 identified articles, only 10 included an explicit description of the rating tool used. Thus, the authors developed a two-dimensional tool that could characterize a hospital pharmacist's recommendations based on the severity of the DRP and the value of that intervention. A broad adoption of this validated tool has been used for characterizing clinical activities in different settings. However, to our knowledge, there is no other up-to-date literature review. Furthermore, since then, with economic constraints growing, aging, burden of chronic disease, patient's lack of compliance, the assessment of quality of PIs is shifting from only clinical to economic and humanistic impacts (e.g., patient's quality of life, compliance, and satisfaction) [13]. Therefore, the purpose of this systematic review is to summarize available tools for assessment of potential significance of a PI and to propose the pragmatic, psychometric and theoretical properties of ideal tools.

2. METHODS

2.1. Research Strategy

A systematic review was performed in the databases MEDLINE (Pubmed) (1986 – February 2013), PASCAL (1997 - February 2013), PsycINFO (1999 - February 2013), CINAHL with full-text (1993 - February 2013), in order to collect studies using tools for assessment of potential significance of an individual PI.

We combined two groups of keywords as the equation search: *drug-related problems AND pharmacist interventions ("drug related problems" OR "drug therapy problems" OR*

"medication therapy problems" OR "medication inappropriateness" OR "pharmaceutical care issues" OR "medicine related problems" OR "medication related problems" OR "medication errors") AND ("pharmaceutical care" OR "pharmaceutical services" OR "medication order review" OR "medication review" OR "pharmacotherapy interventions" OR "pharmacy interventions" OR "drug utilization review" OR "pharmacist recommendations" OR "pharmacist interventions").

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follow: (1) original articles published in English or French; (2) abstract available; (3) published in peer review journals; (4) a study involving pharmacists alone or in cooperation with other healthcare professionals; and (5) having an explicit description of a method for rating the impacts of a PI, called *a tool* in this review.

The exclusion criteria for articles include: (1) literature reviews; (2) studies related to one specific type of DRPs/PIs (e.g., administration errors, drug information service); (3) tools only assessing the actual consequences of DRPs (e.g., ADEs/adverse drug reactions (ADRs)); (4) tools only assessing the actual consequences of a PI; and (5) studies assessing economic impact only; and (6) non-accessible articles. In addition, references listed of articles that met our inclusion criteria, of systematic reviews, and review articles were assessed and, if relevant, were retrieved. Eleven additional articles were also retrieved from a thesis of Quélennec [14] which performed a literature review of tools for evaluation of potential clinical impacts of medication errors (MEs) intercepted through medication conciliation. Finally, hand-search was done to identify articles that were not captured in the electronic database search.

2.3. Screening and data extraction

One author screened (THV) all titles, abstracts and then full-text articles for the first time in February 2013. Another author (CC) independently screened with the same strategies. Additional articles retrieved by the second reviewer were added to the final results. The second reviewer also verified the extraction of relevant data from included articles conducted by the first reviewer. We resolved any disagreement through discussion until consensus was reached.

2.3.1. Content of tools

In order to identify the indicators used in existing tools, theoretical models which are possible to be applied to assess PIs were reviewed. The conceptual models “structure-process-outcome model” by Donabedian [15] suggested that the quality of healthcare interventions was assessed through three types of indicators related to “structural features”- appropriate resources and system design; “process of care”- the method by which health care is provided; and “outcome”- the consequence of the health care provided. The model provided by Kozma et al. [16], placing outcomes into three categories - Economic, Clinical, and Humanistic Outcomes (ECHO model) depict the value of pharmaceutical services. The **Fig. 2** demonstrates the combination of the above two models.

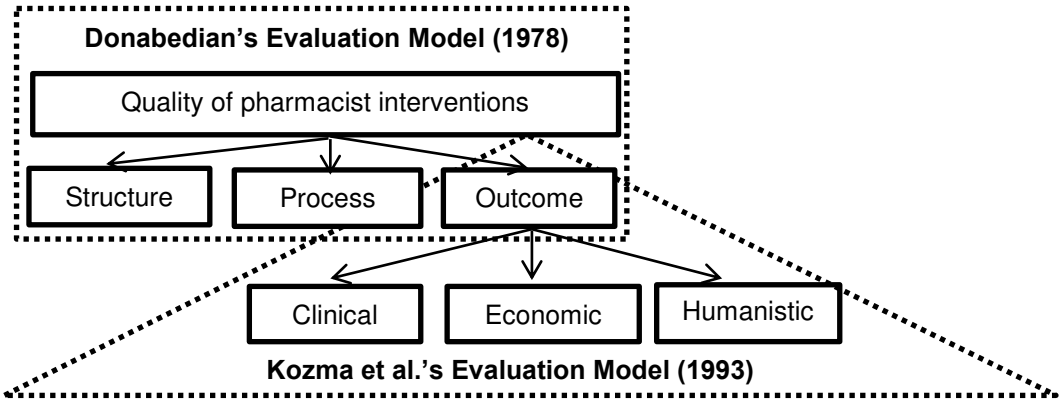

Fig. 2 Evaluation model of PIs based on the Donabedian's and Kozma et al.'s models

According to risk model [17], risks are analyzed by combining severity of consequences and probability in the context of existing situation. Risk matrix are used predominantly in safety risk management of MEs such as National Patient Safety Risk Matrix in UK [17], Safety Assessment Code Matrix in USA [18], Standard for risk management in Australia [19]. An original safety risk matrix assesses a broad range of risks including clinical, financial risks, risks related to reputation, business process, and system, etc. The matrix of clinical risk was simplified to develop some tools assessing the potential significance of a PI [20-24].

According to the basic model of pharmacoeconomics [25], the value of a PI considers both inputs and outputs of a PI compared to the absence of a PI (**Fig. 3**). Inputs can be thought of as resources required implementing the PI. Outputs can be thought of as consequences of a PI, in form of clinical, humanistic, or process-related consequences. The difference between the cost of the original therapy and the new therapy gives the cost savings (or the increase in the cost of therapy). Cost avoidance refers to the prevention of additional health resources which are required to treat drug adverse events if a pharmacist has not intervened such as a hospitalization or a medical visit. Cost of implementation of a PI refers to the expenses of providing the PI such as cost of pharmacist's time, phone calls, etc. In some studies [26, 27], the economic value of a PI is estimated through cost savings plus cost avoidance less cost of implementation of a PI.

Regarding to the content of tools, after combination of the above 4 models which are possible to be applied to assess IPs, we determined and classified indicators used in existing tools into 5 main types of indicators: indicators related to economic, clinical, and humanistic outcomes, process and probability of the impact.

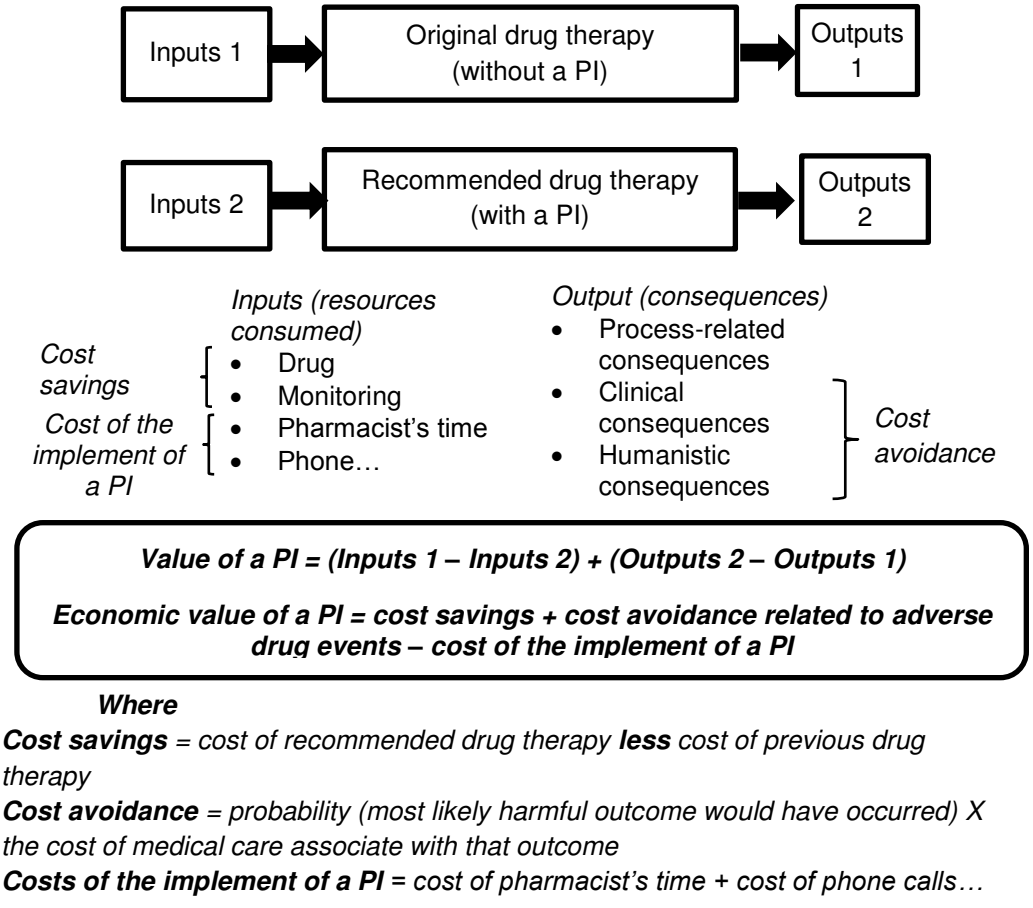

Fig. 3 Economic model for estimation of a pharmacist intervention

2.3.2. Structure of tools

Regarding to the structure of tools, it was classified as *mono-dimensional* or *multidimensional*. One dimension was defined as an independent rating to answer one question related to impacts of a PI. Each dimension was also classified as *nominal* (two or more categories, but there is no intrinsic ordering to the categories, for example, rating PIs into 2 categories: technical or clinical problems [28]) or *ordinal* (there is a clear ordering of the dimension, for example, ordering clinical impacts of PIs into three categories as minor, moderate, major significance [29]). Each aspect of impact of a PI (e.g., clinical, economic aspect) was evaluated *independently* in one dimension or *combinedly* within "significance" dimension with other aspects. For example, clinical impact was evaluated independently into 6-category dimension (adverse significance, no significance, somewhat significant, very significant, extremely significant) and drug cost saving of a PI was evaluated independently in 3-category dimension (drug cost reduction, drug cost increase, no change), respectively in the tool of Briceland et al. [30]. In contrary, drug cost savings was integrated with clinical impact into a 4-category dimension (low, mild, moderate, high significance) in the tool of Williams et al. [31].

2.3.3. Psychometric parameters of tools

Regarding to the psychometric parameters of tools, *validity* aims to check if the tool is measuring what it is supposed to measure; *inter-rater reliability* measures whether, when the same test is applied to the same scenarios by different raters, the same results are produced; *intra-rater reliability* measures whether, when the same test is applied to the same scenarios by the same rater on two different occasions, the same results are produced [32]. We assessed risk of bias in studies which reported results of validity and/or reliability according to the Cochrane Handbook for Systematic Reviews of Interventions [33]. We addressed main components: selection bias, performance bias, detection bias, and others biases. For each study, we placed judgments of low, high, or unclear/unknown risk of bias (see **Electronic Supplementary Material (ESM) 1).**

2.3.3. Assessment of quality of tools

We assessed quality of each tool used in included studies using the criteria outlined in the **ESM 2.** One point is awarded when a criterion is clearly satisfied. The sum of scores presents the quality of a tool for assessing significance of PIs in an included study.

We designed two forms to extract data. The articles were evaluated and summarized by (1) authors, published year, country; (2) structure of tools; (3) approach of assessment; (4) content of tools; (5) notes (see **ESM 3**); and by (6) setting, number of sample, sampling; (7) qualification and number of raters; (8) rating methods; (9) definitions of consensus; (10) validation; (11) inter-rater reliability; (12) intra-rater reliability, (13) risk of bias, and (14) score of quality of a tool (see **ESM 4**). For eligible studies, at least two review authors (THV and CC) independently extracted the data using these form. We resolved discrepancies through discussion until consensus was reached. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details. We conducted this systematic review according to the PRISMA guidelines [34].

3. RESULTS

3.1. Studies identified

A total of 873 articles were retrieved from Pubmed (646), PASCAL (96), PsycINFO (33) and CINAHL with full-text (98). Of these, 833 articles were removed because of repetition or irrelevance and 93 articles were added from reference lists, the review by Quélennec [14], an independent search by the second reviewer, and other sources. Finally, 133 articles [3, 12, 20-24, 28-30, 35-157] were selected and comprised the reviewed data-set (see **ESM 3, 4**). Some studies used a tool or multiple tools which were described in previous studies, there were, therefore, only 82 distinct tools in 133 selected articles. **Fig. 4** presents the systematic review flowchart.

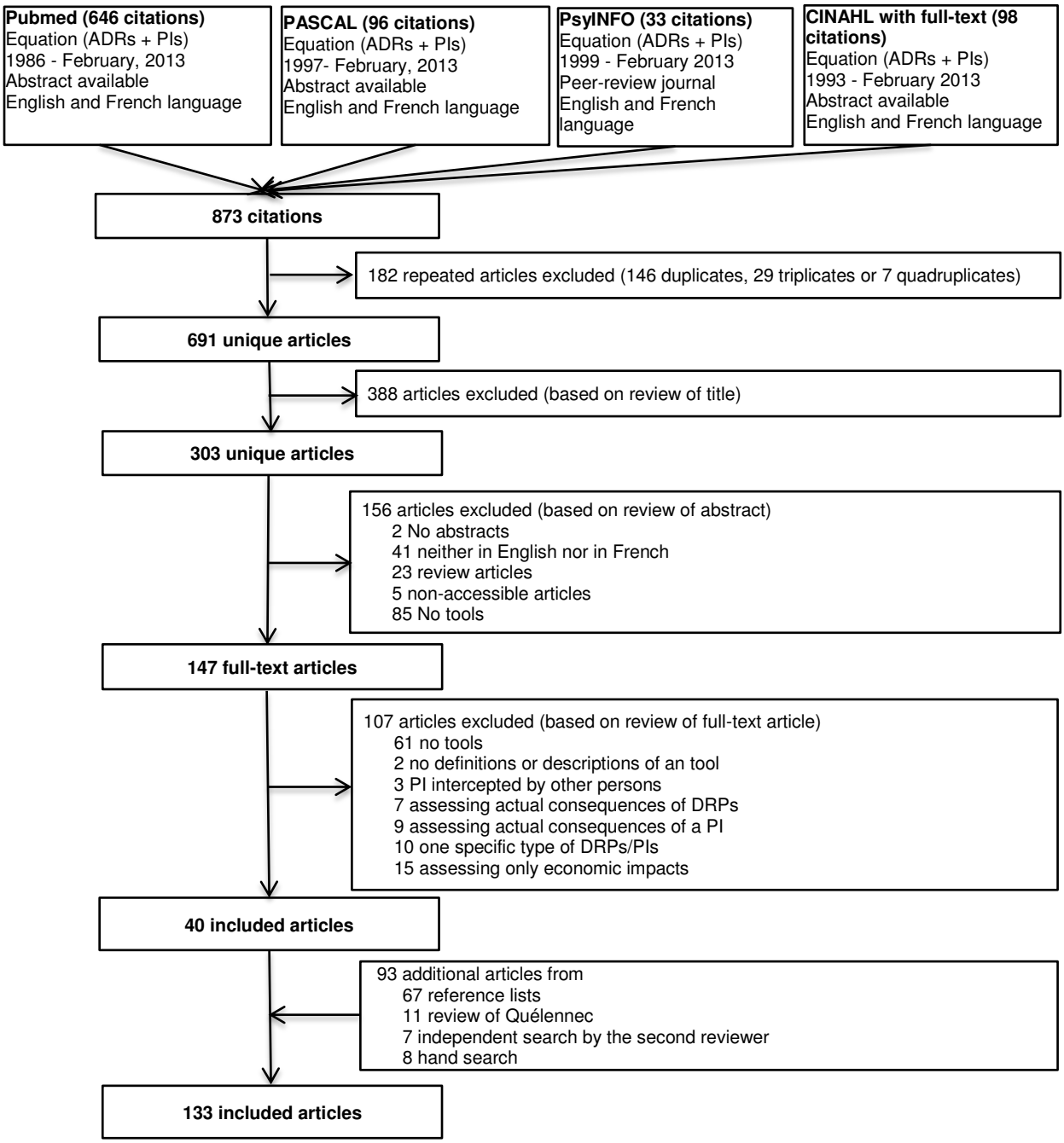

Fig. 4 Systematic review inclusion, exclusion flowchart

Tools were created by research teams in USA (43 studies), UK (19 studies), Canada (16 studies), Australia (15 studies), France (7 studies), Netherlands (5 studies), Sweden (4 studies), Norway (4 studies), Spain (4 studies), Germany (3 studies), Switzerland (3 studies), Belgium (2 studies), Denmark (1 study), Iran (1 study), Israel (1 study), Taiwan (1 study), Ethiopia (1 study), India (1 study), Malaysia (1 study), UK and Saudi Arabia (1 study).

3.2. Content of tools

3.2.1. Main approaches for assessment of significance of PIs

Of 82 distinct tools identified, 30 tools assessed the potential consequences of DRPs (approach 3A in **Fig. 1**) while 46 tools assessed the potential significance of a PI (approach 3B). Six tools applied the multiple-approaches [3, 12, 56, 86, 100, 120]. For example, the tool of Overhage et Lukes assessed both the potential consequences of DRPs (approach 3A) and the potential significance of a PI (approach 3B) [12].

3.2.2. Indicators used in the content of existing tools

The tools can covered only one aspect or a range of aspects of impacts simultaneously. Indicators (not exhaustive) used in existing tools for assessment of potential significance of PIs are summarized (see **ESM 5)**.

Clinical impact

All tools reported clinical aspect as an indispensable aspect of rating the significance of a PI. Ranking clinical significance of PI was realized by assessing effects of DRPs/PIs on *safety* (e.g., adverse health consequence [48], toxicity [44, 55], morbidity [21, 29, 86, 106, 113]); *effectiveness* (e.g., response to medication [87], disease control [53]); and *necessity of drug therapy* [134]; or *characteristics of effects* (e.g., short-term/long-term [106], permanent/temporary [23, 105, 113]), etc.

Humanistic impact

Humanistic outcomes, also called patient-reported outcomes, are the consequences of the disease and/or its treatment as expressed by the patient. Humanistic outcome are now more commonly used in clinical practice [158]. In this review, distinct tools clearly stated some indicators of humanistic outcomes which were *patient's knowledge, compliance, patient's satisfaction, inability to work, and quality of life*. Humanistic aspect was often evaluated combinedly with clinical aspect into "significance" dimension and classified as "low significance" [31, 59, 71, 77, 79, 82, 108, 130] while some distinct tools evaluated independently certain indicators of humanistic impact of a PI [55, 87, 111, 120, 150].

Economic impact

Different studies on the economic impact of a PI employ different terminologies, leading to some confusion in the perspective and components of costs, making the comparison of studies difficult. Cost savings and/or cost avoidance were rated independently in some tools [20, 30, 38, 41, 43, 48, 50, 53, 55, 56, 61, 65, 68, 73, 87, 93, 111, 123, 134]. In some studies, independent rating the economic impact of a PI was used as the first step to determine the monetary value of a PI program [38, 41, 43, 48, 50, 68, 73, 80, 94, 123]. Cost avoidance was estimated through the types of health care resources avoided (e.g., readmission [102, 105, 113] or a scheduled visit to the physician [31, 48]); while cost savings were

evaluated through costs related to drug therapy [20, 38, 43, 61, 66, 109, 111], drug therapy monitoring [38, 61], treatment cost [29], patient cost [43] or reimbursement [66].

Process-related impact

Like humanistic impacts, the process-related impact of a PI was often ignored, incomplete, ambiguous or were mentioned arbitrarily in some tools. They may be grouped into *resolving technical problems [28, 57, 82, 91], informational intervention [31, 38, 53, 57, 71, 75, 82, 94], physician's satisfaction [120], facilitation of continuity of care [55], teamwork support [82], adherence to evidence-based therapy [104, 135], and others [93].*

Structure-related impact

No structured-related indicator (e.g., a comprehensive inventory, record-keeping amenities such as a computer database, a designated area of the pharmacy, trained pharmacists/technicians [159]) was found in the reviewed tools.

Probability

The determination of probability of a consequence for each DRP/PI was used in 20 out of 82 distinct tools [3, 20-24, 48, 56, 70, 86, 89, 109, 112, 113, 115, 116, 121, 132, 135, 138]. The definitions of each level of probability were based on concrete terms with or without a range of numeric probabilities or a Likert score. The number of levels was from 2 to 11. Evaluation of the probability of a consequence of a DRP was useful to evaluate the *confidence of judgment* [70, 116, 135]; classify the *risk* of an adverse heath consequence by combining the severity and the probability of occurrence [20-24]; and/or clarify the estimation of *cost avoidance* of a PI by combining the type of health care resources required to treat an adverse health consequence and its probability [48, 56].

3.3. Structure of tools

The tools were *multidimensional* (one dimension with 2-20 categories, 39/82) or *mono-dimensional* (2-9 dimensions, 43/82), *ordinal* or *nominal* (see **ESM 3**). The majority were presented as classification systems with associated definitions but other tools were based on a visual analog scale[69, 132] or ordinal Likert scales[127].

3.4. Validation process

The validation process was heterogeneous in terms of qualification and number of raters, rating methods, determination of psychometric parameters etc. (see **ESM 4**).

3.4.1. Raters and rating methods

The profile of raters was different: internal or external, blinded or not, junior or senior, generalists or specialists; and with various qualification (e.g., pharmacist, physician, nurse, or

pharmacologist). Rating methods varied: some studies were simply based on a single professional's view (*individual-based rating*) while others used an inter-disciplinary group (*group-based rating*) with up to 30 raters and up to 5 different specialties.

There were a few instances in which a clear definition was presented outlining precisely what constituted consensus. For example, asking a panel of experts to independently judge an event and then combining their opinions using various *mathematical approaches* (e.g., mode [38, 39, 41, 56, 81, 100, 101, 119]; median [24, 100, 130]; mean [39, 41, 53, 56, 60, 69, 81, 83, 89, 100, 122, 136]; sum [59]). Alternatively, a *conservative approach* was used taking the lower category of significance [138, 139] or an *hierarchical approach* in which a more senior expert was consulted when there was a disagreement among the clinical panel) [37, 48, 49, 54, 55, 65, 68, 77, 91, 99, 103, 108, 113, 116, 124, 125, 128, 144, 151-153, 156]. In most studies, the consensus may have been arbitrarily determined; in other words, it was defined simply as a *consensus-based approach* (reached through discussion) [3, 22, 37, 38, 43, 44, 46, 48, 49, 54, 62, 68, 72, 77, 80, 82, 84, 91, 92, 97, 103, 104, 107, 108, 110, 113, 115-118, 120, 121, 123, 124, 132, 134, 135, 150, 152, 153, 160, 161].

3.4.2. Psychometric parameters of tools

Validity was only reported in eight studies (8/133, 6%) [23, 45, 61, 69, 83, 106, 127, 131]. These explored face validity [127] or criteria-based validity (the results of coding by raters were compared to known outcomes in the literature [69, 83] or evidence in patients' medical records [61], to those of other skilled people or consensus of an expert panel [23, 45, 106, 131]. Dean and Barber [69] and Taxis et al. [83] found that there was a clear relationship between potential harm as assessed using their tools and actual harm. Eadon et al. [45] found that there was no significant difference between a pharmacist's scores and three physicians' score (Mann Whiteney U test, $U = 933.5$, $z = 0.034$). Elliott et al. [23] found 93-100% agreement between 2 pharmacists and 1 geriatrician while Knez at al.[131] found 46% agreement between a panel of 3 pharmacists and a physician. In three studies [61, 106, 127] descriptive information was given but no statistical information presented.

Measures of inter- and intra-rater reliability were established in 49 studies (36.8%) (see **ESM 4**). High inter-rater reliability was found in 24 studies: Lesar et al. [63], Rupp at al. [48], Overhage and Lakes [12], Caleo et al. [56], Lewinski et al. [24], Gleason et al. [128], Kwan et al. [110], Wong et al. [118], Chua et al. [146], Midlov et al. [115], Pippins et al. [116], Granas et al. [120], Lee et al. [132] with kappa ≥ 0.7; Chedru et al. [59] with signma x, $y \geq 0.7$; Goarin at al. [129] with t-test $p < 0.05$; Hawkey at al. [20] with Spearman's rank correlation $p < 0.05$; Bayliff et al. [41], Strong et al. [50] and Virani et al. [87] with coefficient of agreement ≥ 0.7; Khalili et al. [151], Hick et al. [81], and Bobb et al. [88] with agreement $\geq 80\%$; Gisev et al. [127] with $W \geq 0.3$; Coffey et al. [119] with $AC1 = 0.69$, $p < 0.01$. Intra-rater reliability was only reported in 2 studies (1.5%) with a poor agreement in a study of Cousins et al. [61] and a good agreement in a study of Dean et al. [69].

While many studies showed that reliability was not affected by the profession of the rater [45, 69, 102, 124, 129], others found that physicians rated DRPs/PIs with lower severity/value than did pharmacists [12, 23, 38, 98]; or on the contrary, pharmacists tended to score PIs as being less clinically significant than physicians [53, 79]. A study by Lee et al.

[100] found that ratings were more consistent between pharmacists than between physicians and pharmacists. However, even within the same profession, reliability was difficult to obtain. A study by Fernandez et al. [149] demonstrated that senior pharmacists rated more consistently than junior pharmacists.

3.5. Assessment of quality of tools

The scores of quality of tools for assessing significance of PIs in 133 included studies were presented in **Table 1**.

Table 1. Scores of quality of tools for assessing significance of PIs in 133 included studies

Sum of scores of quality of each tool	Number of tools
0	5 (3.8%)
1	18 (13.5%)
2	26 (19.5%)
3	22 (16.5%)
4	24 (18.1%)
5	30 (22.6%)
6	6 (4.5%)
7	2 (1.5%)
8	0
9	0

4. DISCUSSION

4.1. Limitation of this review

It was difficult to identify all tools in the literature. We retrieved only four available databases. Tools were sometimes mentioned but not described in detail [162]. Tools only assessing the actual consequences of DRPs (Approach 1 in **Fig. 1**) or the actual consequences of a PI (Approach 2 in **Fig. 1**) were not used for this review because these cover different concepts. We used the outcome terminology proposed by Holdford and Smith [13]. However, identifying classifications of indicators mentioned in existing tools was complicated because of the different terminologies used by authors and institutions. For example, determining whether a tool evaluates humanistic impact of a PI is difficult. The reasons are (1) not all indicators of humanistic outcomes are theoretically well defined, (2) in some tools the terminology of humanistic indicators is confusing, (3) the complex relationships between humanistic, clinical and economic outcomes. An assessment of the significance of PIs is a key to justifying value of pharmacy services. However, between studies methods are heterogeneous which hinders their review and synthesis. Our review is a first attempt to (1) distinguish different approaches used to assess the significance of PIs, (2) evaluate the quality of tools based on theoretical models, and (3) discuss the strengths and weaknesses of existing tools and validation process. We suggest recommendations for an optimal method of evaluation of the significance of PIs.

4.2. Content of tools

The principal indicators of the impact of a PI concern the process and clinical, humanistic and economic outcomes, and probability. These indicators are inconsistently mentioned in tools. Some tools cover many indicators, but a comprehensive tool is not available. One reason may be that few tools were constructed based on theoretical models, a systematic literature review, and input from healthcare professionals.

Pharmacy practitioners and pharmacy managers need to demonstrate that for each PI the benefits outweigh the costs for a given patient, a health care system, and society. According to the economic model, the cost of implementing a PI, cost savings and cost avoidance should be evaluated. Tools should be constructed so as to capture the potential significance of a PI with an estimation of its economic impact (e.g., using the tool of Williams et al. [31], the potential significance had a fairly good correlation with the economic value) and is the first step to conducting a more sophisticated economic evaluation [38, 48, 73, 77, 93, 123].

Most tools focus on patient outcomes. PIs, however, also are useful for the health practitioner. Tools therefore should reflect the possible impacts on both. In order to assign a probability for a potential consequence, it is ideal to know how often it has been described in the literature as well as how often it occurs at the local healthcare facility. However, in most cases, the determination of this probability was difficult to estimate. This is primarily because such probabilities are rarely available in the literature and can vary based on patient risk, co-morbidities or other factors [138]. Generally, in order to improve the consistency of judgment of probability between raters, studies only select and code the most likely harm prevented [19, 23, 48, 56] and request opinion of staff most familiar with these events. A multidimensional matrix of risk which considers many aspects of impacts and the probability of each aspect, such as the matrix developed by National Patient Safety Agency [17] could be used as a framework to construct a new tool for assessing PIs.

Assessing the potential significance of a PI is primarily based on the potential severity of consequences of DRPs that might have occurred if a pharmacist had not intervened. It makes sense to use the same definitions, terminology and grading systems for both the potential significance of a PI and the actual severity of consequence of MEs, ADEs, or ADR [19, 93, 163]. Indeed, the NCC MERP Index [164] for classification of severity of MEs has been used to design new tools for assessing PIs [84, 86, 88, 128]. Furthermore, most tools use a variety of similar terminologies without precise definitions which risks inconsistency of rating.

4.3. Structure of tools

One can argue that a tool for evaluation of impacts of a PI should be as simple as possible. However, a simple tool can hardly detect all possible impacts of PIs and would not provide enough information for practice and research. Therefore, a well-structured tool should provide the main dimensions and the main levels. A stepwise instruction should be developed to guide the use of tools in practice. Such that results of different studies can be compared.

An ordinal tool is preferred in order to prioritize the most significant PIs. Half of tools are mono-dimensional, and often concentrate on clinical impacts of PIs failing to detect other impacts. Multidimensional tools and the independence of evaluation of different impacts of a PI improve the sensitivity and flexibility of evaluation methods. For example, the separation of evaluation of economic impacts (cost savings) and clinical impacts in the tool of Lindblad et al. [111] facilitates estimation of the cost savings by the whole PI program. The numeric-based levels facilitate interpretation of results.

Although the multidimensional tools were used in many studies, the results of each dimension were separately interpreted. Only the study by Lindblad et al. [111] used the method of simultaneous interpretation of mean impacts of many dimensions for *all* PI. For *all* interventions, this study found a mean of 1.4 clinical, 0.8 humanistic, and 0.1 economic outcomes. This method of interpretation of results gives the added value of the whole PI program rather than the individual PI. There is no method for determining these multidimensional impacts of *each* PI.

Many authors adapted existing tools in the literature to their study. In the **ESM 3** and **4**, we grouped studies into sub-groups which used a same tool or a slightly modified tool. The tools which were the most commonly adapted one for use in other studies include: Folli et al. in 1987 [36] (8 studies), Hatoum et al. in 1988[38] (26 studies), Lesar et al. in 1990 [42] (4 studies), Western Australian Clinical Pharmacists Group in 1991 [44] (3 studies), Rupp et al. in 1992 [48] (3 studies), Chedru et al. in 1997 [59] (5 studies), Alderman et al. in 1997 [29] (3 studies), Overhage and Lakes in 1999 [12] (11 studies), Deans et al. in 1999 [69] (6 studies), Hawksworth et al. in 1999 [70] (3 studies), NCC MERP Index in 2001 [164] (5 studies), Society of Hospital Pharmacists of Australia Guideline in 2005 [19] (4 studies), Cornish et al. in 2005 [22] (5 studies), Blix et al. in 2006 [97] (3 studies). The advantages of using existing structured measures are: their reliability and validity have already been undertaken and using measures that have been applied by others enables comparison between studies. However, limitations include difficulties in finding a suitable tool for local use, and the fact that reproducibility of the reliability of a specific tool is not always obvious. For example, Overhage and Lakes's tool [12] had a high inter-rater reliability in their study but this tool adapted by Bosma et al. [98], and Lee et al. [100] Fernandez-Llamazares et al. [149] and Somers et al. [157] showed a low inter-rater reliability.

4.4. Validation process

The criteria-based validity of any method measuring the potential significance of a PI is difficult to assess because there is no generally accepted standard with which to compare [12]. The comparison of the scores given to MEs with known outcomes has limitations because errors resulting in more-severe outcomes may be more likely to be reported in the literature [69]. Nonetheless, the comparison of the individual scores with the consensus results of a group of experts has other limitations. The existence of a consensus does not mean that the "correct" answer has been found [165]. The consensus method is just a means of identifying current medical opinion and areas of disagreement. It recommends that the results should, when possible, be matched to other data in the literature [102], to the actual outcomes

in the patient after following-up [61], to observable events [165] or to other systems of reporting such as MEs and ADEs [89].

Measuring the inter- and intra-rater reliability of methods for assessment of impacts of PIs is a scientific and practical requirement. Indeed, this information provides useful data not only about the reliability of a subjective assessment but can also be used for teaching, peer review and audit purposes [65, 149]. However, this measure was not established for all tools. It is not possible to directly compare the reliability of tools as they used different methods of assessing reliability.

Like the actual severity ratings of ADEs [166-168] or MEs [169, 170], literature shows many inter-rater and intra-rater inconsistencies, within and between healthcare professional groups. Such inconsistencies can be partly attributed to lack of clarity in the tools and scenarios used for validation, shortage of time for proper case reading and coding, and different points of view of the assessors.

The inconsistency of coding between raters prevents individual evaluation. Many studies have used an expert panel. However, there are no strict criteria governing the selection of experts. With regard to medical research, Jones and Hunter [165] defined the term "expert" to be "clinicians practicing in the field under consideration". According to this definition, suitable experts for studies such as those proposed in this paper include pharmacists and medical practitioners. It has been recommended that experts should be selected based on their appropriateness for the study in terms of experience in the therapeutic area, reputation, geographic representation, practice type and specialty, heterogeneity in treatment patterns and willingness to participate in the study [11, 171]. Wright et al. [172] demonstrated that community pharmacists, hospital pharmacists, general practitioners and specialist physicians attribute significantly different values when undertaking these assessments.

4.5. Properties of ideal tools for assessing the potential significance of a PI

Currently, there are no formal guidelines or any standardization of methodology concerning methods of assessment of the potential significance of PIs. Taking into account the results of this review, we suggest some desirable pragmatic, psychometric and theoretical properties:

Theoretical properties

1. Tools should be developed based on (1) comprehensive theoretical models, (2) a systematic literature review of available evidence that reflects the whole range of impacts of a PI and (3) an evaluation of existing tools, and (4) input from healthcare professionals.
2. Tools should be able to demonstrate that the benefits outweigh the costs in a given patient, health care system, and society at the level of each PI.
3. An evaluation from multi-impact perspective, rather than simply focusing on clinical impact, should be used to enhance understanding of the comprehensive effect of PIs. For example, a tool integrating clinical, humanistic, economic, process-related impacts and the probability of these impacts.

4. The views of patients, health care providers, institutions, payers, and society should be considered.

Psychometric properties

1. Tools should be validated prior to its use.
2. Along with the information on clinical case, experts should be provided with a literature review, coding instructions, and examples. Indices for agreement/validity/reliability should be conform to the current guidelines [173].
3. The guideline proposed for the use of experts in pharmacoeconomic studies [174] is suitable for this type of study: description of consensus techniques (e.g., Delphi process, Nominal Group Technique, expert panels); justification in using such methods; and description of selection of experts; provision of a definition of consensus in advance of the execution of a study; information that is provided to panelists in advance must be as objective and as comprehensive as possible; and modification of tool as appropriate with the input from independent experts or pilot-test; appropriate presentation and interpretation of findings.

Pragmatic properties

1. Tools must be brief and not time-consuming. Acceptability to evaluators is also required.
2. Tools should be well defined.
3. Tools must be well-structured as well as flexible to adapt to meet their specific needs (e.g., multidimensional tool, possibility of modification of terminology of economic impact is based on different perspectives or modification of number of levels; independence between dimensions).
4. Tools should have an open, numeric, and hierarchical structure (with main dimensions, main levels of each dimensions, and an open structure to include the option “non-determinable”).
5. Same definitions, terminology and grading systems for both the potential significance of a PI and the actual severity of consequence of MEs/ADEs/ADRs.

4.6. Assessment of quality of tools

Researchers and clinicians may have different needs in relation to a tool for assessing potential significance of PIs. Due to the wide range of tools used in the literature, researchers need consider developing a basis of comparison between tools. Therefore, we tried to assess quality of each tool in included studies using 10 criteria to assist in comparing tools across studies (see **ESM 4**). According to these criteria, the tools with highest scores were: Caleo et al.'s [56] and Hick et al.'s [81] (7 scores), Eadon et al.'s [45], Overhage and Lakes' s[12], Kopp et al.'s [109], Virani et al.'s [87], Lee et al.[100] and Lewinski et al.'s tool [24] (6 scores). No tool could be found that met all of our above criteria. It appears that further research in this filed should be conducted.

5. CONCLUSION

Various structures and contents of tools for evaluation of impacts of PIs were highlighted, as well as suggestions for an optimal evaluation method. Majority of tools focused primarily on assessing clinical aspect and failed to detect other impacts. Variation of tools and assessment process hindered their summarization. Limited and varied results for their validity and reliability questioned the level of evidence of the evaluation of potential significance of PIs for justification of added value of PIs. The development of tools with optimal theoretical, pragmatic and psychometric properties and their integration into daily pharmacists' practice through rational assessment process (e.g., peer review) and standardized documentation systems (e.g., IT tools) are needed.

Compliance with Ethical Standards

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Conflict of interest

Thi-Ha VO, Bruno CHARPIAT, Claire CATOIRE, Michel JUSTE, Renaud ROUBILLE, François-Xavier ROSE, Sébastien CHANOINE, Jean-Luc BOSSON, Ornella CONORT, Benoît ALLENET, and Pierrick BEDOUCH declare that they have no conflict of interest.

Online Resource

Electronic Supplementary Materials may be found in the online resources of this article at the publisher's website:
ESM 1. Assessment of Risk of Bias in Studies
ESM 2: Criteria of quality of a tool for assessing significance of PIs
ESM 3: Content and Structure of tools in 133 identified studies
ESM 4: Process of Validation of tools in 133 identified studies
ESM 5. Indicators used in existing tools for assessment of potential significance of PIs

[In this thesis, all ESM are found at the end of thesis.]

Reference

1. Cipolle RJ, Strand L, Morley P, Cipolle R. Pharmaceutical Care Practice: The Clinician's Guide, 2nd ed. New York: McGraw-Hill Companies; 2004.
2. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.
3. Rothschild JM, Churchill W, Erickson A, Munz K, Schuur JD, Salzberg CA, et al. Medication errors recovered by emergency department pharmacists. Ann Emerg Med. 2010;55:513-21.
4. Strand LM, Cipolle RJ, Morley PC. Documenting the clinical pharmacist's activities: back to basics. Drug Intell Clin Pharm. 1988;22(1):63-7.
5. Vessal G. Detection of prescription errors by a unit-based clinical pharmacist in a nephrology ward. Pharm World Sci. 2010;32:59-65.
6. Dean Franklin B, Vincent C, Schachter M, Barber N. The incidence of prescribing errors in hospital inpatients: an overview of the research methods. Drug Saf. 2005;28(10):891-900.
7. Lee AJ, Boro MS, Knapp KK, Meier JL, Korman NE. Clinical and economic outcomes of pharmacist recommendations in a Veterans Affairs medical center. Am J Health Syst Pharm. 2002;59(21):2070-7.
8. Schmidt IK, Claesson CB, Westerholm B, Nilsson LG. Physician and staff assessments of drug interventions and outcomes in Swedish nursing homes. Ann Pharmacother. 1998;32(1):27-32.
9. McLennan DN, Dooley MJ, Brien JE. Beneficial clinical outcomes resulting from pharmacist interventions. J Oncol Pharm Pract. 1999;5(4):184-9.
10. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
11. Stafford AC, Bindoff IK, Tenni PC, Peterson GM, Doran CM. A methodological framework for estimating the clinical and economic value of community pharmacists' clinical interventions using expert opinion. J Clin Pharm Ther. 2011;37(4):378-85.
12. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. Am J Health Syst Pharm. 1999;56(23):2444-50.
13. Holdford DA, Smith S. Improving the quality of outcomes research involving pharmaceutical services. Am J Health Syst Pharm. 1997;54(12):1434-42.
14. Quélennec B. Assessment of the potential impact of errors found through medication reconciliation [Evaluation de l'impact potentiel des erreurs récupérées par conciliation des traitements médicamenteux] [Thesis]: Université de Strasbourg; 2011.
15. Donabedian A. The quality of medical care. Science. 1978;200(4344):856-64.
16. Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. Clin Ther. 1993;15(6):1121-32.
17. National Patient Safety Agency. A risk matrix for risk managers. 2008 [cited 2015 Oct 19]; Available from: http://www.npsa.nhs.uk/nrls/improvingpatientsafety/patient-safety-tools-and-guidance/risk-assessment-guides/risk-matrix-for-risk-managers/
18. U.S. Department of Veterans Affairs. Safety Assessment Code (SAC) Matrix; 2013. http://www.patientsafety.va.gov/professionals/publications/matrix.asp. Accessed 9 Sept 2015.
19. Society of Hospital Pharmacists of Australia. SHPA Standards of Practice for Clinical Pharmacy. J Pharm Pract Res. 2005;35(2):122-46.
20. Hawkey CJ, Hodgson S, Norman A, Daneshmend TK, Garner ST. Effect of reactive pharmacy intervention on quality of hospital prescribing. BMJ. 1990;300(6730):986-90.
21. Dooley MJ, Allen KM, Doecke CJ, Galbraith KJ, Taylor GR, Bright J, et al. A prospective multicentre study of pharmacist initiated changes to drug therapy and patient management in acute care government funded hospitals. Br J Clin Pharmacol. 2004;57(4):513-21.
22. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9.
23. Elliott RA, Woodward MC. Assessment of Risk Associated with Medication-Related Problems in Elderly Outpatients. J Pharm Pract Res. 2009;39:109-13.
24. Lewinski D, Wind S, Belgardt C, Plate V. Prevalence and safety-relevance of drug-related problems in German community pharmacies. Pharmacoepidemiol Drug Saf. 2010;19(2):141-9.
25. Schumock GT. Methods to assess the economic outcomes of clinical pharmacy services. Pharmacotherapy. 2000;20(10 Pt 2):243S-52S.
26. Benrimoj SI, Langford JH, Berry G, Collins D, Lauchlan R, Stewart K, et al. Economic impact of increased clinical intervention rates in community pharmacy. A randomised trial of the effect of education and a professional allowance. Pharmacoeconomics. 2000;18(5):459-68.

27. Nesbit TW, Shermock KM, Bobek MB, Capozzi DL, Flores PA, Leonard MC, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. Am J Health Syst Pharm. 2001;58(9):784-90.
28. Krahenbuhl JM, Kremer B, Guignard B, Bugnon O. Practical evaluation of the drug-related problem management process in Swiss community pharmacies. Pharm World Sci. 2008;30(6):777-86.
29. Alderman CP. A prospective analysis of clinical pharmacy interventions on an acute psychiatric inpatient unit. J Clin Pharm Ther. 1997;22(1):27-31.
30. Briceland LL, Kane MP, Hamilton RA. Evaluation of patient-care interventions by Pharm.D. clerkship students. Am J Hosp Pharm. 1992;49(5):1130-2.
31. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. Int Journal Clin Pharm. 2012;34:43-52.
32. Carmines EG, Zeller RA. Reliability and validity assessment. London: Sage Publications; 1979.
33. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: The Cochrane Collaboration; 2011. www.cochrane-handbook.org. Accessed 9 Sept 2015.
34. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev.4:1.
35. Iafrate RP, Smith PD. Documenting medication errors averted by pharmacists. Am J Hosp Pharm. 1986;43:1672.
36. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics. 1987;79(5):718-22.
37. Blum KV, Abel SR, Urbanski CJ, Pierce JM. Medication error prevention by pharmacists. Am J Hosp Pharm. 1988;45(9):1902-3.
38. Hatoum HT, Hutchinson RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. Drug Intell Clin Pharm. 1988;22(3):252-9.
39. Hatoum HT, Hutchinson RA, Elliott LR, Kendzierski DL. Physicians' review of significant interventions by clinical pharmacists in inpatient care. Drug Intell Clin Pharm. 1988;22(12):980-2.
40. Neville RG, Robertson F, Livingstone S, Crombie IK. A classification of prescription errors. J R Coll Gen Pract. 1989(39):110-2.
41. Bayliff CD, Einarson TR. Physician assessment of pharmacists' interventions - a method of estimating cost avoidance and determining quality assurance. Can J Hosp Pharm. 1990;43(4):167-71, 95.
42. Lesar TS, Briceland LL, Delcoure K, Parmalee JC, Masta-Gornic V, Pohl H. Medication prescribing errors in a teaching hospital. JAMA. 1990;263(17):2329-34.
43. Mueller BA, Abel SR. Impact of college of pharmacy-based educational services within the hospital. Drug Intell Clin Pharm. 1990;24(4):422-5.
44. Western Australian Clinical Pharmacists Group. Recording clinical pharmacist interventions: is there a better way? Austr J Hosp Pharm. 1991;21(3):158-62.
45. Eadon H. Assessing the quality of ward pharmacist's intervention. Int J Pharm Pract. 1992(1):145-7.
46. Ho L, Brown GR, Millin B. Characterization of errors detected during central order review. Can J Hosp Pharm. 1992;45(5):193-7.
47. Lipton HL, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. Med Care. 1992;30(7):646-58.
48. Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother. 1992;26(12):1580-4.
49. Rupp MT, DeYoung M, Schondelmeyer SW. Prescribing problems and pharmacist interventions in community practice. Med Care. 1992;30(10):926-40.
50. Strong DK, Tsang GW. Focus and impact of pharmacists' interventions. Can J Hosp Pharm. 1993;46(3):101-8.
51. Tang I, Vrahnos D, Hatoum H, Lau A. Effectiveness of clinical pharmacist interventions in a hemodialysis unit. Clin Ther. 1993;15(2):459-64.
52. Mason RN, Pugh CB, Boyer SB, Stiening KK. Computerized documentation of pharmacists' interventions. Am J Hosp Pharm. 1994;51(17):2131-8.
53. Slaughter RL, Erickson SR, Thomson PA. Clinical interventions provided by doctor of pharmacy students. Ann Pharmacother. 1994;28(5):665-70.
54. Chisholm MA, Pittman DG, Longley JM, Mullis SR. Implementation of pharmaceutical care in acute medical cardiovascular patients. Hosp Pharm. 1995;30(7):572-4, 7-8.
55. Wang Chin JM, Muller RJ, Lucarelli CD. A pharmacy intervention program: recognizing pharmacy's contribution to improving patient care. Hosp Pharm. 1995;30(2):120, 3-6, 9-30.
56. Caleo SUE, Benrimoj S, Collins D, Lauchlan R, Stewart KAY. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract. 1996;4(4):221-7.

57. Kettle J, Downie G, Palin A, Chesson R. Pharmaceutical care activities within a mental health team. The Pharmaceutical Journal. 1996;257:814-6.
58. Wernick A, Possidente CJ, Keller EG, Gilroy G. Enhancing continuity of care through pharmacist review of discharge medications. Hosp Pharm. 1996;31:672-6.
59. Chedru V, Juste M. Medical evaluation of the clinical impact of pharmacist interventions [Evaluation médicale de l'impact clinique des interventions pharmaceutiques]. J Pharm Clin. 1997;16(4):254-8.
60. Chisholm MA, Hawkins DW, Taylor AT. Providing pharmaceutical care: are pharmacy students beneficial to patients? Hosp Pharm. 1997;32(3):370-5.
61. Cousins D, Gerrett D, Luscombe D. Reliability and validity of hospital pharmacists' clinical intervention data. Am J Health Syst Pharm. 1997;54(14):1596-603.
62. Grabe DW, Low CL, Bailie GR, Eisele G. Evaluation of drug-related problems in an outpatient hemodialysis unit and the impact of a clinical pharmacist. Clin Nephrol. 1997;47(2):117-21.
63. Lesar TS, Lomaestro BM, Pohl H. Medication-prescribing errors in a teaching hospital. A 9-year experience. Arch Intern Med. 1997;157(14):1569-76.
64. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA. 1997;277(4):312-7.
65. Lucas C, Glare PA, Sykes JV. Contribution of a liaison clinical pharmacist to an inpatient palliative care unit. Palliat Med. 1997;11(3):209-16.
66. Dennehy C, Kroon L, Byrne M, Koda-Kimble M. Increase in Number and Diversity of Clinical Interventions by PharmD. Students Over a Clerkship Rotation. Am J Pharm Educ. 1998;62:373-9.
67. Smythe MA, Shah PP, Spiteri TL, Lucarotti RL, Begle RL. Pharmaceutical care in medical progressive care patients. Ann Pharmacother. 1998;32(3):294-9.
68. Weidle P, Bradley L, Gallina J, Daniel C, Thorn N, Siegel L. Pharmaceutical care intervention documentation program and related cost savings at a University Hospital. Hosp Pharm. 1998;34(1):43-52.
69. Dean BS, Barber ND. A validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm. 1999;56(1):57-62.
70. Hawksworth GM, Corlett aJ, Wright DJ, Chrystyn H. Clinical pharmacy interventions by community pharmacists during the dispensing process. Br J Clin Pharmacol. 1999;47:695-700.
71. Nathan A, Goodyer L, Lovejoy A, Rashid A. 'Brown bag' medication reviews as a means of optimizing patients' use of medication and of identifying potential clinical problems. Fam Pract. 1999;16(3):278-82.
72. Possidente CJ, Bailie GR, Hood VL. Disruptions in drug therapy in long-term dialysis patients who require hospitalization. Am J Health Syst Pharm. 1999;56(19):1961-4.
73. Krass I, Smith C. Impact of medication regimen reviews performed by community pharmacists for ambulatory patients through liaison with general medical practitioners. Int J Pharm Pract. 2000(8):111-20.
74. Lustig A. Medication error prevention by pharmacists - An Israeli solution. Pharm World Sci. 2000;22(1):21-5.
75. Price RN, Rogers A. Intervention monitoring on admissions wards. Hosp Pharm. 2000;7:81-4.
76. Reddick JB, Murphy JE. Evaluating the clinical interventions of students during clerkships using a cognitive services claim form. Am J Pharm Educ. 1999;64:38-43.
77. Taylor CT, Church CO, Byrd DC. Documentation of clinical interventions by pharmacy faculty, residents, and students. Ann Pharmacother. 2000;34(7-8):843-7.
78. Alderman CP, Farmer C. A brief analysis of clinical pharmacy interventions undertaken in an Australian teaching hospital. J Qual Clin Pract. 2001;21(4):99-103.
79. Ewan MA, Greene RJ. Evaluation of mental health care interventions made by three community pharmacists - a pilot study. Int J Pharm Pract. 2001(9):225-34.
80. Guignon AM, Grain F, Allenet B, Brudieu E, Barjhoux C, Bosson J-L, et al. Evaluation de l'impact clinique des opinions pharmaceutiques dans un service de médecine spécialisée. J Pharm Clin. 2001;20(2):118-23.
81. Hick HL, Deady PE, Wright DJ, Silcock J. The impact of the pharmacist on an elective general surgery pre-admission clinic. Pharm World Sci. 2001;23(2):65-9.
82. Needham DS, Wong IC, Campion PD. Evaluation of the effectiveness of UK community pharmacists' interventions in community palliative care. Palliat Med. 2002;16(3):219-25.
83. Taxis K, Dean B, Barber N. The validation of an existing method of scoring the severity of medication administration errors for use in Germany. Pharm World Sci. 2002;24:236-9.
84. Van den Bemt PM, Postma MJ, van Roon EN, Chow MC, Fijn R, Brouwers JR. Cost-benefit analysis of the detection of prescribing errors by hospital pharmacy staff. Drug Saf. 2002;25:135-43.
85. Dale A, Copeland R, Barton R. Prescribing errors on medical wards and the impact of clinical pharmacists. Int J Pharm Pract. 2003:19-24.
86. Davydov L, Caliendo GC, Smith LG, Mehl B. Analysis of clinical intervention documentation by dispensing pharmacists in a teaching hospital. Hosp Pharm. 2003;38(4):346-50.

87. Virani A, Crown N. The Impact of a Clinical Pharmacist on Patient and Economic Outcomes in a Child and Adolescent Mental Health Unit. Can J Hosp Pharm. 2003;56:158-62.
88. Bobb A, Gleason K, Husch M, Feinglass J, Yarnold PR, Noskin GA. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med. 2004;164(7):785-92.
89. Buurma H, De Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol. 2004;58:503-11.
90. Gray S, Woolfrey S, Copeland R, Gill D, Dennett G. Evaluating the potential impact of community pharmacy interventions on patient care in Northumberland. Qual Prim Care. 2004;12:47-51.
91. Prowse A, Scott D. An evaluation of a clinic-based pharmacists and a medicines home delivery service from a transplant outpatient department. The Pharmaceutical Journal. 2004;272:547-51.
92. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance. J Clin Pharm Ther. 2005;30(3):215-23.
93. Fertleman M, Barnett N, Patel T. Improving medication management for patients: the effect of a pharmacist on post-admission ward rounds. Qual Saf Health Care. 2005;14(3):207-11.
94. Ling JM, Mike LA, Rubin J, Abraham P, Howe A, Patka J, et al. Documentation of pharmacist interventions in the emergency department. Am J Health Syst Pharm. 2005;62(17):1793-7.
95. Nickerson A, MacKinnon NJ, Roberts N, Saulnier L. Drug-therapy problems, inconsistencies and omissions identified during a medication reconciliation and seamless care service. Healthc Q. 2005;8 Spec No:65-72.
96. Serrano Fabiá A, Cavero Rodrigo E, Albert Marí A, Almenar Cubells D, Jiménez Torres NV. Pharmaceutical validation as a process of improving the quality of antineoplastic treatment. J Oncol Pharm Pract. 2005;11(2):45-50.
97. Blix HS, Viktil KK, Moger TA, Reikvam A. Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. Pharm World Sci. 2006;28:152-8.
98. Bosma L, Jansman FG, Franken AM, Harting JW, Van den Bemt PM. Evaluation of pharmacist clinical interventions in a Dutch hospital setting. Pharm World Sci. 2008;30:31-8.
99. Grangeasse L, Chaigneau L, Medjoub M, Larosa F, Limat S. Computerized and protocolled prescription of chemotherapy: residual iatrogenic risk and pharmacist interventions [Prescription informatisée et protocolisée des chimiothérapies: risque iatrogène résiduel et interventions pharmaceutiques]. J Pharm Clin. 2006;25:33-8.
100. Lee J, McPherson ML. Outcomes of recommendations by hospice pharmacists. Am J Health Syst Pharm. 2006;63:2235-9.
101. Pham DQ. Evaluating the impact of clinical interventions by PharmD students on internal medicine clerkships: the results of a 3 year study. Ann Pharmacother. 2006;40(9):1541-5.
102. Spinewine A, Dhillon S, Mallet L, Tulkens PM, Wilmotte L, Swine C. Implementation of ward-based clinical pharmacy services in Belgium - description of the impact on a geriatric unit. Ann Pharmacother. 2006;40:720-8.
103. Stubbs J, Haw C, Taylor D. Prescription errors in psychiatry - a multi-centre study. J Psychopharmacol. 2006;20(4):553-61.
104. Viktil KK, Blix HS, Moger TA, Reikvam A. Interview of patients by pharmacists contributes significantly to the identification of drug-related problems. Pharmacoepidemiol Drug Saf. 2006;15:667-74.
105. Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. Qual Saf Health Care. 2006;15(2):122-6.
106. Bayley KB, Savitz LA, Maddalone T, Stoner SE, Hunt JS, Wells R. Evaluation of patient care interventions and recommendations by a transitional care pharmacist. Ther Clin Risk Manag. 2007;3:695-703.
107. Estellat C, Colombet I, Vautier S, Huault-Quentel J, Durieux P, Sabatier B. Impact of pharmacy validation in a computerized physician order entry context. Int J Qual Health Care. 2007;19(5):317-25.
108. Knudsen P, Herborg H, Mortensen AR, Knudsen M, Hellebek A. Preventing medication errors in community pharmacy: frequency and seriousness of medication errors. Qual Saf Health Care. 2007;16:291-6.
109. Kopp BJ, Mrsan M, Erstad BL, Duby JJ. Cost implications of and potential adverse events prevented by interventions of a critical care pharmacist. Am J Health Syst Pharm. 2007;64(23):2483-7.
110. Kwan Y, Fernandes OA, Nagge JJ, Wong GG, Huh JH, Hurn DA, et al. Pharmacist medication assessments in a surgical preadmission clinic. Arch Intern Med. 2007;167(10):1034-40.
111. Lindblad A, Alleyne A, Howorko J. Development and Initial Evaluation of a Software-Based Clinical Workload Measurement System for Pharmacists. Can J Hosp Pharm. 2007;60(5):295-301.
112. Nguyen A, Yu K, Shakib S, Doecke CJ, Boyce M, March G, et al. Classification of findings in the home medicines reviews of post-discharge patients at risk of medication misadventure. J Pharm Pract Res. 2007;37(2):111-4.
113. Struck P, Pharmacist S, Pedersen KH, Moodley P. A pilot study of pharmacist-initiated interventions in drug therapy in an Australian paediatric hospital. EJHP Science. 2007;13:105-12.

114. Lalonde L, Lampron AM, Vanier MC, Levasseur P, Khaddag R, Chaar N. Effectiveness of a medication discharge plan for transitions of care from hospital to outpatient settings. Am J Health Syst Pharm. 2008;65(15):1451-7.
115. Midlov P, Holmdahl L, Eriksson T, Bergkvist A, Ljungberg B, Widner H, et al. Medication report reduces number of medication errors when elderly patients are discharged from hospital. Pharm World Sci. 2008;30(1):92-8.
116. Pippins JR, Gandhi TK, Hamann C, Ndumele CD, Labonville SA, Diedrichsen EK, et al. Classifying and predicting errors of inpatient medication reconciliation. J Gen Intern Med. 2008;23(9):1414-22.
117. Wang HY, Chan AL, Chen MT, Liao CH, Tian YF. Effects of pharmaceutical care intervention by clinical pharmacists in renal transplant clinics. Transplant Proc. 2008;40(7):2319-23.
118. Wong JD, Bajcar JM, Wong GG, Alibhai SM, Huh JH, Cesta A, et al. Medication reconciliation at hospital discharge: evaluating discrepancies. Ann Pharmacother. 2008;42(10):1373-9.
119. Coffey M, Mack L, Streitenberger K, Bishara T, De Faveri L, Matlow A. Prevalence and clinical significance of medication discrepancies at pediatric hospital admission. Acad Pediatr. 2009;9(5):360-5 e1.
120. Granas AG, Berg C, Hjellvik V, Haukereid C, Kronstad A, Blix HS, et al. Evaluating categorisation and clinical relevance of drug-related problems in medication reviews. Pharm World Sci. 2010;32:394-403.
121. Lövgren S, Clark RA, Angley M, Ponniah AP, Colley D, Shakib S. Timeliness and Clinical Impact of Hospital-Initiated Medication Reviews. J Pharm Pract Res. 2009;39.
122. Vasileff HM, Whitten LE, Pink JA, Goldsworthy SJ, Angley MT. The effect on medication errors of pharmacists charting medication in an emergency department. Pharm World Sci. 2009;31(3):373-9.
123. Westerlund T, Marklund B. Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J Clin Pharm Ther. 2009;34(3):319-27.
124. Abdel-Qader DH, Harper L, Cantrill JA, Tully MP. Pharmacists' interventions in prescribing errors at hospital discharge: an observational study in the context of an electronic prescribing system in a UK teaching hospital. Drug Saf. 2010;33:1027-44.
125. Climenté-Marti M, Garcia-Manon ER, Artero-Mora A, Jimenez-Torres NV. Potential risk of medication discrepancies and reconciliation errors at admission and discharge from an inpatient medical service. Ann Pharmacother. 2010;44(11):1747-54.
126. Eichenberger PM, Kahmann IV, Foppe van Mil JW, Hersberger KE. Classification of drug-related problems with new prescriptions using a modified PCNE classification system. Pharm World Sci. 2010;32:362–72.
127. Gisev N, Bell JS, O'Reilly CL, Rosen A, Chen TF. An expert panel assessment of comprehensive medication reviews for clients of community mental health teams. Soc Psychiatry Psychiatr Epidemiol. 2010;45(11):1071-9.
128. Gleason KM, McDaniel MR, Feinglass J, Baker DW, Lindquist L, Liss D, et al. Results of the Medications at Transitions and Clinical Handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission. J Gen Intern Med. 2010;25(5):441-7.
129. Goarin C, Mugnier N. Clinical pharmacist activity in an oncology and haematology unit significantly improves and secures patient care. Pharm Hosp Clin. 2011;46:e24-e32.
130. Haavik S, Soeviknes S, Erdal H, Kjonniksen I, Guttormsen A, Granas AG. Prescriptions from general practitioners and in hospital physicians requiring pharmacists' interventions. Pharmacoepidemiol Drug Saf. 2011;20(1):50-6.
131. Knez L, Laaksonen R, Duggan C. Evaluation of clinical interventions made by pharmacists in chemotherapy preparation. Radiol Oncol. 2010;44:249-56.
132. Lee JY, Leblanc K, Fernandes OA, Huh JH, Wong GG, Hamandi B, et al. Medication reconciliation during internal hospital transfer and impact of computerized prescriber order entry. Ann Pharmacother. 2010;44(12):1887-95.
133. Nerich V, Limat S, Demarchi M, Borg C, Rohrlich PS, Deconinck E, et al. Computerized physician order entry of injectable antineoplastic drugs: an epidemiologic study of prescribing medication errors. Int J Med Inform. 2010;79:699-706.
134. Niquille A, Bugnon O. Relationship between drug-related problems and health outcomes: a cross-sectional study among cardiovascular patients. Pharm World Sci. 2010;32:512-9.
135. Abu-Ramaileh AM, Shane R, Churchill W, Steffenhagen A, Patka J, Rothschild JM. Evaluating and classifying pharmacists' quality interventions in the emergency department. Am J Health Syst Pharm. 2011;68:2271-5.
136. Bourne RS, Dorward BJ. Clinical pharmacist interventions on a UK neurosurgical critical care unit: a 2-week service evaluation. Int J Clin Pharm. 2011;33(5):755-8.
137. Castelino RL, Sathvik BS, Parthasarathi G, Gurudev KC, Shetty MS, Narahari MG. Prevalence of medication-related problems among patients with renal compromise in an Indian hospital. J Clin Pharm Ther. 2011;36(4):481-7.

138. Patanwala AE, Hays DP, Sanders AB, Erstad BL. Severity and probability of harm of medication errors intercepted by an emergency department pharmacist. Int J Pharm Pract. 2011;19:358-62.
139. Patanwala AE, Sanders AB, Thomas MC, Acquisto NM, Weant KA, Baker SN, et al. A prospective, multicenter study of pharmacist activities resulting in medication error interception in the emergency department. Ann Emerg Med. 2011;59(5):369-73.
140. Perera PN, Guy MC, Sweaney AM, Boesen KP. Evaluation of Prescriber Responses to Pharmacist Recommendations Communicated by Fax in a Medication Therapy Management Program (MTMP). J Manag Care Pharm. 2011;17(5):345-54.
141. Schröder S, Martus P, Odin P, Schaefer M. Drug-related problems in Parkinson's disease: the role of community pharmacists in primary care. Int J Clin Pharm. 2011;33(4):674-82.
142. Villanyi D, Fok M, Wong RY. Medication reconciliation: identifying medication discrepancies in acutely ill hospitalized older adults. Am J Geriatr Pharmacother. 2011;9(5):339-44.
143. Williams M, Peterson GM, Tenni PC, Bindoff IK, Curtain C, Hughes J, et al. Drug-Related Problems Detected in Australian Community Pharmacies: The PROMISe Trial (English). Ann Pharmacother. 2011;45(9):1067-76.
144. Bondesson A, Holmdahl L, Midlov P, Hoglund P, Andersson E, Eriksson T. Acceptance and importance of clinical pharmacists' LIMM-based recommendations. Int J Clin Pharm. 2012;34(2):272-6.
145. Cesarz JL, Steffenhagen AL, Svenson J, Hamedani AG. Emergency Department Discharge Prescription Interventions by Emergency Medicine Pharmacists. Ann Emerg Med. 2013;61(2):209-14.e1.
146. Chua SS, Kok LC, Yusof FA, Tang GH, Lee SW, Efendie B, et al. Pharmaceutical care issues identified by pharmacists in patients with diabetes, hypertension or hyperlipidaemia in primary care settings. BMC Health Serv Res. 2012;12:388.
147. Elliott RA, Martinac G, Campbell S, Thorn J, Woodward MC. Pharmacist-led medication review to identify medication-related problems in older people referred to an Aged Care Assessment Team: a randomized comparative study. Drugs Aging. 2012;29(7):593-605.
148. Fernandez-Llamazares CM, Calleja-Hernández M-Á, Manrique-Rodríguez S, Pérez-Sanz C, Durán-García E, Sanjurjo-Sáez M. Prescribing errors intercepted by clinical pharmacists in paediatrics and obstetrics in a tertiary hospital in Spain. Eur J Clin Pharmacol. 2012;68:1339-45.
149. Fernández-Llamazares CM, Manrique-Rodríguez S, Pérez-Sanz C, Durán-García ME, Sanjurjo-Sáez M, Calleja-Hernández MA. Validation of a method for recording pharmaceutical interventions. J Clin Pharm Ther. 2012;37:459-63.
150. Harrison JJ, Wang J, Cervenko J, Jackson L, Munyal D, Hamandi B, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clin Transplant. 2012;26(2):E149-57.
151. Khalili H, Karimzadeh I, Mirzabeigi P, Dashti-Khavidaki S. Evaluation of clinical pharmacist's interventions in an infectious diseases ward and impact on patient's direct medication cost. Eur J Intern Med. 2012;24(3):227-33.
152. Kwint HF, Faber A, Gussekloo J, Bouvy ML. The contribution of patient interviews to the identification of drug-related problems in home medication review. J Clin Pharm Ther. 2012;37(6):674-80.
153. Midlov P, Bahrani L, Seyfali M, Hoglund P, Rickhag E, Eriksson T. The effect of medication reconciliation in elderly patients at hospital discharge. Int J Clin Pharm. 2012;34(1):113-9.
154. Rashed AN, Neubert A, Tomlin S, Jackman J, Alhamdan H, AlShaikh A, et al. Epidemiology and potential associated risk factors of drug-related problems in hospitalised children in the United Kingdom and Saudi Arabia. Eur J Clin Pharmacol. 2012;68(12):1657-66.
155. Mekonnen AB, Yesuf EA, Odegard PS, Wega SS. Implementing ward based clinical pharmacy services in an Ethiopian University Hospital. Pharm Pract (Granada). 2013;11(1):51-7.
156. Quélennec B, Beretz L, Paya D, Blickle JF, Gourieux B, Andres E, et al. Potential clinical impact of medication discrepancies at hospital admission. Eur J Intern Med. 2013;24(6):530-5.
157. Somers A, Robays H, De Paepe P, Van Maele G, Perehudoff K, Petrovic M. Evaluation of clinical pharmacist recommendations in the geriatric ward of a Belgian university hospital. Clin Interv Aging. 2013;8:703-9.
158. Refolo P, Minacori R, Mele V, Sacchini D, Spagnolo AG. Patient-reported outcomes (PROs): the significance of using humanistic measures in clinical trial and clinical practice. Eur Rev Med Pharmacol Sci. 2012;16(10):1319-23.
159. Farris KB, Kirking DM. Assessing the quality of pharmaceutical care. II. Application of concepts of quality assessment from medical care. Ann Pharmacother. 1993;27(2):215-23.
160. Dean B, Schachter M, Vincent C, Barber N. Prescribing errors in hospital inpatients: their incidence and clinical significance. Qual Saf Health Care. 2002;11:340-4.
161. Spinewine A, Dean B. Measuring the impact of medicines information services on patient care: methodological considerations. Pharm World Sci. 2002;24:177-81.

162. Midlands Health Network. Clinical Pharmacy in General Practice - A review of the first nine months. Halmiton; 2012.
163. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA. 1999;282(3):267-70.
164. National Coordinating Council for Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. 2011. http://www.nccmerp.org/types-medication-errors. Accessed 9 Sept 2015.
165. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995;311(7001):376-80.
166. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA. 1995;274(1):29-34.
167. Kunac DL, Reith DM, Kennedy J, Austin NC, Williams SM. Inter- and intra-rater reliability for classification of medication related events in paediatric inpatients. Qual Saf Health Care. 2006;15(3):196-201.
168. Walshe K. Adverse events in health care: issues in measurement. Qual Health Care. 2000;9(1):47-52.
169. Williams SD, Ashcroft DM. Medication errors: how reliable are the severity ratings reported to the national reporting and learning system? Int J Qual Health Care. 2009;21:316-20.
170. Forrey RA, Pedersen CA, Schneider PJ. Interrater agreement with a standard scheme for classifying medication errors. Am J Health Syst Pharm. 2007;64(2):175-81.
171. Evans C. The use of consensus methods and expert panels in pharmacoeconomic studies. Practical applications and methodological shortcomings. Pharmacoeconomics. 1997;12(2 Pt 1):121-9.
172. Wright DJ, Aykroyd RG, Chrystyn H. Rating clinical pharmacy interventions by clinical panels: which health professionals should be included? Br J Clin Pharmacol. 1998;46:278P–305P.
173. Gisev N, Bell JS, Chen TF. Interrater agreement and interrater reliability: key concepts, approaches, and applications. Res Social Adm Pharm. 2013;9(3):330-8.
174. Evans C, Crawford B. Expert judgement in pharmacoeconomic studies. Guidance and future use. Pharmacoeconomics. 2000 Jun;17(6):545-53.

2. Some important tools for assessing potential significance of pharmacist interventions

Due to the wide range of tools used in the literature, researchers need know a basis of comparison between typical tools before deciding to use or develop a new tool. Therefore, we tried to present here some important tools which were commonly used in many studies or had the high score of quality of a tool, or had typical features. We grouped important tools into sub-groups: severity-of-error tools, value-of-service tools, tools of risk assessment, tools of assessment of cost avoidance, and multidimensional tools.

2.1. The severity-of-error tools

The severity-of-tools focused to assess the potential severity of DRPs/MEs to patient avoided by the PI (Approach 3A presented in the **Article 1**).

2.1.1. The tool of Folli et al. developed in 1987 (USA)

The first tool for assessing potential significance of PIs was created by Folli et al. in 1987 (13). The authors classified degree of potential severity of a ME into 3 levels (potential lethal, serious, or significant) with detailed descriptions of definition/explicit examples. However, the authors did not evaluate validity and reliability of this tool. Several investigators adopted this tool, sometimes with minor modifications (Iafrate et al. (198), Blum et al. (199), Lesar et al. (200-202), Ho et al. (203), Overhage et al. (12)).

Table 16. The tool of Folli et al.

Severity of a ME	Definition/Description
Potentially lethal	It could have one or more of the following consequences: (1) the serum level resulting from such a dose is likely to be in the "severe toxicity range" based on common dosage guidelines, e.g., serum theophylline concentrations >30 µg/mL, more than ten times the dose of a chemotherapy agent; (2) the drug being administered has a high potential to cause cardiopulmonary arrest in the dose ordered; (3) the drug being administered has a high potential to cause a life-threatening adverse reaction, such as anaphylaxis, in light of the patient's medical history; (4) the dose of a potentially life-saving drug is too low for a patient having the disease being treated; and (5) the dose of a drug with a very low therapeutic index is too high (ten times the normal dose).
Serious	It could have one or more of the following results: (1) the route of drug administration ordered is inappropriate, with the potential of causing the patient to suffer a severe toxic reaction; (2) the dose of the drug prescribed is too low for a patient with serious disease who is in acute distress;

	(3) the dose of a drug with low therapeutic index is too high-four to ten times the normal dose; (4) the dose of the drug would result in serum drug levels in the toxic range, e.g., serum theophylline levels 20 to 30 µg/mL; (5) the drug ordered could exacerbate the patient's condition, e.g., drug-drug interaction or drug-disease interaction; and (6) the name of the drug is misspelled, creating a risk that the wrong drug might be dispensed.
Significant	An error could have one or more of the following results: (1) the dose of the drug with low therapeutic index is too high - 1/2 to four times the normal dose; (2) the dose is too low for a patient with the condition being treated; (3) the wrong laboratory studies to monitor a specific side effect of a drug are ordered, e.g., CBC and reticulocyte counts are ordered to monitor gentamicin toxicity; (4) the wrong route of administration for the condition being treated is ordered, e.g., the inadvertent change from IV to oral therapy for the treatment of bacterial meningitis; and (5) errors ordering IV fluids are made, e.g., specific additives needed for complete therapy are omitted, or incompatible fluids are ordered.

Source: Reproduction from Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics. 1987;79(5):718-22.

2.1.2. The tool of Lesar et al. developed in 1990 (USA)

Besides the modification of 3 levels of the tool of Folli et al. (13), Lesar et al. (200) added the fourth level - "*problem orders*" to develop a new tool in 1990 (Table 17). In two later studies in 1997 (201, 202), the authors said that consistency and agreement of the tool has been previously reported in a study in 1990 (200). But in fact, this information was not found. However, consistency and agreement of the tool was determined by review of 500 consecutive errors rated as *only* A, B, or C (*not D*) occurring in the last study year by a physician and 2 pharmacists in a study in 1997 (202). All reviewers agreed on the ratings in 485 (97%). Two or more reviewers agreed on 497 (99.5%) of the assigned error severity ratings. Agreement between reviewers as determined by k statistic (0.96, P<.001) was excellent.

Table 17. The tool of Lesar et al.

Potential severity classification for order errors	
A. Potentially Fatal or Severe	1. The dose ordered for a medication with a low therapeutic index was greater than 10 times the normal dose. 2. A dose was ordered for a medication with a very low therapeutic index that would potentially result in pharmacologic effects or serum concentrations associated with severe or fatal toxic reactions. 3. A drug was ordered that had the potential to produce a severe or life-

	threatening reaction in the patient (e.g., anaphylaxis). 4. The dose of a lifesaving drug or drug being used for a severe illness was too low for the patient being treated.
B. Potentially Serious	1. The dose ordered for a medication with a low therapeutic index was 4 to 10 times the normal dose. 2. A dose was ordered for a medication with a very low therapeutic index that would potentially result in serious toxic reactions. 3. The dose ordered for a drug used for a serious illness was too low for the patient. 4. The wrong medication was ordered, with potential serious toxic reactions or inadequate therapy for a serious illness. 5. A route was ordered for a medication that could potentially produce serious toxic reactions or inadequate therapy for a serious illness. 6. A medication order was written illegibly or in such a manner as to result in an error that could produce serious toxic reactions or inadequate therapy for a serious illness. 7. Duplicate therapy with potential for serious toxic reactions was prescribed.
C. Potentially Significant	1. The dose ordered of a medication with a low therapeutic index was 1.5 to 4 times the normal dose, with potential toxic reactions because of the high dose. 2. The dose ordered of any medication was five times or greater than normal, with potential for adverse effects because of the high dose. 3. The dose ordered was inadequate to produce therapeutic effects. 4. The wrong route of administration was ordered, with potential for increased adverse effects or inadequate therapy. 5. The wrong medication was ordered for a non-severe illness and/or there was a potential for side effects from the drug. 6. A medication order was written illegibly or in such a manner as to result in an error producing adverse effects or inadequate therapy. 7. Duplicate therapy was prescribed with a potential for additive toxic reactions.
D. Problem Orders	1. Duplicate therapy was prescribed without potential for increased adverse effects. 2. The order lacked specific drug, dose, dosage strength, formulation, route, or frequency information. 3. The wrong route was ordered without potential for toxic reactions or therapeutic failure. 4. The dose of medication was five times greater than normal but without toxic potential. 5. An errant order was written that was unlikely to be carried out given the nature of drug, dosage forms, route ordered, missing information, etc.
1. Errors were assigned to a specific error class if the error detected met any of the listed criteria for each class.	

Source: Lesar TS, Briceland LL, Delcoure K, Parmalee JC, Masta-Gornic V, Pohl H. Medication prescribing errors in a teaching hospital. JAMA. 1990;263(17):2329-34.

2.1.3. The tool of Deans et al. developed in 1999 (UK)

Deans et al. (204) in UK developed a reliable, validated method of scoring the severity of MEs on the basis of potential patient outcomes in 1999. The raters were asked to score the error cases in terms of their potential clinical significance on a visual-analogue scale from 0 to 10, where 0 represented an incident with no potential effect on the patient and 10 an incident that would result in death. These anchors were chosen to allow as wide a range of responses as possible and thus maximize the sensitivity of the scale.

The 30 health care professionals (10 nurses, 10 physicians, 10 pharmacists) scored independently 50 MEs which were selected from literature with known outcomes. Validity and reliability of the tool was good (204). The Dean and al.'s tool may be better for research as it has been tested on a large sample size and the continuous scale potentially permits more powerful statistical analysis in comparative studies (205, 206). However, this tools may be more time consuming to use because it required at least 4 health care professionals to calculate a reliable mean score for each ME (197, 204).

The tool of Dean et al. was re-validated by Taxis et al. in 2002 in the Germany context(207). However, it required at least 3 health care professionals (not 4) to calculate a reliable mean score for each ME.

2.1.4. The tools inspired from NCC MERP Index developed in 2001 (USA)

In 1995, the United States Pharmacopeia founded the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). In 1996, the Council created an NCC MERP Index to standardize ME definitions and outcome severity categorization. The Index was revised to its current form in 2001 (208). The Index currently consists of 9 discrete categories (A–I) that are further combined into four categories: (1) no error, (2) error, no harm, (3) error, harm, and (4) error, death (*Figure **13***).

Many studies adapted the NCC MERP Index for evaluating potential (and actual) severity of MEs such as studies by Van den Bemt et al. (6 categories) (209), Davydov et al. (10 categories) (210), Bobb et al. (3 categories) (211), Gleason et al. (3 categories) (212), and Quélennec et al. (3 categories) (213). In three studies, results of inter-rater reliability was good: agreement = 75-84% (211), k = 0.61-0.84 (212, 213).

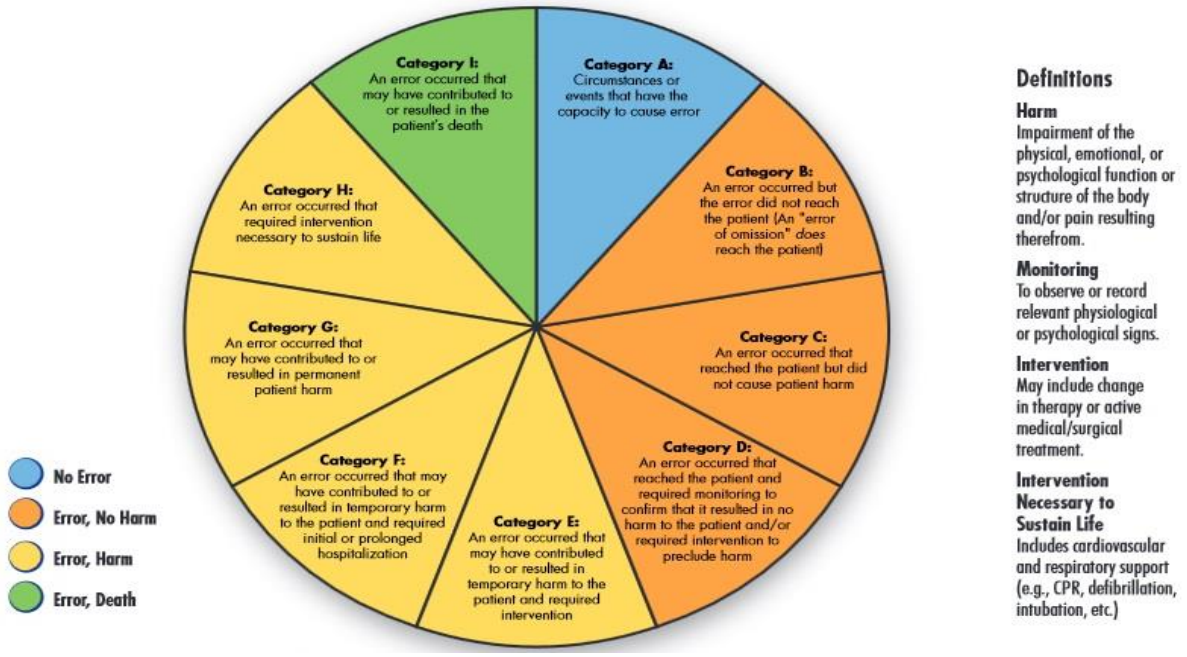


Figure 13. NCC MERP Index for Categorizing Medication Errors

Source: Duplicated from National Coordinating Council for Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. 2011. Available at http://www.nccmerp.org/types-medication-errors.

2.1.5. The tool of Cornish et al. developed in 2005 (Canada)

For assessing unintended medication discrepancies detected during medication reconciliation, Cornish et al. (214) classified each discrepancy for its potential to cause harm as *unlikely*, *possible*, or *probable to cause harm*. There was *fair* inter-rater reliability for judging the potential severity of discrepancies (k = 0.26, 95% CI, 0.16-0.36). This tool has been widely adopted for use in other studies which evaluated unintended medication discrepancies such as Kwan et al. (215), Wong et al. (216), Coffey et al. (217), Villanyi et al. (218), and Lee et al. (206) with good inter-rater reliability (k = 0.63-0.84 or $p < 0.01$).

Table 18. The tool of Cornish et al.

Class	Definitions/Examples
1	Discrepancies were unlikely to cause patient discomfort or clinical deterioration. *Example: a patient prescribed 20 mg/d of atorvastatin calcium on admission, despite reporting a dosage of 10 mg/d on interview.*
2	Discrepancies were those with the potential to cause moderate discomfort or clinical deterioration. *Example: a patient prescribed 25mg of atenolol twice daily on admission, despite reporting a dosage of 25 mg/d on interview.*
3	Discrepancies had the potential to result in severe discomfort or clinical deterioration. *Example: a patient admitted with gastrointestinal hemorrhage who was ordered 2.5 mg/d of ramipril on admission but reported no prior use of ramipril during the interview.*

Source: Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9.

2.2. The impact-of-intervention tools

The impact-of-intervention tools focus on assessing the potential impact of the PI on patient care (Approach 3B presented in the **Article 1**).

2.2.1. The tool of Hatoum et al. developed in 1988 (USA)

The study of Hatoum et al. in 1988 (14) was one of the most important studies in an effort to evaluate the value of CPSs. The objectives of the study were: (1) to evaluate the clinical significance of PIs, (2) to develop a process evaluation of PIs, and (3) to evaluated these PIs in term of economic value.

For the first objective, the authors ranked PIs into 6 levels according to values of service by assessing the potential impact of PIs on patient (Table 19).

For the second objective, process evaluation was proposed as follows:

- **Initial self-review:** all clinical pharmacist providing inpatient care were asked to report two of their daily PIs (one having an impact on the quality of patient care and the other for its potential cost-avoidance) and categorized PIs according to their impact on quality of care or cost.
- **Follow-up and short-term outcomes:** A follow-up concerning physician acceptance and patient's treatment progress was recorded within two working days.
- **Peer-review process and evaluation:** Nine clinical pharmacists served on three peer groups, each consisting of three members. Independently, these reviewers ranked PIs according to their potential for clinical impact on patient therapy. When two or more reviewers gave identical ranks, the mode was the assigned rank. Interventions with inconsistent ranks were discussed until it reached a consensus.

For third objective, based on the results of the process evaluation, a random sample of those interventions with cost impact was subjected to evaluation of economic value. Evaluation focused on five considerations:

- Saving were calculated relative to the estimated **reduction in the cost of drug therapy** (D), e.g, use of less expensive drugs, discontinuance of a drug, conversion to a less expensive drugs (including change of dose, dose interval, route, duration, or form of medication).
- Savings were calculated relative to **a more cost-effective method for drug therapy monitoring** (M), i.e., use of appropriate monitoring variables, cancellation of unnecessary laboratory orders, and identification of therapeutic agents requiring fewer monitoring and/or fewer costly laboratory tests.
- Savings were calculated relative to **avoiding costs attributable to complications of drug therapy** (U), i.e., costs related to the detection and management of such untoward effects as toxic side effects, adverse drug reactions, and therapeutic failures.
- Savings were calculated relative to **a reduction in length of patient hospitalization** (L), i.e., more effective drug therapy resulting in improved therapy and more efficient

management of patient care, thus reducing the length of stay and/or avoiding predictable complications that might increase the hospital stay (e.g.;, preventing an allergic reaction in a patient for whom a known allergy is documented).

- C: Cost of clinical pharmacy services: personnel cost (salaries) + indirect personnel cost (fringe and other employer-paid benefits).

Total economic value (EV) was calculated by a multivariable formula expressed as follows:

$$EV = D + M + U + L - C$$

In this formula, it is possible for any one the four first variables to be positive, negative, or zero.

Table 19. The intervention ranking of Hatoum et al.

Recommendations are ranked according to potential impact on patient care.	
1.Adverse significance	Recommendation supplied by the clinical may lead to adverse outcome. *Example - None reported*
2. No significance	Recommendation is informational (not specifically related or meaningful to the patient in question.) *Example - Chief surgeon asked the clinical pharmacist to explain why one of his patients became hypotensive in the operating room. After reviewing the case, the pharmacist noted the pharmacist noted that vancomycin was given over a period of less than 60 minutes. The pharmacist then provided to the surgery department the appropriate information on the administration techniques of vancomycin. A procedural policy on vancomycin administration was instituted. In this case, the intervention was considered informational because it was after the fact. However, it will most likely have an impact on future use of vancomycin.*
3. Somewhat significant	Benefit of the recommendation to the patient could be neutral depending on professional interpretation (to be differentiated from rank 4 where a standard of practice would support the recommendation). *Example - an order was placed for an aminophylline loading dose followed by maintenance infusion in two separate bags and tubing. Pharmacist intervention: change both orders to the same bag and adjust infusion rate for loading and maintenance doses.*
4. Significant	Recommendation would bring care to a more acceptable and appropriate level (i.e., standard of practice). *Example - Preoperative cultures on patients with stump infection with osteomyelitis were found resistant to cefoxitin. However, patient was placed on cefoxitin postoperatively. Pharmacist intervention: discountinue cefoxitin. Use of the drug was no longer indicated due to the surgical removal of infected tissue through an uncontaminated tissue plane.*
5. Very significant	Recommendation qualified by a potential or existing major organ dysfunction. *Example - Patient with documented previous episode of heparin-induced*

	thrombocytopenia associated with a thrombotic episode was placed on heparin. Pharmacist intervention: substitute dextran 40 for heparin to prevent possible recurrence of thrombocytopenia and/or thrombotic or embotic complications.
6. Extremely significant	Information qualified by life and death situation. *Example - Patient transferred for surgery for intracranial aneurysm was receiving oral narcotic therapy for chronic pain prior to transfer. However, therapy was not reinstated after patient was transferred. Pharmacist intervention: reinstitute narcotic therapy. Perioperative procedure for vascular disease complicated by narcotic withdrawal could cause aneurysm to rupture, leading to fatal hemorrhage. Also, postoperative withdrawal would extent hospital stay.*

Source: Hatoum HT, Hutchinson RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. Drug Intell Clin Pharm. 1988;22(3):252-9.

The original tool of Hatoum al. was not tested for validity and reliability. Only interventions judged as level 5 and 6 by the peer reviewers of 3 pharmacists were under review by a team of physicians to validate the review process (219).

The tool was commonly adopted for use in 31 of 133 studies (23%) identified in the previous systematic review. The results of validity and reliability of Hatoum et al.'s modified tools varied widely. Almost studies adopted only the ranking of clinical significance of PIs. Only Cousins et al. (189) adopted both ranking of clinical significance of PIs and economic indicators to develop a new tool. But the capacity of pharmacists to reliably code indicators of PIs was poor.

2.2.2. The tool of Chedru et al. developed in 1997 (France)

Chedru et al. inspired from the Hatoum et al.'s tool and developed a 4-level tool in 1997 (220), which was used in other studies in France (221-224). The inter-rater reliability of this tool was tested in two studies (220, 223) and was good.

Table 20. The tool of Chedru et al.

Tool for rating pharmacist intervention	
Score	**Significance**
0	**No clinical impact for the patient** The intervention is present an objective, financial or informational exclusively or was proposed after the event; it is therefore without consequence for the patient.
1	**Significant impact** The intervention increases the efficiency and/or safety and/or quality of life of the patient.
2	**Very significant impact** The intervention prevents organ dysfunction, it avoids intensive medical surveillance or an irreversible consequence.

3	**Vital impact** The intervention avoids a potentially fatal accident.

Source: Chedru V, Juste M. Medical evaluation of the clinical impact of pharmacist interventions [Evaluation médicale de l'impact clinique des interventions pharmaceutiques]. J Pharm Clin. 1997;16(4):254-8.

2.3. The multidimensional tools

Some studies combined many previous tools and used at the same time to evaluate impacts of PIs.

2.3.1. The tool of Overhage and Lakes developed in 1999 (USA)

After literature review of articles in a database for the years 1966-1997 and identified 10 rating scale with an explicit description of definition (12). Overhage and Lake constructed a new tool including 2 dimensions: *"severity of error"* (inspired from the classification ranking scale of Folli et al. (13)) and *"value of service"* (based on the ranking system of Hatoum et al. (14)).

Table 21. The tool of Overhage et Lakes

Instrument for characterizing pharmacists' clinical activities	
Severity of error in medication order Assess the inappropriateness of the order or its deviation from the standard of practice.	
A, Potentially lethal	High potential for life-threatening adverse reactions Potentially lifesaving drug at a dosage too low for the disease being treated High dosage (>10 times normal) of drug with low therapeutic index
B, Serious	Route of administration could lead to severe toxicity Low dosage of drug for serious disease in patient with acute distress High dosage (4–10 times normal) of drug with low therapeutic index Dosage resulted in serum drug concentration in potentially toxic range Drug could exacerbate the patient's condition (related to warnings or contraindications) Misspelling or mix-up in medication order could lead to dispensing of wrong drug Documented allergy to drug High dosage (10 times normal) of drug without low therapeutic index Omission of pretest for drug hypersensitivity
C, Significant	High dosage (1.5–4 times normal) of drug with low therapeutic index Drug dosage too low for patient's condition High dosage (1.5–10 times normal) of drug without low therapeutic index Errant dual-drug therapy for single condition Inappropriate dosage interval Omission from medication order
D, Minor	Incomplete information in medication order Unavailable or inappropriate dosage form Non-formulary drug

	Noncompliance with standard formulations and hospital policies Illegible, ambiguous, or nonstandard abbreviation
E, No error	Information or clarification requested by physician or other health care professional from pharmacist Cost savings only
Value of service Assess the potential impact of the pharmacist's recommendation on patient care.	
1, Extremely significant	Recommendation qualified by extremely serious consequences or potential life-and-death situation
2, Very significant	Recommendation qualified by a potential or existing dysfunction in a major organ Avoidance of serious adverse drug interaction or contraindication to use
3, Significant	Recommendation would bring patient care to a more acceptable, appropriate level (e.g., standard of practice), including quality-of-life issues with evidence from the patient or documentation elsewhere, as well as issues of cost and convenience. (Standard of practice is defined by institutional guidelines and protocols and supported by acceptable references to the literature.)
4, Somewhat significant	Patient's benefit from the recommendation could be neutral depending on professional interpretation (to distinguish this rank from rank 3, where a standard of practice would support the recommendation) More information or a clarification must be obtained by the pharmacist from the physician, nurse, or other appropriate health care professional before an order can be processed
5, No significance	Information only Recommendation not patient specific
6, Adverse significance	Recommendation inappropriate; its implementation may lead to adverse outcomes

Source: Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. Am J Health Syst Pharm. 1999;56(23):2444-50.

The inter-rater reliability between of 3 clinical pharmacists and 2 internists was *substantial* (kw = 0.69) for *severity-of-error* and *value-of-service* scales individually. The authors found that *severity of error* and *value of service* were clearly related but that the relationship was not linear. *Value of service* was high for high *severity-of-error* interventions but could also be high for low *severity of error*. Therefore, the *value-of-service* and *severity-of-error* scales measured different dimensions of pharmacist's services (12).

Others adopted the Overhage and Lakes's tool such as Bosma et al.(225), Lee et al.(226), Climenté-Martin et al.(227), Abdel-Qader et al.(54), Fernandez-Llamazares et al.(228, 229), and Somer et al.(230). Some studies (225, 226, 229), however, found *poor* agreement of ratings. There were some risks of bias which were likely to explain high agreement in the study of Overhage and Lakes but not repeatable in other studies (12). Bias concerning selection of raters included: (1) a single pharmacist who retrospectively reviewed and

adjusted the ratings assigned by the pharmacist who made the intervention, which improved the consistency of rating; (2) two internists having fellowship training in clinical pharmacology; and (3) one physician and one pharmacist participated in the refinement of the tools over a one-year period, therefore they understood well the tool. Bias concerning assessment process included: (1) examples and supplemental cues were developed to improve the consistency of ratings; (2) the two experiences raters oriented other raters who had not been involved in the development process.

2.3.2. The tool of Lee et al. developed in 2010 (Canada)

Lee et al.(206) adopted the tool of Cornish et al. (214) and the tool of Deans et al.(204) to rank the clinical impact and severity of unintentional discrepancies detected during medication reconciliation. Each clinician categorized the clinical impact of each discrepancy as *unlikely, possible,* or *probable to cause harm* (214). These were then further categorized as having the *potential to cause discomfort, clinical deterioration,* or *both* and were assessed for severity as *mild, moderate,* or *severe* using a 9-point scale (204). Pairwise k-scores of 2 pharmacists, an internist, and an intensivist ranged from 0.637 to 0.769, indicating a substantial degree of agreement between assessors.

2.3.3. The tool of Hick et al. developed in 2001 (UK)

Hick et al. (205) used both the tool of Dean et al. (204) and the tool of Hatoum et al. (14) in their study.

2.3.4. The tool of Lindblad et al. developed in 2007 (Canada)

According to the tool of Lindblad et al. (231), anticipated health outcomes of PIs were defined according to the ECHO model (*economic, clinical, and humanistic outcomes*) (162). There were 5 clinical outcomes. Humanistic sub-outcomes were combined into a single category to simplify reporting. Economic sub-outcomes were also combined to focus specifically on drug costs that were quantifiable by the pharmacist (Table 22). Each PIs can be assessed to have one or many outcomes. During the study period, pharmacists anticipated that 2,645 PIs would lead to a total of 6,101 outcomes. Over 62% of the anticipated outcomes were clinical, 32.9% were humanistic, and 4.5% were economic. An average of 2.3 outcomes were associated with each PI. For every intervention, there were on average 1.4 clinical outcomes, 0.8 humanistic outcomes, and 0.1 economic outcomes (231). However, a disadvantage of the tool was that 5 clinical outcomes were not hierarchical and were not mutually exclusive. Furthermore, it is difficult to base on categories of clinical outcomes to estimate cost avoidance of a PI.

Table 22. The tool of Lindblad et al.

Anticipated outcomes	Numeric code
Clinical	
Cure a disease	1A
Eliminate or reduce signs or symptoms	1B
Arrest or slow a disease process	1C
Prevent a disease or symptom	1D
Achieve desired alterations in physiologic processes	1E
Humanistic	

Improve physical, mental, or social function or satisfaction with care (feeling better)	2A
Economic	
Drug cost savings of $1 or more/day	3A
Drug cost increase of $1 or more/day	3B

Source: Lindblad A, Alleyne A, Howorko J. Development and Initial Evaluation of a Software-Based Clinical Workload Measurement System for Pharmacists. Can J Hosp Pharm. 2007;60(5):295-301.

2.4. The tools of risk assessment

These tools are based on standards for risk management, where risk is based on an estimate of the likelihood and consequences of an adverse outcome from a DRP, if no IP had made.

2.4.1. The tool of the Society of Hospital Pharmacists of Australia in 2005 (Australia)

The Society of Hospital Pharmacists of Australia's (SHPA) Standards of Practice for Clinical Pharmacy provide a risk-classification system for PIs in hospital inpatients (10). A special feature of the SHPA's tool was that 5 levels of *financial loss* was integrated into the *"consequence"* dimension (Table 23). Struck at al. (123) evaluated inter-rater reliability of a modified tool and found that agreement between 2 pharmacists was *moderate* for the *"consequence"* dimension (kw = 0.51), *slight* for the *"likelihood"* dimension (kw = 0.14), and *fair* for the *"economic benefit"* dimension (kw = 0.39). Elliott et al. (232, 233) adapted the SHPA's tool to develop a new risk-classification system for use in geriatric ambulatory care. Results of validity was *good* (agreement = 93-100%) but inter-rater reliability of risk classification was *fair* (k = 0.24)(233).

Table 23. The tool of the Society of Hospital Pharmacists of Australia's tool

Level/Descriptor	**Consequence or impact**
1. Insignificant	No harm or injuries, low financial loss.
2. Minor	Minor injuries, minor treatment required, no increased length of stay or re-admission, minor financial loss.
3. Moderate	Major temporary injury, increased length of stay or re-admission, cancellation or delay in planned treatment/procedure. Potential for financial loss.
4. Major	Major permanent injury, increased length of stay or re-admission, morbidity at discharge, potential for significant financial loss.
5. Catastrophic	Death, large financial loss and/or threat to goodwill/good name.
Level/Descriptor	**Likelihood of occurrence**
A. Almost certain	Is expected to occur in most circumstances
B. Likely	Will probably occur in most circumstances
C. Possible	Might occur at some time
D. Unlikely	Could occur at some time
E. Rare	May occur only on exceptional circumstances

Risk (consequence x likelihood)					
Likelihood	Insignificant	Minor	Moderate	Major	Catastrophic
A (almost certain)	H	H	E	E	E
B (likely)	M	H	H	E	E
C (possible)	L	M	H	E	E
D (unlikely)	L	L	M	H	E
E (rare)	L	L	M	H	H
E = extreme risk; H = high risk; M = moderate risk; L = low risk					

Source: Society of Hospital Pharmacists of Australia. SHPA Standards of Practice for Clinical Pharmacy. J Pharm Pract Res. 2005;35(2):122-46.

2.4.2. The tool of Lewinski et al. developed in 2010 in Germany

Lewinski et al. (234) constructed a 3x3 matrix of risk assessment of DRPs. Inter-rater reliability in risk assessment was *high* (k = 0.78, 0.83 and 0.87 for three possible rater pairings).

Table 24. The tool of Lewinski et al.

		Severity		
		1	2	3
Probability	1	Low	Significant	High
	2	Low	Significant	Significant
	3	Low	Low	Significant

Severity categories

1 - Reversible, *slight* impairment of health compared to the best possible state of health (e.g. ineffective athlete's foot treatment).

2 - Reversible, *significant* impairment of health compared to the best possible state of health (e.g. causation or prolongation of inability to work).

3 - *Irreversible or serious* impairment of health (e.g. emergency, hospitalization), unwanted pregnancy

Probability categories

1 - p: existent - 0.02 (excl.)

2 - p: 0.02-0.2 (excl.)

3 - p: 0.2 and more, already occurred.

Probability or severe rated 0: Exclusion, that is not safety-relevant, no intervention necessary.

Assessment procedure

First step: Listing and classifying for severity of all possible harms that can be induced by the drug-related problem (Harm can either be an acute event or a prolongation of an ameliorable condition.)

Second step: Assessment of probability for harm occurrence for the harm(s) of the highest severity category

Source: Lewinski D, Wind S, Belgardt C, Plate V. Prevalence and safety-relevance of drug-related problems in German community pharmacies. Pharmacoepidemiol Drug Saf. 2010;19(2):141-9.

2.5. The tools of assessment of cost avoidance

The tools of assessment of cost avoidance of a PI were those that allowed to estimate the resources that would have been required to manage the patient as a result of the DRP. These tools were often used as the first step to conduct an economic study afterward.

2.5.1. The tool of Rupp et al. developed in 1992 (USA)

The purpose of the Rupp et al.'s tool was to estimate the cost avoidance of PIs in community pharmacies (196). The tool contained four questions (*Figure **14***). The cost avoidance was estimated from the cost of each level of care in question 4 multiplied by the probability rated from the question 3. The formula of cost avoidance was:

[cost avoidance] = [probability of consequence] X [cost of level of care]

The cost of each level of care was determined by using information from authoritative sources. For example, the cost of emergency medical attention followed by hospitalization of the patient was estimated to be $2001. The cost of the next three levels of care was estimated to be $110, $60, and $40. Finally, the study determined that the total value of PIs was $76,616, value per intervention $122.98 and value per prescription screened $2.32.

Concerning the inter-rater reliability of a physician and 2 pharmacist, it was *good* agreement for the three first questions (k = 0.68-0.88, k = 0.79-0.82, t-test p > 0.05, respectively) but *poor* agreement for the last question (196, 235).

Pharmacist intervention report evaluation

1. Could this event have resulted in adverse health consequences to the patient if the pharmacist had not intervened ? (check one)
□ no (if no, stop here) □ yes (if yes, please continue)

2. What adverse health consequence do you consider *most likely* to have resulted from this event if the pharmacist had not intervened?
□ toxic or side effects of the drug(s) involved
□ inadequate control of the patient's condition
□ allergy/hypersensitivity reaction
□ other (specify)

3. Based on the available information, what is your estimate of the probability that this event *would* have resulted in the adverse health consequence specified above? (circle one)

	very unlikely	somewhat unlikely	neither likely nor unlikely	somewhat likely	very likely	
0	0.1	0.3	0.5	0.7	0.9	1.0

4. What intensity of healthcare would be need to treat the adverse health consequence specified above, *assuming* that it did occur? (check one)
□ emergency medical attention (hospitalization likely)

□ emergency medical attention (hospitalization unlikely)
□ unscheduled physician contact (urgent care)
□ scheduled physician contact (office visit)
□ self-care (specify)
Comments:

Figure 14. The tool of Rupp et al.

Source: Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother. 1992;26(12):1580-4.

2.5.2. The tool of Caleo et al. developed in 1996 in Australia

Caleo et al. (236) modified the first four questions of the tool of Rupp et al. (196) and added two questions to evaluate the quality of life of a patient and one for the overall outcome. Concerning the inter-rater reliability of 2 clinical pharmacologists, a clinical pharmacist, and a community pharmacist, it was *moderate* to *good* agreement for the question 2 (k = 0.50-0.76) and was *poor* to *moderate* agreement for the rest of questions.

Pharmacist intervention report evaluation

1. Could this event have resulted in adverse health consequences to the patient if the pharmacist had not intervened?

□ No (if no, stop here) □ Yes (if yes, please continue)

2. What adverse health consequence do you consider most likely to have resulted from this event if the pharmacist had not intervened?

□ Toxic or side effects of the drug(s) involved
□ Inadequate control of the patient's condition
□ Allergy/hypersensitivity reaction
□ Other (specify)

3. Based on the available information, what is your estimate of the probability that this event would have resulted in the adverse health consequence specified above? (circle one)

not at all	very unlikely	somewhat unlikely	neither likely nor unlikely	somewhat likely	very likely	definitely
0	0.1	0.3	0.5	0.7	0.9	1.0

4. If the intervention had not occurred, what is your estimate concerning the extent of interference with the patient's everyday activity? (circle one)

no interference	slight	moderate	severe	no normal activity
0	0.25	0.5	0.75	1.0

For how many days would this effect last?.....(give a range if unsure)

5. Based on the available information, what is your estimate of the degree of patient discomfort? (circle one)

no discomfort	slight	moderate	severe	extreme discomfort
0	0.25	0.5	0.75	1.0

For how many days would this discomfort last?.....(give a range if unsure)

6. What intensity of healthcare would be need to treat the adverse health consequence specified above, assuming that it did occur? (tick one)
□ Intensive care - hospital and no. of days.....(give a range if unsure)
□ Standard ward - hospital and no. of days.....(give a range if unsure)
□ Accident and emergency (Casualty) - hospital
□ Urgent physician visit
□ Next regular physician visit
□ Self-care (specify)

7. What is the overall outcome for the patient as a result of this intervention by the pharmacist? (tick one)
□ Negative
□ Neither
□ Positive

Figure 15. The tool of Caleo et al.

Source: Caleo SUE, Benrimoj S, Collins D, Lauchlan R, Stewart KAY. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract. 1996;4(4):221-7.

2.5.3. The tool of Bayliff et al. developed in 1990 (Canada)

Outcomes of PIs were labelled either *detrimental, no effect,* or *beneficial* to patient care (194). The inter-rater reliability of this rating between 4 physicians was *good* (coefficient of agreement = 0.76 ($p>0.05$), effective reliability = 0.93).

The cost avoidance of PIs was estimated through a formula:

[cost avoidance] = [number of days of hospitalization avoided] X [cost per day]

Therefore, raters were required to answer whether the intervention averted a prolonged stay, and if prolonged, the extent of prolongation (1, 3, 5, or a week or more).

The concordance between raters was *lower* for the two final question (coefficient of agreement 0.30-0.38 ($p>0.05$), effective reliability = 0.63-0.71). The study found that of 15 PIs assessed, eight PIs were judged to have a prolonged hospital stay a mean of 3.7 days each or a total of 29.6 days. At the per diem rate of $600 per day this rendered a cost avoidance of $17,760. This method of estimation of cost avoidance of PIs were adopted to use in study of Chedru et al. in France (220).

Evaluation

1. The intervention by the pharmacist resulted in a
□ detrimental effect
□ no effect
□ positive effect
□ minor effect on patient therapy
□ modest effect on patient therapy (Therapy would have been compromised or side effect may have occurred of the intervention did not take place.)
□ marked effect on patient therapy (Had the intervention not taken place, severe, life-threatening events may have occurred.)

2. If the intervention had no occurred, would hospitalization have been prolonged?
□ no □ yes □ don't know

3. If yes, hospital stay may have been prolonged:
□ approximately 1 day
□ approximately 3 days
□ approximately 5 days
□ a week or more

Figure 16. The tool of Bayliff et al.

Source: Bayliff CD, Einarson TR. Physician assessment of pharmacists' interventions - a method of estimating cost avoidance and determining quality assurance. Can J Hosp Pharm. 1990;43(4):167-71, 95.

Strong et al.(237) and Virani et al.(238) in Canada both inspired the Bayliff et al.'s tool to develop their own one. We presented here the tool of Varini et al. whose score of quality of a tool is 6 (see 1. A systematic review of tools for assessing potential significance of pharmacist interventions .

- **The tool of Varani et al. in 2003**

Evaluation Form
1. The intervention by the pharmacist resulted in a
□ detrimental effect
□ no effect
□ positive effect
□ minor effect on patient therapy
□ modest effect on patient therapy (Therapy would have been compromised or side effect may have occurred of the intervention did not take place.)
□ marked effect on patient therapy (Had the intervention not taken place, severe, life-threatening events may have occurred.)

2. The above intervention would result in:

	yes	no	don't know
increase quality of care	☐	☐	☐
avoidance of adverse effects	☐	☐	☐
decrease costs	☐	☐	☐
improve response to medication	☐	☐	☐
improve patient adherence to medication	☐	☐	☐
decrease length of hospital stay	☐	☐	☐

Comments:

Figure 17. The tool of Varini et al.

Source: Virani A, Crown N. The Impact of a Clinical Pharmacist on Patient and Economic Outcomes in a Child and Adolescent Mental Health Unit. Can J Hosp Pharm. 2003;56:158-62.

Instead of assessment of cost avoidance in the study of Bayliff et al., Virani et al.(238) determined the financial impact of having a clinical pharmacist on the mental health unit. A retrospective cost analysis was conducted to determine prescription drug costs, ward stock drug costs, and total number of patient-days on the unit from pharmacy records for the year before and the year immediately after implementation of the position. From these data, the total drug cost per patient-day was calculated and compared for the two 1-year periods, using a matched-pair Student t-test. The study found that total drug cost per patient-day decreased by 14% in the 12 months after implementation of the pharmacy position.

2.5.4. The tool of Buurma et al. developed in 2004 (Netherlands)

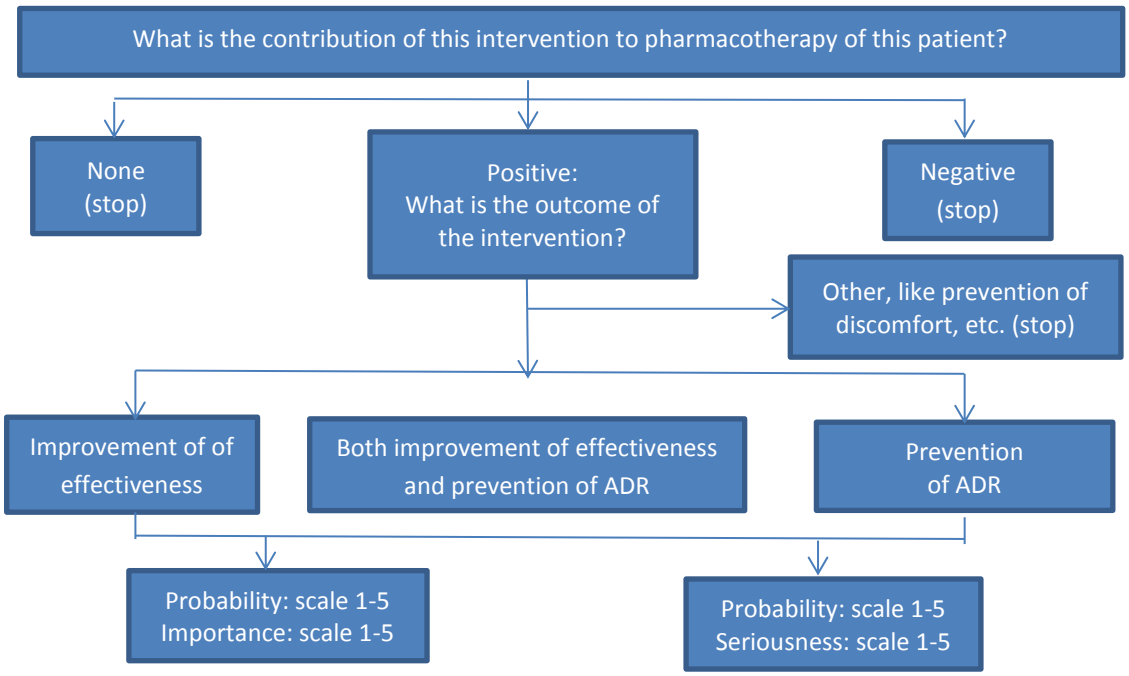


Figure 18. Algorithm representing the low of questions for rating interventions

ADR: adverse drug reaction. *Source:* Buurma H, De Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol. 2004;58:503-11.

The tool of Buurma et al. (239) was developed to use in community pharmacies. The algorithm used by raters for rating PIs is presented in *Figure **18***. According to the tool, assessment process included 3 steps:

- Step 1: Raters had to rate the contribution of each PI proposed in community pharmacies on the pharmacotherapy of the patient as *"positive", "negative"* or *"neutral"*.
- Step 2: In the event of a *"positive"* rating, the rater had to decide whether the PI resulted in an *improvement of effectiveness*, *prevention of an ADR* or *both*.
- Step 3: The judged *improvement of effectiveness* and/or *prevention of ADR* had to be rated on a five-point scale on two further points: *probability* and *importance* or *seriousness.*

The inter-rater reliability of group including a community pharmacist, a hospital pharmacist, a general practitioner and a specialist was *moderate* (k = 0.40-0.49) for the two first steps.

The impact of a PI can be described as "the product of the *probability* and *seriousness* of an ADR" OR as "the product of the *probability* and *importance* of effectiveness improvement" into 4 categories visualized in quadrant diagram: *left upper quadrant A*, *right upper quadrant B*, *left lower quadrant C*, or *right lower quadrant D*.

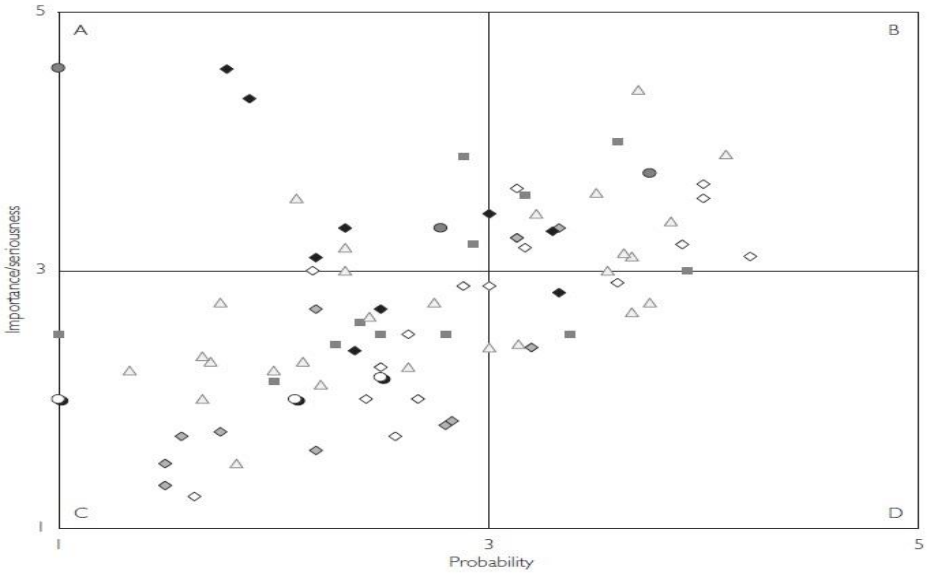


Figure 19. Quadrant diagram

Source: Buurma H, De Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol. 2004;58:503-11.

- **The tool of Westerlund et al. developed in 2009**

Westerlund et al. (195) inspired the algorithm of Buurma et al. to developed "an assessment model of clinical and economic outcomes of PIs" to evaluate PIs in community pharmacies in Sweden (*Figure **20***).

Figure 20. Model used for the assessment of clinical and economic outcomes of PIs

Source: Westerlund T, Marklund B. Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J Clin Pharm Ther. 2009;34(3):319-27.

The assessment process included 2 steps:

- Potential *clinical outcomes* of PIs was categorized as resulting in either an *improvement of the therapeutic effect* or a *prevented/relieved ADR*; or *both*.
- *Economic assessment* of the PIs depended on type of health care resources needed to respond to the ADRs (e.g., cost for primary care visits and hospitalization) that were potentially avoided as a result of the interventions. "Primary care contact" was defined as a patient visit to a general practitioner, patient counselling by general practitioners over the phone, or a visit by a general practitioner to a patient's home.

The formula was applied to calculate *cost avoidance* in the study:

[cost avoidance] = [cost of avoided primary care visit] OR [number of avoided hospitalization days] X [cost per day]

The authors did not include cost due to initiated primary care contacts, thus this cost was zero. The authors did not include indirect societal cost avoidance, such as that for sick leave expenditures and chose also not to use a multiplier to represent the idea that PI may have avoided more than one visit to the doctor in some patients. Finally, the authoer did not adjust for the possibility that some of the visits might have required a specialist, instead of a GP.

The estimated pharmacy personnel costs for identifying, resolving and documenting the DRPs were calculated. Calculations were based on the average time spent per DRP in the study and an estimated average salary, according to the following formula:

[cost of implementation] = [number of identified DRPs] x [time spent/DRP] x [personnel cost time]

Extrapolation of the estimate to the national level, the authors found that the annual potential cost avoidance in Sweden was 357.9 million EUR (51.2 million EUR for avoided primary

care contacts and 306.7 million EUR for avoided hospitalizations). The annual pharmacy personnel costs for identifying, resolving and documenting DRPs was 9.6 million EUR. The ratio between the potential societal cost avoidance and the pharmacy personnel costs was thus 37.3.

2.5.5. The tool of Kopp et al. developed in 2007 (USA)

The authors adopted the tool of Overhage and Lakes (12) to evaluate *severity of potential MEs* and *significance of PIs* and the method of Leape et al.(135) to estimate *cost avoidance* of PIs.

Cost avoidance referred to potential money saved if the potential ADE was caught. To determine cost avoidance of potential ADE, each intervention was determined the *probability* of a potential ADE occurring in the absence of the intervention. Based on a previous investigation, the probability of an ADE was set at 0, 0.01, 0.1, 0.4, or 0.6. Each evaluator's probability values were then multiplied by the estimated cost of a preventable ADE to calculate cost avoidance.

[cost avoidance] = [probability of a potential ADE] X [cost of an estimated ADE]

In this study, *cost savings* refers to money saved, estimated by the evaluators based on differences in medication costs (e.g., intravenous-to oral conversions).

PART 3.

DEVELOPMENT AND VALIDATION OF A NEW TOOL FOR ASSESSMENT OF POTENTIAL IMPACTS OF PHARMACIST INTERVENTIONS

This part will introduce a national documentation system of PIs used commonly in hospitals in France - Act-IP®, a context in which the development of a new tool for assessment of potential impacts of PIs emerged. In the next section, the process of construction of the CLEO multidimensional tool will be presented. Finally, the results of two studies for testing the CLEO tool - one in general context and another in a specific clinical setting will be reported.

1. The tool for documentation of PIs in France - Act-IP©

In 2003, the French Society of Clinical Pharmacy (SFPC) drew attention to the lack of a validated tool for documentation of PIs performed in hospitals (130). Consequently, a special interest group (SIG) ‘‘Standardizing and demonstrating the value of clinical pharmacy activities’’ was formed by eight clinical pharmacists belonging to the SFPC working in six different hospitals. The SIG was charged with developing and validating an instrument for the documentation of clinical PIs (97). This instrument can be used in daily routine, including (1) the identification of DRPs, (2) the PI, (3) the type of drug involved (using ATC classification (Anatomical Therapeutic Chemical)), (4) the acceptance of the intervention by the prescriber. Ten main categories were determined for DRPs and seven for interventions (*Figure 21*). A detailed description of sub-domains for DRPs and interventions is given in Table 25 and Table 26.

For the internal validity of the instrument (240), a panel of 12 French hospital pharmacists assessed 60 PIs which were randomly selected from daily practice in the six hospitals. Each case was composed of a brief description of the medical context and all relevant elements concerning the potential or identified DRP and the intervention suggested by the pharmacist. Of 12 pharmacists, a pair of one pharmacist from the SIG and an independent one was selected from six hospitals. For classification of DRPs, six pharmacists from SIG agreed in 57% of cases with k = 0.77 while six independent ones agreed in 53% of cases with k = 0.75. For classification of PIs, the concordance between six pharmacists from SIG was 77% with k = 0.88 while the concordance between six independent pharmacists was 70% with k = 0.86.

For the *external validity* of the instrument (97), a panel of 12 French speaking clinical pharmacists (six from France; six from foreign French speaking hospitals: two from Canada, two from Switzerland and two from Belgium) was asked to analyze a set of 60 PIs. Sixty cases of intervention were randomly selected from daily practice in the six hospitals participating in the SIG. The level of concordance observed in the validation was 0.76 for DRPs and 0.89 for the type of intervention. Concerning the coding of DRPs, the kappa coefficient for the six foreign experts was excellent (k = 0.82) and good for the six French experts (k = 0.73). Concerning the "type of intervention", kappa was excellent both for the foreign experts (k = 0.91) and for the French experts (k = 0.87). For the user-friendliness of the instrument, eleven experts out of 12 were "very satisfied" or "satisfied" and one "not satisfied" with the tool. Ten out of the 12 experts were ready to use it in daily practice.

Table 25. Description of drug related problems

- *Identification of DRP* is based on the analysis of a drug prescription taking into account the available clinical and paraclinical data on the patient.
- *Only one problem intervention per form:* If the patient's drug regimen analysis reveals several problems, fill out as many intervention forms as there are problems.
- *Question(s)* - Is this patient developing or is he susceptible to develop a symptom linked to a specific drug or is there a drug related problem requiring an intervention to avoid the unnecessary mobilization of resources?

DRP		**Description**
1.1	Non conformity to guidelines or contra-indication	*Non conformity of the drug choice compared to the Formulary:* An equivalent is available on the formulary *Non conformity of the drug choice compared to guidelines:* Another drug has a better benefit/risk ratio or a better cost/efficacy ratio according to current guidelines *There is a physio-pathologic contra-indication for the present drug:* for example: the patient is asthmatic and was prescribed beta-blockers
1.2	Untreated indication	*Valid indication without drug prescription* *A new symptom is not being treated* *A drug is missing after patient transfer* *The patient was not given any pre-medication or prophylactic treatment* *A synergic or corrective drug should be added to the ongoing treatment*
1.3	Subtherapeutic dosage	*Dose too low in this specific case* (daily dose) *Length of the treatment too short.* (for example: antibiotic prescription for 5 days instead of 10 days)
1.4	Supratherapeutic dosage	*Supratherapeutic dose:* Dose too high in this specific case There is a risk for accumulation of the drug *Duplicate prescription:* a same active substance is prescribed several times (for example: oral acetaminophen and the oral association of dextropropoxyphen/acetaminophen)
1.5	Drug without indication	*No justified indication for the drug* *The drug is prescribed for too long* (for example: antibiotics prescribed for 15 days) *Therapeutic redundancy:* prescription of two different molecules from the same therapeutic class
1.6	Drug interaction	*A drug interferes with another drug* and can lead to a non adapted pharmacological impact (over or under expressed) *Level according to the French ''Red Book'' Vidal©* *Interaction reported but not documented in the Vidal©* (specify bibliographic references)
1.7	Adverse drug reaction	*The patient presents an adverse drug reaction with an adequate dosage* (clinical, biological, or kinetic effect)
1.8	Improper administration	The drug is adequate but the mode of administration is not adapted *Another route may be more effective or less costly for the same effectiveness* *The mode of administration is not adequate* (reconstitution, dilution, length of administration) *Inappropriate drug form* *Incomplete formulation* (dosage missing, etc.) *Inappropriate timing of administration*
1.9	Failure to receive drug	*Physicochemical incompatibility between several injectable drugs:* there is a risk of precipitation between drugs during infusion *Patient's non-compliance*
1.10	Drug monitoring	*The patient is not suitably or sufficiently followed-up:* lab tests, kinetics, symptoms (glycemia, EKG, blood pressure, blood concentration of specific drugs, etc.)

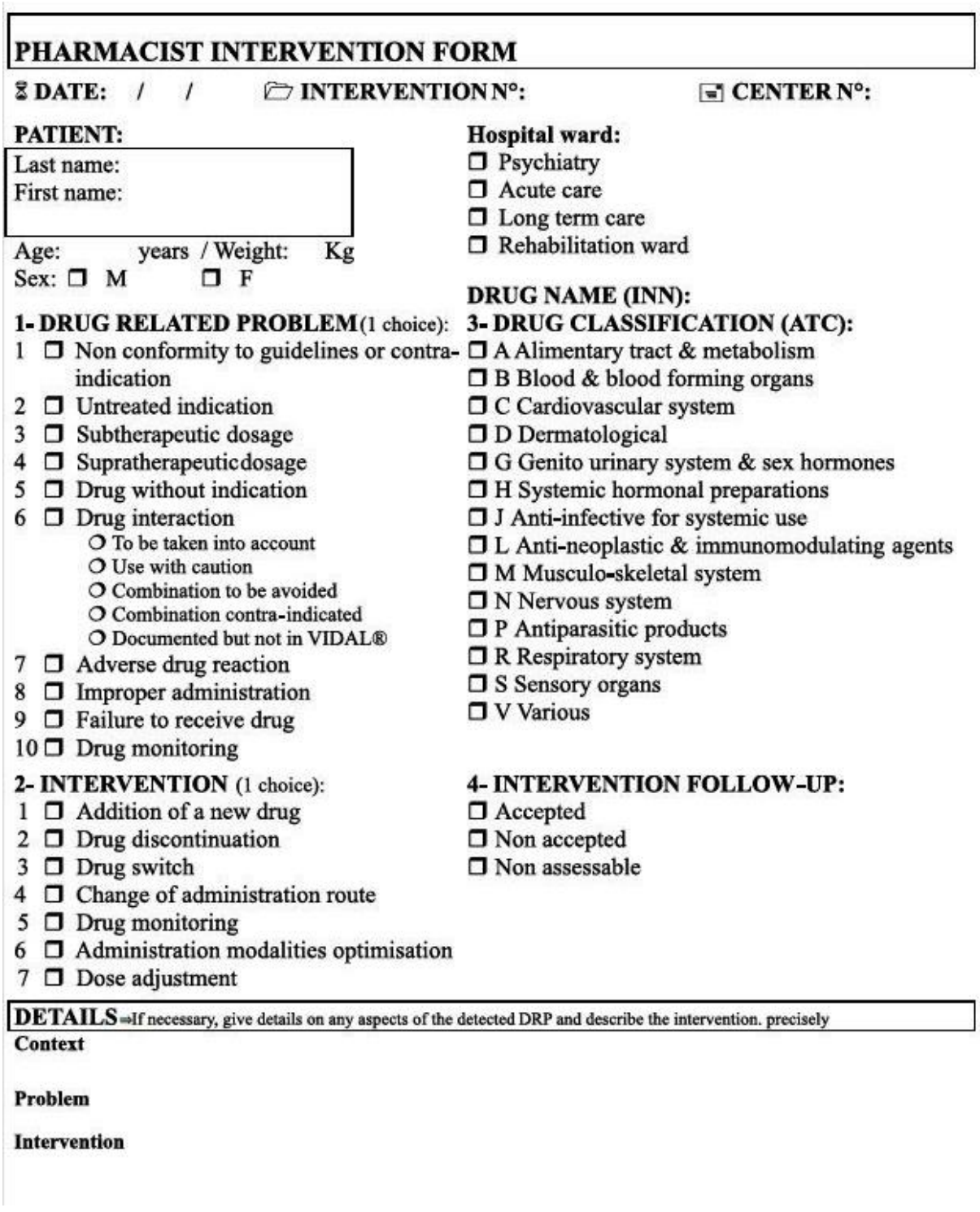
Source: Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006 Aug;28(4):181-8.

Table 26. Description of the pharmacist's interventions

Only one choice per chart

Intervention		Description
2.1	Addition of a new drug	*Addition of a drug to the ongoing treatment*
2.2	Drug discontinuation	*Discontinuation of a drug without any substitution*
2.3	Drug switch	*Switch from the currently administered drug to another drug* Substitution for a generic drug or a therapeutic equivalent (according to the local formulary) Switch following a validated protocol Switch for another drug better adapted to the case
2.4	Change of administration route	*Parenteral/oral switch* Alternative drug with equivalent effectiveness and possible oral administration Alternative oral form of a parenteral drug with the same bioequivalence *Choice of a route of administration better adapted to the case*
2.5	Drug monitoring	*Drug monitoring:* INR, kalemia, kinetics, symptoms, etc *Discontinuation/Request for a new lab test* *Discontinuation/request for a new dosage of a specific drug*
2.6	Administration mode optimization	*Timing of administration* Distribution of doses according to food intake, to drug–food, drug–drug interactions (without modification of the dose) Information on the drug regimen (for example: take on an empty stomach, take during meals, take in the standing position, etc.) *Data on administration procedure* (for example: mode of reconstitution, of dilution, length of infusion, etc.)
2.7	Dose adjustment	*Dose adjustment for a drug with a narrow therapeutic index,* according to its blood level, to renal and hepatic data, or other lab test *Dose adjustment* according to the patient's weight, age, clinical status *Prolongation of treatment*

Source: Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006 Aug;28(4):181-8.



PHARMACIST INTERVENTION FORM

DATE: / / **INTERVENTION N°:** **CENTER N°:**

PATIENT:

Last name:
First name:

Age: years / Weight: Kg
Sex: ❒ M ❒ F

Hospital ward:
❒ Psychiatry
❒ Acute care
❒ Long term care
❒ Rehabilitation ward

DRUG NAME (INN):

1- DRUG RELATED PROBLEM (1 choice):
1 ❒ Non conformity to guidelines or contra-indication
2 ❒ Untreated indication
3 ❒ Subtherapeutic dosage
4 ❒ Supratherapeutic dosage
5 ❒ Drug without indication
6 ❒ Drug interaction
- ❍ To be taken into account
- ❍ Use with caution
- ❍ Combination to be avoided
- ❍ Combination contra-indicated
- ❍ Documented but not in VIDAL®

7 ❒ Adverse drug reaction
8 ❒ Improper administration
9 ❒ Failure to receive drug
10 ❒ Drug monitoring

3- DRUG CLASSIFICATION (ATC):
❒ A Alimentary tract & metabolism
❒ B Blood & blood forming organs
❒ C Cardiovascular system
❒ D Dermatological
❒ G Genito urinary system & sex hormones
❒ H Systemic hormonal preparations
❒ J Anti-infective for systemic use
❒ L Anti-neoplastic & immunomodulating agents
❒ M Musculo-skeletal system
❒ N Nervous system
❒ P Antiparasitic products
❒ R Respiratory system
❒ S Sensory organs
❒ V Various

2- INTERVENTION (1 choice):
1 ❒ Addition of a new drug
2 ❒ Drug discontinuation
3 ❒ Drug switch
4 ❒ Change of administration route
5 ❒ Drug monitoring
6 ❒ Administration modalities optimisation
7 ❒ Dose adjustment

4- INTERVENTION FOLLOW-UP:
❒ Accepted
❒ Non accepted
❒ Non assessable

DETAILS ⇒If necessary, give details on any aspects of the detected DRP and describe the intervention. precisely

Context

Problem

Intervention

Figure 21. The pharmacist intervention form

Source: Duplicated from Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006 Aug;28(4):181-8.

To extend the documentation of these interventions to every French speaking pharmacist, a website, Act-IP®, was put online September 2006 to gather DRPs detected by French hospital pharmacists and their subsequent interventions (241). This computerized documentation system is freely accessible to any pharmacist on the SFPC website. By registering with Act-IP®, pharmacists can develop traceability and analysis of their clinical pharmacy activities using automated queries. The pooling of PIs on the website constitutes an observatory of clinical pharmacy practices (130). Many studies (129, 130, 242) on DRPs and PIs were conducted from this database.

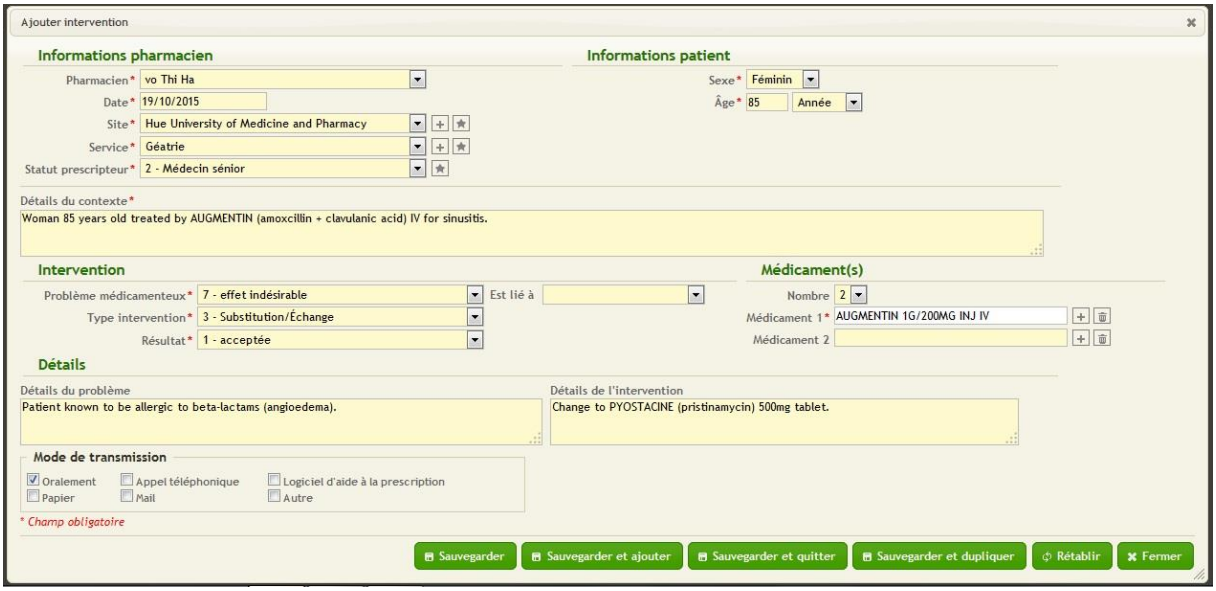


Figure 22. The documentation system of PIs in France - Act-IP®

Source: Available at http://www.actip.sfpc.eu

2. Development of the CLEO tool

Besides description of DRPs and PIs, the evaluation of potential impacts of PIs plays an important role to demonstrate the added value of pharmacists through PIs. In 2004, during the internal validity of the above instrument (240), the ratings of the clinical impact of the PI into three categories (*potential, actual,* or *non-determined*) could not be validated even after repeatedly revised the content of categories. The inter-rater reliability of the clinical impact remained be *moderate*, even in the final validation phase (k = 0.44 for pharmacists from SIG and k = 0.45 for independent pharmacists). Since 2012, we have started to develop and test a new tool for assessment of potential impacts of PIs, based on (1) theoretical models or frameworks of evaluations, (2) a systematic literature review of available tools for assessing impacts of PIs in literature, and (3) input from practice and healthcare professionals' view. The new tool was developed in order to answer to questions as following:

1.1. What indicators does the new tool include?

From the SP(ECH)O-P integrated model for assessment of impacts of PIs (see **3.7. The integrated model for evaluation of impacts of PIs**), the impacts of PIs can be classified into 6 sub-types as structure-related, process-related, clinical, economic and humanistic ones and probability of impacts. However, the systematic review of existing tools for assessment of potential impacts of PIs found that all sub-types existed, except of structure-related impacts. The reason may explain why the PI did not effect on the structure of a setting was: a PI was defined as any action by the pharmacist which changes therapy management at an individual patient. Therefore, the PI focuses on process of care of the particular patient, and never or rarely changes the stable features of structure of the setting. *Therefore, we wanted to develop a new tool which consists of all 5 sub-types of impacts: process-related, clinical, economic and humanistic ones and probability of impacts.*

1.2. How can the new tool be used as first steps to conduct a calculation of value of the PI afterward?

From the economic model of a PI, the value of each PI was estimated from cost savings, cost avoidance and cost of implementation of a PI in most studies. Many existing tools were used as first steps to conduct a calculation of the value of a PI afterward such as Rupp et al.'s (196), Bayliff et al.'s (194), and Westerlund et al.'s tool (195). *We wanted to develop a new tool which is possible to be used as first steps to conduct a calculation of the value of a PI afterward. Furthermore, it is possible to evaluate cost savings, cost avoidance and cost of implementation independently using the new tool.*

"Cost-saving impact" was inspired from Hatoum et al.'s tool which took into consideration two variables: *cost of drug therapy* (positive, negative, zero) and *drug therapy monitoring* (increase, decrease, no change). But we wanted to simplify two variables into *only "cost-saving impact"* (positive, negative, zero) and used a term *"Economic impact"* instead of *"cost-saving impact"* (see ***Figure 23***). Similar to some studies (14, 189), by choosing IPs which have positive or negative on economic impact, we can calculate the cost-savings of a sample of PIs.

"Cost avoidance" can be estimated through health care resources needed to treat harm which were prevented by the PI. Many tools used levels of health care as levels of severity of the DRP or importance of the PI. Therefore, *we wanted to add different types of health care resources avoided by the PI into "Clinical impact" dimension.* The types of health care resources were inspired from the NCC MERP index (243) and the SHPA's tool (233). *Three main levels of care include treatment/monitoring, hospitalization and intensive care/death.*

"Cost of implementation of the PI" will be estimated mostly by the time pharmacists took to propose the PI plus other costs. Like most studies in literature, estimation of cost of implementation of the PI was not tested for validity and reliability. Therefore, we chose to not include it in the new tool.

1.3. How many levels does the "Clinical impact" include?

The 6-level structure of intervention ranking of Hatoum et al.'s tool (244) was used widely in the literature. Furthermore, this ranking included *negative*, *null* and *positive* ranking because although rarely, but it exists cases when a PI can cause harm to the patient (*negative* impact) (136). However, the Hatoum et al.'s intervention ranking did not include different types of health care resources avoided due to the PI. Instead of this, the authors separated intervention ranking with estimation of cost avoidance. *Therefore, we chose a 6-level structure for the "clinical impact" dimension, including: negative (-1), null (0), minor (1), moderate (2), major (3), and vital (4). But we had to find new definitions of levels.*

1.4. How to define six levels of the "Clinical impact" dimension?

In the systematic review of available tools for assessing impacts of PIs, important indicators of humanistic outcomes used were *patient's knowledge, medication compliance, satisfaction, inability to work,* and *quality of life*. Humanistic outcomes was often evaluated combinedly with clinical outcomes into "significance" dimension and classified as "low significance" (96, 220, 245-250). Some tools evaluated independently humanistic impacts of a PI (34, 231, 238, 251, 252) with *poor* inter-rater reliability (236). It is likely that most consequences resulting from PIs will have relatively minor on humanistic outcomes (154). Therefore, we chose to define the *level 1* of the *"clinical impact"* dimension by humanistic indicators (*knowledge, satisfaction, medication compliance and/or quality of life of the patient*) (*Figure **23***).

The *level 2, 3,* and *4* are terminated by main avoidance indicators according to the NCC MERP index (243) and the SHPA's tool (233). The *level 2* is equivalent to *monitoring/treatment avoided* while the *level 3* is equivalent to an *initiated or prolonged hospitalization avoided.* The *level 4* is equivalent to *a potentially intensive care or death of the patient avoided.*

1. Clinical impact

Score	Impact	Definition: The clinical impact is evaluated according to the most likely case expected, not the worst/best case
-1C	**Nuisible**	The PI can lead to adverse outcomes on clinical status, knowledge, satisfaction, patient adherence and/or quality of life of the patient.
0C	**Null**	The PI can have no influence on the patient regarding the clinical status, knowledge, satisfaction, patient adherence and or quality of life of the patient.
1C	**Minor**	The PI can improve knowledge, satisfaction, medication adherence and/or quality of life OR the PI can prevent damage that does not require monitoring/treatment.
2C	**Moderate**	The PI can prevent harm that requires further monitoring/treatment, but does not lead or do not extend a hospital stay of the patient.
3C	**Major**	The PI can prevent harm which causes or lengthens a hospital stay OR causes permanent disability or handicap.
4C	**Lethal**	The PI can prevent an accident that causes a potentially intensive care or death of the patient.
ND	**Non-determined**	The available information does not determine the clinical impact.

- The clinical impact is evaluated for the patient's benefit.
- Harm: alteration of the physical and mental capacities arising from an accident or illness.
- Quality of life: physical function (autonomy, physical abilities, capacity to perform the tasks of daily life ...), psychological (anxiety, depression, emotion ...), social (relative to family environment, friendly or professional, engaging in personal relationships, participation in social and leisure activities ...) and somatic (symptoms related to the disease).
- Monitoring: monitoring clinically relevant (physiological or psychological), biological.
- Treatment: changing therapy or adding an additional medical / surgical treatment.

2. Economic impact

Score	Impact	Definition
-1E	Increase of cost	The PI increases the cost of the drug treatment of the patient.
0E	No change	The PI does not change the cost of drug treatment of the patient.
1E	Decrease of cost	The PI saves the cost of drug treatment of the patient.
ND	Non-determined	The available information does not allow determining the economic impact.

- The cost of drug therapy contains two main elements:
  - o The cost of drugs
  - o The cost of monitoring of drug therapy (e.g., clinical, kinetic, biological monitoring ...).
- The cost of drug therapy is based on the financial cost of the hospital.

3. Organizational impact

Score	Impact	Definition
-1O	**Desfavorable**	The PI reduces the quality of care process.
0O	**Null**	The PI does not change the quality of the care process.
1O	**Favorable**	The PI increases the quality of the care process.
ND	**Non-determined**	The available information does not identify the organizational impact.

- The organizational impact is coded regarding the **overall impact** on the quality of the care process from the **perspective of health care providers** (eg, time savings, improved security, knowledge, job satisfaction of nursing staff; facilitating professional tasks or teamwork, continuity of care, etc.)

Figure 23. The CLEO tool

1. Clinical impact

Score	Impact	Example
-1C	**Nuisible**	Description: Patient treated for ashme by Seretide (salmeterol, fluticasone) 50/25mcg INHAL 3 times/day. DRP: surdose. PI: pharmacist proposed to reduce to the usual dose of 2 times/day. Physician's opinion: no reduction because it was a severe asthma. REFUSED. (Impact of IP was evaluated assuming that it will be accepted by the physician.) **CL = -1, E = 1, O = 0**
0C	**Nul**	Description: patient treated for angina by ROVAMYCINE (spiramycin) 500mg morning and night for 10 days. PM: spiramycin dosage is measured in MUI and is 3 MIU morning and night in case of angina. IP: dosage adjustment of ROVAMYCINE to 3 MIU morning and night. **CL = 0, E = 0, O = 1**
1C	**Minor**	Description: Patient treated for a skin infection (dermatophyte) by KETODERM (ketoconazole) 2% GEL SACHET 6G. PM: daily prescription of KETODERM. IP: conventional dosage is 2 times per week. **CL = 1, E = 1, O = 1**
2C	**Moderate**	Description: respiratory infection in a child of 38 kg with AUGMENTIN (amoxicillin clavulanate) 100 mg/12.5mg oral suspension a weight based dosing 1 time daily for 7 days. PM: risk of underdose. IP: change to 3 times per day. **CL = 2, E = -1, O = 0**
3C	**Major**	Description: Woman 85 years old treated by AUGMENTIN (amoxicillin + clavulanic acid) IV for sinusitis. PM: patient known to be allergic to beta-lactams (angioedema). IP: change to PYOSTACINE (pristinamycin) 500mg tablet. The daily cost of treatment is more expensive. **CL = 3, E = -1, O = 1**
4C	**Vital**	Prescription of COLCHIMAX (colchicine + opium) and PYOSTACINE (Spiramycin) 500MG tablet in a patient. PM: inadvisable association. Increased risk of adverse effects of colchicine with potentially fatal consequences. IP: Stopping COLCHIMAX. **CL = 4, E = 1, O = 0**

2. Economic impact

Score	Impact	Exemple
-1E	**Increase of cost**	Description: DIGOXINE NAT 0.25mg 1 tablet/ day prescribed in a patient for heart failure. PM: K + = 3.1mmol / L (normal range: 3.5 to 5 mmol / l). Hypokalemia increases the toxicity of DIGOXIN (risk of heart rhythm disturbances). IP: Adding Diffu 600MG K, 3 capsules/day and monitoring of serum potassium. **CL = 2, E = -1, O = 0**
0E	**No change**	Description: prescription of ROCEPHINE (ceftriaxone) 1 g/day for a 75 year-old patient for pneumonia. PM: no details on injectable route (IV or IM or SC). IP: suggest IM route. **CL = 1, E = 0, O = 1**
1E	**Reduction of cost**	Description: LOVENOX 30000UI AXa/3ML INJ FL prescribed for a 78 year-old patient with curative dose. PM: scheduled Surgery required discontinuation of LOVENOX but the final date of treatment was unspecified. IP: Suggest a final date of LOVENOX. **CL = 2, E = 1, O = 1**

3. Organizational impact

Score	Impact	Exemple
-1O	**Disfavorable**	Description: prescription of HALDOL (haloperidol) 5MG/1ML SOL INJ AMP and TERCIAN (cyamemazine) 50MG/5ML injectable for an agitated patient. PM: Using the same syringe for mixing. IP: separation because of physicochemical incompatibility. **CL = 2, E = 0, O = -1**
0O	**Null**	Description: 60 year-old patient with prescription of Stilnox (zolpidem) 10MG 2 tablets/day for insomnia. PM: maximum dosage 1tablet/day. IP: reduced to 1 tablet/day. **CL = 2, E = 1, O = 0**
1O	**Favorable**	Description: Patient treated with FOSAVANCE (alendronic acid, cholecalciferol) 70mg/2800UI tablet in a patient at risk of osteoporotic hip fracture. PM: FOSAVANCE was not present in the drug formulary. IP: Suggest to replace by ADROVANCE (alendronic acid, cholecalciferol) 70 mg/2800UI tablet. Price is equivalent. **CL = 0, E = 0, O = 1**

Figure 24. Examples for assessment of impacts of PIs by using the CLEO tool

1.5. How was the probability of consequences of the PI?

To simplify the new tool, we asked evaluators to rate according to *the most likely* consequence expected for the "clinical impact" dimension, not the worst/best one, and did not require determining the numerical probability.

However, if researchers want to calculate the *cost avoidance* or *risk assessment* related to "clinical impacts", they can require raters to estimate the level of probability of impacts after rating "clinical impacts", similar to the tool of Rupp et al. (196) or the tool of the SHPA (10), respectively.

1.6. How was the "process-related impact" of the PI evaluated?

Most tools focus on patient outcomes. PIs, however, also are useful for the health practitioners during care process. Tools therefore should reflect the possible impacts on both. For example, the majority of MEs were formalities regarding information about patient, prescriber and reimbursement. These formal errors and omissions have no direct consequences for the drug therapy and patient safety or cost savings, but they facilitate drug dispensing as the nurses doesn't have to contact the prescriber, patient or relatives to obtain the required information before the drug can be handed out (145). Therefore, we added *the "**O**rganizational impact" dimension* which aims to detect any organizational effects of a PI from HCPs' perspective, such as *time savings, improvement of knowledge or safety for HCPs* (*Figure **23***).

We name this multidimensional tool as **CLEO (CL**inical, **E**conomic, and **O**rganizational) (*Figure **23***). Characteristics of CLEO tool are: terms/indicators are well defined; each dimension consists of 3-6 ordered, numeric levels; each dimension has both *negative, zero,* and *positive* levels, and an open level *"non-determined"* (*Figure **23***).

1.7. How do people use the new tool and interpret the results of ratings?

For each PI, the three dimensions were combined into a three-component code describing the entire impact of a PI (see examples in *Figure **24***). For example, a PI with (2C, -1E, 1O) means that the PI have moderate clinical impact (...) from the patient's perspective, negative economic impact (increase the cost of drug therapy and/or drug monitoring) from the hospital's perspective, and positive organizational impact on process of care from health care providers' perspective.

For a sample of PIs, the results can be expressed as:

- % PIs with -1C, 0C, 1C, 2C, 3C, 4C, ND-C; % PIs with -1E, 0E, 1E, ND-E, and %PIs with -1O, 0O, 1O, ND-O.
- Average/Mean of numerical levels per PI. For example, 2.3 for clinical, 0.8 for economic, and 0.6 for organizational impact per intervention.
- % PIs with different combinations described in Table 27.

Table 27. Matrix for combination of 3 dimensions of the CLEO tool

CL	E	O		CL	E	O		CL	E	O
-1	-1	-1		0	-1	-1		1	-1	-1
-1	-1	0		0	-1	0		1	-1	0
-1	-1	1		0	-1	1		1	-1	1
-1	0	-1		0	0	-1		1	0	-1
-1	0	0		0	0	0		1	0	0
-1	0	1		0	0	1		1	0	1
-1	1	-1		0	1	-1		1	1	-1
-1	1	0		0	1	0		1	1	0
-1	1	1		0	1	1		1	1	1
2	-1	-1		3	-1	-1		4	-1	-1
2	-1	0		3	-1	0		4	-1	0
2	-1	1		3	-1	1		4	-1	1
2	0	-1		3	0	-1		4	0	-1
2	0	0		3	0	0		4	0	0
2	0	1		3	0	1		4	0	1
2	1	-1		3	1	-1		4	1	-1
2	1	0		3	1	0		4	1	0
2	1	1		3	1	1		4	1	1

1.7. Which materials help to use the CLEO?

A CLEO algorithm (*Figure 25*), similar to the NCC MERD algorithm (208), was created for guiding ratings. Some examples of results of rating by using the CLEO tool (*Figure 24*) were selected from validation process by an expert panel.

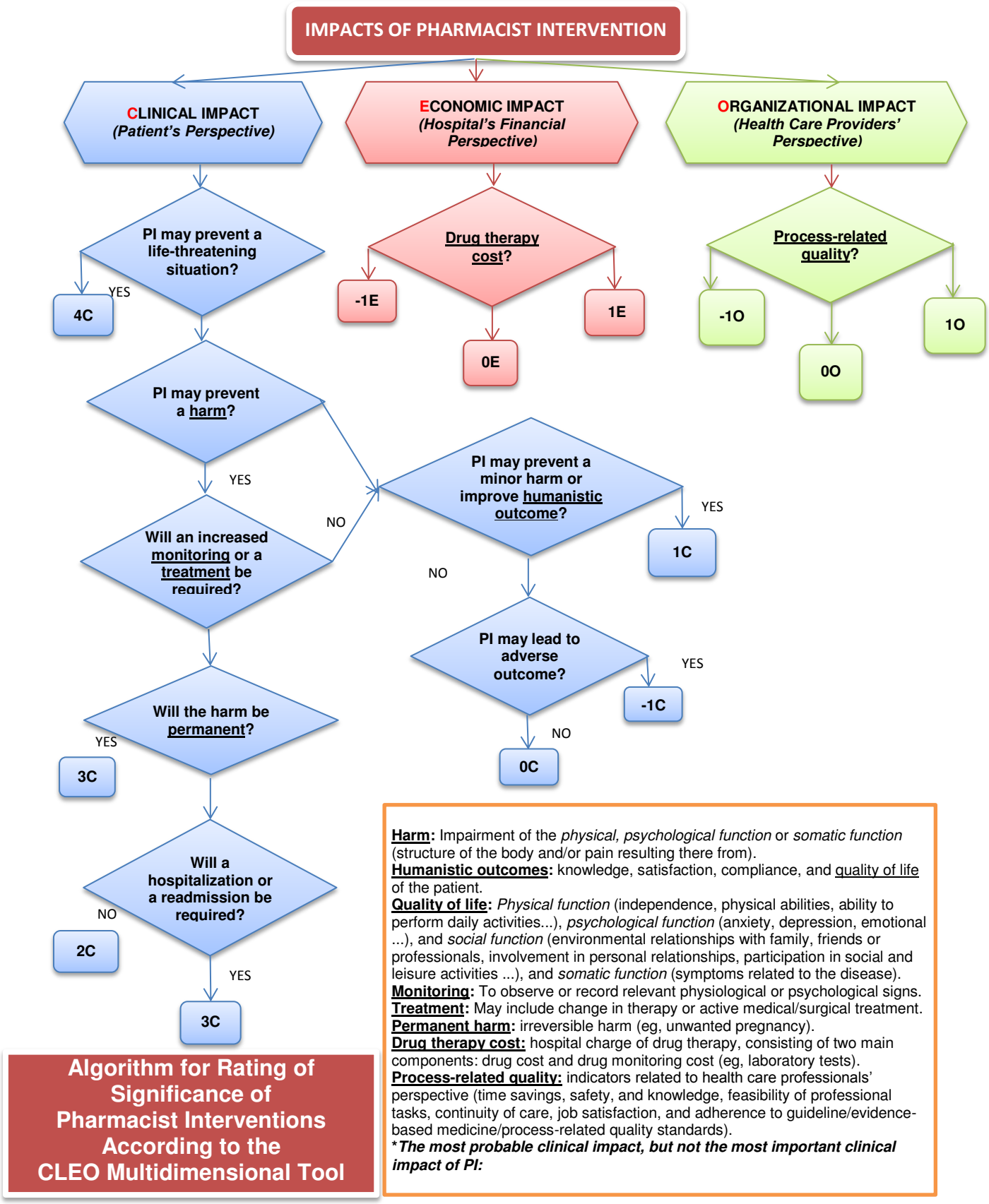


Figure 25. Algorithm for rating of significance of PIs according to the CLEO tool

3. Validation of the CLEO tool

An ideal tool for assessing the potential impacts of PIs should be comprehensive, relatively easy and not too time consuming to use, reliable and validated in different contexts. Therefore, we conducted two studies to test these properties of the CLEO tool. The first one aimed to test and refine the CLEO tool according to results of ratings of samples of PIs extracted from a variety of health care settings by seven expert pharmacists of the SIG. The final CLEO version obtained from the first study then was tested for daily use in a specific setting at the Grenoble University Hospital Center.

3.1. Validation of the CLEO tool in a general practice by a SFPC expert group

Ten years ago, the SIG failed to develop and validate a tool for assessing impacts of PIs. This project started again at the beginning of 2012 as a thesis work of a PhD student collaborated closely with seven pharmacists of the SIG who have worked in six French hospitals. In this first study, we decided to collect non-randomly a sample of PIs to balance types of PIs, scores and clinical specialty areas of practice because we want to assure the CLEO tool will be test in a general practice. PIs were selected from the Act-IP® database or practice of the six hospitals. During a period of 3 year, we asked seven pharmacists to discuss and validate the content of many versions of the CLEO (5 discussion meetings with 6 different versions of tools). Finally, the two versions of the CLEO were tested for inter-rater reliability between pharmacists, named the CLEO v.1 and the CLEO v.2. And the results of inter-rater reliability between pharmacists of the second version CLEO were improved in comparison with the first one. The percentage of agreement increased from 36% to 39% for "Clinical impact", from 65% to 90% for "Economic impact", and from 57% to 62% for "Organizational impact". Similarly, weighted kappa score increased from 0.34 (*fair*) to 0.41 (*moderate*) for "Clinical impact", from 0.65 (*moderate*) to 0.95 (*almost perfect*) for "Economic impact", and 0.26 (*fair*) to 0.39 (*fair*) for "Organizational impact". Intra-rater reliability was *slight* (agreement = 33%, kw = 0.38) for "clinical impact" and *moderate* for "economic impact" (agreement = 80%, kw = 0.70). Most pharmacists satisfied the whole tool, the structure of tool, definitions of keywords, the CLEO algorithm. However, pharmacists judged that CLEO algorithm isn't so useful for facilitating ratings, then we only used the CLEO v.2 with examples for ratings in and without providing the CLEO algorithm.

Article 2.

Validation of CLEO scale for assessment of significance of pharmacist interventions in general context

Thi-Ha VO, Bruno CHARPIAT, Sébastien CHANOINE , Céline GENTY, Michel JUSTE, Renaud ROUBILLE, François-Xavier ROSE, Ornella CONORT, Jean-Luc BOSSON, Benoît ALLENET, Pierrick BEDOUCH

Article 2. Validation of CLEO scale for assessment of significance of pharmacist interventions in general context

Authors: Thi-Ha VO[1,2], Bruno CHARPIAT[3], Sébastien CHANOINE[1,4] , Céline GENTY[1], Michel JUSTE[5], Renaud ROUBILLE[6], François-Xavier ROSE[7], Ornella CONORT[8], Jean-Luc BOSSON[2], Benoît ALLENET[1,2,4], Pierrick BEDOUCH[1,2,4]

1. Univ. Grenoble Alpes, TIMC-IMAG, F-38000 Grenoble, France.
2. CNRS, TIMC-IMAG, F-38000 Grenoble, France.
3. Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Pharmacie, F-69000 Lyon, France.
4. CHU Grenoble, Pôle Pharmacie, F-38000 Grenoble, France.
5. Centre Hospitalier Auban-Moët, Pharmacie, F-51200 Epernay, France.
6. Centre Hospitalier Lucien Hussel, Pharmacie, F-26000 Vienne, France.
7. EPSM-Morbihan, Pharmacie, F-56890 Saint-Avé, France.
8. Assistance Publique des Hôpitaux de Paris, Hôpital Cochin, Pharmacie, F-75000 Paris, France.

on behalf of the Working group "Standardizing and demonstrating the value of clinical pharmacy activities" of the French Society for Clinical Pharmacy.

PURPOSE: This study aims to develop and validate a multidimensional tool for evaluating potential significance of pharmacist interventions (PIs) in general context.

METHODS: Development of a new tool was based from a review of existing tools and evaluation models of health care interventions and inputs of PI practice. A group of 7 experts - 7 hospital clinical pharmacists of the French Society of Clinical Pharmacy coded 50 scenarios extracted from the French national database of PIs by using the CLEO version 1 in order to calculate inter-rater reliability. Satisfaction on the content and structure of the CLEO version 1 by 4-level Likert (not satisfied = 0, somewhat satisfied = 2, satisfied = 4, very satisfied = 6) and suggestion for modification were questioned. Then, the pharmacists coded other 30PIs selected from six hospitals by using the CLEO v2 and recoded 10 cases (randomly select 30 IPs) the second time to calculate the intra-rater reliability.

RESULTS: A first version of a multidimensional scale, named “CLEO”, includes 3 dimensions: clinical (7 categories), economic (4 categories), and process-related dimension (4 categories) with assessment supports (definitions of keywords, an assessment algorithm). The inter-rater reliability of the first ratings showed *fair* agreement for "clinical dimension" (agreement = 82%; kw = 0.34); *moderate* agreement for economic dimension (agreement = 80%; kw = 0.53); and *fair* agreement for organizational dimension (agreement 76%; kw = 0.27). The average scores of satisfaction on the whole tool, the structure of tool, definitions of keywords, the CLEO algorithm were 3.7; 4.9; 3.1; and 3.4, respectively. The CLEO version 1 was modified into a version 2 according to many suggestions collected. The inter-rater reliability of the second rating was *moderate* for "clinical impact" (agreement = 39%; kw = 0.41); *almost perfect* for "economic impact" (agreement = 90%; kw = 0.93); and *fair* for "organizational impact" (agreement = 62%; kw = 0.39). Intra-rater reliability was *slight* (agreement = 33%, kw= 0.38) for "clinical impact" and *moderate* for "economic impact" (agreement = 80%, kw = 0.70).

CONCLUSIONS: A multidimensional scale CLEO for assessing the potential significance of PIs was developed and tested. The highest strength of reliability was found for "economic impact" of the CLEO classification, then "clinical impact". The lowest values were obtained for "organizational impact" dimension. Further study should be conducted to overcome some limitations of this study design, particularly the test for use in a local service is needed.

Introduction

While the pharmaceutical care has undergone dramatic changes since 30 years, pharmacists still need to demonstrate the benefits or added value of services [1]. Pharmaceutical care has been described as a multi-facetted process that aims to result in positive outcomes for the patients. Associated with this process is the delivery of appropriate pharmaceutical services, which include obtaining patient medical history, evaluating laboratory data, reviewing patient records, and performing patient counseling, etc. These activities contribute to medication review of the patient with major outputs in form of PIs. PIs are defined as "any action by a pharmacist that directly resulted in a change in patient management or therapy" [2]. In times of limited resources allocation, it is important to evaluate the impacts and value of PIs proposed during medication review.

A variety of methods [3-7] has been reported for recording of PIs. Most of methods are based on *process-related indicators* (e.g., patient-related information, drug-related information, causes, types of DRPs, action of pharmacists, acceptance by physicians).Some others tried to evaluate *outcome-related indicators* such as *actual patient outcomes of DRPs* [8], *actual patient outcomes of PIs* [9-12]; *potential patient outcomes of PIs* [13-18] or combinations of these [19-23]. Advantages and limitations of each method were described in another article [18, 24]. Of them, the assessment of *potential* impacts of a PI is frequently used because of its practicability when data of actual consequences are lacking, its usefulness in guidance for improving quality of PIs (e.g., hierarchy of potential significance of a PI and target the most potential significant PIs) [24].

We conducted a systematic review [24] of existing tools for rating the potential impact of PIs. Detailed results of this review was reported in another article. In brief, of 873 citations screened, 81 distinct tools were identified from 133 studies. However, the most comprehensive, valid, reliable and practical tool for rating the potential impacts of PIs is not available.

In 2003, the French Society of Clinical Pharmacy (SFPC) drew attention to the lack of a validated tool for documentation of PIs performed in hospitals [25]. Consequently, a special interest group (SIG) ‘‘Standardizing and demonstrating the value of clinical pharmacy activities’’ was charged with developing and validating an instrument for the documentation of clinical PIs [26]. This instrument can be used in daily routine, including (1) the identification of DRPs (Ten main categories), (2) the PI (Ten main categories), (3) the type of drug involved (using ATC classification (Anatomical Therapeutic Chemical)), (4) the acceptance of the intervention by the prescriber. To extend the documentation of these interventions to every French speaking pharmacist, a website, Act-IP©, was put online September 2006 to gather DRPs detected by French hospital pharmacists and their subsequent interventions [27]. The objective of this study is to develop and validate a new tool for assessing potential impacts of PIs which then will be added into the next Act-IP system.

Method

a. Development of a new tool

Construction of a new tool is based from a review of models/frameworks of evaluation of health care interventions, a systematic review of existing tools, and inputs from experience of pharmacists' practice.

Review of Models of Evaluation

We synthetized five models: *the SPO model*, *the ECHO model*, *the SEIPS model*, *the model of Martini*, *the economic model*, and *the risk assessment matrix* into an integrated model for evaluation of impacts of PIs, named *the SP(ECH)O-P*.

According to *the SP(ECH)O-P model (*

Figure 12), the PI can have impacts on structure, process of care and outcomes on the patient (similar to *the SPO model*). The outcomes can include economic, clinical, and humanistic outcomes (similar to *the ECHO model*). Not all impacts of the PI is obvious and certain but a potential to occur (probability). Therefore, it should combine probability of each impacts and severity/importance of each impacts into risk matrix (similar to *the risk matrix*). The value of each PI is the sum of differences of value of the scenario with and without the PI (similar to *the economic model*).

According to the SP(ECH)O-P, there are six types of indicators which provide the comprehensive picture of impacts of PIs: structure-related, process-related impacts, clinical, humanistic, economic outcomes, and probability of each impact.

Literature review of existing tools

After analyzing and synthetizing results of the systematic search of tools for assessing potential impacts of PIs [24], some recommendations for development of new tools were suggested. We decided to develop a new tool to satisfy these recommendations. The tool consists of three dimensions. The **C**linical dimension from patient's perspective is scored from the 6-level structure of Hatoum's tool [28]. Of which, the level 1 is defined by humanistic indicators and the level 2, 3, 4 are terminated according to the NCC MERP index [29] and the tool of the Society of Hospital Pharmacists of Australia [30]. The **E**conomic dimension aims to detect whether a PI induces a cost savings or not from hospital's perspective - a direct cost related to drug and monitoring. The **O**rganizational dimension aims to detect any organizational effects of a PI from health care providers' perspective, such as time savings, improvement of knowledge of health practitioners. We name this multidimensional tool **CLEO** (**CL**inical, **E**conomic, and **O**rganizational) (*Figure **23***). Characteristics of CLEO tool are: terms/indicators are well defined; each dimension consists of 3-6 ordered, numeric levels; each dimension has both negative, zero, positive levels and an open level *"non-determined"***.** The three dimensions were combined into a three-component code describing the entire impact of a PI (see example in *Figure **24***). A CLEO algorithm (***Figure 25***), similar to the NCC MERD algorithm, was created for guiding ratings.

b. Instrument testing

The tool will be validated through three steps. In the first step, after content validation of the tool by a group of 7 clinical pharmacists from SIG in a direct meeting in June 2013, the pharmacists coded 50 scenarios extracted from the French national database of PIs "Act-IP©" in order to test the inter-rater reliability. Each scenarios consisted of a brief description of the medical context (patient information: age, sex, diagnostic) and data that were relevant to the potential or identified DRP (type of ADR, involved drugs), as well as the intervention made by the pharmacist, and acceptance by physicians. Seven clinical pharmacists have worked at 6 different hospitals in France. The overall satisfaction and satisfaction on content and structure of CLEO, and usefulness of the CLEO algorithm by 4-level Likert (not satisfied = 0, somewhat satisfied = 2, satisfied = 4, very satisfied = 6) and suggestion for modification of the tool were questioned.

In the second step, from the experience of the first rating, clinical pharmacists discussed to modify the tool in a direct meeting in October 2013 and through a telephone conference in August 2014. Clinical pharmacists found that lack of access to full clinical data of patients in scenarios extracted retrospectively from the database ACT-IP© may be a major barrier to effectiveness of PI assessment. Therefore, pharmacists were required to collect prospectively new scenarios from their practice and we chose PIs to ensure a balance of types DRPs and PIs and more complete patient's information. Each scenario was more precise regarding medical context: patient information, medical antecedents, medication history, diagnostic, results of examinations, treatment. Seven pharmacists were required to rate 30 PIs to calculate a new inter-rater reliability. The mean time for scoring a PI also was recorded.

In the third step, ten PIs were selected randomly from the same 30 PIs for second recoding by seven pharmacists two month later in order to calculate intra-rater reliability.

The inter-rater reliability is calculated through percent of agreement and weighted kappa. The interpretation of results of weighted kappa is based on the Landis and Koch scale: k values of < 0 indicate *poor* agreement; 0.00-0.20, *slight* agreement, 0.21-0.40, *fair*; 0.41-0.60 *moderate*; 0.61-0.80, *substantial*; 0.81-1.00, *almost perfect* [31]. We also determined which categories of the tool are main sources of disagreement between raters [32]. The statistical analysis was performed using the Stata statistical package, release 9.1 (StataCorp LP, College Station, TX, USA).

Results

Validation of the tool CLEO

The first step

The inter-rater reliability for classification was as follows: *fair* agreement for "clinical impact" (agreement = 36%; kw = 0.34); *moderate* for "economic impact" (agreement = 65%; kw = 0.53); and *fair* agreement for "organizational impact" (agreement = 57%; k = 0.26).

Because *"clinical impact"* dimension has 6 levels, consistency for rating this dimension may be more difficult than others. Therefore, we used weighted kappa to determine which categories of tool are the main sources of disagreement between raters. We found that great sources of disagreement were from ratings between 2C and 3C, then between 1C and 2C.

The average score of satisfaction on the whole tool, structure of tool, definitions of keywords, algorithms was 3.7/6.0; 4.9/6.0; 3.1/6.0; and 3.4/6.0, respectively. Some suggestions for improvement of the first version of the tool were provided such as simplification of expression of 1C, 2C, 3C, 4C and clarification of terms in level 3C, and modification of definition of economic impact.

The second rating

The inter-rater reliability for classification was as follows: *moderate* agreement for clinical impact (agreement = 39%; kw = 0,41); *almost perfect* for economic impact (agreement = 90%; kw = 0,93); and *fair* agreement for organizational impact (agreement = 62%; kw = 0,39). The average time for rating per intervention using the CLEO was of 2.5 minutes.

The third rating

The intra-rater reliability was *fair* (agreement = 33%, kw = 0.38) for "clinical impact" and was *substantial* (agreement = 80% and kw=0.70) for "economic impact".

Table 1: Inter-rater reliability of the CLEO instrument

	Clinical Impact				**Economic Impact**				**Organisational Impact**			
	1 st rating		2nd rating		1 st rating		2nd rating		1 st rating		2nd rating	
	%	kw	%	kw	%	kw	%	kw	%	kw	%	kw
Mean	**36**	**0,34**	**39**	**0,41**	**65**	**0,53**	**90**	**0,93**	**57**	**0,26**	**62**	**0,39**
Upper 95% limit	32	0,29	34	0,37	57	0,42	86	0,91	53	0,20	56	0,30
Lower 95% limit	39	0,39	44	0,45	72	0,65	95	0,95	61	0,31	68	0,49
Agreement	**fair**		**moderate**		**moderate**		**almost perfect**		**fair**		**fair**	

Discussion

Construction of the CLEO tool

Advantages of the CLEO tool are many. Firstly, it added humanistic indicators to level 1 of clinical dimension. Secondly, clinical dimension can detect also levels of cost avoidance (e.g., monitoring/treatment; prolongation of hospital stay; intensive care) while economic

dimension can detect if PI induces cost savings. Therefore, the CLEO can help to extract IPs to conduct economic study. Like some studies, independent rating the economic impact of a PI was used as the first step to determine the monetary value of a PI program [13, 16, 33-40]. A another study in a centralized preparation of cytotoxic drugs unit used the CLEO to extract IPs with -1E or 1E to calculate cost savings and cost increase due to PIs. Thirdly, most tools focus on patient outcomes and/or cost savings. PIs, however, also are useful for health practitioners. For example, there are some PIs which had neither clinical nor economic impact, but they are significant because they improve safety for nurses. Therefore, the organizational dimension of the CLEO aims to detect more sensitively effects of a PI. Fourthly, the CLEO also proposes a multidimensional, comprehensive framework which not only is useful for posterior assessment after implementation of a PI but also for pharmacists to take into consideration before they decide which PIs should be communicated to health care providers or patients. Fifthly, the numeric and independent dimensions help to facilitate the interpretation of results of ratings.

In fact, each PI has many different consequences and each consequence has a probability of occurrence. Some tools allow estimating probability of consequences during rating process [15-17]. However, in most cases, the determination of this probability was difficult to estimate. Therefore, in order to improve consistency of judgment of probability between raters, the clinical impact of the CLEO is evaluated according to the most likely case expected and does not require to estimate probability of consequence. This strategy was applied similarly in other tools [16, 17, 30, 41]. However, estimation of probability of consequences can be added as a supplementary step to the first step - rating by the CLEO if required.

Inter-rater and intra-rater reliability of the CLEO tool

In the CLEO tool, the *"clinical impact"* dimension is scored from the 6-level structure of Hatoum's [28]. Therefore, we extracted from the systematic review [24] only results of reliability of tools which derived from Hatoum's tool and have 5-7 levels to compare with our study's results (Table 2). The highest strength of inter-rater reliability was found in the study of Overhage and Lake (kw=0.76) [19]. However, this good result did not repeat when other studies adopted this tool for use [21, 42, 43]. Our results showed *moderate* agreement for clinical impact (kw = 0.41) in the second rating, which is higher than results obtained by Cousin et al. (k=0.26)[44]; by Bosma et al. (kw=0.20)[42]; by Lee et al. (k=0.14-0.31)[21]; by Fernandez-Llamazarez et al. (k=0.24)[43]; and by Somers et al. (k=0.15-0.25)[45].

Table 2: Reliability and validity of tools which derived from Hatoum's

No	Author(s), Year, Country	Tool	N° of PIs	Rater(s)	Validity and/or Reliability
1	Lucas et al.* [46] 1997, Australia	**S6**[1]	56	1 intervening pharmacist + 1 internal physician + 2 external physicians	**Internal inter-rater reliability** (1 intervening pharmacist *vs* 1 internal physician): agreement = **83%**, t-test **p>0.05**: no different **External inter-rater reliability** (1 internal physician *vs* the first external physician) agreement = **48%**, **63%**; t-test **p>0.05** no different (1 internal physician vs the second external physician)

					agreement = 63%; t-test **p<0.05** different
2	Cousins et al.* [44] 1997, UK	**S6**[1]	584[a] 62[b]	pharmacists	**Intra-rater reliability** (12 intervening pharmacists): Wilcoxon matched-pairs signed-rank test **p=0.01-0.69** **Inter-rater reliability** (12 pharmacists): **k=0.26**
3	Overhage et al.* [19] 1999, USA	**S6**[1]	300	3 pharmacists, 2 physicians	**Inter-rater reliability** **kw=0.76**
4	Hick et al. [47] 2001, UK	**S6**[1]	155	3 senior pharmacists	**Inter-rater reliability** agreement = **85%** of case: at least 2 out of 3 raters agreed on the rated grades.
5	Bosma et al. [42] 2006, Netherland	**S7**[2]	255	1 hospital pharmacist + 1 internal medicine specialist	**Inter-rater reliability** **kw=0.20**
6	Lee et al.* [21] 2006, USA	**S6**[1]	98	2 pharmacists + 1 physician + 2 principal investigators	**Inter-rater reliability of each pairs** agreement = **63-80%, k=0.14-0.31**
7	Spinewine et al.* [48] 2006, Belgium	**S5**[3]	700	2 Belgian geriatricians + 1 Canadian clinical pharmacist	**Inter-rater reliability** agreement = **33%**
8	Fernandez-Llamazares et al. [43] 2012, Spain	**S6**[1]	20	4 senior pharmacists + 5 junior pharmacists	**Inter-rater reliability** agreement=**66%**, **k=0.24** (0.15-0.32) for all raters; agreement = **72%**, **k=0.27**(0.16-0.38) for senior pharmacists; agreement = **64%**, **k=0.10** (0.00-0.20) for junior pharmacists
9	Somers et al. [45] 2013, Belgium	**S6**[1]	304	2 clinical pharmacologists + 2 clinical pharmacists	**Inter-rater reliability** **k = 0.15-0.25**
10	Vo et al., 2015, France	**C7**[4]	30-50	7 clinical pharmacists	**2nd rating** **Inter-rater reliability** **39%** (95%CI 34-44); **kw= 0,41** (95%CI 0,37-0,45)
S6: Clinical impact consists of 6 levels: adverse significance, no significance, somewhat significant, significant, very significant, extremely significant **S7:** Clinical impact consists of 7 levels: no intervention, adverse significance, not significant, somewhat significant, significant, very significant, extremely significant **S5:** Clinical significance consists of 5 levels: deleterious, minor, moderate, major, extreme **C7:** Clinical impact consists of 7 levels: nuisible, null, minor, moderate, major, lethal, non-determined					

The highest strength of agreement was found for *"economic impact"* dimension (agreement = 90% and kw = 0.93) in the second rating. In many cases, it is quite easy to determine "economic impact". For example, types of PIs such as adding a new drug, switching to more expensive drug have a 1E code while discontinuation of a drug or a monitoring test have a -1E code. In the literature, only the study of Cousin et al. [44] determined the inter-rater reliability of economic impact. However, its coding was different. In the study of Cousin et al., up to four of five economic codes could be assigned to each intervention: (i) savings in cost of drug therapy, (ii) increase in cost of drug therapy, (iii) savings in cost of laboratory tests, (iv) savings in cost of complications, and (v) savings in costs of hospitalization time. The study of Cousin et al. reported worse results for this variable with an overall kappa of 0.27 indicating *fair* agreement among panel members.

The *"organizational impact"* dimension aims to detect any beneficial effects of a PI on quality of process of care from point of view of health care providers. The lowest score of kappa were obtained for *"organizational impact"* (agreement = 62% and kw = 0.39). There are some reasons for explanation of this result. Firstly, the evaluators found that it was difficult to consider many different indicators of process of care (e.g., time savings, improved security, knowledge, job satisfaction of nursing staff; facilitating professional tasks or teamwork, continuity of care...) and points of view of different health care providers (physicians, pharmacists, nurses) to make a global opinion of organizational impact. For example, some IPs such as adding a new medication may require nurses more time to administer drugs to patients but such IPs can improve job satisfaction from pharmacists and physicians' view. Another reason is that there was no precious definition and/or examples of the indicators of organizational impact (e.g., improve security of nursing staff; facilitating professional tasks or teamwork, continuity of care).

Consistency between raters improves for all three dimensions in the second rating, particularly economic dimension. Modification of the CLEO tool, providing examples and more information of clinical cases for rating may be reasons for this improvement.

Limitations

The main threats to internal validity are confounding, maturation, testing, selection bias, and analytic methods.

Concerning threat of confounding, results of agreement between raters in the two studies may be effected by perceptions of raters themselves rather than functionality of the tool itself. Threat of maturation is present when evaluators rate more consistently over time due to their experience/familiarity with the tool. The seven pharmacists have involved in process of development and the refinement of the tool over a two-year period, therefore they understood well the tool. This was a bias.

Testing bias occurs when evaluators are aware of that their ratings will be compared to ones of their colleagues; then they are likely to rate based on what researchers expect rather than based on their true perceptions. To minimize this threat, we informed clearly all evaluators that the objective of studies aims to test the functionality of the tool and not achieve perfect concordance between raters. Such that, all evaluators were required to rate based on their true opinions.

Selection bias of PIs could threaten the internal validity of a study when PIs are selected in a nonrandom fashion. In this study, we selected non-randomly PIs to balance sample size, variety of interventions, scores.

Evaluating agreement or reliability is fundamental to the evaluation of research tools. Agreement is defined as the degree to which scores/ratings are identical, whereas reliability relates to the extent of variability and error inherent in a measurement [49]. Hence, we used both agreement and reliability but focused more in reliability. Although the kappa score was

commonly used to assess the reliability between raters in literature, the k statistic may be difficult to interpret. First, mathematically, a value of +1 is difficult to achieve and is only observed in extreme circumstances. Second, the k score depends on the number of categories [49]. The more categories there are, the more difficult it is to classify correctly and the lower the resulting k value. In our results, the strength of agreement and reliability of *"clinical impact"* (kw = 0.41) can be considered quite high given the large number of categories (seven categories) involved. However, the *"organizational impact"* dimension had similar kw score (kw = 0.39) but has fewer categories (four categories). Therefore, we thought that the inter-rater reliability of *"clinical impact"* dimension of the CLEO tool is acceptable and reliable enough to use in practice but not *"organizational impact"*. Third, kappa is sensitive to bias between raters and the overall prevalence of responses. In some instances, a relatively high proportion of observed agreement can result in a low kappa value and an unbalanced or biased distribution of responses can result in a higher kappa value than a more balanced distribution of responses. Hence, a low kappa value may not always be indicative of low agreement [49]. This event occurred in our studies for *"organizational impact"* dimension in which a high agreement (62%) existed with a low kappa (kw = 0.39).

Conclusions

A multidimensional scale CLEO for assessing the potential significance of PIs was developed and tested. The highest strength of reliability was found for "economic impact" of the CLEO classification, then "clinical impact". The lowest values were obtained for "organizational impact" dimension. Further study should be conducted to overcome some limitations of this study design; particularly the test for use in a local service is needed.

Reference

1. Indritz ME, Artz MB. Value added to health by pharmacists. Soc Sci Med. 1999 Mar;48(5):647-60.
2. The Society of Hospital Pharmacists of Australia Committee of Specialty Practice in Clinical Pharmacy. SHPA standards of practice for clinical pharmacy. In: Johnstone J, Vienet MD, editors. Practice Standards and Definitions. Melbourne: The Society of Hospital Pharmacists of Australia; 1996.
3. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.
4. Schaefer M. Discussing basic principles for a coding system of drug-related problems: the case of PI-Doc. Pharm World Sci. 2002 Aug;24(4):120-7.
5. Hohmann C, Eickhoff C, Klotz JM, Schulz M, Radziwill R. Development of a classification system for drug-related problems in the hospital setting (APS-Doc) and assessment of the inter-rater reliability. J Clin Pharm Ther. 2012 Jun;37(3):276-81.
6. Pharmaceutical Care Network Europe Foundation. Classification of Drug Related Problems (revised 14-01-2010vm) V6.2. 2010 [cited 2013 January 20]; Available from: http://www.pcne.org/sig/drp/documents/PCNE%20classification%20V6-2.pdf
7. AbuRuz SM, Bulatova NR, Yousef AM. Validation of a comprehensive classification tool for treatment-related problems. Pharm World Sci. 2006 Aug;28(4):222-32.
8. Vessal G. Detection of prescription errors by a unit-based clinical pharmacist in a nephrology ward. Pharm World Sci. 2010;32:59-65.
9. Lee AJ, Boro MS, Knapp KK, Meier JL, Korman NE. Clinical and economic outcomes of pharmacist recommendations in a Veterans Affairs medical center. Am J Health Syst Pharm. 2002 Nov 1;59(21):2070-7.
10. Schmidt IK, Claesson CB, Westerholm B, Nilsson LG. Physician and staff assessments of drug interventions and outcomes in Swedish nursing homes. Ann Pharmacother. 1998;32(1):27-32.
11. McLennan DN, Dooley MJ, Brien JE. Beneficial clinical outcomes resulting from pharmacist interventions. J Oncol Pharm Pract. 1999;5(4):184-9.
12. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
13. Hatoum HT, Hutchinson RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. Drug Intell Clin Pharm. 1988;22(3):252-9.
14. Neville RG, Robertson F, Livingstone S, Crombie IK. A classification of prescription errors. J R Coll Gen Pract. 1989(39):110-2.
15. Hawkey CJ, Hodgson S, Norman A, Daneshmend TK, Garner ST. Effect of reactive pharmacy intervention on quality of hospital prescribing. BMJ. 1990;300(6730):986-90.
16. Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother. 1992;26(12):1580-4.
17. Caleo SUE, Benrimoj S, Collins D, Lauchlan R, Stewart KAY. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract. 1996;4(4):221-7.
18. Dean BS, Barber ND. A validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm. 1999;56(1):57-62.
19. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. Am J Health Syst Pharm. 1999;56(23):2444-50.
20. Davydov L, Caliendo GC, Smith LG, Mehl B. Analysis of clinical intervention documentation by dispensing pharmacists in a teaching hospital. Hosp Pharm. 2003;38(4):346-50.
21. Lee J, McPherson ML. Outcomes of recommendations by hospice pharmacists. Am J Health Syst Pharm. 2006;63:2235-9.
22. Rothschild JM, Churchill W, Erickson A, Munz K, Schuur JD, Salzberg CA, et al. Medication errors recovered by emergency department pharmacists. Ann Emerg Med. 2010;55:513-21.
23. Harrison JJ, Wang J, Cervenko J, Jackson L, Munyal D, Hamandi B, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clin Transplant. 2012;26(2):E149-57.

24. Vo T.-H., Charpiat B., Catoire C., Juste M., Roubille R., Rose F.-X., et al. Methods assessing the potential significance of a pharmacist intervention – a systematic review. Drug Safety (In revision).
25. Bedouch P, Sylvoz N, Charpiat B, Juste M, Roubille R, Rose FX, et al. Trends in pharmacists' medication order review in French hospitals from 2006 to 2009: analysis of pharmacists' interventions from the Act-IP(c) website observatory. J Clin Pharm Ther. 2014 Oct 10.
26. Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006 Aug;28(4):181-8.
27. Bedouch P, Charpiat B, Roubille R, Juste M, Rose FX, Escofier L, et al. [The French Society of Clinical Pharmacy website for the documentation and analysis of pharmacist's interventions: purpose, instructions and perspectives]. J Pharm Clin. 2007;26:40-4.
28. Hatoum HT, Hutchison RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. 1988. p. 252-9.
29. National Coordinating Council for Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. 2013 [cited; Available from: http://www.nccmerp.org/pdf/indexColor2001-06-12.pdf
30. Elliott RA, Woodward MC. Assessment of Risk Associated with Medication-Related Problems in Elderly Outpatients. J Pharm Pract Res. 2009;39:109-13.
31. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74.
32. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther. 2005 Mar;85(3):257-68.
33. Krass I, Smith C. Impact of medication regimen reviews performed by community pharmacists for ambulatory patients through liaison with general medical practitioners. Int J Pharm Pract. 2000(8):111-20.
34. Mueller BA, Abel SR. Impact of college of pharmacy-based educational services within the hospital. Drug Intell Clin Pharm. 1990;24(4):422-5.
35. Strong DK, Tsang GW. Focus and impact of pharmacists' interventions. Can J Hosp Pharm. 1993;46(3):101-8.
36. Weidle P, Bradley L, Gallina J, Daniel C, Thorn N, Siegel L. Pharmaceutical care intervention documentation program and related cost savings at a University Hospital. Hosp Pharm. 1998;34(1):43-52.
37. Westerlund T, Marklund B. Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J Clin Pharm Ther. 2009;34(3):319-27.
38. Bayliff CD, Einarson TR. Physician assessment of pharmacists' interventions - a method of estimating cost avoidance and determining quality assurance. Can J Hosp Pharm. 1990;43(4):167-71, 95.
39. Ling JM, Mike LA, Rubin J, Abraham P, Howe A, Patka J, et al. Documentation of pharmacist interventions in the emergency department. Am J Health Syst Pharm. 2005;62(17):1793-7.
40. Guignon AM, Grain F, Allenet B, Brudieu E, Barjhoux C, Bosson J-L, et al. Evaluation de l'impact clinique des opinions pharmaceutiques dans un service de médecine spécialisée. J Pharm Clin. 2001;20(2):118-23.
41. Society of Hospital Pharmacists of Australia. SHPA Standards of Practice for Clinical Pharmacy. J Pharm Pract Res. 2005;35(2):122-46.
42. Bosma L, Jansman FG, Franken AM, Harting JW, Van den Bemt PM. Evaluation of pharmacist clinical interventions in a Dutch hospital setting. Pharm World Sci. 2008;30:31-8.
43. Fernández-Llamazares CM, Manrique-Rodríguez S, Pérez-Sanz C, Durán-García ME, Sanjurjo-Sáez M, Calleja-Hernández MA. Validation of a method for recording pharmaceutical interventions. J Clin Pharm Ther. 2012;37:459-63.
44. Cousins D, Gerrett D, Luscombe D. Reliability and validity of hospital pharmacists' clinical intervention data. Am J Health Syst Pharm. 1997;54(14):1596-603.
45. Somers A, Robays H, De Paepe P, Van Maele G, Perehudoff K, Petrovic M. Evaluation of clinical pharmacist recommendations in the geriatric ward of a Belgian university hospital. Clin Interv Aging. 2013;8:703-9.

46. Lucas C, Glare PA, Sykes JV. Contribution of a liaison clinical pharmacist to an inpatient palliative care unit. Palliat Med. 1997;11(3):209-16.
47. Hick HL, Deady PE, Wright DJ, Silcock J. The impact of the pharmacist on an elective general surgery pre-admission clinic. Pharm World Sci. 2001;23(2):65-9.
48. Spinewine A, Dhillon S, Mallet L, Tulkens PM, Wilmotte L, Swine C. Implementation of ward-based clinical pharmacy services in Belgium - description of the impact on a geriatric unit. Ann Pharmacother. 2006;40:720-8.
49. Gisev N, Bell JS, Chen TF. Interrater agreement and interrater reliability: key concepts, approaches, and applications. Res Social Adm Pharm. 2013;9(3):330-8.

3.2. Validation process of the CLEO tool in clinical practice

Results of validation of a method of assessment depend on many factors: scale (content, structure), process of assessment (quality of information of scenarios, retrospective or prospective rating, etc.), and profiles of evaluators (professional, number of experience years, etc.). Limitations of the previous study were only rating retrospectively PIs by external pharmacists, testing the reliability among pharmacists only, and rating PIs extracted from the general pharmacy practice. Therefore, this study aims to test prospectively both validity and reliability of the method of assessment of potential significance of PIs using the CLEO tool in a specific setting - a centralized preparation of cytotoxic drugs unit (CPU) at the Grenoble University Hospital Center. We choose the CPU for a practical reason rather than a methodological reason. When we finished the first study of validation of the CLEO tool with the SIG, there was an emergent requirement for assessing impacts of PIs conducted in the CPU. This unit has found since 20 years and there were many studies that measured the production of PIs and acceptance rate of PIs. However, no study measured potential outcomes of PIs. Therefore, we collaborated with clinical pharmacists and pharmacy residents in this unit to use and test the CLEO v.2. In this setting, there are two types of pharmacists, ones reviewed the patient's electronic medical record at the CPU before preparation of drugs and a full-time on-ward of clinical pharmacists who participated in medical teams. And we wanted to know how agreement of ratings between two types of pharmacists was. Another question was how agreement of ratings between pharmacists and opinions in consensus of multidisciplinary groups.

All 237 PIs made by pharmacists in the CPU were recorded from July to September 2014 and then were divided into 4 specific therapeutic domains: hematology, oncology-radiotherapy, pneumology, hepato-gastroenterology (HGE). Four expert panels were constituted respectively. Each expert panel consists of 4 members: a medical specialist of the domain, a clinical pharmacy specialist, a pharmacist working in the CPU, a pharmacovigilance expert. The inter-rater reliability between two pharmacists was *moderate* agreement for clinical (agreement=51%; kw=0.48); *substantial* for economic (agreement=71%; kw=0.61); and *fair* agreement for organizational dimension (agreement=60%; kw=0.27). The validity when comparing ratings between a pharmacist in the CPU and panels was *fair* agreement for "Clinical impact" (agreement=41%; kw=0.32); *substantial* agreement for "Economic impact" (agreement=68%; kw=0.53); and *slight* agreement for "Organizational dimension" (agreement=57%; kw=0.17).

Comparing to inter-rater reliability of the CLEO in the first study, the results of this study was better for "Clinical impact" (from kw=0.41 to 0.48), was worse (but was still *substantial* agreement) (from kw=0.93 to 0.61) for "Economic impact" but worse much for "Organizational impact" (from kw=0.39 to 0.27). The results of this study helped to confirm that it was difficult to achieve high kappa score (kw > 0.6) for "Clinical impact" and we considered a kw score in range of 0.4-0.6 as acceptable for "Clinical impact". In conclusion, the "Clinical impact" and "Economic impact" were valid and reliable enough to use. The explorations of reasons of low agreement concerning "Organization impact" in this study are useful to refine this dimension in further study.

Finally, reproducibility of validity and reliability of the CLEO in a local setting is not always obvious. Subgroup analyses used in this study to target the main source of disagreement (panel experts, pharmacists or types of PIs) were useful for further training of rating and peer-review process to improve agreement afterward.

Article 3.

Validation process of the CLEO tool for assessment of significance of pharmacist interventions in clinical practice: oncology service

Thi-Ha VO, Céline ZECCHINI, Isabelle FEDERSPIEL, Sébastien CHANOINE, Bruno CHARPIAT, Jean-Luc BOSSON, Benoît ALLENET, Pierrick BEDOUCH

Article 3. Validation process of the CLEO tool for assessment of significance of pharmacist interventions in clinical practice: oncology service

Authors: Thi-Ha VO[1,2], Céline ZECCHINI[3], Isabelle FEDERSPIEL[3], Sébastien CHANOINE[3], Bruno CHARPIAT[4], Jean-Luc BOSSON[2], Benoît ALLENET[1,2,3], Pierrick BEDOUCH[1,2,3]

1. Univ. Grenoble Alpes, TIMC-IMAG, F-38000 Grenoble, France.

2. CNRS, TIMC-IMAG, F-38000 Grenoble, France.

3. CHU Grenoble, Pôle Pharmacie, F-38000 Grenoble, France.

4. Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Pharmacie, F-69000 Lyon, France.

Background and Objective: The CLEO tool (including 3 independent dimensions: 7-category clinical, 4-categogry economic, and 4-category organizational) for evaluation of potential significance of a pharmacist intervention (PI) was validated in general practice. This study aims to test the validity and reliability of CLEO tool for PIs from pharmacist analysis of prescriptions in a centralized chemotherapy preparation unit (CPU).
Setting and Method: The inter-rater reliability is a concordance between intervening pharmacists (2 pharmacy residents and 3 senior pharmacists working in the CPU) and a peer reviewer pharmacist. The validity is a concordance between intervening pharmacists and consensus opinions of expert panels (ie: multidisciplinary expert committees). All 237 PIs recorded from July to September 2014 were divided into 4 specific therapeutic domains: hematology (43PIs), oncology-radiotherapy (146PIs), pneumology (33PIs), hepato-gastroenterology (HGE) (15PIs). Four expert panels were constituted respectively. Each expert panel consists of 4 members: a medical specialist of the domain, a clinical pharmacy specialist, a pharmacist working in the CPU, a pharmacovigilance expert. Subgroup analyses were also conducted.
Main outcome measures: Inter-rater reliability, validity, factors affecting agreement
Results: The inter-rater reliability was moderate agreement for clinical (agreement=51%; kw=0.48); substantial for economic (agreement=71%; kw=0.61); and fair agreement for organizational dimension (agreement=60%; kw=0.27). The validity was fair agreement for clinical (agreement=41%; kw=0.32); substantial agreement for economic (agreement=68%; kw=0.53); and slight agreement for organizational dimension (agreement=57%; kw=0.17). The peer pharmacist rated more consistently with expert panels than pharmacists in the CPU; pharmacy residents rated more consistently than senior pharmacists. Ratings were less consistent with the expert panel of HGE. Validity of the CLEO was higher if evaluators rated accepted PIs than refused PIs.
Conclusion: The highest strength of agreement was found for economic dimension of the CLEO classification, then clinical dimension. The lowest values were obtained for organizational dimension. Reproducibility of validity and reliability of the CLEO in a local setting is not always obvious. Subgroup analyses is useful to target the main source of disagreement (panel experts, pharmacists or types of PIs) and further training of rating and peer-review process is necessary to improve agreement.

INTRODUCTION

The special interest group “Standardizing and demonstrating the value of clinical pharmacy activities” of the French Society of Clinical Pharmacy (SFPC) developed and validated a multidimensional tool for determining the impacts of pharmacist interventions (PIs), named the CLEO [1]. Construction of the CLEO was based on a review of models of evaluation of PIs, a systematic review of existing tools [2], selection and examination of impacts of 200 PIs. The CLEO includes three independent dimensions: clinical impact of a PI from the point of view of patient (C), economic impact of a PI from point of view of the hospital setting (E), and organizational impact of a PI from point of view of health care providers (O). Each dimension consists of many numeric levels; and has both negative, zero, positive values and an open level *"non-determined"* (*Figure **23***). The three dimensions were combined into a three-component code describing the whole impacts of PI (see examples in *Figure **24***).

The scale was validated through three steps of rating by a group of 7 clinical pharmacists of SFPC. They coded retrospectively 30 or 50 scenarios extracted from the general pharmacy practice in order to estimate the reliability (% agreement and kw). The second rating showed *moderate* agreement for clinical dimension (agreement = 39% and kw = 0.41); *almost perfect* agreement for economic dimension (agreement = 90% and kw = 0.93); and *fair* agreement for organizational dimension (agreement = 62% and kw = 0.39). The information of validation process of the CLEO was presented in the another article [1].

Results of validation of a method of assessment depends on many factors: scale (content, structure), process of assessment (quality of information of scenarios, retrospective or prospective rating, etc.), profiles of evaluators (professional, number of experience years, etc.) [2]. Limitations of the previous study were only rating retrospectively PIs by external pharmacists, testing the reliability among pharmacists only, and rating PIs extracted from the general pharmacy practice. Therefore, this study aims to test prospectively both validity and reliability of the method of assessment of potential significance of PIs using the CLEO tool in a specific setting - a centralized preparation of cytotoxic drugs unit (CPU). This study was designed to determine if the CLEO tool is reliable for daily use in a specific setting.

Method

Grenoble University Hospital is a 2000-bed, public hospital. Since late 1995, all of the injectable chemotherapy for all onco-hematology services are prepared at a CPU. Three pharmacists and 2 pharmacy residents work at CPU.

In 1999, the hospital implemented an electronic medical record system covering all the aspects of patient care and a CPOE program for chemotherapy prescription (Cristal-link ©), which provides access to patient demographic information, laboratory results, drugs dispensed and medication administration records. Firstly, all anti-cancer medication are prescribed through predefined order sets which was validated by pharmacists and physicians. These order sets include drugs, doses, administration (route, infusion time, solvent used), and associated premedication. Once the prescription was signed electronically by the physician,

prescriptions automatically appear on the pharmacy computer screen. Then pharmacists in the CPU analyze the prescription and call physicians when a DRP is identified during the medication order validation process. PIs are daily recorded. A preparation sheet is then sent to pharmacy technicians.

In the Hematology service, the hospital integrates a clinical pharmacy resident as a full-time staff member. The clinical pharmacy resident has completed 5-year pharmacy studies and has chosen to specialize, pursuing a hospital residency program lasting 4 years divided into rotations of 6 months in different services. Pharmacy residents work under the supervision of a clinical pharmacist. The main mission of clinical pharmacy residents is to assist physicians with drug therapy, by taking medication histories directly from patients at admission, participating in physicians' ward rounds, validating medication orders (except validation of anti-cancer drugs was done by pharmacists in the CPU) and performing patient education before discharge.

Data collection

All consecutive PIs proposed by pharmacists in the CPU were recorded for the whole duration of the study. In fact, 237 PIs were recorded from 7 July to 14 September 2014. The clinical pharmacy resident on ward recorded prospectively PIs into a report form, including: patient characteristics (sex, age, weight, height, body surface area); medical history; cancer drugs and cancer protocols used, the types of DRPs and PIs were classified according to the validated tool of the SFPC[3]; description of DRPs and PIs in detail; whether or not it was accepted by the physician. These forms were provided to expert panels at the end of the study for rating.

Rating

The study's objective is to determine *inter-rater reliability* (concordance between intervening pharmacists and second pharmacist as peer reviewer) and *validity* (concordance between intervening pharmacist and an expert panel) of the CLEO tool. Pharmacists in the CPU rated PIs as soon as they intervened while the clinical pharmacy resident on ward rated PIs after collecting data and filling in a report form. There are 2 pharmacy residents and 3 pharmacists in the CPU who participated to rate PIs. At the end of the study, all 237 PIs were devided into 4 specific therapeutic domain: hematology (43PIs), oncology-radiotherapy (146PIs), pneumology (33PIs), hepato-gastroenterology (15PIs). Therefore, 4 panels of experts were formed respectively. Each expert panel consists of 4 members: a medical specialist, a pharmacy specialist, a pharmacist working in the CPU, a pharmacist working in a pharmacovigilance center. The CLEO version 3 and 12 examples for rating were sent to members of expert panels one week before the day of face-to-face direct meeting. During the meeting, after the clinical pharmacy resident on ward read each PI, each rater evaluated independently and then discussed until reaching the consensus (3 or more raters agree).

Statistical analysis

The reliability and validity is calculated through percentage of agreement and weighted kappa. The interpretation of results of weighted kappa is based on the Landis and Koch scale (k values of < 0 indicate poor agreement; 0.00-0.20, slight agreement, 0.21-0.40, fair; 0.41-0.60 moderate; 0.61-0.80, substantial; 0.81-1.00, almost perfect)[4]. Subgroup analyses were conducted for 5 pharmacists in the CPU, 4 specific therapeutic domains, and whether or not a PI was accepted by the physician. The statistical analysis was performed using the Stata statistical package, release 9.1 (StataCorp LP, College Station, TX, USA).

Results

Reliablity and validity of assessment method

The inter-rater reliability between pharmacists for classification was as follows: *moderate* agreement for clinical impact (agreement = 51%; kw = 0.48); *substantial* for economic impact (agreement = 71%; kw = 0.61); and *fair* agreement for organizational impact (agreement = 60%; kw = 0.27) (Table 1).

The validity (concordance between pharmacists in the CPU and an expert panel) for classification was as follows: *fair* agreement for clinical impact (agreement = 41%; kw = 0.32); *substantial* agreement for economic impact (agreement = 68%; kw = 0.53); and *slight* agreement for organizational impact (agreement = 57%; kw = 0.17).

Table 1: Reliablity and validity of assessment method

Type		Cinical Impact		Economic Impact		Organizational Impact	
		%	kw	%	kw	%	kw
General	R (P1-P2)	**51**	**0.48**	**71**	**0.61**	**60**	**0.27**
	V (P1-C)	**41**	**0.32**	**68**	**0.53**	**57**	**0.17**

R: reliability. V: validity. P1: pharmacist on ward. P2: pharmacist in the CPU

Subgroup analyses of validity

Compare validity of CLEO between the clinical pharmacy resident on ward and pharmacists in the CPU

Ratings of the clinical pharmacy resident on ward was more consistent with those of expert panels than the pharmacists in the CPU in term of clinical and economic impact, but less consistent in term of organizational impact (Table 2). Validity of clinical impact was *moderate* (agreement = 54%; kw = 0.56) and *fair* (agreement = 41%; kw = 0.32), respectively. Validity of economic impact was *substantial* (agreement = 81%; kw = 0.75) and

moderate agreement (agreement = 68%; kw = 0.53), respectively. Validity of organizational impact was *slight* (agreement = 49% and 57%; kw = 0.11 and 0.17 respectively).

Table 2. Subgroup analyses of validity of assessment method

Sub-analysis		**Validity**	**Cinical Impact**		**Economic Impact**		**Organizational Impact**	
			%	**kw**	**%**	**kw**	**%**	**kw**
Which pharmacist	Pharmacists in the CPU	V(P1-C)	**41**	**0.32**	**68**	**0.53**	**57**	**0.17**
	Pharmacist on ward	V(P2-C)	**54**	**0.56**	**81**	**0.75**	**49**	**0.11**
Which Expert panel	Hepato-gastroenterology	V (P1-C)	**20**	**0.36**	**87**	**0.42**	**73**	**0.44**
	Hematology	V (P1-C)	**60**	**0.48**	**84**	**0.80**	**40**	**-0.13**
	Pneumology	V (P1-C)	**66**	**0.50**	**89**	**0.87**	**49**	**0.22**
	Oncology-Radiotherapy	V (P1-C)	**52**	**0.58**	**78**	**0.72**	**50**	**0.15**
Which type of PIs	Accepted PI	V(P1-C)	**58**	**0.58**	**86**	**0.83**	**52**	**0.12**
	Refused PI	V(P1-C)	**41**	**0.34**	**66**	**0.50**	**41**	**0.05**
Which pharmacists in the CPU	If P1 is the Interne 1	V(P1-C)	**44**	**0.37**	**79**	**0.70**	**50**	**0.15**
	If P1 is the Interne 1	V(P1-C)	**54**	**0.42**	**66**	**0.48**	**59**	**0.23**
	If P1 is the Pharmacist 1	V(P1-C)	**32**	**0.21**	**55**	**0.29**	**59**	**0.13**
	If P1 is the Pharmacist 2	V(P1-C)	**36**	**0.31**	**77**	**0.67**	**69**	**0.28**
	If P1 is the Pharmacist 3	V(P1-C)	**28**	**0.08**	**50**	**0.24**	**28**	**0.07**

V: validity. P1: pharmacist on ward. P2: pharmacist in the CPU. C: expert panel

Compare validity of CLEO among groups of expert panels

Ratings of pharmacists in the CPU were less consistent with those of expert panel of hepato-gastroenterology than other expert panels in term of *clinical impact and economic impact*. But ratings of pharmacists in the CPU were less consistent with those of expert panel of hematology and oncology-radiotherapy in term of *organizational impact*.

Compare validity of CLEO between accepted PIs and refused PIs

Validity score of CLEO were higher if evaluators rated accepted PIs than refused PIs.

Compare validity of CLEO between different pharmacists in the CPU

Validity score of CLEO was higher if evaluators in the CPU were clinical pharmacy residents than clinical pharmacists. Particularly, the clinical pharmacist 1 and 3 rated the worst.

DISCUSSION

We agreed with Hatoum et al. [5] that building consensus on the positive contribution of clinical pharmacy services to patient care mandates both inter- and intra-professional evaluation. Therefore, in this study each IP was evaluated independently by 2 practicing pharmacists and a multidisciplinary expert panel. Unlike the study of Hatoum et al., only PIs which have been considered clinically significant with ranks 5 and 6 by pharmacists, were subjected to the physician-review process; in our study all PI were evaluated by expert panels.

Concerning *inter-rater reliabilit*y of *"clinical impact",* our results showed *moderate* agreement for clinical impact (kw = 0.48), which is similar to the result when the CLEO tool was used in general pharmacy practice (kw = 0.41) in our previous study. Both are higher than other studies [6], [7], [8], [9], [10]. Therefore, we thought that the inter-rater reliability of clinical dimension of the CLEO tool is acceptable and reliable enough to use in practice.

Concerning the *validity* of the tool, it is difficult to assess validity of any method measuring the potential significance of a PI because there is no generally accepted standard with which to compare [11]. The comparison of the scores given by evaluators with known outcomes in the literature as in the study of Dean et al.[12] and Taxis et al.[13] has limitations because errors resulting in more-severe outcomes may be more likely to be reported in the literature [12]. There were studies in which the validation was determined by comparing results of ranking of practicing pharmacists with a senior expert (e.g., a pharmacy manager [14], an academic pharmacist [15], an internal physician [16], an external physician [15, 16]. Nonetheless, no study aimed to compare results of ranking of practicing pharmacists with the consensus results of a group of experts like in our study. We found 4 specific panel experts and each panel expert consists of 4 members (a medical specialist, a pharmacy specialist, a pharmacist working in the CPU, a pharmacist working in the pharmacovigilance center), which aims to assure the validity of consensus opinions of panel experts. Our results showed *slight* agreement for clinical impact (agreement = 41%; kw = 0.32).

The highest strength of agreement was found for *"economic impact"* dimension (agreement = 71% and kw = 0.61 for inter-rater reliability; agreement = 68% and kw = 0.53 for validity). However, these results were lower when the CLEO was used in the previous study (agreement = 90%, kw = 0.93).

The organizational dimension aims to detect any beneficial effects of a PI on quality of process of care from point of view of health care providers. The lowest values were obtained for organizational impact (agreement = 60% and kw = 0.27 for reliability; agreement = 57% and kw = 0.17 for validity). These results were lower than ones in the previous study (agreement = 62% , kw = 0.39). The reasons for explanation of this low result were found as same as in the previous study. One difficulty is to choose the point of view. Because health care providers such as physicians, pharmacists, nurses are involved in process of care, we then choose to evaluate from the point of view of health care providers. However, in many cases, the points of view were different between professional groups. For example, in meetings of

multidisciplinary groups in the second study, switching from intravenous (IV) to oral (PO) therapy as soon as patients are clinically stable sometimes were considered as having no effect on "organizational impact" by physicians while pharmacists judged the PI as having positive impact because it saved times for nurses. The CLEO tool did not specify which professional groups' view was used, which results in the ambiguity in ratings. Purpose of the CLEO tool is to be used independently by pharmacists in daily practice and pharmacists often have to consider potential impacts from different points of view before deciding to intervene or not. Therefore, one suggestion for refining "Organizational impact" may be that "The organizational impact is coded regarding the overall impact on process of care from *pharmacists' judgement/perception"*.

Second difficulty is to how to evaluate many organizational indicators in a simple way. We decided to combine many organizational indicators into a single global opinion to simplify reporting. However, impacts of a PI on different organizational indicators sometimes are not the same and then contributing a global impact on "Organizational impact" is difficult. For example, in the second study for cancer patients, many times pharmacists found that patients used cancer drugs whose dose needed to be adapted to patients' renal function without update information of creatinine levels of patients. Pharmacists reminded physicians to update. However, physicians responded that physicians already considered the update creatinine level into dosing adaption but physicians did not save this new information in patients' medical record. This type of PIs requires more times by both pharmacists and physicians (negative impact) but they are necessary tasks of teamwork (positive impact). One suggestion is to separate organizational indictors, to evaluate them independently, and to have just 3 choices (yes/no/don't know) instead of 4 choices (negative/no/positive/don't know). Further studies need to be conducted to refine "Organizational impact" dimension and retest its validity and reliability.

Measuring the reliability and validity of methods for assessment of impacts of PIs not only provide an credibility/evidence of a subjective assessment but can also be used for training, peer review and audit purposes [9, 16]. Therefore, subgroup analyses can be conducted to target the main source of disagreement. Ratings of clinical pharmacy resident in ward was more much consistent with those of expert panels than the pharmacists in the CPU in term of clinical and economic impact (agreement = 54% and kw = 0.56 for clinical impact; agreement = 81% and kw = 0.75 for economic impact) (Table 2). The reason may be the clinical pharmacist on ward who practiced in the service, contacted directly with patients and health care team, and rated impacts of PIs only after collecting complete patient information while pharmacists in the CPU who only access to patient information in the computer and had to rate impacts of PIs as soon as they intervened. This result confirms the opinion of Hatoum et al. [5] that peer-review process added further credibility to results presented.

Compare validity of CLEO among groups of expert panels, the worst results of consistency of clinical impact and economic impact is between pharmacists in the CPU and expert panel of hepato-gastroenterology. Therefore, it is necessary to extract PIs of hepato-gastroenterology in which it exists divergence to discuss further among members and then to provide more

examples of rating. Validity of CLEO was higher if evaluators rated accepted PIs than refused PIs. In the literature, there is no information about that. Sub-analysis of validity of CLEO between different pharmacists in the CPU found that pharmacy residents rated better than clinical pharmacists did. Particularly, the clinical pharmacist 1 and 3 rated the worst. This result is contrary to findings of study conducted by Fernandez-Llamazarez et al. [9] in which senior pharmacists rated more consistently than junior pharmacists.

Limitations

Inevitably, the evaluated studies suffered from some problems with external validity. The study sample may have included unique characteristics which make the results unique to the study. The tool was used by pharmacists and physicians in one CPU. And the specific characteristics of this service (e.g., types of DRPs and PIs) may be not representative for other services or settings. Other more broad-based, multicenter, and longitudinal studies are needed to validate the CLEO tool in a variety settings.

In fact, reproducibility of reliability of a specific tool in a local setting is not always obvious because it depends on not only the structure and content of tools, but also process of assessment. Therefore, sub-analysis of validity is useful to target panel experts, pharmacists or types of PIs in which it exists great divergence in order to improve agreement.

CONCLUSION

The highest strength of agreement was found for economic dimension of the CLEO, then clinical dimension. The lowest values were obtained for organizational dimension. Reproducibility of validity and reliability of the CLEO in a local setting is not always obvious. Subgroup analyses is useful to target the main source of disagreement (panel experts, pharmacists or types of PIs) and further training of rating and peer-review process is necessary to improve agreement.

Reference

1. Vo T.-H., Charpiat B., Chanoine S, Genty C, Juste M., Roubille R. et al. Validation of the CLEO tool for assessment of significance of pharmacist interventions in general context (In redaction).
2. Vo T.-H., Charpiat B., Catoire C., Juste M., Roubille R., Rose F.-X., et al. Methods assessing the potential significance of a pharmacist intervention – a systematic review. Drug Safety (In revision).
3. Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006 Aug;28(4):181-8.
4. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74.
5. Hatoum HT, Hutchinson RA, Elliott LR, Kendzierski DL. Physicians' review of significant interventions by clinical pharmacists in inpatient care. Drug Intell Clin Pharm. 1988;22(12):980-2.
6. Cousins D, Gerrett D, Luscombe D. Reliability and validity of hospital pharmacists' clinical intervention data. Am J Health Syst Pharm. 1997;54(14):1596-603.
7. Bosma L, Jansman FG, Franken AM, Harting JW, Van den Bemt PM. Evaluation of pharmacist clinical interventions in a Dutch hospital setting. Pharm World Sci. 2008;30:31-8.
8. Lee J, McPherson ML. Outcomes of recommendations by hospice pharmacists. Am J Health Syst Pharm. 2006;63:2235-9.
9. Fernández-Llamazares CM, Manrique-Rodríguez S, Pérez-Sanz C, Durán-García ME, Sanjurjo-Sáez M, Calleja-Hernández MA. Validation of a method for recording pharmaceutical interventions. J Clin Pharm Ther. 2012;37:459-63.
10. Somers A, Robays H, De Paepe P, Van Maele G, Perehudoff K, Petrovic M. Evaluation of clinical pharmacist recommendations in the geriatric ward of a Belgian university hospital. Clin Interv Aging. 2013;8:703-9.
11. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. Am J Health Syst Pharm. 1999;56(23):2444-50.
12. Dean BS, Barber ND. A validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm. 1999;56(1):57-62.
13. Taxis K, Dean B, Barber N. The validation of an existing method of scoring the severity of medication administration errors for use in Germany. Pharm World Sci. 2002;24:236-9.
14. Bayley KB, Savitz LA, Maddalone T, Stoner SE, Hunt JS, Wells R. Evaluation of patient care interventions and recommendations by a transitional care pharmacist. Ther Clin Risk Manag. 2007;3:695-703.
15. Elliott RA, Martinac G, Campbell S, Thorn J, Woodward MC. Pharmacist-led medication review to identify medication-related problems in older people referred to an Aged Care Assessment Team: a randomized comparative study. Drugs Aging. 2012;29(7):593-605.
16. Lucas C, Glare PA, Sykes JV. Contribution of a liaison clinical pharmacist to an inpatient palliative care unit. Palliat Med. 1997;11(3):209-16.
17. Hick HL, Deady PE, Wright DJ, Silcock J. The impact of the pharmacist on an elective general surgery pre-admission clinic. Pharm World Sci. 2001;23(2):65-9.
18. Spinewine A, Dhillon S, Mallet L, Tulkens PM, Wilmotte L, Swine C. Implementation of ward-based clinical pharmacy services in Belgium - description of the impact on a geriatric unit. Ann Pharmacother. 2006;40:720-8.

PART 4.

DISCUSSION AND PERSPECTIVES

More complex patient care resulting from new technology, higher acuity of illness or higher burden of chronic diseases are placing heavier demands on health care practitioners. These trends are reflected in the increasing number, types and cost of prescribed drugs. The optimal drug use may best be achieved by using an interdisciplinary approach. The direct involvement of a pharmacist throughout the medication-use process helps ensure continuity of care and has the potential to minimize risk, lower the cost, and improve the outcomes associated with drug therapy (175).

While the pharmaceutical care has undergone dramatic changes since 30 years, pharmacists still need to demonstrate the benefits or added value of services because demonstration of value defines professional contribution (253). Pharmaceutical care has been described as a multi-faceted process that aims to result in positive outcomes for the patients. Associated with this process is the delivery of appropriate clinical pharmaceutical services, which include obtaining patient medical history, evaluating laboratory data, reviewing patient records, and performing patient counseling, etc. These activities contribute to medication reconciliation and medication review of the patient with major outputs in form of PIs. In times of limited resources allocation, it is important to evaluate the impacts and value of PIs proposed during medication review. The present work aimed to develop methodologies for assessment of impacts and value of PIs.

1. Principal findings of this work

When evaluating our work as a whole, several important and new findings can be identified.

First, many theoretical models and frameworks can be applied to evaluate impacts of PIs. However, only a few studies measured more than one types of impacts. In order to obtain a comprehensive picture of the impact of PIs, we constructed an integrated model, named the SP(ECH)O-P model, which synthetized six types of impacts from many evaluation models in literature. All impacts of this model should be measured when possible.

Second, a systematic review of existing tool for assessment of the potential significance of PIs was conducted with a rigor method[1]. This review helps to update a previous review of Overhage and Lakes in 1999 (12). A variety of tools and methodologies for estimate of value of PIs were found and analyzed. For the first time in the literature, an attempt to classification of these tools based on the 10-criteria scale of quality of tools was conducted, which will provide useful information for researchers who want to adopt or develop a new tool for local use. From the results of review, some recommendations on characteristics of optimal tools for assessing potential impacts of PIs were suggested.

Third, we developed a new multidimensional tool, named CLEO, which aimed to satisfy the above recommendations for optimal tools. The CLEO tool was a result from a review of theoretical models of evaluation, existing tools and inputs of clinical pharmacists' practice. The CLEO tool allows to evaluate **CL**inical and humanistic outcomes from the patient's

[1] Thi Ha VO et al. A systematic review of tools for assessing potential significance of pharmacist interventions. Drug Safety (in press).

perspective, **E**conomic impacts (cost savings) from the hospital's perspective and **O**rganizational impacts from HCPs' perspective. The original features of the CLEO tool is to include many humanistic outcomes integrated into "clinical impact" dimension. Furthermore, for the first time in the literature, an independent dimension for evaluating "organizational impacts" of PIs on process of care from HCPs' perspective was developed and tested. This 3-dimension tool allows to interpret different impacts together in order to obtain a complete picture of impacts of PIs.

The new tool was tested for validity and inter-rater and intra-rater reliability, and user-friendliness in two studies[2,3] In the first one[2], a research group of 7 expert pharmacists from the SFPC was required to assess retrospectively PIs selected from the database Act-IP© or their practice. Many steps of refinement of the tools were conducted and the results of inter-rater reliability were improved over time. After that, the final version of the CLEO tool was used prospectively in daily practice in a specific hospital service in the second study. We anticipated the condition/context in which the tool was used will influence profoundly results of ratings. Therefore, we designed a study which allowed practitioners to use the tool in realistic study conditions. An evaluation process included three steps: (i) an initial and immediate evaluation by the pharmacist who intervened, (ii) a peer-review evaluation by the ward-based pharmacist who can access to more complete patient information several days later, and (iii) an evaluation in consensus by multi-disciplinary panels two month later. By sub-analysis of results of concordance between raters/panels, these results of the second study not only allow to test validity and inter-rater reliability, but also supply useful information to improve concordance measure. Concerning inter-rater reliability, the results obtained were *substantial* for "economic impact" dimension (kw = 0.93 and 0.61, respectively); *moderate* for "clinical impact" dimension (kw = 0.41 and 0.48, respectively); and *fair* (kw = 0.39 and 0.27, respectively) for "organizational impact" dimension in the two studies. Concerning intra-rater reliability, results were *sligh* (kw = 0.38) for clinical impact and were *moderate* (kw = 0.70) for economic impact. Concerning validity tested in the second study, ratings of the pharmacist on ward were more consistent with those of expert panels than the pharmacists in the centralized preparation unit in term of clinical and economic impact (kw = 0.56 and 0.32 for clinical; kw = 0.75 and 0.53 for economic, respectively), but less consistent in terms of organizational impact (kw = 0.11 and 0.17, respectively). Comparing to results of other tools in literature, we found that clinical and economic dimension are likely to be reliable and valid enough to be able to use independently in daily practice by pharmacists. However, inter-rater reliability of organizational dimension was better in the first study and worse in the second study, which requires further research. We will discuss this point in more detail in the next section.

[2] Thi Ha VO et al. Validation of the CLEO tool for assessment of significance of pharmacist interventions in general context.

[3] Thi Ha VO et al. Validation process of the CLEO tool in clinical practice: oncology service.

2. Validity of findings

The validity of research approach of this work need to be discussed to raise questions about the quality of the CLEO tool and the internal and external validity of findings of the studies, its advantages, limitations and further perspectives of research.

2.1. Quality of the CLEO tool

Currently, there are no formal guidelines or any recommendations concerning methods of assessing the potential impacts of PIs. Taking into account the results of our systematic review of existing tools in literature, we suggested 12 recommendations as follows:

Table 28. Recommendations of methods of assessment of potential impacts of PIs

Theoretical properties
R1. Tools should be developed based on (1) comprehensive theoretical models, (2) a systematic literature review of available evidence that reflects the whole range of impacts of a PI and (3) an evaluation of existing tools, and (4) input from healthcare professionals.
R2. Tools should be able to demonstrate that the benefits outweigh the costs in a given patient, health care system, and society at the level of each PI.
R3. An evaluation from multi-impact perspective, rather than simply focusing on clinical impact, should be used to enhance understanding of the comprehensive effect of PIs. For example, a tool integrating clinical, humanistic, economic, process-related impacts and the probability of these impacts.
R4. The views of patients, health care providers, institutions, payers, and society should be considered.
Psychometric properties
R5. Tools should be validated prior to its use.
R6. Along with the information on clinical case, experts should be provided with a literature review, coding instructions, and examples. Indices for agreement/validity/reliability should be conform to the current guidelines.
R7. The guideline proposed for the use of experts in pharmacoeconomic studies is suitable for this type of study including description of consensus techniques; justification in using such methods; and description of selection of experts; provision of a definition of consensus in advance of the execution of a study; information that is provided to panelists in advance must be as objective and as comprehensive as possible; and modification of tool as appropriate with the input from independent experts or pilot-test; appropriate presentation and interpretation of findings.
Pragmatic properties
R8. Tools must be brief and not time-consuming. Acceptability to evaluators is also required.
R9. Tools should be well defined.
R10. Tools must be well-structured as well as flexible to adapt to meet their specific needs (e.g., multidimensional tool, possibility of modification of terminology of economic impact is based on different perspectives or modification of number of levels; independence between dimensions).
R11. Tools should have an open, numeric, and hierarchical structure (with main dimensions, main levels of each dimensions, and an open structure to include the option “non-determinable”).
R12. Same definitions, terminology and grading systems for both the potential significance of a PI and the actual severity of consequence of MEs/ADEs/ADRs.

Researchers and clinicians may have different needs in relation to a tool for assessing potential significance of PIs. Due to the wide range of tools used in the literature, researchers need consider developing a basis of comparison between tools. Therefore, we tried to assess quality of each tool using 10 criteria to assist in comparing tools across studies.

Table 29. Criteria of quality of a tool for assessing significance of PIs and the score of the CLEO tool

A. Structure of a tool	**Score**	**The CLEO**
A1. A tool has 2 or more dimensions	1	x
A2. A tool has at least one dimension which has 4 or more categories	1	x
B. Content of a tool		
B3. A tool applies 2 or more approaches of assessment	1	0
B4. A tool consists of indicator(s) related to cost savings	1	x
B5. A tool consists of indicator(s) related to cost avoidance	1	x
B6. A tool consists of humanistic indicator(s)	1	x
B7. A tool consists of process-related indicator(s)	1	x
B8. A tool consists of indicator(s) related to probability of consequences	1	0
C. Psychometric parameters of tools		
C9. A tool has at least one of psychometric parameters (validity, inter- or intra-rater reliability) which presented a moderate or good agreement.	1	0
C10. Risk of bias of a study which tested validity, inter- or intra-rater reliability of a tool was low.	1	0
Sum of scores:	**10**	**6**

Comparing the CLEO to these recommendations and criteria, some questions were raised: How does the CLEO tool satisfy these recommendations and criteria? What are advantages and disadvantages of the CLEO tool? How to improve the CLEO tool?

The CLEO tool was developed based on reviewing many theoretical models and existing tools in literature and inputs from expert pharmacists of the SFPC. Ideally, a tool should evaluate impact of PIs on *structure, process of care, clinical, humanistic, economic outcomes* with the *probability* of its impacts. We will discuss each type of impacts assessed in the CLEO tool below.

2.1.1. Clinical impact

There are some advantages of "clinical impact" of the CLEO. Firstly, "Clinical impact" includes the levels 2, 3, and 4 which are terminated by main cost-avoidance indicators (level 2 = monitoring/treatment avoided; level 3 = an initiated or prolonged hospitalization avoided; and level 4 = a potentially intensive care or death avoided). Secondly, many definitions and terminology used in "clinical impact" are similar to the NCC MERP Index - a famous grading system for the actual severity of MEs. Thirdly, the six-level structure of "clinical impact" was inspired from the structure of a famous tool of Hatoum et al. used most widely in literature, which will facilitate better comparison of results across studies.

There are two perspectives for improvement of "clinical impact": (i) improvement of concordance of rating potential clinical impact and (ii) establishment of relationship between potential and actual clinical impacts of PIs. In our first study, for the first time in literature, we also determined which levels of "clinical impact" were main sources of disagreement between raters. Both the statistic method and opinions of expert pharmacists shown that great sources of disagreement were from ratings between level 2C and 3C. One limitation of "clinical impact" was that its weighted kappa score was *moderate* which were higher than many other tools' in literature. However, it still needs to be improved. And a strategy is to give more examples, training and discussion on PIs having the 2C or 3C impact code.

Potential clinical impacts of PIs are only intermediate (surrogate) outcomes for proving the benefits of PIs. The fact that a positive intermediate outcome may not lead to a positive end-point outcome such as death and cure. However, the measurement of end-point outcomes is limited by measurement difficulties and design complications (11). Therefore, studies are needed to establish correlation between potential and actual clinical impacts of PIs. Such that, measures of potential impacts of PIs can be validly used as a measure of quality and value provided by pharmacists.

2.1.2. Humanistic impact

We decided to combine humanistic indicators into a single category (the level 1C) of "clinical impact" for simplifying reporting. Another reason is that this integration may be increase sensitivity to detect humanistic impacts. In fact, a majority of PIs such as undertaking monitoring, adding additional drugs, changing administration schedule or providing drug information to the patient, which have no remarked effect on symptoms or disease control. The impact of these on quality of life is likely to be minimal or event undetectable. Furthermore, some interventions may have a brief or delayed effect on quality of life and the timescale used in studies cannot detect benefits (40). However, PIs can improve the patient's satisfaction or knowledge which attributes a positive score (the level +1C).

However, this integration is likely to fail to describe humanistic impacts of the PI in detail on the patient. Further studies should develop separate tools that incorporate drug-use-specific and disease-specific measures because MR tends to have small effects on QOL and generic measures of QOL are likely to be somewhat insensitive. Some tools related to drug use were developed. Several relate to medication compliance and belief of the patient such as Beliefs about Medicines Questionnaire (254), Brief Medication Questionnaire (255), Medication Adherence Scale (256). Others relate to the provision of information about medicines (for example the Satisfaction with Information about Medicines Scale (257), the Desire for Information Scale (258)). Another scales measure patients' satisfaction with pharmaceutical care service (259, 260). Although all these are important, they focused on one aspect of medicines use or pharmaceutical care. Other measures are more global, including the Drug Therapy Concerns Questionnaire (261) and the Medicines-Related Quality of Life Measure(262). Again the sensitive of such a measure to PI should be much greater than that of generic quality-of-life measure(40).

2.1.3. Economic impact

The "Economic impact" dimension of the CLEO tool indeed evaluate just "cost saving" of PIs related to drug and monitoring costs. This strategy is used in other tools. A new advantage of the CLEO tool, as mentioned in arguments for development of the CLEO tool, is possible to use the first results of ratings impact of PIs in order to calculate the economic value of PIs afterward. The value of PIs can be estimated through 3 variables: cost of implementation, cost savings and cost avoidance of PIs. In the same study in the CPU at the Grenoble University Hospital, we selected PIs with positive or negative economic impact to estimate cost savings of PIs. Another study should calculate also cost avoidance, cost of providing medication review to estimate the benefit: cost ratio. It is possible to estimate the benefit: cost ratio for each PI or the whole medication review program in a setting. Each approach has different purposes. The estimate of the benefit: cost ratio for each PI is useful for pharmacists to target PIs which provide most value while the estimate of the benefit: cost for the whole medication review program in a setting helps directors of pharmacy or hospital to choose best investment among clinical pharmacy services.

The estimated value of PIs was often limited in the analysis to the projected direct costs of medical care that was avoided as a result of the pharmacists' actions. Studies rarely included in this estimate indirect costs (costs attributable to losses in patient productivity or their families, and costs arising from possible litigation against physicians or pharmacists) and intangible costs (costs related to humanistic outcomes). Therefore, another perspective for economic research on MR is to develop methods for evaluating indirect and intangible costs that were always ignored in literature.

2.1.4. Organizational impact

The development and process of validation of the CLEO tool emerged a lot of reflections on "Organizational impact": What is definition? How will evaluation be operated? Is it valid and reliable?

From the Sructure-Process-Outcome model of Donabedian, we can confirm that the PI not only influence on patient outcomes but also on structure and process of care. To clarify elements and component of structure and process of care, it is necessary to look the broader picture as "pharmacy work systems" presented in the Systems Engineering Initiative for Patient Safety (SEIPS) model According to this model, PIs can influence on "work system or structure" (including Person, Organization, Technologies and tools, Tasks), Process and Outcomes (including Emloyee and organizational outcomes and Patient outcomes). However, in reality, a PI was defined as any action by the pharmacist, which changes therapy management at an individual patient. The PI then focuses on process of care of the particular patient, and never or rarely changes the stable features of *structure* of the setting. Therefore, the CLEO tried to capture process-related indicators but not structure-related ones. We also inspired from process-related indicators used in other tools to develop "Organizational impact" dimension such as time savings, improved security, knowledge, job satisfaction of staff; facilitation professional tasks, continuation of care, or teamwork.

One difficulty is to choose the point of view. Because health care providers such as physicians, pharmacists, nurses are involved in process of care, we then choose to evaluate from the point of view of HCPs. However, in many cases, the points of view were different between professional groups. For example, in meetings of multidisciplinary groups in the second study, switching from intravenous (IV) to oral (PO) therapy as soon as patients are clinically stable sometimes were considered as having no effect on "organizational impact" by physicians while pharmacists judged the PI as having positive impact because it saved times for nurses. The CLEO tool did not specify which professional groups' view was used, which results in the ambiguity in ratings. Purpose of the CLEO tool is to be used independently by pharmacists in daily practice and pharmacists often have to consider potential impacts from different points of view before deciding to intervene or not. Therefore, one suggestion for refining "Organizational impact" may be that "The organizational impact is coded regarding the overall impact on process of care from *pharmacists' judgement/perception".*

Second difficulty is how to evaluate many organizational indicators in a simple way. We decided to combine many organizational indicators into a single global opinion to simplify reporting. However, impacts of a PI on different organizational indicators sometimes are not the same and then contributing a global impact on "Organizational impact" is difficult. For example, in the second study for cancer patients, many times pharmacists found that patients used cancer drugs whose dose needed to be adapted to patients' renal function without update information of creatinine levels of patients. Pharmacists reminded physicians to update. However, physicians responded that physicians already considered the update creatinine level into dosing adaption but physicians did not save this new information in patients' medical record. This type of PIs requires more times by both pharmacists and physicians (negative impact) but they are necessary tasks of teamwork (positive impact). One suggestion is to separate organizational indicators, to evaluate them independently, and to have just 3 choices (yes/no/don't know) instead of 4 choices (negative/no/positive/don't know) like the tool of Lindblad et al. (231) or the tool of Virani et al. (238). An example of suggestions for modification of "Organizational impact" dimension:

Organization impact

The organizational impact is coded regarding the overall impact on process of care from pharmacists' judgement/perception.

Indicators	**yes**	**no**	**don't know**
Time savings			
Improved security of working			
Improved knowledge			
Facilitating professional tasks			
Facilitating teamwork			
Facilitating continuity of care			

With regard to the organizational impacts of PIs, it is clear that further study should aim to refine and clarify these impacts. Firstly, benefits of PIs from perceptions of different HCPs

including physicians, nurses can be exploited through qualitative studies. Then, these data can be useful to give clear definitions of the "organizational impact" dimension and examples for ratings.

2.1.5. Probability

As explained in the section "Development of the CLEO tool", in most cases, the determination of the probability of impacts of PIs was difficult to estimate. Generally, in order to improve the consistency of judgement of probability between raters, studies only select and code the most likely harm prevented, request opinion of experts most familiar with these events and review how often it occurred in the literature. To simplify the new tool, we asked evaluators to rate according to the most likely consequence expected for the "clinical impact" dimension, not the worst/best one, and did not require determining the numerical probability.

However, if researchers want to calculate the cost avoidance related to "clinical impact", the estimate of probability is necessary to specify the cost avoidance as many methods presented in the section "**Methods for estimation of cost avoidance related to pharmacist interventions**". Furthermore, the probability can be used to classify risk levels as presented in the section "**Tools of risk assessment**".

2.1.6. Use of the CLEO tool and interpretation of results of ratings

Each dimension can be used independently. For examples, some studies prefer to use only "Clinical impact" dimension, others want to use both "Clinical impact" and "Economic impact" while others will use all three dimensions. When we can conduct an economic study with a rigor method to calculate the benefit: cost ratio of each PI as discussed above, it is easy to judge the value of the PI and compare it to other PIs. However, it is time consuming and difficult to conduct. Then, one question raised is that how to combine three codes of impacts for each PI into a single code when we don't conduct an economic study with a rigor method. Whether do we judge one impact (e.g. clinical impact) more important than other impacts (e.g. economic or organizational impact)? If yes, how is this distribution of importance and is it the same for all types PIs. There are 9 x 6 = 54 different combinations of three codes of the CLEO (page 133). It is obvious the PIs having the (4C, 1E, 1O) code is likely to provide more value than the PIs having the (-1C, -1E, -1O). However, other comparisons are not always easy. One factors need to be considered is the costs for providing the PI (e.g. time of pharmacists involved). Further studies need to be conducted to response to these questions.

2.1.7. Modification of the CLEO tool for use in community pharmacies

The CLEO tool which was constructed and tested to evaluate the impacts of PIs done in hospitals; therefore, without modification it is not suitable to be used in ambulatory care settings (such as community pharmacy). The context of practice by pharmacists between hospitals and community pharmacies is different. Firstly, hospital pharmacists are likely to expect that their PIs can prevent the inpatient from the initiated or lengthened hospitalization while community pharmacists are likely to expect that their PIs can prevent the outpatient from physician office visit. Secondly, community pharmacists often provide a majority of PIs

aiming to optimization of drug use such as change of drug form, administration schedule, drug equivalence or providing advice/information in health promotion while few PIs have a major impacts. Therefore, a tool used in community pharmacy need to be specific and sensitive enough to detect these minor impacts. Thirdly, medication adherence/compliance is one of major problems for outpatients who visited community pharmacy compared to higher medication compliance for inpatients in hospital. How a specific tool can not only evaluate the impact of PIs but also favor the role of community pharmacy in improvement in medication adherence need to be discussed. Concerning the "Economic impact", from which point of view, the cost savings related to drug/monitoring induced by the PI should be evaluated: the patient's, medical insurances', community pharmacy's or the society's? Concerning the "Organization impact", there are some raised questions. Is the "Organization impact" still necessary to keep in a tool? If we keep this dimension, how should we modify it? In hospital, pharmacists always work closely with physicians and nurses in big teams. In many cases, hospital pharmacists contact more frequently health care providers (HCPs) than patients. Therefore, HCPs become "major clients" of their services and PIs. Therefore, many PIs have organization impacts from the HCPs' point of view. However, in community pharmacy, pharmacists work in a small and simple organizational system, focus more in the patients and have a "weak" relationship with other HCPs. It is likely that the "Organizational impact" is not so essential.

2.2. Validity of research methods

2.2.1. Internal validity

The main threats to internal validity are confounding, maturation, testing, selection bias, and analytic methods.

Concerning threat of confounding, results of agreement between raters in the two studies may be effected by perceptions of raters themselves rather than functionality of the tool itself. Threat of maturation is present when evaluators rate more consistently over time due to their experience/familiarity with the tool. To minimize this threat, we chose a variety of raters with different profiles. In the first study, seven pharmacists who practice in six different French hospitals were included. These seven pharmacists were involved in process of development and the refinement of the tool over a two-year period; therefore, they understood well the tool. This was a bias. To overcome this bias, in the second study, we required pharmacists and physicians who did not belong to research group rated their PIs in daily practice. The pharmacists who intervened in the CPU, the ward-base pharmacist and four multi-disciplinary groups of expert (each consisting of a specialist, a pharmacist at the CPU, a clinical pharmacist, a pharmacist in pharmacovigilance center) were required to raise their opinions on impacts of PIs by using the CLEO tool. However, for intra-rater reliability in the first study, results of one rater were missing. Thus, the result may be biased.

Testing bias occurs when evaluators are aware of that their ratings will be compared to ones of their colleagues; then they are likely to rate based on what researchers expect rather than based on their true perceptions. To minimize this threat, we informed clearly all evaluators

that the objective of studies aims to test the functionality of the tool and not achieve perfect concordance between raters. Such that, all evaluators were required to rate based on their true opinions.

Selection bias of PIs could threaten the internal validity of a study when PIs are selected in a nonrandom fashion. In the first study, we selected non-randomly PIs to balance sample size, variety of interventions, scores. In the second study, we selected all PIs during a 10-week study period. Two different sampling strategies help to overcome the weakness and take the advantages of each one.

Concerning analytic method, evaluating interrater agreement (IRA) or interrater reliability (IRR) is fundamental to the evaluation of research tools. However, many statistical tests exist and there is debate in the statistical literature about the appropriateness of the different statistical tests. IRA is defined as the degree to which scores/ratings are identical, whereas reliability relates to the extent of variability and error inherent in a measurement (263). Hence, we used both IRA and IRR but focused more in IRR. Although the kappa score was commonly used to assess the IRR between raters in literature, the k statistic may be difficult to interpret. First, mathematically, a value of +1 is difficult to achieve and is only observed in extreme circumstances. It has been suggested that this upper limit is unnecessarily high and realistically may not be achievable in the context of some research studies. Second, the k score depends on the number of categories (263). The more categories there are, the more difficult it is to classify correctly and the lower the resulting k value. In our results, the strength of agreement and reliability can be considered quite high given the large number of categories, raters and PIs involved. Third, kappa is sensitive to bias between raters and the overall prevalence of responses. In some instances, a relatively high proportion of observed agreement can result in a low kappa value and an unbalanced or biased distribution of responses can result in a higher kappa value than a more balanced distribution of responses. Hence, a low kappa value may not always be indicative of low agreement (263). This event occurred in our studies for *"organizational impact"* dimension in which a high agreement (62%) existed with a low kappa (kw = 0.39) in the first study of validation of the CLEO tool[4]. Further statistical analysis is needed to correct for any potential bias in the kappa value. Furthermore, we used the weighted kappa instead of kappa because it is more suitable for rating items that have between 3 and 10 ordinal categories, and as expected, weighted kappa values tend to be higher than unweighted kappa values. Therefore, comparison to other studies need to consider this point.

2.2.2. External validity

Inevitably, the evaluated studies suffered from some problems with external validity. The study sample may have included unique characteristics that make the results unique to the study.

[4] Thi Ha VO et al. Validation of the CLEO tool for assessment of significance of pharmacist interventions in general context.

First, in the first study, seven raters were involved to develop another tool for assessing impacts of PIs in 2004. Their previous experience may influence research results of this work. However, it may be a minor concern because it occurred ten years ago.

Second, in the first study, to improve the results obtained during the second rating, if the investigator found one evaluator rated differently with majority of raters, he/she could be required to rate again in blinding others' rating and his/her previous rating. The objective was to prevent cognitive or unintentional errors of evaluators. However, only few PIs were needed to do so. Therefore, this bias was minor.

Third, in the second study, the tool was used by pharmacists and physicians in one CPU. And the specific characteristics of this service (e.g., types of DRPs and PIs) may be not representative for other services or settings. Other more broad-based, multicenter, and longitudinal studies are needed to assess the CLEO tool in a variety of settings. In the near future, the CLEO tool will be tested for use in a geriatric service at a hospital in Lyon, France.

Fifth, the reproducibility of results of validation of the French-written CLEO tool needs to be tested in other languages and countries. The CLEO tool was originally constructed and written in French and was tested in two studies by French pharmacists and physicians for PIs conducted in hospitals. The translation and adaptation of the tool from one language and culture/country to another needs follow the International Test Commission guidelines on the adapting of tests (264). Four kinds of equivalence need to be considered: linguistic equivalence, conceptual equivalence, functional equivalence and metric equivalence. There are a variety of different approaches to test adaptation: one might develop a new tool to meet one's needs, others want to validate the same CLEO tool in their countries. Steps in the translation and adaptation process includes: translate and adapt the tool, review the translated of adapted version of the tool, adapt the draft tool on the basis of the comments of the reviewers, pilot-test the tool, field-test the tool, standardize the score, perform validation research as needed, develop a manual and other documents for users of the tool, train users, collect reactions from users (264). We are planning to cooperate with Swiss and Vietnamese colleagues for the translation and adaptation of the CLEO tool in these two countries.

3. Perspectives

The present work generates some perspectives. We presented some perspectives for further research on the above section "Validity of findings". Here we will discuss other approaches for research.

3.1. Role of pharmacists in outcome research

Outcome studies have emerged as a primary research focus for pharmacy and other medical disciplines as a result of demands by health care payers and the public for justification of the rising costs of care. The role of pharmacists in pharmaceutical outcomes research should be to determine the value of pharmaceutical services on the basis of their relative impact. To achieve this, research should be directed toward:

- Improving our knowledge of which pharmaceutical processes and structures improve specific patient outcomes,
- Determining the degree to which these processes and structures improve outcomes,
- Assessing the types of outcomes most affected by pharmaceutical services and programs, and
- Improving methods of measuring outcomes.

Some studies show promise of positive impacts of pharmaceutical services. However, it is possible that some of pharmacy's high-profile, heavily promoted services and products do not provide significant improvement in outcomes. Some pharmacists may worry that pharmacy, as widely practiced, may not have as much of an effect on outcomes as once believed. Pharmacists must be sufficiently committed to improving outcomes to accept this possibility and the possibility that some services and products may need to be altered or discarded (11).

Pharmacists promote their value best within their own professional journals. However, if pharmacist published more in non-pharmacy literature, this would allow other health care professionals the opportunity to see how pharmacists add value.

3.2. Evaluation of impact of PIs

3.2.1. Integration of the CLEO tool into the Act-IP© website for quality improvement

The initial purpose of development of the CLEO tool is to integrate it into the Act-IP© website. The Act-IP© website was created 10 years ago. Before that time, practice of MR by French pharmacists in hospitals has just started and varied across hospital settings. The leading group "Standardizing and Demonstrating the value of clinical pharmacy activities" belonging to the SFPC had a good vision that developed a valid and standardized instrument for documentation of PIs. Diffusion of this instrument has created the first national trend of enhancement of MR in France through practice, collection and analysis of data and quality improvement (130). However, this instrument just describes characteristics of PIs, which means only process of PI practice collected. Furthermore, nowadays, in the period of economic crisis, the role of demonstration of value of PIs in term of both costs and potential outcomes is so important.

In a review of studies published between 1995 and 2008 in French hospitals by Morice et al. (121), of 24 studies selected, almost all studies (83%) measure the production of PI and 58% measure acceptance rate of PI. Few studies (25%) assess the potential clinical impact of PI and a poor number of studies (17%) evaluate the homogeneity of PI production among pharmacists. The French 4-level tool of Chedru et al.(220) which was developed in 1997 by modification of the Hatoum's tool was widely used in other studies in France. The inter-rater reliability of this tool was good in two studies. However, this tool has some limitations including (i) the cost saving was combined into "clinical impact" and was considered as "null impact", (ii) the number of levels was only four and (iii) validation process was not rigor. With many advantages of the new CLEO tool as well as some limitations needed to be improved, we hoped that our work will trigger many studies adopt it widely for testing and

use. At present, only the "Clinical impact" and "Economic impact" of the CLEO tool were valid, reliable and practical enough to will be integrated into the Act-IP© in the near future. This integration is expected to create the second national trend of enhancement of MR in France through demonstration of outcomes of PIs. A variety of epidemiological studies of MR can be conducted more effectively with this complete observatory of MR. Some kinds of these studies will be discussed in the below section.

3.2.2. Relationship between characteristics of medication review and their impacts

The impacts of MR depends mainly on how MR is conducted. Therefore, exploration of the relationship between characteristics of MR (e.g., level of MR, skills of pharmacists for providing MR, type of pharmacists, hospitals or ambulatory settings, whether PIs were accepted or not) and their impacts are needed. These data allow to improve quality and value of MR. For example, the study of Denneboom et al., the authors developed a risk-model for detecting patients at risk of DRPs, considered the inclusion of clinical relevance (265). DRPs were classified into those with low and those with (potential) clinical relevance. Factors possibly associated with DRPs (both for all and relevant problems) were identified. When including clinical relevance a shift in main problem categories is observed. Furthermore, the risk model for problems with clinical relevance contains more factors than the model which considered all problems.

It is also important that the intervention is reproducible, and this in turn depends upon a clear description of the intervention (37). There are different levels of MR, for example, from opportunistic review (level 0) to a clinical medication review involving the patient, the clinical records and the actual drugs (level 3) (46). Although the level 3 of MR may be seen as the golf standard, it is also the most expensive in time and other resources, and may not always be necessary (37). In contrary, a subgroup meta-analysis of 36 studies found that *clinical MR* but not *adherence support review* reduced hospitalization (9). Further studies should be conducted to determine when, where and how different types of MRs will be performed effectively.

The training, skills and experience of the pharmacist conducting the review are also important. While a very prescriptive protocol-led review may reduce the need for training, it also limits the potential of the review which takes account of the patient's individual situation and needs (37). Pharmacists should possess uniformity in skills for providing medication review according to recommendations of Singhal et al. (38). This can be addressed through uniform training, with skills assessment. If uniform training cannot be achieved or skill cannot be assessed, an alternative is to measure the level of pharmaceutical care provision through scales such as the Behavioral Pharmaceutical Care scale (266), the Pharmacist Implementation of Pharmaceutical Care Scale (267), or the Purdue Pharmacist Directive Guidance Scale (268). Differences in pharmaceutical care provision could then be incorporated into study results through statistical techniques such as ANCOVA (38).

Pharmacist-led medication review in community pharmacies or primary-care teams is expanding that is needed to evaluate.

3.2.3. Other methodologies of evaluation of impacts of PIs

Researchers have measured the process and outcomes of MR in many ways. These have varied from the observational to the randomized controlled trial (RCT), prospective to retrospective. Benefits of PIs proven in randomized, controlled, multicenter trials are considered as "gold evidence". Thus, such studies are needed. Power in study design can be improved through using larger great sample size, designing more effective interventions, choosing valid and sensitive variables of impacts and studying homogeneous high-risk populations, such as the elderly or AIDS patients who will likely benefits from pharmaceutical services.

4. Conclusion

The commitment to pharmaceutical care has given pharmacists new roles and responsibilities, namely to detect, resolve and prevent DRPs through PIs. The impacts and value of PIs to the patient, the health care system, healthcare providers and society are needed to be evaluated and documented in order to expand clinical pharmacy services.

We addressed some issues in this thesis. The work of the thesis:

1. Described a variety of theoretical models and frameworks which can be applied to evaluate impacts of PIs and synthetize them into an integrated model - the SP(ECH)O model which can provide the comprehensive picture of impacts of PIs.

2. Reviewed systematically existing tools for assessment potential significance of PIs. A variety of tools and methodologies for estimate of value of PIs were found and analyzed. An attempt to classification of these tools based on the 10-criteria scale of quality of tools was conducted, which will provide useful information for researchers who want to adopt or develop a new tool for local use. Some recommendations on characteristics of optimal tools for assessing potential impacts of PIs were suggested.

3. Developed and tested a new multidimensional tool, named the CLEO, for assessing potential impacts of PIs. The CLEO tool was a result from a review of theoretical models of evaluation, existing tools and inputs of clinical pharmacists' practice. The CLEO tool allows to evaluate **CL**inical and humanistic outcomes from the patient's perspective, **E**conomic impacts (cost savings) from the hospital's perspective and **O**rganizational impacts from HCPs' perspective. This 3-dimension tool allows interpreting different impacts together in order to obtain a complete picture of impacts of PIs.

4. Tested the CLEO tool for validity and inter-rater and intra-rater reliability, and user-friendliness in two studies. In the first study, a research group of 7 pharmacists was required to assess retrospectively PIs selected from the database Act-IP or their practice. The final version of the CLEO tool was used prospectively in daily practice in a specific service in the second study. An evaluation process included three steps: (i) an initial and immediate evaluation by the pharmacist who intervened, (ii) a peer-review evaluation by the ward-based pharmacist who can access to more complete patient information several days later, and (iii)

an evaluation in consensus by multi-disciplinary panels two month later. Concerning inter-rater reliability, the results obtained were *almost perfect* or *substantial* for "economic impact" dimension (kw = 0.93 and 0.61, respectively); *moderate* for "clinical impact" dimension (kw = 0.41 and 0.48, respectively); and *fair* (kw = 0.39 and 0.27, respectively) for "organizational impact" dimension in the two studies. Concerning intra-rater reliability, results were *slight* (kw = 0.38) for "clinical impact" and were *moderate* (kw = 0.70) for "economic impact" in the first study. Concerning validity tested in the second study, ratings of the pharmacist on ward were more consistent with those of expert panels than the pharmacists in the CPU in terms of "clinical impact" and "economic impact" (kw = 0.56 and 0.32 for clinical; kw = 0.75 and 0.53 for economic, respectively), but less consistent in term of "organizational impact" (kw = 0.11 and 0.17, respectively). Comparing to results of other tools in literature, we found that "clinical and economic impact" dimension are likely to be reliable and valid enough to be able to use independently in daily practice by pharmacists. However, inter-rater reliability of "organizational impact" dimension was better in the first study and worse in the second study, which requires further research.

Outcome studies have emerged as a primary research focus for pharmacy and other medical disciplines as a result of demands by health care payers and the public for justification of the rising costs of care. The role of pharmacists should be to determine the value of PIs and target PIs which have most value. The CLEO tool will contribute as a new multidimensional tool to research and evaluate value of PIs. For application the CLEO tool in other settings, it is necessary to keep in mind that whether the results of ratings using the CLEO tool are valid and reliable which not only depend on the functionality of the tool itself but also depend on factors related to process of ratings and opinions of evaluators. Therefore, strategies such as providing examples, training of ratings, review by a peer or review by a multidisciplinary panel need to be conducted in order to improve continuously validity and reliability of results of independent ratings by pharmacists.

REFERENCES

1. Agency for Healthcare Research and Quality. Medication errors. 2015 [updated 2015 March 2015; cited 2015 9 July]; Available from: http://psnet.ahrq.gov/primer.aspx?primerID=23.
2. Grabe DW, Low CL, Bailie GR, Eisele G. Evaluation of drug-related problems in an outpatient hemodialysis unit and the impact of a clinical pharmacist. Clin Nephrol. 1997;47(2):117-21.
3. Lakshmanan MC, Hershey CO, Breslau D. Hospital admissions caused by iatrogenic disease. Arch Intern Med. 1986 Oct;146(10):1931-4.
4. McKenney JM, Harrison WL. Drug-related hospital admissions. Am J Hosp Pharm. 1976 Aug;33(8):792-5.
5. Michel P, Quenon J, Djihoud A, Tricaud-Vialle S, de Sarasqueta A, Demecq S. Les événements indésirables graves liés aux soins observés dans les établissements de santé : premiers résultats d'une étude nationale (Enquête ENEIS). DRESS Etudes et Résultats 2005(398):1-16.
6. Trinh Duc A, Trombert Paviot B, Queneau P, Carpentier F, Bannwarth B, J B. Coût hospitalier des effets indésirables médicamenteux. Projection nationale à partir d'une enquête dans neuf Services d'Accueil et d'Urgences Journal d'Economie Médicale. 2006;24(1):19-27.
7. Kohn LT, Corrigan JM, Donaldson MS, editors. To Err is Human. Building a Safer Health System. Washington: National Academy Press; 1999.
8. ACCP. The definition of clinical pharmacy. Pharmacotherapy. 2008 Jun;28(6):816-7.
9. Hatah E, Braund R, Tordoff J, Duffull SB. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol. 2013 Jan;77(1):102-15.
10. Society of Hospital Pharmacists of Australia. SHPA Standards of Practice for Clinical Pharmacy. J Pharm Pract Res. 2005;35(2):122-46.
11. Holdford DA, Smith S. Improving the quality of outcomes research involving pharmaceutical services. Am J Health Syst Pharm. 1997;54(12):1434-42.
12. Overhage JM, Lukes A. Practical, reliable, comprehensive method for characterizing pharmacists' clinical activities. Am J Health Syst Pharm. 1999;56(23):2444-50.
13. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics. 1987;79(5):718-22.
14. Hatoum HT, Hutchinson RA, Witte KW, Newby GP. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction. Drug Intell Clin Pharm. 1988;22(3):252-9.
15. Ackroyd-Stolarz S, Hartnell N, Mackinnon NJ. Demystifying medication safety: making sense of the terminology. Res Social Adm Pharm. 2006 Jun;2(2):280-9.
16. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.
17. Hepler CD. Understanding adverse drug therapy outcomes. In: Hepler CD SR, editor. Preventing Medication Errors and Improving Drug Therapy Outcomes. Boca Raton: CRC Press; 2003.
18. Hepler CD, Grainger-Rousseau TJ. Pharmaceutical care versus traditional drug treatment. Is there a difference? Drugs. 1995 Jan;49(1):1-10.
19. American Society of Health-System Pharmacists. Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events, and adverse drug reactions. Am J Health Syst Pharm. 1998 Jan 15;55(2):165-6.

20. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med. 1995 Apr;10(4):199-205.
21. Reason J. Human Error. Cambridge: Cambridge University Press; 1990.
22. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991 Feb 7;324(6):377-84.
23. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care. 2000 Mar;38(3):261-71.
24. Franklin BD, Birch S, Savage I, Wong I, Woloshynowych M, Jacklin A, et al. Methodological variability in detecting prescribing errors and consequences for the evaluation of interventions. Pharmacoepidemiol Drug Saf. 2009 Nov;18(11):992-9.
25. Bernheim C, Schimitt E, Dufay E. Iatrogénie médicamenteuse nosocomiale et gestion des risques d'erreur méducamenteuse : à propos de l'analyse des notifications du réseau REEM. Oncologie. 2005;7(104-119).
26. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. JAMA. 1995;274(1):29-34.
27. Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983 and 1993. Lancet. 1998 Feb 28;351(9103):643-4.
28. Castelino RL, Sathvik BS, Parthasarathi G, Gurudev KC, Shetty MS, Narahari MG. Prevalence of medication-related problems among patients with renal compromise in an Indian hospital. J Clin Pharm Ther. 2011;36(4):481-7.
29. Reason J. Human error: models and management. BMJ. 2000 Mar 18;320(7237):768-70.
30. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA. 1995 Jul 5;274(1):35-43.
31. Fortescue EB, Kaushal R, Landrigan CP, McKenna KJ, Clapp MD, Federico F, et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. Pediatrics. 2003 Apr;111(4 Pt 1):722-9.
32. Czubak R, Tucker J, Zarowitz BJ. Optimizing drug prescribing in managed care populations - Improving clinical and economic outcomes. Dis Manage Health Outcomes 2004;12(3):147-67.
33. Bond CA, Raehl CL, Franke T. Clinical pharmacy services, hospital pharmacy staffing, and medication errors in United States hospitals. Pharmacotherapy. 2002 Feb;22(2):134-47.
34. Harrison JJ, Wang J, Cervenko J, Jackson L, Munyal D, Hamandi B, et al. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clin Transplant. 2012;26(2):E149-57.
35. Kaboli PJ, Hoth AB, McClimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care : A systematic review (English). Archives of internal medicine (1960). 2006;166(9):955-64.
36. Bond CA, Raehl CL. Clinical pharmacy services, pharmacy staffing, and hospital mortality rates. Pharmacotherapy. 2007 Apr;27(4):481-93.
37. Zermansky AG, Silcock J. Is medication review by primary-care pharmacists for older people cost effective?: a narrative review of the literature, focusing on costs and benefits. Pharmacoeconomics. 2009;27(1):11-24.

38. Singhal PK, Raisch DW, Gupchup GV. The impact of pharmaceutical services in community and ambulatory care settings: evidence and recommendations for future research. Ann Pharmacother. 1999 Dec;33(12):1336-55.
39. Chisholm-Burns MA, Kim Lee J, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, et al. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. Med Care. 2010 Oct;48(10):923-33.
40. Krska J, Rowe PH. Outcome measures: a sensitive approach. Int J Pharm Pract. 2010 Apr;18(2):125-7.
41. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol. 2008 Mar;65(3):303-16.
42. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Arch Intern Med. 2008 Apr 14;168(7):687-94.
43. Bond CA, Raehl CL, Franke T. Clinical pharmacy services, pharmacy staffing, and the total cost of care in United States hospitals. Pharmacotherapy. 2000 Jun;20(6):609-21.
44. Perez A, Doloresco F, Hoffman JM, Meek PD, Touchette DR, Vermeulen LC, et al. ACCP: economic evaluations of clinical pharmacy services: 2001-2005. Pharmacotherapy. 2009 Jan;29(1):128.
45. Pickard AS, Hung SY. An update on evidence of clinical pharmacy services' impact on health-related quality of life. Ann Pharmacother. 2006 Sep;40(9):1623-34.
46. Clyne W, Blenkinsopp A, Seal R. A Guide to Medication Review. 2008. Available at http://www.npc.nhs.uk/review_medicines/intro/resources/agtmr_web1.pdf (last accessed November 2011). 2008.
47. American Pharmacist Association and National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model. Available at http://www.pharmacist.com/sites/default/files/files/core_elements_of_an_mtm_practice.pdf (last accessed November 2011). 2008.
48. Australia Government, Department of Human Services. Home Medicines Review (HMR). Available at http://www.medicareaustralia.gov.au/provider/pbs/fourthagreement/hmr.jsp (last accessed August 2010). 2012.
49. Ontario Ministry of Health and Long-Term Care. MedsCheck. Availabe at http://www.health.gov.on.ca/en/pro/programs/drugs/medscheck/medscheck_original.aspx (last accessed September 2012). 2011.
50. Pharmacy Council of New Zealand. Medicines management: definition, levels, competence framework. Available at http://www.pharmacycouncil.org.nz/cms_show_download.php?id=124 (last accessed August 2011). 2006.
51. Société français de pharmacie clinique. Recommandation de Bonne Pratique de Pharmacie Clinique - Analyse Ordonnance. Available at http://www.sfpc.eu/fr/item1/finish/34-documents-sfpc-public/432-sfpcrecommandationbppharmacieclinqiueanalyseordonnancesept12/0.html (last accessed August 2014). 2012.
52. Dooley MJ, Allen KM, Doecke CJ, Galbraith KJ, Taylor GR, Bright J, et al. A prospective multicentre study of pharmacist initiated changes to drug therapy and patient management in acute care government funded hospitals. Br J Clin Pharmacol. 2004;57(4):513-21.

53. Rothschild JM, Churchill W, Erickson A, Munz K, Schuur JD, Salzberg CA, et al. Medication errors recovered by emergency department pharmacists. Ann Emerg Med. 2010;55:513-21.
54. Abdel-Qader DH, Harper L, Cantrill JA, Tully MP. Pharmacists' interventions in prescribing errors at hospital discharge: an observational study in the context of an electronic prescribing system in a UK teaching hospital. Drug Saf. 2010;33:1027-44.
55. The Society of Hospital Pharmacists of Australia Committee of Specialty Practice in Clinical Pharmacy. SHPA standards of practice for clinical pharmacy. In: Johnstone J, Vienet MD, editors. Practice Standards and Definitions. Melbourne: The Society of Hospital Pharmacists of Australia; 1996.
56. Koecheler JA, Abramowitz PW, Swim SE, Daniels CE. Indicators for the selection of ambulatory patients who warrant pharmacist monitoring. Am J Hosp Pharm. 1989 Apr;46(4):729-32.
57. Isaksen SF, Jonassen J, Malone DC, Billups SJ, Carter BL, Sintek CD. Estimating risk factors for patients with potential drug-related problems using electronic pharmacy data. IMPROVE investigators. Ann Pharmacother. 1999 Apr;33(4):406-12.
58. Barenholtz Levy H. Self-administered medication-risk questionnaire in an elderly population. Ann Pharmacother. 2003 Jul-Aug;37(7-8):982-7.
59. Gordon KJ, Smith FJ, Dhillon S. The development and validation of a screening tool for the identification of patients experiencing medication-related problems. The International Journal of Pharmacy Practice. 2005;13(4):187-93.
60. Krahenbuhl JM, Decollogny A, Bugnon O. Using the costs of drug therapy to screen patients for a community pharmacy-based medication review program. Pharm World Sci. 2008 Dec;30(6):816-22.
61. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. Ann Pharmacother. 2004 Sep;38(9):1369-76.
62. Roten I, Marty S, Beney J. Electronic screening of medical records to detect inpatients at risk of drug-related problems. Pharm World Sci. 2010 Feb;32(1):103-7.
63. Dreischulte T, Grant AM, McCowan C, McAnaw JJ, Guthrie B. Quality and safety of medication use in primary care: consensus validation of a new set of explicit medication assessment criteria and prioritisation of topics for improvement. BMC Clin Pharmacol. 2012;12:5.
64. Cottrell R, Caldwell M, Jardine G. Developing and implementing a pharmacy risk screening tool. Hospital Pharmacy Europe. 2013(71).
65. Falconer N, Nand S, Liow D, Jackson A, Seddon M. Development of an electronic patient prioritization tool for clinical pharmacist interventions. Am J Health Syst Pharm. 2014 Feb 15;71(4):311-20.
66. Rovers J, Miller MJ, Koenigsfeld C, Haack S, Hegge K, McCleeary E. A guided interview process to improve student pharmacists' identification of drug therapy problems. Am J Pharm Educ. 2011 Feb 10;75(1):16.
67. Meyer LD, Raymond CB, Rodrigue CM. Development and evaluation of a checklist for medication order review by pharmacists. Can J Hosp Pharm. 2011 May;64(3):199-206.
68. Calop J. Algoithme de validation de l'ordonnance. In: Calop J., Limat S., Fernandez B., editors. Pharmacie clinique et thérapeutique 3ème ed. Paris: Elsevie Masson; 2008.
69. Thérèse Dupin-Spriet. La validation d'ordonnance. Le moniteur des pharmacies et des laboratoires. 2003;2510(2):10-1.
70. Han-Dupont D. La validation d'ordonnance. Le moniteur des pharmacies et des laboratoires. 2003;2510(2):13-5.

71. Kassam R, Farris KB, Cox CE, Volume CI, Cave A, Schopflocher DP, et al. Tools used to help community pharmacists implement comprehensive pharmaceutical care. J Am Pharm Assoc (Wash). 1999 Nov-Dec;39(6):843-56.
72. Northern Health and Social Services Board. A guide to patient medication review. 2003.
73. Hurley SC. A Method of Documenting Pharmaceutical Care Utilizing Pharmaceutical Diagnosis. American Journal of Pharmaceutical Education. 1998;62:119-27.
74. Weed LL. Medical Records, Medical Education and Patient Care, Case Western Reserve Press, Cleveland OH. 1970.
75. Wallace C, Franson KL. Incorporation of ability-based outcome education into pharmacotherapeutics using an expanded S.O.A.P. format. Am J Pharm Educ. 1996;60:87-93.
76. Donnelly WJ, Brauner DJ. Why SOAP is bad for the medical record. Arch Intern Med. 1992 Mar;152(3):481-4.
77. Canaday BR, Yarborough PC. Documenting pharmaceutical care: creating a standard. Ann Pharmacother. 1994 Nov;28(11):1292-6.
78. Strand LM, Cipolle RJ, Morley PC. Documenting the clinical pharmacist's activities: back to basics. Drug Intell Clin Pharm. 1988;22(1):63-7.
79. Winslade NE, Bajcar JM, Bombassaro AM, Caravaggio CD, Strong DK, Yamashita SK. Pharmacist's management of drug-related problems: a tool for teaching and providing pharmaceutical care. Pharmacotherapy. 1997 Jul-Aug;17(4):801-9.
80. ASHP guidelines on a standardized method for pharmaceutical care. American Society of Health-System Pharmacists. Am J Health Syst Pharm. 1996 Jul 15;53(14):1713-6.
81. Pharmaceutical Care Network Europe Foundation. Classification of Drug Related Problems (revised 14-01-2010vm) V6.2. 2010 [updated 2010; cited 2013 January 20]; Available from: http://www.pcne.org/sig/drp/documents/PCNE%20classification%20V6-2.pdf.
82. Schaefer M. Discussing basic principles for a coding system of drug-related problems: the case of PI-Doc. Pharm World Sci. 2002 Aug;24(4):120-7.
83. van Mil JW, Westerlund LO, Hersberger KE, Schaefer MA. Drug-related problem classification systems. Ann Pharmacother. 2004 May;38(5):859-67.
84. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992 Oct;45(10):1045-51.
85. Morris CJ, Cantrill JA, Hepler CD, Noyce PR. Preventing drug-related morbidity--determining valid indicators. Int J Qual Health Care. 2002 Jun;14(3):183-98.
86. De Smet PA, Denneboom W, Kramers C, Grol R. A composite screening tool for medication reviews of outpatients: general issues with specific examples. Drugs Aging. 2007;24(9):733-60.
87. Bulloch MN, Olin JL. Instruments for evaluating medication use and prescribing in older adults. J Am Pharm Assoc. 2003 Sep-Oct;54(5):530-7.
88. Desrochers JF, Lemieux JP, Morin-Belanger C, Paradis FS, Lord A, Bell R, et al. Development and validation of the PAIR (Pharmacotherapy Assessment in Chronic Renal Disease) criteria to assess medication safety and use issues in patients with CKD. Am J Kidney Dis. 2011 Oct;58(4):527-35.
89. Cipolle RJ, Strand L, Morley P, Cipolle R. Pharmaceutical Care Practice: The Clinician's Guide, 2nd ed. New York: McGraw-Hill Companies; 2004 [cited.
90. ASHP Council on Professional Affairs. ASHP guidelines on documenting pharmaceutical care in patient medical records. Am J Health Syst Pharm. 2003 Apr 1;60(7):705-7.

91. Currie JD, Doucette WR, Kuhle J, Sobotka J, Miller WA, McDonough RP, et al. Identification of essential elements in the documentation of pharmacist-provided care. J Am Pharm Assoc (Wash). 2003 Jan-Feb;43(1):41-7; quiz 8-9.
92. AbuRuz SM, Bulatova NR, Yousef AM. Validation of a comprehensive classification tool for treatment-related problems. Pharm World Sci. 2006 Aug;28(4):222-32.
93. Hohmann C, Eickhoff C, Klotz JM, Schulz M, Radziwill R. Development of a classification system for drug-related problems in the hospital setting (APS-Doc) and assessment of the inter-rater reliability. J Clin Pharm Ther. 2012 Jun;37(3):276-81.
94. Hoth AB, Carter BL, Ness J, Bhattacharyya A, Shorr RI, Rosenthal GE, et al. Development and reliability testing of the clinical pharmacist recommendation taxonomy. Pharmacotherapy. 2007 May;27(5):639-46.
95. Westerlund T, Almarsdottir AB, Melander A. Drug-related problems and pharmacy interventions in community practice Int J Pharm Pract. 1999(7):40-50.
96. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. Int Journal Clin Pharm. 2012;34:43-52.
97. Allenet B, Bedouch P, Rose FX, Escofier L, Roubille R, Charpiat B, et al. Validation of an instrument for the documentation of clinical pharmacists' interventions. Pharm World Sci. 2006 Aug;28(4):181-8.
98. Schumock GT, Hutchinson RA, Bilek BA. Comparison of two systems for documenting pharmacist interventions in patient care. Am J Hosp Pharm. 1992 Sep;49(9):2211-4.
99. MacKinnon III GE, MacKinnon NJ. Documentation of Pharmacy Services. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy - A pathophysiologic Approach 7th New York: The McGraw-Hill Companies; 2008.
100. Boardman H, Fitzpatrick R. Self reported clinical pharmacist interventions under-estimate their input to patient care. Pharm World Sci. 2001 Apr;23(2):55-9.
101. Brock KA, Casper KA, Green TR, Pedersen CA. Documentation of patient care services in a community pharmacy setting. J Am Pharm Assoc (2003). 2006 May-Jun;46(3):378-84.
102. Rough SS, McDaniel M, Rinehart JR. Effective use of workload and productivity monitoring tools in health-system pharmacy, part 2. Am J Health Syst Pharm. 2010 Mar 1;67(5):380-8.
103. Rough SS, McDaniel M, Rinehart JR. Effective use of workload and productivity monitoring tools in health-system pharmacy, part 1. Am J Health Syst Pharm. 2010 Feb 15;67(4):300-11.
104. Pawloski P, Cusick D, Amborn L. Development of clinical pharmacy productivity metrics. Am J Health Syst Pharm. 2012 Jan 1;69(1):49-54.
105. Naseman RW, Lopez BR, Forrey RA, Weber RJ, Kipp KM. Development of an inpatient operational pharmacy productivity model. Am J Health Syst Pharm. 2015 Feb 1;72(3):206-11.
106. Gupta SR, Wojtynek JE, Walton SM, Botticelli JT, Shields KL, Quad JE, et al. Monitoring of pharmacy staffing, workload, and productivity in community hospitals. Am J Health Syst Pharm. 2006 Sep 15;63(18):1728-34.
107. Société français de pharmacie clinique. Recommandation de Bonne Pratique de Pharmacie Clinique - Niveaux Analyse Pharmaceutique. Available at http://www.sfpc.eu/fr/item1/finish/34-documents-sfpc-public/454-sfpcrecommandationbppharmacieclinique niveauanalysesept12/0.html (last accessed August 2014). 2012.

108. Gurwich EL. Comparison of medication histories acquired by pharmacists and physicians. Am J Hosp Pharm. 1983 Sep;40(9):1541-2.
109. Nester TM, Hale LS. Effectiveness of a pharmacist-acquired medication history in promoting patient safety. Am J Health Syst Pharm. 2002 Nov 15;59(22):2221-5.
110. Kwint HF, Faber A, Gussekloo J, Bouvy ML. The contribution of patient interviews to the identification of drug-related problems in home medication review. J Clin Pharm Ther. 2012;37(6):674-80.
111. Jameson JP, VanNoord GR. Pharmacotherapy consultation on polypharmacy patients in ambulatory care. Ann Pharmacother. 2001 Jul-Aug;35(7-8):835-40.
112. Ellis SL, Billups SJ, Malone DC, Carter BL, Covey D, Mason B, et al. Types of interventions made by clinical pharmacists in the IMPROVE study. Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers. Pharmacotherapy. 2000 Apr;20(4):429-35.
113. Shaw J, Seal R, Pilling M. Task force on medicines partnership and the national collaborative medicines management services programme. Room for review: a guide to medication review. . 2002 [updated 2002; cited 2013 6 Decembre]; Available from: http://www.npc.nhs.uk/review_medicines/intro/resources/room_for_review.pdf.
114. Barnett NL, Sanghani P. A coaching approach to improving concordance. International Journal of Pharmacy Practice. 2013;21(4):270-2.
115. Knez L, Laaksonen R, Duggan C. Evaluation of clinical interventions made by pharmacists in chemotherapy preparation. Radiol Oncol. 2010;44:249-56.
116. Kwint HF, Bermingham L, Faber A, Gussekloo J, Bouvy ML. The relationship between the extent of collaboration of general practitioners and pharmacists and the implementation of recommendations arising from medication review: a systematic review. Drugs Aging. 2013 Feb;30(2):91-102.
117. Currie JD, Chrischilles EA, Kuehl AK, Buser RA. Effect of a training program on community pharmacists' detection of and intervention in drug-related problems. J Am Pharm Assoc (Wash). 1997 Mar-Apr;NS37(2):182-91.
118. Kwint HF, Faber A, Gussekloo J, Bouvy ML. Completeness of medication reviews provided by community pharmacists. J Clin Pharm Ther. 2014 Feb 13.
119. Freeman CR, Cottrell WN, Kyle G, Williams ID, Nissen L. An evaluation of medication review reports across different settings. Int J Clin Pharm. 2013 Feb;35(1):5-13.
120. Marino J, Caballero J, Llosent M, Hinkes R. Differences in Pharmacy Interventions at a Psychiatric Hospital: Comparison of Staff Pharmacists, Pharmacy Faculty, and Student Pharmacists. Hosp Pharm. 2010;45(4):314-9.
121. Morice E, Gabriel-Bordenave C, Auclair V, Juste M, Roberge C. [Evaluation of prescription checking practices and interventions by pharmacists in French hospitals] Pharm Hosp Clin. 2011;46(4):e33–48.
122. Charpiat B, Conort O, Juste M, Rose FX, Roubille R, Bedouch P, et al. Mise à disposition de l'outil de codification des interventions pharmaceutiques de la Société française de pharmacie clinique : bilan à 10 ans et perspectives. Pharm Hosp Clin. 2015;50(1):125-35.
123. Struck P, Pharmacist S, Pedersen KH, Moodley P. A pilot study of pharmacist-initiated interventions in drug therapy in an Australian paediatric hospital. EJHP Science. 2007;13:105-12.
124. Hawkey CJ, Hodgson S, Norman A, Daneshmend TK, Garner ST. Effect of reactive pharmacy intervention on quality of hospital prescribing. BMJ. 1990;300(6730):986-90.
125. ISMP Canada. ISMP list of high-alert medications in community and ambulatory healthcare settings. 2014 [updated 2014; cited 2014 16 december]; Available from: https://www.ismp.org/communityRx/tools/ambulatoryhighalert.asp.

126. ISMP Canada. ISMP list of high-alert medications in acute care settings. 2014 [updated 2014; cited 2014 16 december]; Available from: https://www.ismp.org/tools/institutionalhighAlert.asp.
127. Institute for Healthcare Improvement. How-to Guide: Prevent Harm from High-Alert Medications. 2012 [updated 2012; cited 2014 16 december]; Available from: http://www.ihi.org/resources/Pages/Tools/HowtoGuidePreventHarmfromHighAlertMedications.aspx.
128. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol. 2007 Feb;63(2):136-47.
129. Bedouch P, Charpiat B, Conort O, Rose FX, Escofier L, Juste M, et al. Assessment of clinical pharmacists' interventions in French hospitals: results of a multicenter study. Ann Pharmacother. 2008 Jul;42(7):1095-103.
130. Bedouch P, Sylvoz N, Charpiat B, Juste M, Roubille R, Rose FX, et al. Trends in pharmacists' medication order review in French hospitals from 2006 to 2009: analysis of pharmacists' interventions from the Act-IP(c) website observatory. J Clin Pharm Ther. 2014 Oct 10.
131. Klopfer JD, Einarson TR. Acceptance of pharmacists' suggestions by prescribers: a literature review. Hosp Pharm. 1990 Sep;25(9):830-2, 4-6.
132. Barber ND, Batty R, Ridout DA. Predicting the rate of physician-accepted interventions by hospital pharmacists in the United Kingdom. Am J Health Syst Pharm. 1997 Feb 15;54(4):397-405.
133. Scarsi KK, Fotis MA, Noskin GA. Pharmacist participation in medical rounds reduces medication errors. Am J Health Syst Pharm. 2002 Nov 1;59(21):2089-92.
134. Anderegg SV, DeMik DE, Carter BL, Dawson JD, Farris K, Shelsky C, et al. Acceptance of Recommendations by Inpatient Pharmacy Case Managers: Unintended Consequences of Hospitalist and Specialist Care. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2013;33(1):11-21.
135. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA. 1999;282(3):267-70.
136. Lee AJ, Boro MS, Knapp KK, Meier JL, Korman NE. Clinical and economic outcomes of pharmacist recommendations in a Veterans Affairs medical center. Am J Health Syst Pharm. 2002 Nov 1;59(21):2070-7.
137. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units (English). Archives of internal medicine (1960). 2003;163(17):2014-8.
138. de Almeida Neto AC, Chen TF. When pharmacotherapeutic recommendations may lead to the reverse effect on physician decision-making. Pharm World Sci. 2008 Jan;30(1):3-8.
139. Fijn R, Van den Bemt PM, Chow M, De Blaey CJ, De Jong-Van den Berg LT, Brouwers JR. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol. 2002 Mar;53(3):326-31.
140. Koh Y, Kutty FB, Li SC. Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. Ther Clin Risk Manag. 2005 Mar;1(1):39-48.
141. Vessal G. Detection of prescription errors by a unit-based clinical pharmacist in a nephrology ward. Pharm World Sci. 2010;32:59-65.
142. Niquille A, Bugnon O. Relationship between drug-related problems and health outcomes: a cross-sectional study among cardiovascular patients. Pharm World Sci. 2010;32:512-9.

143. Société français de pharmacie clinique, editor. Pharmacie clinique générale. Paris MEDSI/McGRAW-HILL; 1990.
144. Buurma H, de Smet PA, van den Hoff OP, Egberts AC. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol. 2001 Jul;52(1):85-91.
145. Haavik S, Soeviknes S, Erdal H. Prescriptions from general practitioners and in hospital physicians requiring pharmacists ' interventions y. 2010.
146. Neville RG, Robertson F, Livingstone S, Crombie IK. A classification of prescription errors. J R Coll Gen Pract. 1989(39):110-2.
147. Kaushal R, Bates DW, Abramson EL, Soukup JR, Goldmann DA. Unit-based clinical pharmacists' prevention of serious medication errors in pediatric inpatients. Am J Health Syst Pharm. 2008 Jul 1;65(13):1254-60.
148. Kopp BJ, Mrsan M, Erstad BL, Duby JJ. Cost implications of and potential adverse events prevented by interventions of a critical care pharmacist. Am J Health Syst Pharm. 2007;64(23):2483-7.
149. Holland R, Smith R, Harvey I. Where now for pharmacist led medication review? J Epidemiol Community Health. 2006 Feb;60(2):92-3.
150. Holland R, Lenaghan E, Harvey I, Smith R, Shepstone L, Lipp A, et al. Does home based medication review keep older people out of hospital? The HOMER randomised controlled trial. BMJ. 2005 Feb 5;330(7486):293.
151. Grymonpre RE, Williamson DA, Montgomery PR. Impact of a pharmaceutical care model for noninstitutionalised elderly: results of a randomised, controlled trial. Int J Pharm Pract. 2001;9:235-41.
152. Donabedian A. The quality of medical care. Science. 1978;200(4344):856-64.
153. Donabedian A. Evaluating the quality of medical care. Milbank Mem Fund Q. 1966 Jul;44(3):Suppl:166-206.
154. Stafford AC, Bindoff IK, Tenni PC, Peterson GM, Doran CM. A methodological framework for estimating the clinical and economic value of community pharmacists' clinical interventions using expert opinion. J Clin Pharm Ther. 2011;37(4):378-85.
155. Farris KB, Kirking DM. Assessing the quality of pharmaceutical care. II. Application of concepts of quality assessment from medical care. Ann Pharmacother. 1993;27(2):215-23.
156. Schmidt IK, Claesson CB, Westerholm B, Nilsson LG. Physician and staff assessments of drug interventions and outcomes in Swedish nursing homes. Ann Pharmacother. 1998;32(1):27-32.
157. McLennan DN, Dooley MJ, Brien JE. Beneficial clinical outcomes resulting from pharmacist interventions. J Oncol Pharm Pract. 1999;5(4):184-9.
158. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
159. Carayon P, Schoofs Hundt A, Karsh BT, Gurses AP, Alvarado CJ, Smith M, et al. Work system design for patient safety: the SEIPS model. Qual Saf Health Care. 2006 Dec;15 Suppl 1:i50-8.
160. Chui MA, Mott DA, Maxwell L. A qualitative assessment of a community pharmacy cognitive pharmaceutical services program, using a work system approach. Res Social Adm Pharm. 2012 May-Jun;8(3):206-16.
161. Martini M. La qualité de l'analyse pharmaceutique des traitements médicamenteux au centre hospitalier de Luneville Nancy: Université Henri Poincare - Nancy 1; 2010.
162. Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. Clin Ther. 1993;15(6):1121-32.

163. Grauer D, Lee J, Odom T, Osterhaus J, Sanchez L, Touchette D, editors. Pharmacoeconomics and Outcomes. Kansas, USA: American College of Clinical Pharmacy 2003.
164. National Patient Safety Agency. A risk matrix for risk managers. London; 2008 [updated 2008; cited 2015 Oct 19]; Available from: http://www.npsa.nhs.uk/nrls/improvingpatientsafety/patient-safety-tools-and-guidance/risk-assessment-guides/risk-matrix-for-risk-managers/.
165. U.S. Department of Veterans Affairs. Safety Assessment Code (SAC) Matrix; 2013. http://www.patientsafety.va.gov/professionals/publications/matrix.asp. Accessed 9 Sept 2015.
166. Schumock GT. Methods to assess the economic outcomes of clinical pharmacy services. Pharmacotherapy. 2000;20(10 Pt 2):243S-52S.
167. Svensson S, Menkes DB, Lexchin J. Surrogate outcomes in clinical trials: a cautionary tale. JAMA Intern Med. 2013 Apr 22;173(8):611-2.
168. Gyllensten H, Jonsson AK, Rehnberg C, Carlsten A. How are the costs of drug-related morbidity measured?: a systematic literature review. Drug Saf. 2012 Mar 1;35(3):207-19.
169. Drummond M, Stoddart G, Torrance G, editors. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford Medical Publications; 1997.
170. Schumock GT, Michaud J, Guenette AJ. Re-engineering: an opportunity to advance clinical practice in a community hospital. Am J Health Syst Pharm. 1999 Oct 1;56(19):1945-9.
171. Harrison DL, Bootman JL, Cox ER. Cost-effectiveness of consultant pharmacists in managing drug-related morbidity and mortality at nursing facilities. Am J Health Syst Pharm. 1998 Aug 1;55(15):1588-94.
172. Lai L. Benefit analysis of pharmaceutical care in a medicaid population—from a budgetary perspective. J Manag Care Pharmacy. 1998;4(3):303-8.
173. Schulman K, Burke J, Drummond M, Davies L, Carlsson P, Gruger J, et al. Resource costing for multinational neurologic clinical trials: methods and results. Health Econ. 1998 Nov;7(7):629-38.
174. Benrimoj SI, Langford JH, Berry G, Collins D, Lauchlan R, Stewart K, et al. Economic impact of increased clinical intervention rates in community pharmacy. A randomised trial of the effect of education and a professional allowance. Pharmacoeconomics. 2000;18(5):459-68.
175. Nesbit TW, Shermock KM, Bobek MB, Capozzi DL, Flores PA, Leonard MC, et al. Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. Am J Health Syst Pharm. 2001;58(9):784-90.
176. Crealey GE, Sturgess IK, McElnay JC, Hughes CM. Pharmaceutical care programmes for the elderly: Economic issues (English). PharmacoEconomics (Auckland). 2003;21(7):455-65.
177. Chisholm-Burns MA, Graff Zivin JS, Lee JK, Spivey CA, Slack M, Herrier RN, et al. Economic effects of pharmacists on health outcomes in the United States: A systematic review. Am J Health Syst Pharm. 2010 Oct 1;67(19):1624-34.
178. Peterson G, Tenni P, Jackson S, Bereznicki L, Hughes J, Kong D, et al. PROMISe Intervention Study - Final report to the Pharmacy Guild of Australia. 2003 [updated 2003; cited 2015 Sept 28]; Available from: http://goo.gl/hUI1Mi.
179. de Clifford J-M, Blewitt P, Lam SS, Leung BK. How do Clinical Pharmacists spend their Working Day? A Time-and-Motion Study. Journal of Pharmacy Practice and Research. 2012;42:134-9.
180. Hubault M. Analyse pharmaceutique des prescriptions en services de rééducation neurologique : Étude de situations à risque d'erreur de prescription & Évaluation de l'impact

clinique et économique des interventions pharmaceutiques. Lyon: Université Claude Bernard – Lyon 1; 2015.
181. Nerich V, Borg C, Villanueva C, Thiery-Vuillemin A, Helias P, Rohrlich PS, et al. Economic impact of prescribing error prevention with computerized physician order entry of injectable antineoplastic drugs. J Oncol Pharm Pract. 2013 Mar;19(1):8-17.
182. Armoiry X, Lassiaz C, Jurus V, Charpiat B. Analyse pharmaceutique des prescriptions avant et après informatisation. La Presse Médicale. 2007;36(3):410-8.
183. Rose F-X, Escofier L, Conort O, Charpiat B, Roubille R, Juste M, et al. Etude multicentrique de l'impact économique des interventions pharmaceutiques. Gestions hospitalières. 2009(490):548-54.
184. Coursier S, Bontemps H, Brantus JF, Allenet B. [Economic impact of pharmacist's interventions: illustration in a rheumatology ward]. J Pharm Belg. 2008 Dec;63(4):103-9.
185. Mutnick AH, Sterba KJ, Peroutka JA, Sloan NE, Beltz EA, Sorenson MK. Cost savings and avoidance from clinical interventions. Am J Health Syst Pharm. 1997 Feb 15;54(4):392-6.
186. Kausch C, Sean P, Boelle P-Y, Paye F, Beaussier M, Parc R, et al. Impact économique et intégration d'un pharmacien clinicien dans un service de chirurgie digestive. J Pharm Clin. 2005;24(2):90-7.
187. Carter BL, Malone DC, Valuck RJ, Barnette DJ, Sintek CD, Billups SJ. The IMPROVE study: background and study design. Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers. Am J Health Syst Pharm. 1998 Jan 1;55(1):62-7.
188. Bedouch P, Allenet B, Labarere J, Foroni L, Leger S, François D, et al. Analyse médico-économique des pratiques de prescription des fluoroquinolones injectables. J Econ Medicale. 2004;22(6):199-306.
189. Cousins D, Gerrett D, Luscombe D. Reliability and validity of hospital pharmacists' clinical intervention data. Am J Health Syst Pharm. 1997;54(14):1596-603.
190. Kausch C, Sean PT, Boelle P-Y, Paye F, Beaussier M, Parc R, et al. Impact économique et intégration d'un pharmacien clinicien dans un service de chirurgie digestive. J Pharm Clin. 2005;24(2):90-7.
191. Neville HL, Chevalier B, Daley C, Nodwell L, Harding C, Hiltz A, et al. Clinical benefits and economic impact of post-surgical care provided by pharmacists in a Canadian hospital. Int J Pharm Pract. Jun;22(3):216-22.
192. Rose F-X, Escofier L, Conort O, Charpiat B, R. R. Etude multicentrique de l'impact économique des interventions pharmaceutiques. Gestions hospitalières. 2009(490):548-54.
193. Gyllensten H, Hakkarainen KM, Jonsson AK, Andersson Sundell K, Hagg S, Rehnberg C, et al. Modelling drug-related morbidity in Sweden using an expert panel of pharmacists'. Int J Clin Pharm. 2012 Aug;34(4):538-46.
194. Bayliff CD, Einarson TR. Physician assessment of pharmacists' interventions - a method of estimating cost avoidance and determining quality assurance. Can J Hosp Pharm. 1990;43(4):167-71, 95.
195. Westerlund T, Marklund B. Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J Clin Pharm Ther. 2009;34(3):319-27.
196. Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother. 1992;26(12):1580-4.
197. Garfield S, Reynolds M, Dermont L, Franklin BD. Measuring the severity of prescribing errors: a systematic review. Drug Saf. 2013 Dec;36(12):1151-7.
198. Iafrate RP, Smith PD. Documenting medication errors averted by pharmacists. Am J Hosp Pharm. 1986;43:1672.

199. Blum KV, Abel SR, Urbanski CJ, Pierce JM. Medication error prevention by pharmacists. Am J Hosp Pharm. 1988;45(9):1902-3.
200. Lesar TS, Briceland LL, Delcoure K, Parmalee JC, Masta-Gornic V, Pohl H. Medication prescribing errors in a teaching hospital. JAMA. 1990;263(17):2329-34.
201. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA. 1997;277(4):312-7.
202. Lesar TS, Lomaestro BM, Pohl H. Medication-prescribing errors in a teaching hospital. A 9-year experience. Arch Intern Med. 1997;157(14):1569-76.
203. Ho L, Brown GR, Millin B. Characterization of errors detected during central order review. Can J Hosp Pharm. 1992;45(5):193-7.
204. Dean BS, Barber ND. A validated, reliable method of scoring the severity of medication errors. Am J Health Syst Pharm. 1999;56(1):57-62.
205. Hick HL, Deady PE, Wright DJ, Silcock J. The impact of the pharmacist on an elective general surgery pre-admission clinic. Pharm World Sci. 2001;23(2):65-9.
206. Lee JY, Leblanc K, Fernandes OA, Huh JH, Wong GG, Hamandi B, et al. Medication reconciliation during internal hospital transfer and impact of computerized prescriber order entry. Ann Pharmacother. 2010;44(12):1887-95.
207. Taxis K, Dean B, Barber N. The validation of an existing method of scoring the severity of medication administration errors for use in Germany. Pharm World Sci. 2002;24:236-9.
208. National Coordinating Council for Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. 2011. http://www.nccmerp.org/types-medication-errors. Accessed 9 Sept 2015 [cited 2013 March 5].
209. Van den Bemt PM, Postma MJ, van Roon EN, Chow MC, Fijn R, Brouwers JR. Cost-benefit analysis of the detection of prescribing errors by hospital pharmacy staff. Drug Saf. 2002;25:135-43.
210. Davydov L, Caliendo GC, Smith LG, Mehl B. Analysis of clinical intervention documentation by dispensing pharmacists in a teaching hospital. Hosp Pharm. 2003;38(4):346-50.
211. Bobb A, Gleason K, Husch M, Feinglass J, Yarnold PR, Noskin GA. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med. 2004;164(7):785-92.
212. Gleason KM, McDaniel MR, Feinglass J, Baker DW, Lindquist L, Liss D, et al. Results of the Medications at Transitions and Clinical Handoffs (MATCH) study: an analysis of medication reconciliation errors and risk factors at hospital admission. J Gen Intern Med. 2010;25(5):441-7.
213. Quélennec B, Beretz L, Paya D, Blickle JF, Gourieux B, Andres E, et al. Potential clinical impact of medication discrepancies at hospital admission. Eur J Intern Med. 2013;24(6):530-5.
214. Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, et al. Unintended medication discrepancies at the time of hospital admission. Arch Intern Med. 2005;165(4):424-9.
215. Kwan Y, Fernandes OA, Nagge JJ, Wong GG, Huh JH, Hurn DA, et al. Pharmacist medication assessments in a surgical preadmission clinic. Arch Intern Med. 2007;167(10):1034-40.
216. Wong JD, Bajcar JM, Wong GG, Alibhai SM, Huh JH, Cesta A, et al. Medication reconciliation at hospital discharge: evaluating discrepancies. Ann Pharmacother. 2008;42(10):1373-9.

217. Coffey M, Mack L, Streitenberger K, Bishara T, De Faveri L, Matlow A. Prevalence and clinical significance of medication discrepancies at pediatric hospital admission. Acad Pediatr. 2009;9(5):360-5 e1.
218. Villanyi D, Fok M, Wong RY. Medication reconciliation: identifying medication discrepancies in acutely ill hospitalized older adults. Am J Geriatr Pharmacother. 2011;9(5):339-44.
219. Hatoum HT, Hutchinson RA, Elliott LR, Kendzierski DL. Physicians' review of significant interventions by clinical pharmacists in inpatient care. Drug Intell Clin Pharm. 1988;22(12):980-2.
220. Chedru V, Juste M. Medical evaluation of the clinical impact of pharmacist interventions [Evaluation médicale de l'impact clinique des interventions pharmaceutiques]. J Pharm Clin. 1997;16(4):254-8.
221. Guignon AM, Grain F, Allenet B, Brudieu E, Barjhoux C, Bosson J-L, et al. Evaluation de l'impact clinique des opinions pharmaceutiques dans un service de médecine spécialisée. J Pharm Clin. 2001;20(2):118-23.
222. Grangeasse L, Chaigneau L, Medjoub M, Larosa F, Limat S. Computerized and protocolled prescription of chemotherapy: residual iatrogenic risk and pharmacist interventions [Prescription informatisée et protocolisée des chimiothérapies: risque iatrogène résiduel et interventions pharmaceutiques]. J Pharm Clin. 2006;25:33-8.
223. Goarin C, Mugnier N. Clinical pharmacist activity in an oncology and haematology unit significantly improves and secures patient care. Pharm Hosp Clin. 2011;46:e24-e32.
224. Nerich V, Limat S, Demarchi M, Borg C, Rohrlich PS, Deconinck E, et al. Computerized physician order entry of injectable antineoplastic drugs: an epidemiologic study of prescribing medication errors. Int J Med Inform. 2010;79:699-706.
225. Bosma L, Jansman FG, Franken AM, Harting JW, Van den Bemt PM. Evaluation of pharmacist clinical interventions in a Dutch hospital setting. Pharm World Sci. 2008;30:31-8.
226. Lee J, McPherson ML. Outcomes of recommendations by hospice pharmacists. Am J Health Syst Pharm. 2006;63:2235-9.
227. Climenté-Marti M, Garcia-Manon ER, Artero-Mora A, Jimenez-Torres NV. Potential risk of medication discrepancies and reconciliation errors at admission and discharge from an inpatient medical service. Ann Pharmacother. 2010;44(11):1747-54.
228. Fernandez-Llamazares CM, Calleja-Hernández M-Á, Manrique-Rodríguez S, Pérez-Sanz C, Durán-García E, Sanjurjo-Sáez M. Prescribing errors intercepted by clinical pharmacists in paediatrics and obstetrics in a tertiary hospital in Spain. Eur J Clin Pharmacol. 2012;68:1339-45.
229. Fernández-Llamazares CM, Manrique-Rodríguez S, Pérez-Sanz C, Durán-García ME, Sanjurjo-Sáez M, Calleja-Hernández MA. Validation of a method for recording pharmaceutical interventions. J Clin Pharm Ther. 2012;37:459-63.
230. Somers A, Robays H, De Paepe P, Van Maele G, Perehudoff K, Petrovic M. Evaluation of clinical pharmacist recommendations in the geriatric ward of a Belgian university hospital. Clin Interv Aging. 2013;8:703-9.
231. Lindblad A, Alleyne A, Howorko J. Development and Initial Evaluation of a Software-Based Clinical Workload Measurement System for Pharmacists. Can J Hosp Pharm. 2007;60(5):295-301.
232. Elliott RA, Martinac G, Campbell S, Thorn J, Woodward MC. Pharmacist-led medication review to identify medication-related problems in older people referred to an Aged Care Assessment Team: a randomized comparative study. Drugs Aging. 2012;29(7):593-605.
233. Elliott RA, Woodward MC. Assessment of Risk Associated with Medication-Related Problems in Elderly Outpatients. J Pharm Pract Res. 2009;39:109-13.

234. Lewinski D, Wind S, Belgardt C, Plate V. Prevalence and safety-relevance of drug-related problems in German community pharmacies. Pharmacoepidemiol Drug Saf. 2010;19(2):141-9.
235. Rupp MT, DeYoung M, Schondelmeyer SW. Prescribing problems and pharmacist interventions in community practice. Med Care. 1992;30(10):926-40.
236. Caleo SUE, Benrimoj S, Collins D, Lauchlan R, Stewart KAY. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract. 1996;4(4):221-7.
237. Strong DK, Tsang GW. Focus and impact of pharmacists' interventions. Can J Hosp Pharm. 1993;46(3):101-8.
238. Virani A, Crown N. The Impact of a Clinical Pharmacist on Patient and Economic Outcomes in a Child and Adolescent Mental Health Unit. Can J Hosp Pharm. 2003;56:158-62.
239. Buurma H, De Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol. 2004;58:503-11.
240. Conort O BP, Juste M, Augereau L, Charpiat B, Roubille R, Allenet B. Validation d'un outil de codification des interventions de pharmacie clinique. J Pharm Clin. 2004;23(3):141-7.
241. Bedouch P, Charpiat B, Roubille R, Juste M, Rose FX, Escofier L, et al. [The French Society of Clinical Pharmacy website for the documentation and analysis of pharmacist's interventions: purpose, instructions and perspectives]. J Pharm Clin. 2007;26:40-4.
242. Charpiat B, Bedouch P, Conort O, Juste M, Rose FX, Roubille R, et al. Pharmacists' interventions on intravenous to oral conversion for potassium. Int J Clin Pharm. 2014 Jun;36(3):513-8.
243. National Coordinating Council for Medication Error Reporting and Prevention. NCC MERP index for categorizing medication errors. 2013 [updated 2013; cited]; Available from: http://www.nccmerp.org/pdf/indexColor2001-06-12.pdf.
244. Evaluation of the contribution of clinical pharmacists: inpatient care and cost reduction, 1988).
245. Nathan A, Goodyer L, Lovejoy A, Rashid A. 'Brown bag' medication reviews as a means of optimizing patients' use of medication and of identifying potential clinical problems. Fam Pract. 1999;16(3):278-82.
246. Taylor CT, Church CO, Byrd DC. Documentation of clinical interventions by pharmacy faculty, residents, and students. Ann Pharmacother. 2000;34(7-8):843-7.
247. Ewan MA, Greene RJ. Evaluation of mental health care interventions made by three community pharmacists - a pilot study. Int J Pharm Pract. 2001(9):225-34.
248. Needham DS, Wong IC, Campion PD. Evaluation of the effectiveness of UK community pharmacists' interventions in community palliative care. Palliat Med. 2002;16(3):219-25.
249. Knudsen P, Herborg H, Mortensen AR, Knudsen M, Hellebek A. Preventing medication errors in community pharmacy: frequency and seriousness of medication errors. Qual Saf Health Care. 2007;16:291-6.
250. Haavik S, Soeviknes S, Erdal H, Kjonniksen I, Guttormsen A, Granas AG. Prescriptions from general practitioners and in hospital physicians requiring pharmacists' interventions. Pharmacoepidemiol Drug Saf. 2011;20(1):50-6.
251. Granas AG, Berg C, Hjellvik V, Haukereid C, Kronstad A, Blix HS, et al. Evaluating categorisation and clinical relevance of drug-related problems in medication reviews. Pharm World Sci. 2010;32:394-403.
252. Wang Chin JM, Muller RJ, Lucarelli CD. A pharmacy intervention program: recognizing pharmacy's contribution to improving patient care. Hosp Pharm. 1995;30(2):120, 3-6, 9-30.

253. Indritz ME, Artz MB. Value added to health by pharmacists. Soc Sci Med. 1999 Mar;48(5):647-60.
254. Horne R, Weinmanb J, Hankinscd M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14:1-24.
255. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns. 1999 Jun;37(2):113-24.
256. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986 Jan;24(1):67-74.
257. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. Qual Health Care. 2001 Sep;10(3):135-40.
258. Duggan C, Bates I. Development and evaluation of a survey tool to explore patients' perceptions of their precribed drugs and need for drug information. Int J Pharm Pract. 2000;8:42-52.
259. Gourley GK, Gourley DR, La Monica Rigolosi E, Reed P, Solomon DK, Washington E. Development and validation of the pharmaceutical care satisfaction questionnaire. Am J Manag Care. 2001 May;7(5):461-6.
260. MacKeigan LD, Larson LN. Development and validation of an instrument to measure patient satisfaction with pharmacy services. Med Care. 1989 May;27(5):522-36.
261. Blalock SJ, Patel RA. Drug therapy concerns questionnaire: initial development and refinement. J Am Pharm Assoc (2003). 2005 Mar-Apr;45(2):160-9.
262. Krska J, Morecroft C, Poole H, Rowe P, Auckland R. Developing a medicines-related quality of life measure. Pharm World Sci. 2009;31:501.
263. Gisev N, Bell JS, Chen TF. Interrater agreement and interrater reliability: key concepts, approaches, and applications. Res Social Adm Pharm. 2013;9(3):330-8.
264. Geisinger KF. Testing and asessment in cross-cultural psychology. Handbook of Psychology: Assessment Psychology: John Wiley & Sons; 2003. p. 95-117.
265. Denneboom W, Dautzenberg MG, Grol R, De Smet PA. User-related pharmaceutical care problems and factors affecting them: the importance of clinical relevance. J Clin Pharm Ther. 2005;30(3):215-23.
266. Odedina FT, Segal R. Behavioral pharmaceutical care scale for measuring pharmacists' activities. Am J Health Syst Pharm. 1996 Apr 15;53(8):855-65.
267. Odedina FT, Hepler CD, Segal R, Miller D. The Pharmacists' Implementation of Pharmaceutical Care (PIPC) model. Pharm Res. 1997 Feb;14(2):135-44.
268. Gupchup GV, Wolfgang AP, Thomas J, 3rd. Development of a scale to measure directive guidance by pharmacists. Ann Pharmacother. 1996 Dec;30(12):1369-75.

Electronic Supplementary Material

ESM 1. Assessment of Risk of Bias in Studies

Risk of Bias	Score
A. The rigor of the sampling methodology of DRPs/PIs/patients (checking for possible selection bias)	
1. Number of DRPs/PIs/patients was less than 5 times the maximum number of categories of a dimension of a tool	1
2. Sampling of DRPs/PIs/patients was selected non-randomly or non-consecutively or from a setting which probably didn't cover all types of DRPs/PIs/patients	1
B. The profile of evaluators (checking for possible performance bias)	
3. Only 2 raters	1
4. Raters from only one group of health care professionals	1
5. Only internal or external raters	1
6. More half of raters involved in tool construction/data collection	1
C. The process of evaluation (checking for possible detection bias)	
7. Raters did not assess independently cases	1
8. The method did not blind raters from knowledge of which PIs were accepted by physicians	1
9. The method did not blind raters from knowledge of actual outcome of following-up of patient	1
D. Other bias	1
Total Score:	**10**
Assessment of Risk of Bias (ROB)	
High (H):	≥ 1
Low (L):	0
Unclear (U):	not enough information reported to judge

ESM 2: Criteria of quality of a tool for assessing significance of PIs

A. Structure of a tool	**Score**
1. A tool has 2 or more dimensions	1
2. A tool has at least one dimension which has 4 or more categories	1
B. Content of a tool	
3. A tool applies 2 or more approaches of assessment	1
4. A tool consists of indicator(s) related to cost savings	1
5. A tool consists of indicator(s) related to cost avoidance	1
6. A tool consists of humanistic indicator(s)	1
7. A tool consists of process-related indicator(s)	1
8. A tool consists of indicator(s) related to probability of consequences	1
C. Psychometric parameters of tools	
9. A tool has at least one of psychometric parameters (validity, inter- or intra-rater reliability) which presented a moderate or good agreement.	1
10. Risk of bias of a study which tested validity, inter- or intra-rater reliability of a tool was low.	1
Sum of scores:	**10**

ESM 3. Content and Structure of tools in 133 identified studies

- **Structure of each dimension of a tool is coded by 3 or 4-character code**; of which:

+ The **final number** indicates the **number of categories** of the dimension;

+ The **next final character** (**N** or **O**, respectively) indicates a **nominal** or **ordinal** dimension, respectively;

+ **One or two first characters** (**S, E, E1, E2, C, H, Pc**, **Pb**, or R, respectively) indicate aspect of impacts (**significance, economic impact, cost savings, cost avoidance, clinical impact, humanistic impact, process-related impact**, **probability**, or **risk,** respectively).

- **Approach of assessment:** Approach **3** is the estimation of potential significance of a PI. The approach **3A –** prediction of the potential consequences of DRPs in absence of a PI; approach **3B -** prediction of the potential consequences of an implemented PI.
- **PI** = pharmacist intervention**. DRP** = drug related problem**. "_"** = Not reported. **"+"** Reported. **"±"** Non-determined. "*" = Distinct tool

No.	Author(s), Published Year, Country	Structure of a tool	Approach of Assessment	Content of a tool					Notes
				Economic (E)	Clinical (C)	Humanistic (H)	Process-related (Pc)	Probability (Pb)	
1.1	Folli et al.* [36] 1987, USA	**CO3/**Severity of error (significant, serious, potentially lethal)	3A	_	+	_	_	_	The tool was adapted for use in many studies (Iafrate et al. [35], Blum et al. [37], Lesar et al. [42, 63, 64], Ho et al. [46], Overhage et al. [12])
1.2	Iafrate et al. [35] 1986, USA	**CO4/**Severity of error (minor, significant, serious, potentially lethal)	3A	_	+	_	_	_	Folli et al. [36]
1.3	Blum et al. [37] 1988, USA	**CO4/**Severity of error (minor, significant, serious, potential lethal)	3A	_	+	_	_	_	Folli et al. [36]

1.4	Lesar et al. [42] 1990, USA	**CO4/**Severity of error (problem order errors, potentially significant, potentially serious, potentially fatal or severe)	3A	_	+	_	_	_	Folli et al. [36]
1.5	Lesar et al. [63] 1997, USA	**CO4/**Severity of error (problem order errors, potentially significant, potentially serious, potentially fatal or severe)	3A	_	+	_	_	_	Adaption from the tool of Folli et al. [36]
1.6	Lesar et al. [64] 1997, USA	**CO4/**Severity of error (problem order errors, potentially significant, potentially serious, potentially fatal or severe)	3A						Adaption from the tool of Folli et al. [36]
1.7	Ho et al. [46] 1992, Canada	The tool of Folli et al. [36]	3A						
2.1	Hatoum et al.* [38] 1988, USA	(1) **SO6/**Impact on patient care (adverse significance, no significance, somewhat significant, very significant, extremely significant) (2) **E1O3/**Cost savings of drug therapy (negative, zero, positive) (3) **E1O3/**Cost savings of drug therapy monitoring (negative, zero, positive) (4) **E2O3/**Savings attributable to complication of drug therapy (negative, zero, positive) (5) **E2O3/**Savings in length of patient hospitalization (negative, zero, positive)	3B	E1, E2	+	±	+	_	The first dimension of the tool is the most commonly adapted one for use in other studies (26 of 133 studies)
2.2	Hatoum et al. [39] 1988, USA	The tool of Hatoum et al. [38]	3B						
2.3	Briceland et al. [30] 1992, USA	(1) **SO6/**Significance (Adverse significance, no significance, somewhat significant, significant, very significant, extremely significant) (2) **E1O3/**Cost savings (positive, no change, negative)	3B	E1	+	±	±	_	Hatoum et al. [38]
2.4	Eadon et al. [45] 1992, UK	Adaption from the tool of Hatoum et al. [38]	3B						

2.5	Chisholm et al. [54] 1995, USA	Adaption from the tool of Hatoum et al. [38]	3B						
2.6	Wernick et al. [58] 1996, USA	Adaption from the tool of Hatoum et al. [38]	3B						
2.7	Lucas et al. [65] 1997, Australia	(1) **SO6/**Clinical significance (adverse significance, no significance, somewhat significant, significant, very significant, extremely significant) (2) **E1O2/**Cost savings (yes/no)	3B	E1	+	±	±	_	Hatoum et al. [38] Eadon et al. [45]
2.8	Chisholm et al. [60] 1997, USA	Adaption from the tool of Hatoum et al. [38]	3B						
2.9	Grabe et al. [62] 1997, USA	Adaption from the tool of Hatoum et al. [38]	3B						
2.10	Smythe et al. [67] 1998, USA	Adaptation from the tool of Hatoum et al. [38]	3B						
2.11	Possidente et al. [72] 1999, USA	Adaption from the tool of Hatoum et al. [38]	3B						
2.12	Reddick et al.[76] 1999 USA	**SO5/**Significance (adverse significance, no significance, somewhat significant, significant, very significant)	3B	±	+	±	±	_	Hatoum et al. [38]
2.13	Nickerson et al. [95] 2005, Canada	Adaption from the tool of Hatoum et al. [38]	3B						
2.14	Wang et al. [117] 2008, Taiwan	Adaption from the tool of Hatoum et al. [38]	3B						
2.15	Bondesson et al. [144] 2012, Sweden	Adaption from the tool of Hatoum et al. [38]	3B						

3	Mueller et al.* [43] 1990, USA	(1) **SO6/**Clinical impact (adverse significance, no significance, somewhat significant, significant, very significant, extremely significant) (2) **E1O3/**Influence on drug cost (increase, decrease, no change) (3) **E1O3/**Influence on patient cost (increase, decrease, no change)	3B	E1	+	±	+	_	Hatoum et al. [38]
4.1	Chedru et al.* [59] 1997, France	**SO4/**Significance (no significance, significant, very significant, fatal)	3B	E1	+	+	_	_	Hatoum et al. [38]
4.2	Guignon et al.[80] 2001, France	Adaption from the tool of Chedru et al. [59]	3B						
4.3	Grangeasse et al. [99] 2006, France	Adaption from the tool of Chedru et al. [59] and of Hatoum et al. [38]	3B						
4.4	Goarin et al. [129] 2010, France	The tool of Chedru et al. [59]	3B						
4.5	Nerich et al. [133] 2010, France	The tool of Chedru et al. [59]	3B						x
5	Cousins et al.* [61] 1997, UK	(1) **SO6/**Significance (adverse significance, no significance, somewhat significant, very significant, extremely significant) (2) **EN5/**Economic impact (Savings in cost of drug therapy, Increase in cost of drug therapy, Savings in cost of laboratory tests, Savings in cost of complications, Savings in costs of hospitalization time)	3B	E1, E2	+	±	+	_	Modified the tool of Hatoum et al. [38]

6.1	Overhage et al.* [12] 1999, USA	(1) **CO5/**Severity of error (no error, minor, significant, serious, potentially lethal) (2) **SO6/**Value of service (adverse significance, not significant, somewhat significant, significant, very significant, extremely significant)	3A + 3B	E1	+	±	+	_	After reviewing literature, the two -dimension tool was constructed, tested and determined to be reliable. The tool was developed from the two famous tools: one of Hatoum et al. [38] et another of Folli et al. [36].
6.2	Bosma et al. [98] 2006, Netherland	Adaption from the tool of Overhage and Lukes [12]	3A + 3 B						
6.3	Lee et al. [100] 2006, USA	(1) **CO5/**Severity of drug related problems (not applicable, minor, significant, serious, potentially lethal) (2) **SO6/**Value of pharmacist intervention (adverse significance, not significant, somewhat significant, significant, very significant, extremely significant)							The tool was modified from the tool of Overhage and Lukes [12] for home-based hospice care.
6.4	Climenté-Marti et al. [125] 2010, Spain	Severity scores were adapted from the tool of Overhage et Lukes [12]	3A + 3B						x
6.5	Abdel-Qader et al. [124] 2010, UK	Adaption from the tool of Overhage and Lukes [12]	3A + 3B						x
6.6	Fernandez-Llamazares et al. [149] 2012, Spain	Adaption from the tool of Overhage and Lukes [12] (2) **SO6/**Value of service (adverse significance, not significant, somewhat significant, significant, very significant, extremely significant)	3A + 3B						
6.7	Fernandez-Llamazares et al. [148]	Impact of pharmacy service was modified slightly from the tool of Overhage and Lukes [12]	3A + 3B						

	2012, Spain								
6.8	Somers et al. [157] 2013, Belgium	Adaption from the tool of Overhage et al. [12]	3A + 3B						
7	Kopp et al.* [109] 2007, USA	(1) **SO5/**Severity of error (no error, minor, significant, serious, potentially lethal) (2) **SO6/**Value of service (adverse significance, not significant, somewhat significant, very significant, extremely significant) (3) CN4/Probability of Adverse Drug Events (none, potential, preventable-actual, nonpreventable-actual) (4) **E1O2/**Cost saving(yes/no) (5) **PbO5/**Probability of ADE occurring in the absence of the intervention (0; 0.01; 0.1; 0.4; 0.6)	3A + 3B	E1, E2	+	_	_	+	Leape et al.[163] and Overhage et al. [12]
8	Spinewine et al.* [102] 2006, Belgium	**SO5/**Clinical significance (deleterious, minor, moderate, major, extreme)	3B	E2	+	±	±	_	Hatoum et al. [38] Dooley et al. [21]
9	Neville et al.* [40] 1989, UK	**SO4/**Classification of error (potentially serious to patient, major nuisance, minor nuisance, trivial)	3A	_	+	+	+	_	
10	Hawkey et al.* [20] 1990, UK	(1) **CO4/**Degree of harm (unnoticed, noticed, harmful, lethal) (2) **PbO3/**Likelihood of occurrence (<5%, 5-20%, >20%) (3) **RO4/** Risk (none, minor, appreciable, major) (4) **E1O5/**Savings of drug cost (decrease of drug cost <50p, decrease of drug cost >50p, no change, increase of drug costs <50p, increase of drug costs >50p)	3A	E1	+	_	_	+	

11	Bayliff et al.* [41] 1990, Canada	(1) **SO5/**Effect (detrimental effect, no effect, minor positive effect, modest effect, marked effect) (2) **E2O2/**Avoided hospitalization (yes/no) (3) **E2O4/**Duration of prolonged hospitalization (1, 3, 5 days, a week or more)	3B	E2	+	±	_	_	
12	Strong et al.* [50] 1993, Canada	(1) **CO3/**Effect (detrimental effect, no effect, positive effect) (2) **CO2/**Life- saving (yes/no) (3) **SO2/**Increased quality of care (yes/no) (4) **CO2/**Avoidance of adverse effects (yes/no) (5) **E2O2/**Reduction of hospital stay (yes/no) (6) **E1O2/**Cost saving (yes/no) (7) **PcO3/**Physician education (yes/no)	3B	E1, E2	+	±	+	_	
13	Virani et al.* [87] 2003, Canada	(1) **SO5/**Perceived impact on patient care (detrimental effect, no effect, minor positive effect, moderate positive effect, marked positive effect) (2) **SO2/**Increased quality of care (yes/no) (3) **CO2/**Avoidance of adverse effect (yes/no) (4) **E1O2/**Potential cost savings (yes/no) (5) **CO2/**Improved response to medication (yes/no) (6) **HO2/**Improved patient adherence to medication (yes/no) (7) **E2O2/**Decreased hospital length of stay (yes/no)	3B	E1, E2	+	+	±	_	Strong et al. [50] Bayliff et al. [41]
14	Western Australian Clinical Pharmacists Group* [44] 1991, Australia	**SO4/**Clinical significance (minor, optimizing drug therapy, preventing major toxicity or end-organ damage, potentially life-saving)	3B	_	+	±	_	_	

15.1	Krass et al.* [73] 2000 Australia	(1) **SO6/**Clinical significance (negative effect, no effect, minor significance, significant, very significant, potentially life savings) (2) **E1O2/**Cost savings (yes/no)	3B	E1	+	±	±	_	Western Australian Clinical Pharmacists' Group [44]
15.2	Lövgren et al. [121] 2009, Australia	**SO6/**Clinical impact (negative, none , minor, significant, very significant, potentially life-saving)	3B	_	+	+	_	+	Western Australian Clinical Pharmacists Group [44]
16	Struck et al.* [113] 2007, Australia	(1) **SO5/**Severity (insignificant, minor, moderate, major, catastrophic) (2) **PbO5/**Possibility (3) **E?**	3A	E2, E?	+	_	_	+	Society of Hospital Pharmacists of Australia's guideline [19]
17.1	Elliott et al.* [23] 2009, Australia	(1) **SO5/**Severity of medication-related problem (insignificant, minor, moderate, major, catastrophic) (2) **PbO5/**Likelihood of consequence (rare, low, possible, likely, almost certain) (3) **RO5** (no, low, moderate, high, extreme)	3A	E2	+	_	_	+	Society of Hospital Pharmacists of Australia's guideline [19]. This is a risk matrix 5x5.
17.2	Elliott et al. [147] 2012, Australia	The tool of Elliott et al. 2009 [23]	3A						
18	Khalili et al.* [151] 2012, Iran	(1) **SO5/**Clinical significance (insignificant, minor, moderate, major, catastrophic) (2) **EO4/**Economic significance (insignificant, minor, moderate, major)	3A	+	+	±	_	_	Clinical significance was based on the Guideline of Society of Hospital Pharmacy of Australia [19]. Economic significance was adapted from the IMPROVE study.
19.1	Lipton et al.* [47] 1992, USA	**SO3/**Severity (0 = no problem, 1 = clinically significant but not life threatening, 2 = potentially life threatening or leading to serious injury or hospitalization, 9 = not enough information to make an assessment)	3A	E2	+	_	_	_	Numeric tool
19.2	Lalonde et al. [114] 2008, Canada	**SO3/**Significance (not clinically significant, clinically significant but not life-threatening, serious, not enough information to judge or not applicable)	3A	E2	+	_	_	_	Adaption of the tool of Lipton et al. [47]

20.1	Rupp et al.* [48] 1992, USA	(1) **CO2/**Adverse health consequence (yes/no) (2) **CN4/**Type of adverse health consequence (toxic, side effects; inadequate control; allergy/hypersensitivity; others) (3) **PbO7/**Probability of adverse health consequence (not at all, very unlikely, somewhat unlikely, neither unlikely or likely, somewhat likely, very likely, definitely) (4) **E2O5/**Intensity of health care utilization (hospital admission, urgent or emergence care, scheduled physician visit, self-care, or other)	3A	E2	+	_	_	+	A typical tool for estimating the cost avoidance of a PI
20.2	Rupp et al. [49] 1992, USA	**CO2/**Adverse health consequence (yes/no)	3A	_	+	_	_	_	The tool of Rupp et al. [48]
21	Tang et al.* [51] 1993, USA	(1) **SN3/**Effect of PIs (improvement of quality of care, reduce of cost, both) (2) **SO6/**Clinical significance (detrimental to patient, general information, a choice among several equally acceptable actions, improve level of care to acceptable standards, preserve one or more major organs, life-saving)	3B	E1	+	±	+	_	
22	Mason et al.* [52] 1994, USA	**SO4/**Clinical importance (cost savings only, minimal, moderate, and high clinical importance)	3A	E1	+	_	_	_	Lesar et al. [42]
23	Slaughter et al.* [53] 1994, Canada	(1) **PcN2/**Type of intervention (intervention event, information event) (2) **SO9/**Quality of intervention (extreme adverse significance, very adverse significance, adverse significance, somewhat adverse significance, no significance, somewhat significant, significant, very significant, extremely significant) (3) **E1O3/**Cost savings (decrease, increase, no change)	3B	E1	+	_	+	_	

24	Wang Chin et al.* [55] 1995, USA	(1) **CO2/**Decrease toxicity (yes/no) (2) **CO2/**Increase efficacy (yes/no) (3) **CO2/**Avoid drug interaction/allergy (yes/no) (4) **E1O2/**Decrease cost (yes/no) (5) **HO2/**Increase compliance (yes/no) (6) **SO2/**Others (yes/no)	3B	E1	+	+	_	_	
		Other piloted version: (1) **CO2/**Prevent toxicity/side effects (yes/no) (2) **CO2/**Prevent allergy/interaction (yes/no) (3) **CO2/**Improve efficacy (yes/no) (4) **HO2/**Improve compliance (yes/no) (5) **PcO2/**Facilitate continuity of care (yes/no) (6) **SO3/**Clinical significance (somewhat significant, significant, very significant) (7) **E1O2/**Financial significance (cost saving likely, cost saving unlikely)	3B	E1	+	+	+	_	
25	Caleo et al.* [56] 1996, Australia	(1) **CO2/**Adverse health consequence (yes/no) (2) **CN4/**Type of adverse health consequence (toxic, side effects; inadequate control; allergy/hypersensitivity; others) (3) **PbO7/** Probability of adverse health consequence (not at all, very unlikely, somewhat unlikely, neither unlikely or likely, somewhat likely, very likely, definitely) (4) **HO5/**Inference with the patient's everyday activity (no, slight, moderate, severe inference, no normal activity) (5) **HO5/**Degree of patient discomfort (no, slight, moderate, severe, extreme discomfort) (6) **E2O6/**Intensity of health care utilization (intensive care-hospital, standard ward-hospital, accident and emergency-hospital, urgent physician visit, next regular physician	3A + 3B	E2	+	+	_	+	The first four questions are similar with the tool of Rupp et al. [48]. However, they added the three questions 5, 6, 7 to evaluate the quality of life of a patient and the overall outcome.

		visit, self-care) (7) **SO3/**Overall outcome (negative, positive, neither)							
26	Kettle et al.* [57] 1996, UK	(1) **SN7/**Impact on therapy (problem identified, problem resolved, problem prevented, problem unresolved, improved drug therapy, improved drug supply, monitoring) (2) **SO3/**Intervention rating (not significant, useful, significant)	3B	_	+	_	+	_	
27.1	Alderman et al.* [29] 1997, Australia	**SO3/**Significance (minor, moderate, major)	3B	E1, E2	+	±	±	_	
27.2	Alderman et al. [78] 2001, Australia	The tool of Alderman et al. [29]	3B						
27.3	Castelino et al. [137] 2011, India	Adaption from the tool of Alderman et al. [29]	3B						
28	Dennehy et al.* [66] 1998, USA	(1) **SN5/**Potential outcome (optimizing drug therapy, minimizing ADRs or drug toxicity, decreasing drug costs, increasing reimbursement, increasing patient satisfaction) (2) **SO3/**Significance (low, moderate, high)	3B	E1, E2	+	+	_	_	
29	Weidle et al.* [68] 1998, USA	(1) **SO3/** Severity of intervention (low, typical, high) (2) **E1O3/**Cost savings (no cost saving, low cost saving, high cost saving)	3B	E1	+	_	_	_	
30.1	Dean et al.* [69] 1999, UK	**CO11/**A visual-analogue tool from 0 to 10	3A	_	+	_	_	_	A visual-analogue tool.
30.2	Taxis et al. [83] 2002, Germany	The tool of Dean et al. [69]	3A						
30.3	Hick et al. [81] 2001, UK	(1) The tool of Dean et al. [69] (2) Adaption from the tool of Hatoum et al.	3A + 3B	E1, E2	+	±	+	_	

		[38]							
30.4	Bourne et al. [136] 2011, UK	Adaption from the tool of Deans et al. [69]	3A						
31	Hawksworth et al.* [70] 1999, UK	(1) **SN4/** Clinical impact (detrimental, improved the efficacy, prevented harm, prevented a hospital admission) (2) **PbO11/**Confidence (0="definitely not" to 10 = "definitely")	3B	E2	+	_	_	+	
32	Lewinski et al.* [24] 2010, Germany	(1) **CO4/**Severity (no impairment; reversible, slight impairment of health; reversible, significant impairment of health; irreversible or serious impairment of health compared to the best possible state of health) (2) **PbO4/**Probability (impossible; existent-0.02; 0.02-0.2; 0.2 and more, already occurred) (3) **RO4/**Safety-relevance (no intervention necessary, low, significant, high)	3A	E2	+	+	_	+	Hawksworth et al. [70]. This is a risk matrix.
33	Gisev et al.* [127] 2010, Australia	(1) **SO5/**Finding agreement (Five-point Likert-type scale) (2) **SO5/**Recommendation appropriateness (Five-point Likert-type scale) (3) **SO5/**Implementation probability (Five-point Likert-type scale) (4) **SO5/**Overall expected clinical outcome for each client (detrimental, improved the efficacy, prevented harm, prevented a hospital admission, no change in the management of the client)	3B	E2	+	_	+	_	Hawksworth et al. [70]
34	Nathan et al.* [71] 1999, UK	**SO4/**Clinical significance (no clinical intervention necessary, patient's knowledge improved, improved outcome if therapy	3B	E2	+	+	_	_	

		changed, hospital admission prevented)							
35	Ewan et al.* [79] 2001, UK	(1) **SO2/**Appropriateness of the intervention (yes, no) (2) **SO4/**Clinical significance of the intervention (no clinical intervention necessary, patient's knowledge improved, improved outcome if therapy changed, hospital admission prevented)	3B	E2	+	+	_	_	Nathan et al. [71]
36	Lustig et al.* [74] 2000 Israel	**SO3/**Severity (non-clinically significant, clinically significant, potentially serious)	3B	E2	+	_	_	_	
37	Price et al.* [75] 2000, UK	(1) **SN4/**Reasons for interventions (effectiveness, safety, patient care, value of money) (2) **SN6/**Results of interventions (prescription altered, information, prescription the same and advice taken, resolved without doctor, prescription the same and advice not taken, other) (3) **SO4/**Significance of interventions (no difference, minor, moderate, severe)	3B	E1	+	±	+	_	
38	Taylor et al.* [77] 2000, USA	**SO3/**Severity of intervention (low, medium, high)	3B	_	+	+	±	_	
39	Needham et al.* [82] 2002, UK	(1) **SN4/**Type of intervention (clinical/pharmaceutical support, teamwork or communication, medication supply related, other) (2) **SO6/**Impact of intervention (improve symptom control, prevent deterioration of the patient, improve patient compliance, worthwhile but effected no change, unnecessary or inappropriate, be detrimental to	3B	_	+	+	_	_	

		the patient's well-being)							
40	van den Bemt et al.* [84] 2002, Netherlands	**SO6/**Seriousness of prescribing error (not be misunderstood, nurse need gather additional information, no clinical consequences, need for an increased patient monitoring, damage, death)	3A	E2	+	_	+	_	a modified version of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy of medication errors [164]
41	Davydov et al.* [86] 2003, USA	**SO10/***Errors that reached the patient* (no harm, increased monitoring, need for treatment or intervention and temporary harm, initial or prolonged hospitalization and temporary harm, permanent harm, near-death event, death); & *Errors that did not reach the patient* (would have resulted in significant morbidity or mortality, could have resulted in significant morbidity or mortality, low potential for negative patient outcome)	1 + 3A	E2	+	_	_	+	A modified version of NCC MERP taxonomy [164]. The tool evaluates separately errors that "reached" and "did not reach the patient".
42	Bobb et al.* [88] 2004, USA	**SO3/**Potential error severity (no harm, monitoring required, harmful)	3A	E2	+	_	_	_	A modified version of NCC MERP taxonomy [164]
43.1	Gleason et al.* [128] 2010, USA	**SO3/**Severity of medication error (no potential harm; monitoring or intervention potentially required to preclude harm; potential harm)	3A	E2	+	_	_	_	Adaption from the NCC MERP taxonomy [164]
43.2	Quélennec et al. [156] 2013, France	Adaption from the tool of Gleason et al. [128]	3A						
44	Dooley et al.* [21] 2003, Australia	**SO5/**Clinical significance (no clinically significance, minor, moderate, major, life-savings)	3B	E2	+	±	±	+	
45	Dale et al.* [85] 2003, UK	**SO6/**Outcome (harmful, neutral, minor, major, life- saving, no code)	3B	E2	+	_	_	_	

46	Buurma et al.* [89] 2004, Netherlands	(1) **SO3/**Contribution to patient (negative, positive, none) (2) **SN4/**Type of positive impact (improvement of effectiveness, prevention of ADR, both, other) (3) **PbO5/**Probability of positive impact (1-5) (4) **SO5/**Importance of positive impact (1-5)	3B	_	+	±	_	+	An algorithm representing the flow of questions for rating interventions.
47	Westerlund et al.* [123] 2009, Sweden	(1) **CN3/**Expected clinical patient outcomes (improved therapeutic effects, prevented or relieved ADRs, and both) (2) **E2O4/**Hypothesized expected patient outcomes (hospitalization avoided , primary care contact neither initiated nor avoided, a primary care contact initiated, a primary care contact avoided)	3B	E2	+	_	_	_	Buurma et al. [89]
48	Gray et al.* [90] 2004, UK	(1) **SN4/**Type of intervention (safety, quality of life, concordance, value for money) (2) **SO4/**Significance of intervention (potentially harmful, not significant, significant, very significant)	3B	+	+	+	_	_	
49	Prowse et al.* [91] 2004, UK	**SO4/**Clinical significance (nil, minor, moderate, severe)	3B	E1, E2	+	+	+	_	A specific tool for a transplant department
50.1	Cornish et al.* [22] 2005, Canada	**SO3/**Significance (unlikely cause discomfort or clinical deterioration; potential to cause moderate discomfort or clinical deterioration; potential to cause severe discomfort or clinical deterioration)	3A	_	+	+	_	+	The tool was used in some other studies related to medication conciliation such as studies by Kwan et al. [110], Wong et al. [118], Coffey et al. [119], and Villanyi et al. [142]
50.2	Kwan et al. [110] 2007, Canada	Adaption from the tool of Cornish et al. [22]	3A						
50.3	Wong et al. [118] 2008, Canada	Adaption from the tool of Cornish et al. [22]	3A						

50.4	Coffey et al. [119] 2009, Canada	Adaption from the tool of Cornish et al. [22]							
50.5	Villanyi et al. [142] 2011, Canada	Adaption from the tool of Cornish et al. [22]	3A						
51	Denneboom et al.* [92] 2005, Netherlands	**CO2/**Clinical relevance (low, potential or high)	3A	_	+	_	_	_	
52	Fertleman et al.* [93] 2005, UK	(1) **RO5/**Risk matrix considered potential or actual impacts on patient, number of patients affected, impact on organization and has 5 level of risk (no, minor, moderate, major, catastrophic) (2) **E1O2/**Actual medication cost savings between admission and discharge (yes/no)	3A	E1	+	_	+	_	Adaption from the Nation Patient Safety risk matrix [17]
53	Knudsen et al.* [108] 2007, Denmark	**SO3/**Potential seriousness score (minor potential inconvenience to the patient, potentially influence the treatment of the patient but correctable, potentially influence the treatment of the patient to the extent that intensive treatment would be necessary)	3A	E2	+	+	_	_	Safety Assessment Code score [17]
54	Haavik et al.* [130] 2010, Norway	**SO4/**Seriousness of error (no influence on the patient's treatment, minor potential inconvenience to the patient, potentially influence the treatment of the patient, but correctable, potentially influence the treatment of the patient to the extent that intensive treatment would be necessary, eg. admission to hospital)	3A	E2	+	+	_	_	Adaption from the Safety Assessment Code score [17]
55	Serrano et al.* [96] 2005, Spain	**SO9/**Clinical significance (no medication error occurred; medication error without harm to patient and without necessitating change in medical treatment; change in treatment	3B	E2	+	_	_	_	

		required without change in vital signs; increasing monitoring without change in vital signs; change in vital signs, or additional laboratory test/invasive procedures required; increased length of hospital stay with additional treatment; transfer to intensive care unit without permanent harm; permanent harm resulted; death)							
56	Ling et al.* [94] 2005, USA	**SN20/**20 subcategories belonging to 8 categories of cost avoidance (no resource utilization; no medication-related problem; drug information; drug therapy modification; additional tests or treatments or noninvasive procedures; additional tests or treatments or noninvasive procedures and increased length of stay or drug-related admission; any resource utilization in level 4, long-term-care admission, or required transfer to intensive care unit; death)	3B	E1, E2	+	_	+	_	The tool was used for estimating cost avoidance.
57.1	Blix et al.* [97] 2006, Norway	**SO4/**Clinical significance (minor, moderate, major, extremely important)	3B	_	+	±	±	_	
57.2	Viktil et al. [104] 2006, Norway	The tool of Blix et al. [97]	3B						
57.3	Schröder et al. [141] 2011, Germany	Adaption from the tool of Viktil et al. [104]	3B						
58	Vira et al.* [105] 2006, Canada	**SO2/**Clinical significance (clinically important or not)	3A	E2	+	_	_	_	
59.1	Stubbs et al.* [103] 2006, UK	**CO4/**Severity of error (doubtful or negligible importance, minor adverse effects or worsening condition, serious effects or relapse, fatality)	3A	_	+	_	_	_	

59.2	Chua et al. [146] 2012, Malaysia	Adaption from the tool of Stubbs et al. [103]	3A						
60	Pham et al.* [101] 2006, USA	**SO3/**Significance (high, medium, low)	3B	E2	+	+	+	_	
61	Estellat et al.* [107] 2007, France	**CO3/**Potential severity of prescription error (none, purely preventive; significant or serious; life-threatening)	3A	_	+	_	_	_	
62.1	Lindblad et al.* [111] 2007, Canada	(1) **CO2/**Cure a disease = 1A (yes/no) (2) **CO2/**Eliminate or reduce signs or symptoms = 1B (yes/no) (3) **CO2/**Arrest or slow a disease process = 1C (yes/no) (4) **CO2/**Prevent a disease or symptom = 1D (yes/no) (5) **CO2/**Achieve desired alterations in physiologic processes = 1E (yes/no) (6) **HO2/**Improve physical, mental, or social function or satisfaction with care = 2A (yes/no) (7) **E1O2/**Drug cost savings of $1 or more/day = 3A(yes/no) (8) **E1O2/**Drug cost increases of $1 or more/day = 3B (yes/no)	3B	E1	+	+	+	_	The coding system was developed according to the ECHO model (economic, clinical and humanistic outcome)[16]. An average of outcomes was calculated for each PI.
62.2	Harrison et al. [150] 2012, Canada	(1) **SO6/**Potential clinical significance (adverse significance, insignificant, somewhat significant, significant, very significant, extremely significant) ***Anticipated clinical outcome*** (2) **CO2/**Cure a disease (yes/no) (3) **CO2/**Eliminate or reduce signs or symptoms (yes/no); (4) **CO2/**Arrest or slow a disease process (yes/no)	3B	_	+	+	+	_	Used the tool of Hatoum et al. and [38] and the tool of Lindblad et al. [111]

		(5) **CO2/**Prevent a disease or symptom (yes/no) (6) **CO2/**Achieve desired alterations in physiologic processes (yes/no) (7) **PcO2/**Prevent a potential drug therapy problem (yes/no) (8) **HO2/**Anticipated humanistic outcome (improve physical, mental, or social function or satisfaction with care)							
63	Nguyen et al.* [112] 2007, Australia	**SO6/**Clinical impact of issues (negative impact, no impact, minor impact, significant impact, very significant impact, potentially lifesaving)	3B	_	+	±	±	+	Numeric tool from -1 to 4.
64	Bayley et al.* [106] 2007, USA	(1) **SO4/**Importance of intervention (cost and product selection, prevented potential ADE or standard of practice, prevent serious morbidity, prevent mortality) (2) **SN4/**Expected time-frame of impact (short-term, long-term, both, not rated)	3B	E1	+	±	+	_	
65.1	Midlov et al.* [115] 2008, Sweden	**SO3/**Clinical risk (no/low, moderate, high)	3A	_	+	_	_	+	
65.2	Midlov et al. [153] 2012, Sweden	The tool of Midlov et al. [115]	3A						
66	Krahenbuhl et al.* [28] 2008, Switzerland	(1) **CN2/**Type of problems (technical, clinical problem) (2) **CN6/**Types of potential negative outcome (not indicated, indication not treated, quantitative ineffectiveness, non-quantitative ineffectiveness, non-quantitative safety, quantitative safety)	3A	_	+	_	_	_	

67	Pippins et al.* [116] 2008, USA	(1) **SO3** Significance (significant, serious, life-threatening) (2) **PbO6/**Confidence (little or no confidence, slight to modest confidence, less than 50–50 but close call, more than 50–50 but close call, strong confidence, virtually certain confidence)	3A	_	+	+	_	+	Bates et al. [166]
68	Rothschild et al.* [3] 2010, USA	(1) **CN3/**Type of recovered medication error (intercepted potential adverse drug event; mitigated adverse drug event; ameliorated adverse drug event) (2) **PbO5/**Presence of a recovered medication error (definitely, probable, probably not, definitely not, unsure) (3) **CO4/**Potential severity of harm (insignificant, significant, serious, life-threatening, unable to determine)	1 + 3A	_	+	_	_	+	Bates et al. [166]
69	Abu-Ramaileh et al.* [135] 2011, USA	(1) **SN2/**Quality intervention (yes/no) (2) **PbO5/**Confidence of judgment (little or no confidence, modest confidence, medium confidence, strong confidence, virtually certain confidence) (3) **SN4/**Type of quality intervention (avoid overuse of medication, underuse of medication, and misuse of medication, improve adherence with current evidence based medicine/nationally adopted quality standards)	3B	_	+	_	+	+	PIs were classified into PIs prevent medication errors (rated by the tool of Rothschild et al. [3]) and Quality Interventions (rated by the tool of Abu-Ramaileh et al. [135])
70.1	Patanwala et al.* [138] 2011, USA	(1) **CO4/**Severity (minor, significant, serious, potentially lethal) (2) **PbO5/**Probability of harm (no harm expected 0, very low 0.01, low 0.1, medium 0.4, high 0.6)	3A	_	+	_	_	+	Adopted the tool of Overhage et al. [12] and the tool of Rothschild et al. [3]
70.2	Patanwala et al. [139] 2011, USA	The tool of Patanwala et al. [138]	3A	_	+	_	_	_	

71	Granas et al.* [120] 2009, Norway	(1) **SO3/**Clinical relevance of DRP (low, medium, high); (2) **HO3/**Quality of the PI with the patient (good, satisfaction, not satisfaction) (3) **PcO3/**Quality of the PI with the physician (good, satisfaction, not satisfaction)	3A + 3B	_	+	+	+	_	
72	Vasileff et al.* [122] 2009, Australia	**SO5/**Clinical significance (nil, minor, significant, very significant, life-savings)	3B	_	+	±	_	_	
73	Lee et al.* [132] 2010, Canada	(1) **PbO3/**Potential of patient harm (unlikely, possible, probable) (2) **SN3/**Type of patient harm (discomfort, clinical deterioration, or both) (3) **SO3/**Severity of patient harm (minor, moderate and severe by 9-point tool of Deans et al. [69])	3A	_	+	+	_	+	Deans et al. [69]
74	Rashed et al.* [154] 2012, UK and Saudi Arabia	**CO3/**Severity (minor outcome, moderate outcome, severe outcome)	3A	_	+	_	_	_	Adopted the tool of Dean et al. [69]
75	Niquille et al.* [134] 2010, Switzerland	(1) **SN3/**Type of possible negative clinical outcome (necessity, effectiveness, safety) (2) **SO4/**Clinical problem (harmful; interesting in theory, but not applicable in the case of the patient; revaluated at the next visit; implemented as soon as possible) (3) **E1O2/**Expense problem (yes/no)	3A	E1	+	_	_	_	
76	Eichenberger et al.* 2010, Switzerland	**PcO4/**Outcome (outcome unknown, problem solved, problem partially solved, problem not solved)	3B	_	_	_	+	_	Adaptation from the PCNE V.5.01.
77	Knez et al.* [131] 2010, UK	**CO5/**Clinical significance (insignificant, minor significant, significant, very significant, potentially life-savings)	3B	_	+	_	_	_	

78	Williams et al.* [31] 2011, Australia	**SO4/**Clinical significance (low, mild, moderate, high)	3B	E2	+	+	+	_	
79	Cesarz et al.* [145] 2012, USA	**SN2/**Type of intervention (error prevention, optimization of medication therapy)	3B	_	+	±	±		
80	Perera et al.* [140] 2010, USA	**SN3/**Intervention category (cost savings, safety, guideline adherence)	3B	E1	+	_	+	_	
81	Kwint et al.* [152] 2012, Netherlands	Three parameters of clinical relevance of DRP consists (1) **SO3/**High priority to be discussed with the physician (low, medium, high) (2) **SN2/**Recommendation for drug change (yes/no) (3) **SN2/**Implemented recommendation for drug change (yes/no)	_	_	+	_	+	_	
82	Mekonnen et al.* [155] 2012, Ethiopia	(1) **SO4/**Clinical importance of intervention (mild, moderate, major, extreme)	3B	_	+	_	+	_	

ESM 4. Process of validation of tools in 133 identified studies

Note: "IN" = individual-based rating. "GR" = group-based rating. "ND" = non-determined. "_" = Not reported. "*" = Distinct tool. "ME" = medication error. "PI" = pharmacist intervention. [1, 2] Number of PIs, sampling were presented and risk of bias/limits was assessed for only studies which reported validity or reliability results. "U" = unclear risk of bias. "H" = high risk of bias. "L" = low risk of bias

No.	Author(s), Published year, Country	Setting, Number of PIs, Sampling[1]	Quality and Number of Raters	Rating Method	Definitions of Consensus	Validity	Inter-rater Reliability	Intra-rater Reliability	Risk of Bias/Limits[2]	Score of Quality of a Tool
1.1	**Folli et al. [36] 1987, USA**	2 children's hospitals	1 member of the pediatric faculty or 1 attending physician + 2 pediatric clinical pharmacist practitioners	GR	ND	_	_	_	_	0
1.2	**Iafrate et al. [35] 1986, USA**	a hospital	1 clinical supervisor + 1 clinical resident	GR	ND	_	_	_	_	1
1.3	**Blum et al. [37] 1988, USA**	a hospital	4 pharmacists + 1 physician	GR	consensus + hierarchical approach	_	_	_	_	1
1.4	**Lesar et al. [42] 1990, USA**	a hospital	investigators	ND	ND	_	_	_	_	1
1.5	**Lesar et al. [63] 1997, USA**	a hospital, 500 MEs, consecutive sampling	1 physician + 2 pharmacists	IN	IN	_	agreement = 97%, Cohen k = 0.96, $p < 0.001$: excellent agreement	_	U	2
1.6	**Lesar et al. [64] 1997, USA**	a hospital	investigators	ND	ND	_	_	_	_	1

1.7	**Ho et al. [46] 1992, Canada**	a hospital	1 practicing pharmacist + 1 practicing physician	GR	consensus	_	_	_	_	1
2.1	**Hatoum et al.* [38] 1988, USA**	a hospital	3 physicians	GR	mode and mean	_	_	_	_	5
2.2	**Hatoum et al. [39] 1988, USA**	a hospital	practicing clinical pharmacists + peer-review process (9 practicing clinical pharmacists served on 3 reviewing teams)	GR	mode + consensus	_	_	_	_	5
2.3	**Briceland et al. [30] 1992, USA**	a hospital	1 clinical pharmacy preceptor	IN	IN	_	_	_	_	5
2.4	**Eadon et al. [45] 1992, UK**	a hospital, 25 PIs, random sampling	1 pharmacist + 3 physicians (1 transplant registrar + 1 research registrar + 1 senior registrar)	IN	IN	Mann Whitney U = 933.5, z=0.034: no significant difference	_	_	- sampling of few PIs from one hospital - no results of agreement between pharmacists (H)	6
2.5	**Chisholm et al. [54] 1995, USA**	a hospital	1 pharmacy resident + 2 pharmacy practitioners + 1 fourth pharmacy practitioner served as arbitrator	GR	consensus + hierarchical approach	_	_	_	_	5
2.6	**Wernick et al. [58] 1996, USA**	a hospital	1 practicing pharmacist + a panel of 3 clinical pharmacists	GR	ND	_	_	_	_	5
2.7	**Lucas et al.**	an inpatient	1 pharmacist (P1) + 1	IN	hierarchical		**P1** *vs* **P2:**	_	- sampling of	5

	[65] 1997, Australia	palliative care unit, 62 PIs, consecutive sampling	internal physician (P2) + 2 external physicians (P3, P4)		approach		agreement = 83%, t-test p = 0.495 > 0.05: no significant difference **P2** *vs* **P3:** agreement = 48% **P2** *vs* **P4:** agreement = 63% **P1** *vs* **P3:** t-test p = 0.983 > 0.05: no significant difference **P1** *vs* **P4:** t-test p = 0.02 < 0.05: significant difference		PIs from only one unit - no result of agreement between 2 pharmacists (H)	
2.8	**Chisholm et al. [60] 1997, USA**	a hospital	1 preceptor + 1 practicing pharmacist	GR	mean	_	_	_	_	5
2.9	**Grabe et al. [62] 1997, USA**	a hospital	4 investigators	GR	consensus	_	_	_	_	5
2.10	**Smythe et al. [67] 1998, USA**	a step-down unit for the medical ICU, 235 PIs, consecutive sampling	2 intensivists + 2 internists blinded to as to whether recommendations were accepted	IN	IN	_	weighted kappa = 0.342 for intensivists; weighted kappa = 0.258 for internists	_	- sampling of only one unit - there were no pharmacists as raters (H)	5
2.11	**Possidente et al. [72] 1999, USA**	a hospital	2 pharmacists + 1 nephrologist	GR	consensus	_	_	_	_	5

2.12	**Reddick et al. [76] 1999 USA**	27 clerkship sites of pharmacy students	pharmacy students	IN	IN	_	_	_	_	5
2.13	**Nickerson et al. [95] 2005, Canada**	2 general medicine units	1 seamless care pharmacist + 1 clinical pharmacist	GR	ND	_	_	_	_	5
2.14	**Wang et al. [117] 2008, Taiwan**	a medical center	1 practicing pharmacist + 1 other physician	GR	consensus	_	_	_	_	5
2.15	**Bondesson et al. [144] 2012, Sweden**	a hospital	Two pairs of evaluators (each including 1 clinical pharmacist + 1 geriatrician or 1 general physician with special interest in geriatrics); the third clinical pharmacist served as a tiebreaker	GR	hierarchical approach	_	_	_	_	5
3	**Mueller et al.* [43] 1990, USA**	a hospital	investigators	GR	consensus	_	_	_	_	4
4.1	**Chedru et al.* [59] 1997, France**	2 departments of a hospital, 18 PIs, non-random sampling	2 external physicians	IN	sum	_	signmax 0.8, signmay 0.7	_	- sampling of few PIs - non-random sampling - there were no pharmacists as raters (H)	4
4.2	**Guignon et al. [80]**	a hospital	1 external hospital pharmacist + 1	GR	consensus	_	_	_	_	3

	2001, France		physician of the regional center of pharmacovigilance							
4.3	**Grangeasse et al. [99]** **2006, France**	a hospital	a center of clinical pharmacy of oncology + 1 physician reviewed	GR	hierarchical approach	_	_	_	_	3
4.4	**Goarin et al. [129]** **2010, France**	an oncology and haematology ward in a hospital, 188 PIs, consecutive sampling	1 physician from a pharmacovigilance center + 1 pharmacist of a centralized cytotoxic service	IN	One parameter of the relevance of a PI is that score of a PI is > 0 by at least one assessors	_	t-test $p < 0.05$: no significant difference	_	- only 2 raters - PIs from only a ward (H)	4
4.5	**Nerich et al. [133]** **2010, France**	a hospital	6 medical oncologists + 3 pneumologists + 3 hematologists	GR	ND	_	_	_	_	3
5	**Cousins et al.* [61]** **1997, UK**	a hospital, 584 PIs for intra-reliability test; 62 PIs for inter-reliability test	12 pharmacists	IN	IN	patients' medical records of 62 PIs were inspected for evidence of the interventions	(1) kappa = 0.26 (2) kappa = 0.27	(1) Wilcoxon matched-pairs signed-rank test $p = 0.01, 0.03, 0.13, 0.18, 0.32, 0.37, 0.38, 0.46, 0.55, 0.58, 0.60, 0.69$ (2) agreement = 48%; kappa < 0	- there were no physicians as raters - raters involved in practice of medication review and data collection (H)	5
6.1	**Overhage et al.* [12]** **1999, USA**	a hospital, 300 PIs, sampling strategy to balance	1 pharmacist retrospectively viewed + an expert panel of 2 clinical pharmacists and 2 internists with	IN	IN	_	(1) kw = 0.69 (2) kw = 0.69	_	- non-random sampling of only one hospital - 2 internists	6

		sample size, variety of interventions	fellowship training in clinical pharmacology						with fellowship training in clinical pharmacology - 2 raters participated in the refinement of the instrument (H)	
6.2	**Bosma et al. [98] 2006, Netherland**	a hospital, 255 PIs, consecutive sampling	1 hospital pharmacist + 1 internal medicine specialist - clinical pharmacologist	IN	IN	_	(1) kw = 0.30 (2) kw = 0.20	_	- sampling of only one hospital - only 2 raters (H)	5
6.3	**Lee et al. [100] 2006, USA**	three hospice programs, 98 DRPs 87 PIs, consecutive sampling	3 hospice experts (2 pharmacists + 1 physician) + 2 principal investigators	IN	mean, mode and median	_	(1) agreement = 60-70%, k = 0.19-0.47 (2) agreement = 63-80%, k = 0.14-0.31		(L)	6
6.4	**Climenté-Marti et al. [125] 2010, Spain**	a hospital	1 pharmacist + 1 physician + another physician or pharmacist (sometimes a third internist)	GR	hierarchical	_	_	_	_	5
6.5	**Abdel-Qader et al. [124] 2010, UK**	a hospital	practicing pharmacists + meetings among the research team	GR	consensus, hierarchical	_	_	_	_	5
6.6	**Fernandez-Llamazares et al. [149] 2012, Spain**	a hospital, 20 PIs, random sampling	4 senior pharmacists + 5 junior pharmacists	IN	IN	_	(2) agreement = 66%, k = 0.24 (95% CI 0.15-0.32) for all raters; agreement	_	- few PIs tested - PIs were not evaluated by physicians (H)	5

							= 72%, k = 0.27(95% CI 0.16-0.38) for senior pharmacists; agreement = 64%, k = 0.10 (95% CI 0.00-0.20) for junior pharmacists			
6.7	**Fernandez-Llamazares et al. [148] 2012, Spain**	a hospital	clinical pharmacists	IN	IN	_	_	_	_	5
6.8	**Somers et al. [157] 2013, Belgium**	a geriatric ward of a hospital, 304 PIs, consecutive sampling	2 clinical pharmacologists + 2 clinical pharmacists	IN	IN	_	k = 0.15-0.25: poor agreement	_	- only one ward - PIs done by only one clinical pharmacist (H)	5
7	**Kopp et al.* [109] 2007, USA**	a surgical intensive care unit of a hospital, 129 PIs, consecutive sampling	2 pharmacists not involved in data collection	IN	consensus	_	(1) agreement = 62.8%; kappa = 0.25; (5) agreement = 69.8%; kappa = 0.41 (prevalence-adjusted and bias-adjusted kappa)	_	- PIs from only a surgical intensive care unit - there were no physicians as raters (H)	6
8	**Spinewine et al.* [102] 2006, Belgium**	a geriatric unit of a hospital, 700 PIs	2 geriatricians + 1 clinical pharmacist	IN	consensus	_	(1) agreement = 33%	_	- sampling of PIs of only a geriatric unit - raters did not	2

									blind to as to whether PIs were accepted by physicians (H)	
9	**Neville et al.* [40] 1989, UK**	a health center	ND	ND	ND	_	_	_	_	3
10	**Hawkey et al.* [20] 1990, UK**	6 hospitals, 103 PIs, non-random sampling	2 physicians	IN	IN	_	(3) Spearman's rank correlation coefficient R = 0.83, p<0.001: a significant correlation	_	- only 2 raters - there were no pharmacists as raters (H)	5
11	**Bayliff et al.* [41] 1990, Canada**	a hospital, 15 PIs, non-random sampling	4 physicians (2 clinical pharmacologists + 2 chief residents in medicine)	GR	mean, mode	_	(1) coefficient of agreement = 0.76 (p>0.05), effective reliability = 0.93: "reasonably good" agreement (2) coefficient of agreement 0.38 (p>0.05), effective reliability = 0.71 (3) coefficient of agreement 0.30 (p>0.05), effective reliability = 0.63	_	- sampling of few PIs from only one hospital - there were no pharmacists as raters (H)	4
12	**Strong et al.* [50] 1993, Canada**	a hospital, each rater received 11 identical	7 physicians with clinical pharmacology experience	IN	IN	_	(1) Coefficient of agreement = 0.86: good	_	- non-random sampling of few PIs from	5

		cases, non-random sampling					agreement		only one hospital - no results of agreement between pharmacist (H)	
13	**Virani et al.* [87] 2003, Canada**	a mental health unit, 8 PIs, consecutive sampling	2 internal clinical pharmacists + 1 child and adolescent psychiatrist	IN	ND	_	coefficient of agreement = 0.7: reasonably good agreement	_	- sampling of few PIs (H)	6
14	**Western Australian Clinical Pharmacists Group* [44] 1991, Australia**	12 hospitals	6 clinical pharmacists	GR	consensus	_	_	_	_	1
15.1	**Krass et al.* [73] 2000 Australia**	community pharmacies	1 clinical pharmacist + 1 clinical pharmacologist + 1 general medical practitioner + 1 consultant physician	ND	ND	_	_	_	_	3
15.2	**Lövgren et al. [121] 2009, Australia**	a hospital	1 consultant pharmacologist + 1 academic pharmacist	GR	consensus	_	_	_	_	3
16	**Struck et al.* [113] 2007, Australia**	a hospital, 656 PIs, consecutive sampling	2 clinical pharmacists (1 third clinical pharmacist as needed)	IN	consensus + hierarchical approach	_	(1) agreement = 65% (95% CI 61-68%), kw = 0.51 (95% CI 0.46-0.56): moderate	_	- there were no physicians as raters - raters did not blind to as to	4

							agreement (2) agreement = 37% (95% CI 33-40), kw = 0.14 (95%CI 0.09-0.18): very poor agreement (3) agreement = 68% (95% CI 65-72), kw = 0.39 (95% CI 0.34-0.45): poor agreement		whether PIs were accepted by physicians (H)	
17.1	**Elliott et al.* [23] 2009, Australia**	aged care and memory clinics at a hospital, 113 DRPs	2 clinical pharmacist + 2 physician	IN	IN	Face validity reviewed 30 DRPs by 2 pharmacists + 1 senior geriatrician (agreement = 93-100%)	(3) k = 0.24 for all raters, k = 0.55 for pharmacists, k = 0.20 for physicians	_	- PIs proposed by one pharmacist from aged care and memory clinics - only external raters - some raters were not provided with the risk table (H)	4
17.2	**Elliott et al. [147]**	Aged Care Assessment Teams	1 geriatrician + 1 pharmacist	GR	consensus	_	_	_	_	4
18	**Khalili et al.* [151] 2012, Iran**	an infectious diseases ward of a hospital, 231 PIs, consecutive	1 clinical pharmacist + 1 physician	IN	hierarchical approach (physician's opinions)	_	(1) agreement = 93.6%: good agreement	_	- raters probably did not blinded to as to whether PIs were	4

		sampling							accepted by physicians - PIs of only one ward (H)	
19.1	**Lipton et al.* [47] 1992, USA**	a hospital	a principal investigator and a panel of 5 physicians, 2 clinical pharmacists	GR	mean + hierarchical approach	_	_	_	_	1
19.2	**Lalonde et al. [114] 2008, Canada**	a hospital and pharmacies	1 clinical pharmacist + 1 family-medicine physician	GR	ND	_	_	_	_	1
20.1	**Rupp et al.* [48] 1992, USA**	89 community pharmacies, 176 PIs, consecutive sampling	1 physician + 1 pharmacist + 1 third pharmacist served as a tiebreaker	IN	consensus + hierarchical approach	_	(1) agreement = 87-95%; kappa = 0.68-0.88: moderately strong agreement (2) agreement = 87-88%; kappa = 0.79-0.82: (3) $p > 0.05$ (4) low agreement	_	- the tool was tested in community pharmacies, not in hospitals - raters did not blind to the outcomes of PIs (H)	5
20.2	**Rupp et al. [49] 1992, USA**	89 community pharmacies, 623 DRPs, consecutive sampling	1 physician + 1 pharmacist + 1 third pharmacist served as a tiebreaker)	IN	consensus + hierarchical approach	_	agreement = 87%, kappa = 0.68: moderately strong agreement	_	- the tool was tested in community pharmacies, not in hospitals - raters did not blind to the outcomes of PIs (H)	5

21	**Tang et al.* [51] 1993, USA**	a hospital	2 clinical pharmacists	ND	ND	_	_	_	_	4
22	**Mason et al.* [52] 1994, USA**	a medical center	practicing pharmacists	IN	IN	_	_	_	_	2
23	**Slaughter et al.* [53] 1994, Canada**	hospitals and an ambulatory care site	1 physician (clinical preceptor) + 1 pharmacist (internal medicine faculty preceptor)	GR	mean	_	_	_	_	4
24	**Wang Chin et al.* [55] 1995, USA**	a cancer center	practicing pharmacists + 1 investigator	GR	hierarchical approach	_	_	_	_	3
25	**Caleo et al.* [56] 1996, Australia**	30 community pharmacies, 50 PIs, random sampling	2 clinical pharmacologists + 1 clinical pharmacist + 1 community pharmacist	GR	mean, mode	_	(1) weighted kappa (kw) < 0 (2) kw = 0.50-0.76: moderate to good agreement (4) kw with poor agreement (5) kw with poor agreement (6) kw with poor to moderate agreement (7) kw with poor to moderate agreement	_	- there were no physicians raters - the tool was tested in community pharmacies, not in hospitals (H)	7
26	**Kettle et al.* [57] 1996, UK**	a hospital-based community mental health team	1 trust pharmacy manager + 1 consultant psychiatrist	GR	ND	_	_	_	_	3

27.1	**Alderman et al.* [29] 1997, Australia**	a hospital	ND	ND	ND	_	_	_	_	2
27.2	**Alderman et al. [78] 2001, Australia**	a hospital	ND	ND	ND	_	_	_	_	2
27.3	**Castelino et al. [137] 2011, India**	a hospital	ND	ND	ND	_	_	_	_	2
28	**Dennehy et al.* [66] 1998, USA**	hospital(s)	intervening student + 2 pharmacists + committee of 8 pharmacists	GR	consensus + hierarchical approach	_	_	_	_	5
29	**Weidle et al.* [68] 1998, USA**	a hospital	recording pharmacist + Pharmaceutical Council (Pharmaceutical Care Team leaders + Associate Director of Pharmacy)	GR	consensus + hierarchical approach	_	_	_	_	2
30.1	**Dean et al.* [69] 1999, USA**	_ 50 MEs, non-random sampling	10 physicians + 10 pharmacists + 10 nurses	IN	mean (a mean score was reliable if it was calculated from scores given by 4 health professionals)	clear relationship between patient outcomes and severity scores	Generalizability coefficient = 0.587 (A generalizability coefficient of 0.8 or more was considered to represent an acceptable level of reliability).	Generalizability coefficient = 0.780	- only external raters (H)	2

30.2	**Taxis et al. [83] 2002, Germany**	_ 50 MEs, non - random sampling	10 physicians + 10 pharmacists + 10 nurses	GR	mean (a mean score was reliable if it was calculated from scores given by 3 health professionals)	Clear relationship between severity scores with known outcomes	not reported	not reported	- only external raters	2
30.3	**Hick et al. [81] 2001, UK**	an pre-admission clinic, 155 PIs, consecutive sampling	4 senior pharmacists for each tool	IN	(1) mean score (2) mode + fourth rater as a casting vote	_	(1) ANOVA p < 0.001: no significant agreement (2) agreement = 85% of cases two out of 3 assessors agreed	_	- sampling of PIs from only one clinic - there were no physicians as raters (H)	7
30.4	**Bourne et al. [136] 2011, UK**	a critical care unit	3 clinical pharmacists + 1 specialist nurse + 1 intensive care consultant	GR	mean	_	_	_	_	1
31	**Hawksworth et al.* [70] 1999, UK**	14 community pharmacies	ND	GR	ND	_	_	_	_	4
32	**Lewinski et al.* [24] 2010, Germany**	69 community pharmacies, 638 patients, consecutive sampling	2 pharmacists + 1 physician	IN	median	_	(1) Cohen k = 0.78: substantial agreement (2) Cohen k = 0.83: almost perfect agreement (3) Cohen k = 0.87: almost	_	- uncompleted or deficient cases was excluded from the analysis - no internal raters (H)	6

							perfect agreement			
33	**Gisev et al.* [127] 2010, Australia**	5 community mental health teams, 208 PIs, consecutive sampling	1 consultant psychiatrist + 1 general medical practitioner + 1 specialist psychiatric pharmacist + 1 medication review accredited pharmacist	IN	IN	Face validity by an independent pharmacist	(1) moderately consistent (2) W = 0.41: moderately consistent (3) W = 0.40: moderately consistent (4) ND (W = Kendall coefficient of concordance)	_	- criteria-based validity was not tested - sampling of only patients with mental illness (H)	5
34	**Nathan et al.* [71] 1999, UK**	23 pharmacies	1 geriatrician + 1 physician + 1 hospital clinical pharmacist + 1 community pharmacist	GR	ND	_	_	_	_	3
35	**Ewan et al.*[79] 2001, UK**	community pharmacies, 94 DRPs, consecutive sampling	2 pharmacists (R1 and R2) + 1 consultant psychiatrist (R3)	IN	IN	_	(1) **R1** *vs* **R3**: agreement = 86, k = 0.31 **R1** *vs* **R2**: agreement = 90, k = 0.20 **R2** *vs* **R3**: agreement = 90, k=0.26 (2) **R1** *vs* **R3**: k = 0.33 **R1** *vs* **R2**: k = 0.25 **R2** *vs* **R3**: k = 0.28	_	- the tool was tested in community pharmacies, not in hospitals - sampling of only mentally ill patients (H)	4

36	**Lustig et al.* [74] 2000 Israel**	a hospital	ND	ND	ND	_	_	_	_	1
37	**Price et al.* [75] 2000, UK**	a hospital	2 pharmacists + pharmacy services managers	GR	ND	_	_	_	_	4
38	**Taylor et al.* [77] 2000, USA**	a hospital	pharmacy residents + pharmacy patient care leaders + 1 pharmacy manager	GR	consensus + hierarchical approach	_	_	_	_	1
39	**Needham et al.* [82] 2002, UK**	14 community palliative care teams	1 nurse + 1 consultant in palliative care + 1 hospital pharmacist	GR	consensus	_	_	_	_	3
40	**van den Bemt et al.* [84] 2002, Netherlands**	2 hospitals	2 hospital pharmacists	GR	consensus	_	_	_	_	3
41	**Davydov et al.* [86] 2003, USA**	a hospital	ND	IN	IN	_	_	_		4
42	**Bobb et al.* [88] 2004, USA**	a medical center, 56 MEs, random sampling	3 pharmacists	IN	IN	_	agreement = 75.0-83.6% (effect strength = 57.1-68.5): excellent agreement	_	- sampling of one medical center - there were no physicians as raters (H)	2
43.1	**Gleason et al.* [128] 2010, USA**	a hospital, 309 MEs, random sampling	2 pharmacists + 1 internist (the second physician as needed)	IN	hierarchical	_	Cohen's k= 0.84: high agreement	_	- no external raters - raters involved in medication review and data	2

									collection (H)	
43.2	**Quélennec et al. [156] 2013, France**	an internal medicine department, 173 unintentional discrepancies, consecutive sampling	2 pharmacists + 2 internists	IN	hierarchical approach	_	Cohen's k= 0.61: substantial agreement	_	- sampling of only patients ≥ 65 years in only one department (H)	2
44	**Dooley et al.* [21] 2003, Australia**	8 hospitals	ND	GR	ND	_	_	_	_	3
45	**Dale et al.* [85] 2003, UK**	2 medical wards of a hospital, 740 MEs, consecutive sampling	1 consultant physician + 1 pharmacist	IN	IN	_	agreement = 41% for the intervention group and 46% for the control group	_	- only 2 raters (H)	2
46	**Buurma et al.* [89] 2004, Netherlands**	141 community pharmacies, 72 PIs, random sampling	5 groups and each group including 1 community pharmacist + 1 hospital pharmacist + 1 general practitioner + 1 specialist or other non-practicing medical/pharmaceutical experts)	IN	mean	_	(1,2) kappa = 0.40 (2) kappa = 0.49 for all raters, 0.35 for physicians, 0.58 for pharmacists;	_	- the tool was tested in community pharmacies, not in hospitals (H)	3
47	**Westerlund et al.* [123] 2009, Sweden**	89 pharmacies	1 pharmacist + 1 physician	GR	consensus	_	_	_	_	3

48	**Gray et al.* [90] 2004, UK**	21 pharmacies	2 pharmacists	GR	ND	_	_	_	_	4
49	**Prowse et al.* [91] 2004, UK**		1 clinical pharmacist + a multidisciplinary panel (1 consultant nephrologist + 1 transplant nurse practitioner + 1 specialist pharmacist in transplantation + 1 pharmacist)	GR	consensus + hierarchical approach	_	_	_	_	5
50.1	**Cornish et al.* [22] 2005, Canada**	a hospital, 140 unintended discrepancies, consecutive sampling	3 general internal medicine hospitalists	IN	consensus	_	Fleiss's k = 0.26 (95% CI 0.16-0.36)	_	- sampling of unintended discrepancies from only one hospital - there were no pharmacists as raters (H)	2
50.2	**Kwan et al. [110] 2007, Canada**	a surgical preadmission clinic, 46 medication discrepancies , unclear	3 pharmacists	GR	consensus	_	mean Cohen k= 0.84: substantial agreement	_	- sampling of only PI of only one clinic - there were no physicians as raters (H)	3
50.3	**Wong et al. [118] 2008, Canada**	a hospital, 105 actual unintentional discharge discrepancies, consecutive	1 general internist + 2 pharmacists not involved in the direct care	GR	consensus	_	mean Fleiss's k = 0.76 (pairwise k = 0.72 - 0.80)	_	- only actual unintentional discrepancies were assessed for clinical impact	3

		sampling							- only external raters (H)	
50.4	**Coffey et al. [119] 2009, Canada**	general pediatric unit, 59 patients with at least one unintentional discrepancy, non-consecutive sampling	3 physicians	IN	mode	_	AC1 = 0.69, p<0.01: good agreement	_	- non-representative sampling - only external raters - no pharmacists as raters (H)	3
50.5	**Villanyi et al. [142] 2011, Canada**	a hospital	1 external pharmacist	IN	IN	_	_	_	_	2
51	**Denneboom et al.* [92] 2005, Netherlands**	9 pharmacies	1 pharmacist + 1 general practitioner	GR	consensus	_	_	_	_	0
52	**Fertleman et al.* [93] 2005, UK**	a hospital	ND	GR	ND	_	_	_	_	4
53	**Knudsen et al.* [108] 2007, Denmark**	40 community pharmacies	3 pharmacists + 1 chief researcher	GR	consensus + hierarchical approach	_	_	_	_	2
54	**Haavik et al.* [130] 2010, Norway**	12 pharmacies, 124 MEs, non-random sampling	3 hospital pharmacists + 5 community pharmacists + 6 hospital physicians + 2 emergency care	IN	median, a clinically relevant error was defined as	_	k = 0.093-0.115	_	- non-random sampling - information of clinical cases was probably	3

			physicians		median score > =1				insufficient - no pilot phase of assessment (H)	
55	**Serrano et al.* [96] 2005, Spain**	a hospital	ND	ND	ND	_	_	_	_	2
56	**Ling et al.* [94] 2005, USA**	a hospital	practicing pharmacists	IN	IN	_	_	_	_	4
57.1	**Blix et al.* [97] 2006, Norway**	5 hospitals	1 professor in pharmacotherapeutics + 2 specialists in hospital pharmacy	GR	consensus	_	_	_	_	1
57.2	**Viktil et al. [104] 2006, Norway**	4 hospitals	1 professor in pharmacotherapeutics, who is also a specialist in internal medicine + 2 specialists	GR	consensus	_	_	_	_	1
57.3	**Schröder et al. [141] 2011, Germany**	community pharmacies	4 physicians + 1 pharmacist	GR	consensus	_	_	_	_	1
58	**Vira et al.* [105] 2006, Canada**	a hospital	1 internist	IN	IN	_	_	_	_	1
59.1	**Stubbs et al.* [103] 2006, UK**	mental health units	2 pharmacists + a panel of 5 psychopharmacists	GR	hierarchical approach + consensus	_	_	_	_	1
59.2	**Chua et al. [146] 2012, Malaysia**	44 primary care clinics, 706 DRPs, consecutive	1 clinician + 1 pharmacist who were not involved in the study	IN	hierarchical approach	_	Cohen's k = 0.729: good agreement	_	- only 2 raters - classification of the clinical significance of	2

		sampling							DRPs was not re-tested (H)	
60	**Pham et al.* [101] 2006, USA**	a hospital	2 faculty members + 10 external pharmacists	GR	mode	_	_	_	_	3
61	**Estellat et al.* [107] 2007, France**	hospital	3 physicians + 1 pharmacist	GR	consensus	_	_	_	_	0
62.1	**Lindblad et al.* [111] 2007, Canada**	a hospital	practicing pharmacists	IN	IN	_	_	_	_	4
62.2	**Harrison et al. [150] 2012, Canada**	an outpatient lung transplant clinic	1 respirologist + 1 advanced practice nurse + 1 transplant nurse coordinator + 1 transplant pharmacist	GR	consensus	_	_	_	_	4
63	**Nguyen et al.* [112] 2007, Australia**	a hospital	1 liaison pharmacist	IN	IN	_	_	_	_	2
64	**Bayley et al.* [106] 2007, USA**	a hospital, 927 PIs	1 intervening pharmacist + 1 pharmacy manager + 1 pharmacist	IN	IN	Few different between an intervening pharmacist and a pharmacy manager and a study author	_	_	- result of validity was not reported in detail - no physicians as raters (H)	5
65.1	**Midlov et al.* [115] 2008, Sweden**	three departments of a hospital, 197 patients with at least	2 physicians	IN	consensus	_	Cohen's k = 0.85 (95% CI 0.78-0.92)	_	- sampling of patients of 65 years or older - only 2 raters - there were no	2

		one medication error							pharmacists as raters (H)	
65.2	**Midlov et al. [153] 2012, Sweden**	a hospital	3 persons	GR	consensus + hierarchical approach	_	_	_	_	1
66	**Krahenbuhl et al.* [28] 2008, Switzerland**	20 community pharmacies	intervening pharmacists	IN	IN	_	_	_	_	2
67	**Pippins et al.* [116] 2008, USA**	2 hospitals, 939 unintentional discrepancies	2 physicians from a pool of six (the third judicator as needed)	GR	consensus + hierarchical approach	_	(1) k = 0.95 (2) k = 0.94	_	- sampling of only unintentional discrepancies - only external raters - there were no pharmacists as raters - only two raters (H)	5
68	**Rothschild et al.* [3] 2010, USA**	4 emergency departments, 504 MEs, consecutive sampling	Pairs of physician and pharmacist	IN	consensus	_	(1-2) k = 0.23 (3) k = 0.22	_	- MEs from only emergency departments - only 2 raters evaluated each ME (H)	4
69	**Abu-Ramaileh et al.* [135] 2011, USA**	an emergency department of 4 medical centers, 130	pairs of a physician and a pharmacist	GR	consensus	_	(1) k = 0.21 (3) k = 0.30	_	- only 2 raters evaluated a PI - non-random sampling of PIs	4

		PIs, non-random sampling							- PIs from only emergency departments (H)	
70.1	**Patanwala et al.* [138] 2011, USA**	an emergency departments, 237 MEs, consecutive sampling	2 pharmacists + 1 physician investigator not involved in the data collection process	IN	conservative	_	(1) agreement = 76%, kw =0.35 (2) agreement = 77%, kw = 0.42 after "dichotomization of severity scale and probability scale"		- PIs done by only a pharmacist in an emergency department - MEs did not consists of name misspellings or other inconsequential events (H)	3
70.2	**Patanwala et al. [139] 2011, USA**	4 emergency departments, 401 MEs, consecutive sampling	1 pharmacist + 1 physician not involved in the data collection process and blinded to the study site	IN	conservative approach	_	(1) agreement 83%, kw = 0.3	_	- only 2 raters - PIs from only emergency departments (H)	3
71	**Granas et al.* [120] 2009, Norway**	23 community pharmacies, 88 DRPs, consecutive sampling	1 physician + 2 hospital-based clinical pharmacists + 1 community pharmacist	GR	consensus	_	(1) k' = 0.5 (2) k' = 0.64; (3) k' = 0.81 (modified Fleiss' kappa)	_	- patient notes from physician was not available - a meeting organized for understanding of the concept of categorisation of DRPs	4

									(H)	
72	**Vasileff et al.* [122] 2009, Australia**	an emergency department of a hospital, 111 unintentional discrepancies, consecutive sampling	3 hospital pharmacists + 3 physicians + 1 academic pharmacist + 1 pharmacy researcher	GR	mean and rounded to the nearest clinical significance category	_	Of the 15 possible pairings of raters, 11 gamma statistics indicated moderate agreement, 3 indicated weak agreement and 1 indicated strong agreement	_	- sampling of only unintentional discrepancies of an emergency department - assumptions made when assessing the clinical significance of discrepancies (H)	2
73	**Lee et al.* [132] 2010, Canada**	10 inpatient units at 2 tertiary care hospitals, 250 unintentional discrepancies	2 pharmacists + 1 internist + 1 intensivist not involved in the direct care of the patient	IN	consensus	_	(1-3) k = 0.637-0.769	_	- sampling of only medication discrepancies - a series of assumptions applied before assessment (H)	4
74	**Rashed et al.* [154] 2012, UK and Saudi Arabia**	2 hospitals	1 consultant pediatrician + 1 clinical pharmacist + 1 researcher	GR	consensus	_	_	_	_	0
75	**Niquille et al.* [134] 2010, Switzerland**	community pharmacies	General practitioners + 2 pharmacists	IN and GR	IN and consensus	_	_	_	_	3
76	**Eichenberger**	64 community	Pharmacy students	IN	IN	_	_	_	_	2

	et al.* [126] 2010, Switzerland	pharmacies								
77	**Knez et al.* [131] 2010, UK**	a chemotherapy preparation unit at a cancer center, 13 PIs, random sampling	a consultant in medical oncology and a panel of 1 head of preparation service + 2 clinical oncology pharmacists + 1 specialist in drug manufacture and drug stability	GR	Modified nominal group consensus method	Validated the panel's decisions by a consultant in medical oncology (agreement = 46%)	_	_	- few PIs - PIs from on a chemotherapy preparation unit - the study did not test inter- and intra-reliability (H)	1
78	**Williams et al.* [31] 2011, Australia**	community pharmacies	intervening pharmacists	IN	IN	_	_	_	_	4
79	**Cesarz et al.* [145] 2011, USA**	a medical center	4 intervening pharmacists	IN	IN	_	_	_	_	0
80	**Perera et al.* [140] 2011, USA**	Medication Therapy Management Program	pharmacists	IN	IN	_	_	_	_	2
81	**Kwint et al.* [152] 2012, Netherlands**	10 community pharmacies	3 pharmacists	ND	consensus + hierarchical approach	_	_	_	_	2
82	**Mekonnen et al.* [155] 2013, Ethiopia**	a hospital	1 internist + 1 clinical pharmacologist + 1 clinical pharmacist	GR	hierarchical approach	_	_	_		2

ESM 5. Indicators used in existing tools for assessment of potential significance of PIs

Impact	Indicators used
Clinical	**Safety** [28, 75, 134, 140, 158], adverse health consequence [48], adverse effect [50, 77, 87, 101, 103], ADE [3, 102, 106], harmful effect [21], ADR [66, 89, 123], detrimental effect [104], clinical deterioration [22, 132], toxicity [44, 55, 66], side effects/allergy/interaction [55, 66], damage [84, 91], harm/injury [3, 23, 47, 96, 113, 128], relapse [103], graft loss [91], organ loss [66], impairment of health [24], morbidity [21, 29, 86, 106, 113]; change in vital signs [96], mortality/life-threatening/lethal effect [3, 12, 20, 23, 30, 38, 43, 44, 47, 51, 59, 61, 65, 66, 76, 77, 84-86, 94, 96, 100-103, 106, 107, 112, 116, 122, 138, 150] **Effectiveness** of drug therapy [21, 28, 29, 75, 89, 134], efficacy [55], response to medication [87], efficacy of the patient's therapeutic management[70], therapy effect [57, 123], disease control [53], treatment failure [66], curing a disease, slowing a disease process [111, 150], disease-related complication [91], signs or symptom control [3, 82, 100, 111, 116, 150], major organ dysfunction [3, 12, 30, 38, 43, 44, 51, 59, 61, 65, 76, 100, 102, 150], alteration in physiological process [111, 150], alteration of life functions [3, 116], treatment failure [77, 101] **Necessity** [134] **Characteristics of effects**: short-term/long-term [106]; (ir)reversible [24, 59, 99, 104, 129, 133]; permanent/temporary [23, 96, 105, 113], theoretical/(un)detectable/(un)noticed [20, 21]; trivial/minor/major/serious [40]; doubtful or negligible [103] **Others**: clinical relevance [92, 120], examples of groups of similar MEs [12, 35-37, 42], preventability [154]
Humanistic	**Patient's knowledge** [71, 79] **Compliance** [31, 53, 55, 66, 71, 77, 82, 158], adherence [87, 101] **Patient's satisfaction** [66, 120], (in)convenience [91, 100, 108, 159], distress [100], (dis)comfort to patient [22, 56, 66, 132] **Inability to work** [24, 105], inference with the patient's everyday activity [56] **Quality of life** of patient [59, 100, 158], patient's well-being [66, 82], standard of patient health [112, 121], state of health [24], physical, mental or social function or satisfaction with care (feeling better) [111, 150], lifetime disability [66]
Economic	**Cost savings** [30, 31, 50, 51, 53, 55, 65, 68, 73, 87, 106, 140], expense problem [134], value for money [75, 158], cost of drug therapy [20, 38, 43, 61, 66, 109, 111], savings from drug therapy monitoring [38, 61], influence on patient cost [43], reduction in treatment cost [29], increasing reimbursement [66]. **Cost avoidance**: Health care resources avoided such as a reduction in hospital stay [21, 29, 38, 41, 47, 50, 61, 66, 77, 85, 87, 94, 96, 101, 105, 113], hospital admission [21, 23, 24, 31, 48, 70, 71, 74, 79, 85, 94, 101, 105, 113, 123, 127, 159], readmission [66, 102, 105, 113], schedule physician visit [31, 48, 66],

	long-term-care admission [94], regular nurse visit or residential care [31], transfer to intensive care unit [94, 96, 159], urgent or emergency care [24, 48, 66], primary care contact [123], self-care [48], monitoring [59, 74, 84, 86, 88, 91, 96, 105, 128], additional laboratory test/invasive procedures [96], treatment or change in therapy [23, 74, 75, 86, 91, 94, 96, 105, 108, 113, 152, 159], additional investigation/intervention/tests, noninvasive procedures [85, 94, 128].
Process-related	**Resolving technical problems**: medication supply [57, 82], legally or technical problems/formulary [28, 91] **Informational intervention** [31, 38, 53, 57, 71, 75, 82, 94], physician education [50], nurse need gather additional information [84] **Physician's satisfaction** [120], inconvenience to physician and pharmacist [40, 91, 100], **Facilitation of continuity of care** [55], cancellation or delay in planned treatment/procedure [40, 113], service closure [93] **Teamwork**, pharmaceutical support, or communication [82] **Adherence to evidence-based therapy**, nationally adopted quality standards [104, 135], guideline adherence [140], adherence to unit protocols [91] **Others**: loss of confidence in the organization, litigation [93]
Structure-related	**No indicator**
Probability	**Probability/** chance/ likelihood of adverse health consequence [3, 20, 23, 48, 56, 109, 113, 132] **Confidence of judgment** [70, 116, 135]. Probability as an intermediate indicator in order to classify **risk** [20-24] Probability as an intermediate indicator in order to calculate **cost avoidance** [48, 56, 109]
Significance	**Quality of care** [50, 51, 87], bringing care to a more acceptable and appropriate level [38, 51, 102], overall care of patient [77, 101], patient care [75, 87], standard of practice [38, 51, 102, 106] **Improved patient outcome** [71, 91], health outcome [122] Being neutral depending on **professional interpretation** [38, 53, 102], a choice among several equally acceptable actions [51] **Priority** to be discussed with the physician [152], priority into implementation [134] **Effect**: negative, no, positive effect [41, 50, 56, 87], significant/useful [57] **Optimizing drug therapy** [21, 44, 66, 160], rationalization of medication to reduce medication burden [91], adjustments [21, 29] **Problem** identified/resolved/unresolved/prevented [57, 111, 126, 150, 160] **Appropriateness** [79]

PI: pharmacist intervention, ME: medication error

ESM 6. The French-written CLEO tool

EVALUATION DES IMPACTS D'UNE INTERVENTION PHARMACEUTIQUE PAR L'ECHELLE CLEO v3

1. IMPACT CLINIQUE (CL)

Score	Impact	**Définition:** L'impact clinique est évalué selon le scénario prévu le plus probable et non pas le pire/meilleur scénario
-1C	**Nuisible**	L'IP peut conduire à des résultats défavorables concernant l'état clinique, la connaissance, la satisfaction, l'adhésion médicamenteuse et/ou la qualité de vie du patient.
0C	**Nul**	L'IP n'a pas d'influence sur le patient concernant l'état clinique, la connaissance, la satisfaction, l'adhésion médicamenteuse et/ou la qualité de vie du patient.
1C	**Mineur**	L'IP peut améliorer la connaissance, la satisfaction, l'adhésion médicamenteuse, et/ou la qualité de vie OU l'IP peut empêcher un dommage qui ne requiert pas de surveillance/traitement
2C	**Moyen**	L'IP peut empêcher un dommage qui requiert une surveillance accrue ou un traitement, mais n'entraine pas ou n'allonge pas un séjour hospitalier du patient.
3C	**Majeur**	L'IP peut empêcher un dommage qui entraine ou allonge un séjour hospitalier OU entraine une incapacité permanente ou un handicap.
4C	**Vital**	L'IP peut empêcher un accident qui entraine potentiellement un soin intensif ou le décès du patient.
ND	**Non-déterminé**	Les informations disponibles ne permettent pas de déterminer l'impact clinique.

- L'impact clinique est évalué du point de vue **clinique chez le patient.**
- **Dommage**: dommage corporel - altération des *capacités physiques* et *psychiques* survenant au décours d'un accident ou d'une maladie.
- **Qualité de vie**: fonction *physique* (autonomie, capacités physiques, capacités à réaliser les tâches de la vie quotidienne...), *psychologique* (anxiété, dépression, émotivité...), *sociale* (rapport à l'environnement familial, amical ou professionnel, engagement dans des relations personnelles, participation aux activités sociales et de loisirs...) et *somatique* (symptômes liés à la maladie).
- **Surveillance**: *Suivi clinique (physiologique* ou *psychologique), biologique* pertinent.
- **Traitement**: *Changement* de thérapie ou *ajout* d'un traitement médical/chirurgical supplémentaire.

2. IMPACT ECONOMIQUE (E)

Score	Impact	Definition
-1E	**Augmentation du coût**	L'IP augmente le coût de la prise en charge médicamenteuse du patient.
0E	**Pas de changement**	L'IP ne modifie pas le coût de la prise en charge médicamenteuse du patient.
1E	**Réduction du coût**	L'IP économise le coût de la prise en charge médicamenteuse du patient.
ND	**Non-déterminé**	Les informations disponibles ne permettent pas de déterminer l'impact économique.

- Le **coût de la prise en charge médicamenteuse** contient deux éléments principaux :
  - *Le coût des médicaments*
  - *Le coût de surveillance de la prise en charge médicamenteuse (par exemple, suivi clinique, cinétique, biologique...).*
- Le **coût de la prise en charge médicamenteuse** se base sur le **coût financier de l'hôpital.**

3. IMPACT ORGANISATIONEL (O)

Score	Impact	Definition
-1O	**Défavorable**	L'IP diminue la qualité du processus des soins.
0O	**Nul**	L'IP ne change pas la qualité du processus des soins.
1O	**Favorable**	L'IP augmente la qualité du processus des soins.
ND	**Non-déterminé**	Les informations disponibles ne permettent pas de déterminer l'impact organisationnel.

- L'impact organisationnel est codé selon **l'impact global sur la qualité du processus des soins selon la perspective des personnels soignants** (eg, *économies de temps ; amélioration de connaissance, de satisfaction au travail ou de sécurité des personnels soignants ; facilitation des tâches professionnelles ou du travail d'équipe, de continuité des soins ; etc.)*

TITRE en français : Évaluation de l'impact potentiel des interventions pharmaceutiques : développement et validation de l'outil multidimensionel CLEO

RESUME en francais :

Dans le contexte de ressources limitées actuelles, il est nécessaire pour les pharmaciens de justifier la valeur ajoutée de leurs interventions pharmaceutiques (IP) formulées lors de l'analyse pharmaceutique (AP). L'objectif de ce travail de thèse est de mener une recherche sur les méthodes d'évaluation de la pertinence des IPs et développer un nouvel outil pour l'évaluation de l'impact potentiel des IPs. Le travail se décompose en 3 grandes parties : (i) contexte de l'AP, et méthodes d'évaluation de l'impact des IPs, (ii) revue systématique des outils pour évaluer la pertinence potentielle des IPs, (iii) processus de développement et de validation du nouvel outil multidimensionnel - nommé CLEO pour évaluer l'impact potentiel des IPs. Les résultats de cette recherche apportent des éléments nouveaux pour l'évaluation et la démonstration de la valeur des IPs dans un objectif global de déploiement des services de pharmacie clinique.

TITRE en anglais : Evaluation of the potential impact of pharmacist interventions : development and validation of the CLEO multidimensional tool

RESUME en anglais :

In times of limited resources allocation, it is necessary for pharmacists to justify the added value of their pharmacist interventions (PIs) made during medication review (MR). The purpose of this thesis work is to research on methodologies of evaluation of value of PIs as well as development and validation of a new tool for assessing potential impacts of PIs. The work consists of 3 major parties: (i) context in which MR locates, characteristics of practice of MR, and methodologies of evaluation of impacts of PIs, (ii) systematic review of tools for assessing the potential significance of PIs in literature , (iii) process of development and validation of the new multidimensional tool - named CLEO for assessing potential impacts of PIs. The whole results of this research are useful to evaluate and demonstrate the value of PIs in efforts to expand clinical pharmacy services.

MOTS-CLES : interventions pharmaceutiques, évaluation, outil, impacts

MOT-CLES en anglais: pharmacist interventions, evaluation, tool, impacts

DISCIPLINE

Modèles, Méthodes et Algorithmes en Biologie

INTITULE ET ADRESSE DE L'U.F.R OU DU LABORATOIRE

Laboratoire TIMC-IMAG, Equipe ThEMAS "Techiniques pour l'Evaluation et la Modélisation des Actions de Santé" UMR CNRS 5525 - Université Grenoble Alpes

Pavillon Taillefert -Faculté de Médecine de Grenoble - 38700 La Tronche