

**Clinical pharmacy services within  
a multiprofessional healthcare team**



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**CLINICAL PHARMACY SERVICES  
WITHIN A MULTIPROFESSIONAL  
HEALTHCARE TEAM**

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**CLINICAL PHARMACY SERVICES WITHIN A MULTIPROFESSIONAL  
HEALTHCARE TEAM**

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## Abstract

Hellström, Lina, (2012). *Clinical pharmacy services within a multiprofessional healthcare team*. Linnaeus University Dissertations No 84/2012. ISBN: 978-91-86983-47-5. Written in English with a summary in Swedish.

**Background:** The purpose of drug treatment is to reduce morbidity and mortality, and to improve health-related quality of life. However, there are frequent problems associated with drug treatment, especially among the elderly. The aim of this thesis was to investigate the impact of clinical pharmacy services within a multiprofessional healthcare team on quality and safety of patients' drug therapy, and to study the frequency and nature of medication history errors on admission to hospital.

**Methods:** A model for clinical pharmacy services within a multiprofessional healthcare team (the Lund Integrated Medicines Management model, LIMM) was introduced in three hospital wards. On admission of patients to hospital, clinical pharmacists conducted medication reconciliation (i.e. identified the most accurate list of a patient's current medications) to identify any errors in the hospital medication list. To identify, solve and prevent any other drug-related problems, the clinical pharmacists interviewed patients and performed medication reviews and monitoring of drug therapy. Drug-related problems were discussed within the multiprofessional team and the physicians adjusted the drug therapy as appropriate.

**Results:** On admission to hospital, drug-related problems, such as low adherence to drug therapy and concerns about treatment, were identified. Different statistical approaches to present results from ordinal data on adherence and beliefs about medicines were suggested. Approximately half of the patients were affected by errors in the medication history at admission to hospital; patients who had many prescription drugs had a higher risk for errors. Medication reconciliation and review reduced the number of inappropriate medications and reduced drug-related hospital revisits. No impact on all-cause hospital revisits was demonstrated.

**Conclusion:** Patients admitted to hospital are at high risk for being affected by medication history errors and there is a high potential to improve their drug therapy. By reducing medication history errors and improving medication appropriateness, clinical pharmacy services within a multiprofessional healthcare team improve the quality and safety of patients' drug therapy. The impact of routine implementation of medication reconciliation and review on healthcare visits will need further evaluation; the results from this thesis suggest that drug-related hospital revisits could be reduced.

### Keywords

Clinical pharmacy services, pharmacist, medication review, medication reconciliation, medication errors, drug-related problems, inappropriate prescribing, elderly, inpatients, patient readmissions, hospitalisation, multiprofessional, patient care team, continuity of patient care



To my family



Build a bridge, not a barrier  
Make a friend, not a fuss  
Find a cause, not a controversy  
Be a cheerleader, not a critic  
Seek a solution, not a standoff  
(Source unknown)



## List of papers

The thesis is based on the following original papers, which are referred to in the text by their Roman numerals.

- I Bondesson Å, Hellström L, Eriksson T, Höglund P. A structured questionnaire to assess patient compliance and beliefs about medicines taking into account the ordered categorical structure of data. *Journal of Evaluation in Clinical Practice* 2009; 15(4): 713-723.
- II Hellström LM, Bondesson Å, Höglund P, Midlöv P, Holmdahl L, Rickhag E, Eriksson T. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. *European Journal of Clinical Pharmacology* 2011; 67(7): 741-752.
- III Hellström LM, Bondesson Å, Höglund P, Eriksson T. Errors in medication history at hospital admission: prevalence and predicting factors. *BMC Clinical Pharmacology* 2012; 12:9.
- IV Hellström LM, Höglund P, Bondesson Å, Petersson G, Eriksson T. Clinical implementation of systematic medication reconciliation and review. (Submitted)



## Populärvetenskaplig sammanfattning

Behandling med läkemedel avser att minska patienters sjuklighet och dödlighet och leda till bättre livskvalitet. Det händer emellertid att patienter drabbas av så kallade läkemedelsrelaterade problem, särskilt vanligt är detta bland äldre. Läkemedelsrelaterade problem kan till exempel vara biverkningar eller otillräcklig effekt av ett läkemedel. Läkemedelsfel i övergångar mellan olika vårdenheter är också vanligt. Syftet med denna avhandling var att undersöka hur en modell för klinisk farmaci på sjukhus påverkar läkemedelsbehandlings kvaliteten och säkerheten. Ett ytterligare syfte var att studera hur många och vilken typ av läkemedelsfel som uppkommer i sjukhusets läkemedelslistor när patienter skrivs in på sjukhus.

En modell där kliniska apotekare ingår i ett multiprofessionellt vårdteam (Lund Integrated Medicines Management, LIMM) infördes på tre sjukhusavdelningar. När patienter skrevs in på avdelningarna gjorde kliniska apotekare en läkemedelsavstämning (dvs de identifierade den mest korrekta listan över patientens aktuella läkemedel). Apotekarna intervjuade även patienterna samt genomförde läkemedelsgenomgångar och uppföljning av läkemedelsbehandlingen under sjukhusvistelsen för att lösa och förebygga läkemedelsrelaterade problem. De läkemedelsrelaterade problemen och läkemedelsfelen som hittades diskuterades inom vårdteamet och läkaren ansvarade för att göra förändringar i patientens läkemedelsbehandling.

Vid patientintervjuerna upptäcktes olika läkemedelsrelaterade problem, till exempel låg följsamhet och oro för behandlingen. Ett antal statistiska metoder som kan användas för att presentera resultaten från frågeformulär om följsamhet och attityder till behandlingen togs fram. Hos ungefär hälften av patienterna hittades minst ett fel i sjukhusets läkemedelslista vid jämförelse med vilka läkemedel patienten behandlades med precis före sjukhusinläggningen. De patienter som hade många receptbelagda läkemedel hade en högre risk för läkemedelsfel. Läkemedelsavstämning och läkemedelsgenomgångar minskade antalet olämpliga läkemedel och minskade läkemedelsorsakade återbesök på sjukhus. Någon effekt på totala antalet återbesök på sjukhus kunde inte visas. Sammanfattningsvis löper patienter inlagda på sjukhus stor risk för att drabbas av felmedicinering och det finns en stor potential att förbättra kvaliteten i deras läkemedelsbehandling. Genom att minska läkemedelsfelen och minska antalet olämpliga läkemedel så kan kliniska farmaceuter i ett multiprofessionellt vårdteam förbättra läkemedelsbehandlings kvaliteten och säkerheten. Ytterligare studier behövs för att undersöka om läkemedelsavstämning och läkemedelsgenomgångar påverkar patienternas behov av sjukvård efter utskrivning från sjukhuset; resultatet från denna avhandling tyder dock på att läkemedelsrelaterade återbesök till sjukhus kan minskas.



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## Abbreviations

BMQ	Beliefs about Medicines Questionnaire
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DRP	Drug-Related Problem
EHR	Electronic Health Record
GP	General Practitioner
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IMM	Integrated Medicines Management
ITT	Intention-To-Treat
LIMM	Lund Integrated Medicines Management
MAI	Medication Appropriateness Index
OR	Odds Ratio
PP	Per Protocol
QALY	Quality-Adjusted Life Year

## **Introduction**

Drug treatment is an essential component of medical care to prevent, cure and control disease. Its purpose is to decrease morbidity and mortality and to increase health-related quality of life (HRQoL). Treatment with medicines is a prerequisite for many people in order to function well and be able to live in their own homes as long as possible [1]. However, problems associated with drug treatment such as medication errors and adverse drug events are frequent, especially among the elderly [2-4]. It has been shown that at least 5% of hospital admissions are caused by drug-related problems; higher prevalences have typically been found in the elderly population and among psychiatric patients [5, 6]. Fatal adverse drug reactions has been estimated to be the seventh most common cause of death in Sweden [7]. Thus, there is an urgent need for methods that improve quality and safety of prescribing and reduce adverse drug events. There is a large potential to improve the situation as the majority of drug-related admissions to hospital has been estimated to be preventable [8, 9]. Given the complexity of the process leading to medication errors and adverse drug events [8, 10-12], it is likely that interventions for solving and preventing drug-related problems need to be multifaceted.

## **Drug safety issues in the elderly**

The elderly population is steadily increasing throughout most of the world [13]. According to a report from the United Nations, the proportion of individuals over 60 years is expected to reach 22% in 2050, compared with 11% in 2009 [13]. In Sweden, 24.7% of the population was over 60 years already in 2009; only three countries in the world had a higher proportion of persons over 60 years [13]. A major challenge in relation to this demographic shift is to ensure that drug treatment when needed in the elderly is safe and effective. This is a complex task, especially in patients with age-related physiological changes, multimorbidity and polypharmacy [14]. Many elderly have a number of co-morbid chronic diseases and, therefore, are often prescribed a number of different drugs to be used concurrently (known as polypharmacy). The prevalence of polypharmacy has increased during recent years [15]. Polypharmacy can be justified in patients with multiple co-morbidities, but may also be inappropriate [14]. In any case, the risk of adverse drug reactions and drug interactions increase exponentially with the number of drugs taken [14, 16]. On the other hand, undertreatment or therapeutic failure may also occur in the elderly [17].

## Appropriate prescribing

Appropriate prescribing is a general phrase to express the quality of prescribing of medications for the individual patient [18]. In a wide sense, appropriate prescribing encompasses a number of values, including the desires of the patient, the scientific and technical rationale for the use of the medication, and the general good that is expected to be derived from the use of the medication (societal and family-related) [18]. No set definition of inappropriate prescribing has been established [18, 19], but it can be described as: *“the use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition”* [16]. The under-use of beneficial medicines that are clinically indicated but not prescribed for irrational reasons may also be defined as inappropriate prescribing [16].

Measures to assess potentially inappropriate prescribing can be based on predetermined criteria (explicit criteria) or clinical judgment (implicit criteria) [18]. As most measures of appropriate prescribing evaluate only pharmacological and sometimes economic appropriateness [18, 20], they reduce the complexity of the concept of appropriate prescribing. Hence, these measures cannot be used as substitutes for careful clinical decision-making, but they are still useful to alert physicians and pharmacists to the likelihood of inappropriateness [20]. Also, they are valuable in research for evaluating the effect of interventions aiming at improving quality of prescribing [21].

Explicit criteria for inappropriate prescribing include lists of drugs that should be avoided in elderly people, doses that should not be exceeded, drugs that should be avoided in patients with specific diagnoses, or drugs that are indicated and should be started [18, 22-26]. Among the most commonly used explicit criteria are the Beers criteria [27, 28], the McLeods criteria [23], the IPET (Improved prescribing in the elderly tool) [24], and the STOPP/START (Screening tool of older persons' prescription/Screening tool to alert doctors to right treatment) [26]. The prevalence of potentially inappropriate medications in European elderly home care patients were reported to be 19.8% as defined by the Beers 1997 criteria [27], the Beers 2003 criteria [22], or McLeod criteria [23] (range 5.8% in Denmark to 41.1% in the Czech Republic) [29]. A shortcoming with the use of Beers and McLeod's criteria in Europe is that a significant number of the medications listed in the criteria are not approved in Europe. Moreover, there are a number of potentially inappropriate medications that are available in Europe, but not in the US. Thus, higher prevalence of potentially inappropriate medication has been found when applying Beers criteria in the US [16].

An explicit measure (quality indicators) for evaluation of appropriateness of drug therapy in the elderly have been developed by the Swedish National Board of Health and Welfare [25]. These indicators include drugs to be avoided, inappropriate doses and drug combinations to avoid, as well as diagnosis specific indicators. When applying five of these drug-specific indicators to prescribing data among Swedish nursing home residents, over 70% had one or more potentially inappropriate prescriptions [30]. In an investigation of exposure to at least one of four drug-specific quality indicators, 30% of the institutionalised elderly and 12% of the home-dwelling elderly used potentially inappropriate drugs [31]. Patients using multi-dose drug dispensing seem to be more exposed to potentially inappropriate drugs [32, 33]. Other predictors for potentially inappropriate drugs judged by explicit measures are the number of prescribed drugs [34-36], and lower education [37]. The association between age and potentially inappropriate drug use is unclear; some studies have reported a higher risk with increasing age [34, 36], while others have reported a lower risk [31, 38].

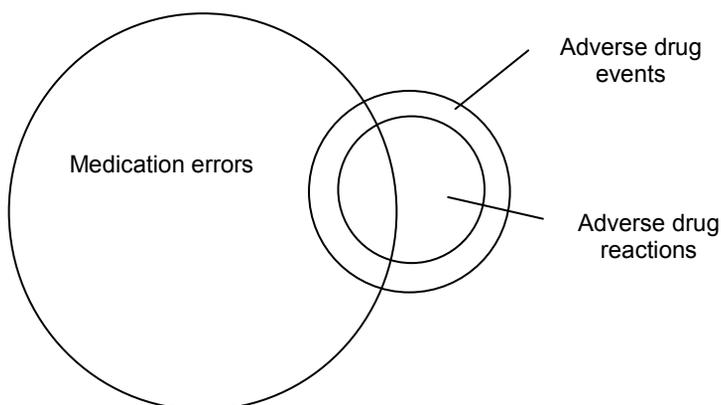
In implicit measures, clinicians judge the appropriateness of a patient's prescription [18]. In order for such measures to be reliable and valid, detailed specifications, instruments to obtain data, and training of data collectors are necessary [18]. Although, the Medication Appropriateness Index (MAI) is an implicit measure, it incorporates operational definitions and explicit instructions, which standardise the rating process [18, 39]. The MAI evaluates appropriateness based on ten items: indication, drug effectiveness, correct dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, drug duplication, duration of treatment, and expense [39]. However, underprescribing is not assessed by the MAI and it is time-consuming to use. The Lipton's criteria include some of the MAI items and also less-than-optimal choice of a drug and drug allergy [40]. The Inappropriate Medication Use and Prescribing Indicators Tool includes all MAI items except correct directions, and also underprescribing and elements that assess the medication management appropriateness, e.g. monitoring and additional tests [41].

When inappropriate prescribing is assessed by clinical judgement (i.e. by implicit criteria), higher number of patients affected by potentially inappropriate prescriptions is reported relative to studies using explicit criteria [42-45]. Two US studies in Veteran Affairs medical centres (>97% males) found that over 90% of patients in hospital [42] and ambulatory care [43] received at least one inappropriate medication according to the MAI; 74%-78% of the drugs had at least one inappropriate rating. In a Danish study in primary care, 94.3% of elderly patients exposed to polypharmacy (five or more drugs) had one or more inappropriate ratings among their medications; 39.5%

of the medications were inappropriate [44]. Among patients admitted to an acute geriatric ward in Belgium, 60% of the medications had one or more inappropriate MAI-rating [45].

### **Drug-related problems**

Drug-related problems (DRP) may occur in all steps of the medication pathway, from the prescribing of the medication, the administration and use of the medication, and the follow up evaluation of the effects of the medication [46]. DRPs include adverse drug events and adverse drug reactions; also, other problems such as the need for additional drug therapy [47], or patient dissatisfaction with treatment [48] may be included depending on the choice of DRP definition and classification system [49]. DRPs are often caused by medication errors, but there might be no error at all involved [49]. Furthermore, DRPs can be split into actual problems, which are manifest and influence outcome and potential problems, which are not manifest but may possibly influence outcome [49, 50]. There are a number of different classification systems for DRPs [48-51]. The systems differ in respect to their assessment processes, structures, and number and type of categories. There are strengths and weaknesses with all classification systems [49]; the use of different systems in different studies hampers comparison of results. A variety of definitions of DRPs, medication errors, adverse drug reactions, and adverse drug events are in use; definitions used in this thesis are shown in Table 1 and their relationship is depicted in Figure 1.



**Figure 1. Relationship between medication errors, adverse drug events, and adverse drug reactions**

**Table 1. Definitions of drug-related problems, medication errors, adverse drug reactions, and adverse drug events**

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Drug-related problem	An undesirable patient experience that involves drug therapy and that actually or potentially interferes with the desired patient outcome [47]
Medication error	Any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not [52]
Adverse drug reaction	A response to a medicinal product which is noxious and unintended (and a causal relationship is at least a reasonable possibility) [53]
Adverse drug event	An injury related to the use of a drug, regardless of whether a therapeutically appropriate dosage is used, although the causality of this relationship may not be proven [52]

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Medication errors include errors in planning actions or errors in executing correctly-planned actions [54]; they are preventable and may or may not result in patient harm [52, 54, 55]. It has been estimated that 1% to 10% of medication errors result in harm [4, 56], but the results depend on the method for detection as well as the definitions of medication errors [55]. Today, there is inconsistency between studies in defining medication errors [55].

It has been suggested that 25% [57] to 46% [4] of adverse drug events are due to medication errors and hence possibly preventable. An even larger part of adverse drug events may be preventable if drug therapy is continuously and actively monitored, managed and reassessed over time [58]. Dose-dependent adverse drug reactions are potentially preventable by dose adjustments based on the individual patient's clinical status (e.g. kidney function and potential drug-drug interactions) [59]. In other words, adverse drug reactions may be prevented by identification of risk factors that contribute to the development of the reaction [59].

### **Errors in medication history**

Errors in medication history can be described as errors made when compiling medication lists in connection with patients' admission to a care unit [60]. Such errors do not include inappropriate treatment from a clinical perspective. In order to prevent adverse drug events, an accurate, current medication list is essential [61]. A common situation where there is a risk for errors in

medication history is at admission to and discharge from hospital. As many as 67% of the patients admitted to hospital have been reported to experience at least one discrepancy between their 'home' medication list and the hospital medication list [60]; drugs may be mistakenly omitted or added to the drug list, or prescribed in the wrong dose. The errors in medication histories might be related to the system, e.g. failure to transfer information between health care providers in a timely way or heavy workload; or the healthcare staff, e.g. absence of verification of medication charts and poor documentation of prescribing decisions [62-65].

The term 'medication error', or more specifically 'medication history error', has been widely used when describing discrepancies between the medication list in hospital and the home-medication list [60, 62]. The term 'medication discrepancy' is also commonly used [60, 66]. In some cases, the terms medication error and medication discrepancy might be considered to be synonymous, but medication error is only used to describe unintentional changes in the drug list, while medication discrepancy also may comprise intentional changes [60].

### **Implications of age-related physiological changes on the effect of drugs**

Important pharmacokinetic and pharmacodynamic changes may occur with increasing age [67]. Many elderly are frail (e.g. have kidney and/or liver dysfunction, or dementia) making them more vulnerable to adverse drug reactions. However, it is likely that co-morbid conditions such as hypertension, diabetes mellitus, and chronic heart disease are more important than ageing *per se* with regard to their effect on the pharmacological changes [14], with some older persons being as fit and in a similar condition as younger patients.

The most important age-related changes of the body are reductions in renal and liver mass and blood flow, affecting metabolism and excretion [14]. This may result in higher plasma concentrations of the drug and the subsequent risk of toxicity [14, 67]. Conversely, the bioavailability of the active metabolites of prodrugs that require activation in the liver to become effective may be decreased (e.g. enalapril) [14, 67]. Absorption and distribution are affected to a much lesser extent by age-related physiological changes than metabolism and excretion [14].

Age-dependent pharmacodynamic changes may also occur [16, 67]. Such changes include end-organ responsiveness to drugs at the receptor or post-receptor level, and subsequent increased sensitivity to some drugs (e.g. opiates, warfarin) [16, 67]. Furthermore, elderly people are particularly sensitive to

drugs acting on the central nervous system (e.g. benzodiazepines) and anticholinergic drugs (e.g. tricyclic antidepressants) [67]. Adverse drug reactions of central nervous system active drugs include sedation, confusion, and impaired balance, possibly resulting in falls and fractures [68]. Anticholinergic drugs may for example cause constipation, dry mouth, and cognitive decline [69, 70].

### **Drug-related healthcare contacts**

Reported estimates of the prevalence of hospital admissions caused by DRPs range between 0.1% and 54% [6]. The results vary as a function of the setting, studied population, choice of outcome, the method of data collection, and geographical area (continent) [6]. High prevalence has been found among elderly (10.2%) and psychiatric patients (23.1%), patients who had been admitted previously because of a drug-related problem (17.7% to 19.5%), and in patients with polypharmacy (6.6%) [6]. Numerous studies have included only adverse drug reactions as a cause for hospital admissions; prevalence rates vary between 0.16% and 15.7%, with a median rate of 6.5% in adults [5]. A Swedish study reported a prevalence of 13.8% for adverse drug reactions as a cause for hospital admissions [71], and a Dutch study found a prevalence of 5.1% [72].

The most common drugs causing DRPs resulting in hospital admissions are antiplatelets [71, 73], diuretics [73], nonsteroidal anti-inflammatory drugs [73], anticoagulants [71, 73], betablockers [71, 73, 74], opioid analgesics [73] and other central nervous system agents [5, 71]. Many drug-related hospital visits are preventable [8, 75], especially among the elderly [75].

### **Patients' perspectives on drug use**

Patients possess fundamental knowledge about drug use derived from own experience [76]. Patients' knowledge, experience, and medication related behaviours are important factors that may influence outcomes of drug treatment [77]. There is a considerable reluctance to take drugs and a preference to take as little as possible according to lay experiences of medication taking [78]. In a Swedish study among elderly individuals using at least five medications, co-existing positive and negative attitudes towards their medications emerged [79]. The participants expressed gratitude that medications exist, but it was also revealed that participants used medicines because they 'had to', and they expressed emotions such as worry, fear and uncertainty about adverse effects and interactions [79]. It has been suggested that patients balance the perceived benefits against the perceived risks and

decide whether they should reject, passively accept or actively modify the prescribed therapy [78, 80, 81].

The terms compliance and adherence both relate to the extent to which patients take medications as prescribed, but the terms are not synonymous. Compliance suggests that patients should passively follow the doctor's orders [82]; whereas adherence is intended to be non-judgmental, a statement of fact rather than of blame of the patient [77]. The term concordance includes a consensual agreement about drug treatment established between patient and provider, and does not refer to a patient's medicine-taking behaviour [77]. Questionnaires can be used to assess patients' adherence to drug treatment and their beliefs about medications. The Morisky four-item scale [83], and eight-item scale [84], are questionnaires for assessing adherence. The Beliefs about Medicines Questionnaire-specific (BMQ-specific) includes statements about necessity and concerns of medication therapy [85]. There is a correlation between beliefs about medication and adherence; with negative beliefs correlating with non-adherence and positive beliefs with adherence [81, 86].

In the same way as polypharmacy and the use of inappropriate medicines may result in negative clinical consequences, the opposite (i.e. patients' underuse of medicines) may cause poor health outcomes [77, 87-90] as well as increased healthcare costs [90]. The adherence rate for long-term medication used for prevention, treatment or cure is reported to range from 33% to 94% [91]. The adherence rates to long-term therapy tend to reach at most 50%, regardless of the illness or setting [77].

## **Strategies to improve drug use**

### **Medication reconciliation**

Problems with inaccurate information during transitions between care settings, e.g. medication history errors, can jeopardise the quality of prescribing and result in adverse drug events [92-94]. Medication reconciliation has been endorsed by patient safety organisations and authorities in a number of countries as a method of improving the accuracy of patients' medication lists [62, 95, 96]. The Institute for Healthcare Improvement in the US has described medication reconciliation as being "*the process of identifying the most accurate list of a patient's current medicines – including the name, dosage, frequency, and route – and comparing them to the current list in use, recognising any discrepancies, and documenting any changes, thus resulting in a complete list of medications, accurately communicated*" [62]. Medication reconciliation can be conducted at all transitions between care

settings, e.g. admission to hospital, discharge from hospital, or at the return to a nursing home [62].

Clinical pharmacists, as key members of a multiprofessional healthcare team, are very well suited to perform such systematic medication reconciliations [97, 98]. Based on the ability to reduce medication errors, there is evidence that pharmacist interventions are the most cost effective among studied medication reconciliation interventions [62]. However, also other interventions appear beneficial such as a package of interventions including personnel and documentation changes and systems to better transfer information from the general practitioner to hospital [62]. In addition, there are many promising and emerging technologies that may be effective in medication reconciliation [62, 99, 100].

There is evidence for a positive impact of medication reconciliation procedures on medication errors [101-106]. Fewer high-quality studies have evaluated the impact of medication reconciliation on adverse drug events or other patient-related outcomes. However, in a randomized study of pharmacist medication reconciliation, patient counselling and follow-up telephone call, intervention patients had fewer preventable adverse drug events and medication-related hospital revisits within 30 days, than patients who received routine review of medication orders by a ward-based pharmacist and medication discharge counselling by a nurse [107]. No difference in total adverse drug events or total healthcare utilisation between the groups was demonstrated [107]. Another randomised study comparing a pharmacy discharge plan for hospitalised elderly patients with standard discharge letters, reported no differences in hospital readmissions, outpatient visits or mortality at 3 or 6 months [108]. In two before-after studies, medication reconciliation upon admission [61] and discharge [61, 109] was associated with fewer adverse drug events caused by erroneous medication changes. A home-based medication reconciliation program in the US had no impact on emergency department visits, rehospitalisations or ambulatory visits when compared with usual care [110]. However, an adjusted hazard ratio (HR) showed that the intervention group had a 78% reduction in the risk of death [110].

### **Medication review**

No set definition for a medication review exists, but the Pharmaceutical Care Network Europe has suggested the following definition: “*Medication review is an evaluation of patient’s medicines with the aim of managing the risk and optimising the outcome of medicine therapy by detecting, solving and preventing drug-related problems*” [111]. Medication review can be provided in different settings, and by different healthcare professionals (e.g. in community

pharmacies without any access to patient medical records, in primary care, or in hospital within a multiprofessional team). A patient interview is often, but not always, included as part of the medication review. Hence, medication review is not a straightforward term, which must be taken into consideration when comparing the results of research studies.

Medication reviews conducted in primary care, nursing homes and in hospital, reduce DRPs as well as prescribing of inappropriate drugs [45, 112-119]. The evidence of an impact of medication reviews on clinical outcomes, such as morbidity, and healthcare use is inconclusive [117, 118], and more high-quality studies should be undertaken. However, clinical medication reviews in multiprofessional teams, including medication reconciliation procedures at admission and discharge, can reduce the length of hospital stay and reduce rates of hospital readmission [115, 120-122].

### **Interventions to improve patient adherence**

A number of different methods to improve adherence to prescribed drugs have been studied, including simplifying the dosage regimen, more thorough patient instructions and counselling, reminders, close follow-up, motivational interviewing, and telephone follow-up [77, 123]. For short-term treatments several quite simple interventions are effective, but strategies for improving adherence with long-term medication prescriptions are not very effective [77]. Therefore, research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders should be prioritised [77].

### **Information systems**

There is increasing evidence that information systems, such as computerised physician order entry, ePrescribing, clinical decision support systems, software for medication reviews, and electronic medication reconciliation are key components of strategies to prevent medication errors and DRPs [124-126]. However, the scientific basis of its benefits remains to be firmly established [125], and the understanding of how and why eHealth interventions do or do not work in clinical practice is currently insufficient [125].

It is expected that a joint-order database for drugs or a shared electronic health record (EHR) for both the primary and hospital care will decrease the problem of access to information regarding patients' current drug lists, and reduce medication errors when patients are transferred between healthcare settings [127-129]. A qualitative study of Swedish physicians' experiences of a shared EHR showed that physicians regarded the EHR to have many

advantages [130]; it was practical and efficient as it had increased the availability of data and information. However, the expectation of the shared EHR to provide a reliable single source about patients' current medication list had not been fulfilled; there were still multiple ways of transferring information about patients' current prescribed medicines besides the list in the EHR (e.g. separate schedules of warfarin treatment kept on paper, multi-dose dispensing order lists, or discharge letters). In addition, the medication list in the EHR was not always accurate, as changes had not been updated [130]. Electronic medication reconciliation applications, integrated into the computerised order system for medications, may facilitate medication reconciliation procedures [124]. There is preliminary evidence that such applications are effective in reducing errors in medication history and potential adverse drug events [99, 100].

## **The multiprofessional team**

All healthcare professionals in hospital are more or less involved in the drug therapy process. Physicians' role is evident as they have the overall responsibility for prescribing drugs. Nurses administer most drugs, and may also monitor patients' clinical condition in relation to drug therapy (e.g. effects and adverse events). Assistant nurses may contribute by reporting patients' complaints or symptoms to the healthcare team. Also, the critical role played by pharmacists in the areas of medication safety and management has been recognised [131, 132]. Clinical pharmacists are especially well suited for performing medication reconciliations [97, 98], and their deep knowledge in pharmacokinetics, pharmacodynamics, and drug formulation is valuable when conducting medication reviews [122, 132]. Counselling patients during the hospital stay, at discharge and after discharge are also activities that have shown to be successfully conducted by clinical pharmacists and which have contributed to improved patient outcomes [117, 133].

Pharmacists may not only contribute to improved use of medications in hospital settings, but also in community pharmacies [134], primary care centres [135, 136], and nursing homes [114]. Until recently, very few Swedish pharmacists have worked within healthcare performing direct patient services. In other countries, such as the US, the UK and Canada, the role of pharmacists as members of the healthcare team has expanded beyond conventional medication dispensing decades ago [132].

However, the knowledge and skills of clinical pharmacists are best utilised in cooperation with other professionals in multiprofessional healthcare teams [132]. The work within such teams involves a negotiated agreement between

professionals which value the expertise and contributions that various healthcare professionals bring to patient care [137]. It has been suggested that important factors for successful collaborative relationships are: the behaviour of the professionals when initiating a new relationship; trustworthiness i.e. trust or confidence in another's abilities which can result in greater dialogue about problems encountered during patient care; and role specification, a factor which addresses the interactions between professionals in which they reach agreement on roles and responsibilities for each other in caring for mutual patients [138].

### **The concepts of medicines management, medication therapy management and pharmaceutical care**

Much of the work by clinical pharmacists is described as clinical pharmacy, medicines management, or pharmaceutical care [139-141]. Medicines management and pharmaceutical care do not explicitly require a specific profession to provide care, and also, they are oriented toward outcomes of care. There are more similarities than differences between these two concepts, as their core process is to identify, resolve, and prevent DRPs in order to improve patient outcomes [139, 141]. Clinical pharmacy, on the other hand, comprises processes carried out by pharmacists without specific references to outcomes [142].

Medicines management is originally a British concept and has been defined as: *"A concept that seeks to maximise health through the optimum use of medical drugs and which covers several aspects of the use of medications, from appropriate prescribing to the ways in which the drugs are taken or not taken by the patients"* [139]. The definition can vary, though, between countries or even regions. Earlier, there was an emphasis of rationalising medications primarily for the organisation, but more recently, it has developed to include managing medicines for patients [139].

The concept of pharmaceutical care originated in the US, and can be described as a philosophy that focuses on the responsibility of the pharmacist to meet all of the patient's drug-related needs [140]. The original definition of pharmaceutical care by Hepler and Strand is *"Responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the patient's quality of life"*; a distinctively patient centred concept [141]. Medication therapy management is another concept which can be viewed as a strategy, including payment for services rendered, to incorporate the philosophy of pharmaceutical care into everyday pharmacy practice for a defined patient population [140].

## **Lund Integrated Medicines Management (LIMM) model**

Since year 2000, the LIMM model has been continuously developed as a quality improvement and research project. The model offers a systematic approach for individualising and optimising drug treatment for inpatients. Today, the LIMM model is used in clinical practice in a number of hospitals in Sweden and Norway.

The model is based on multiprofessional teamwork in hospital wards. The activities of the LIMM model are performed by physicians, clinical pharmacists, and nurses and include: medication reconciliation at admission, medication review and monitoring during the hospital stay, and medication reconciliation at discharge (Table 2). In addition, nurses in the wards are educated in pharmacotherapy, and drug-information leaflets for patients have been developed to improve counselling of patients by nurses during the hospital stay. The clinical pharmacists are trained by experienced clinical pharmacists or attend a Master programme in clinical pharmacy before starting to work in the wards.

The activities of the LIMM model have been evaluated, both separately [102, 143-145] and in combination with each other [146]. We have demonstrated reduced rates of medication errors [102, 144] and healthcare contacts after hospital discharge [143], improved appropriateness of therapy [146], improved skills of the team to identify DRPs [145], and positive attitudes among the healthcare professionals in the wards [145].

**Table 2. The Lund Integrated Medicines Management (LIMM) model**

Activities performed in the hospital wards for each patient, the responsible professional groups, and the tools used to perform the activities.

When	How often	Activity	Responsibility	Tool
At admission	Once for each patient	Admission medication reconciliation	Clinical pharmacist	LIMM Medication Interview Questionnaire: Part 1: identification of the most accurate medication list for the patient Part 2: addition of questions concerning the patient's practical handling, knowledge of the medications and adherence to the medical regimen Part 3: addition of more detailed questions concerning the patient's adherence to the medical regimen [83] and beliefs about medications [85] LIMM Medication Review Form
During hospital stay	At regular intervals for each patient	Medication review and monitoring Symptom assessment	Clinical pharmacist Nurse (or clinical pharmacist) Physician	LIMM Symptom Assessment Form Documented in the patient health record
At discharge	Once for each patient Occasionally	Discharge medication reconciliation Quality control of discharge medication reconciliation	Physician Clinical pharmacist	LIMM Discharge Information Form, including a Medication Report and a Medication List LIMM Quality Control form for Discharge Medication Reconciliation

<sup>a</sup>The quality control of discharge medication reconciliation is not performed for all patients. It can be done either before discharge, with immediate feedback to the physician, or retrospectively

## **Aim and objectives**

The overall aim of this thesis was to investigate the impact of clinical pharmacy services within a multiprofessional healthcare team on quality and safety of patients' drug therapy, and to study the occurrence of medication history errors on admission to hospital.

More specifically, the objectives of the studies were:

- To describe and evaluate a structured medication questionnaire and to improve data handling of results from the Morisky four-item adherence scale and the Beliefs about medicines questionnaire-specific (paper I)
- To examine the impact of medication reconciliation upon admission and inpatient medication review on the number of inappropriate medications and unscheduled drug-related hospital revisits (paper II).
- To describe the frequency, type and predictors of medication history errors identified by pharmacists performing medication reconciliations (paper III).
- To examine the impact of routine implementation of medication reconciliation upon admission and inpatient medication review on all-cause hospital revisits after discharge (paper IV).

## Methods

All studies in this thesis were conducted at three internal medicine wards at the University hospital of Lund during the years 2002 until 2008 (Table 3); two descriptive studies (papers I and III), and two interventional studies (paper II and IV). In paper I, a patient sample from Landskrona hospital was also included.

**Table 3. An overview of papers in the thesis**

Paper	Study period	n	Study design	Clinical pharmacy services	Data sources for outcome assessment	Outcome measures
I	2002-2003 and 2005-2006	115	Descriptive	Medication reconciliation and interview	Pharmacist documents Patient questionnaires	Medication history errors Adherence Beliefs about medicines
II	2006-2008	210	Controlled intervention	Medication reconciliation and interview Medication review	Pharmacist documents EHR	Medication appropriateness Drug-related hospital revisits
III	2007	670	Descriptive	Medication reconciliation and interview	Pharmacist documents EHR	Medication history errors
IV	2006-2008	3974	Controlled intervention	Medication reconciliation and interview Medication review	Healthcare register	ED revisits ED revisit, rehospitalisation or death (combined outcome)

ED, Emergency Department; EHR, Electronic Health Record

## **The clinical pharmacy services**

In the studies of this thesis, two out of the three main activities of the L IMM model outlined in Table 2, have been studied: medication reconciliation at admission including a medication interview with the patient, and medication review and monitoring during the hospital stay.

### **Admission medication reconciliation and patient interview**

The admission medication reconciliation was performed on week-days, shortly after the patient had been admitted by using the L IMM Medication Interview Questionnaire parts 1-3 (Table 2, Appendix 1).

- The most accurate patient medication list was identified (part 1 of the Medication Interview Questionnaire). The current medication list in the EHR was compared with lists from other sources, including the patient. The use of over-the-counter drugs and herbal drugs was also documented.
- Patients who took responsibility for their own drug treatment at home were interviewed about other aspects of their drug use in part 2 of the interview.
- If the patient was capable and willing to participate, in-depth questions concerning adherence to the drug regimen [83] and beliefs about the medication [85] were added to the interview (part 3).
- Any problems concerning the patient's drug use emerging during the interview were addressed by the pharmacist by means of counselling and/or written information, including ward-specific drug information leaflets.
- On the basis of identified discrepancies between the medication list in the EHR and non-hospital based medication lists, the pharmacist suggested changes to the current medication list in a face-to-face discussion with a ward physician.
- All data were documented on the L IMM Medication Interview Questionnaire (Appendix 1).

### **Medication review and monitoring**

On week-days, before morning rounds, the pharmacists identified DRPs by conducting structured medication reviews (Table 2, Appendix 2), which addressed the following categories of risk:

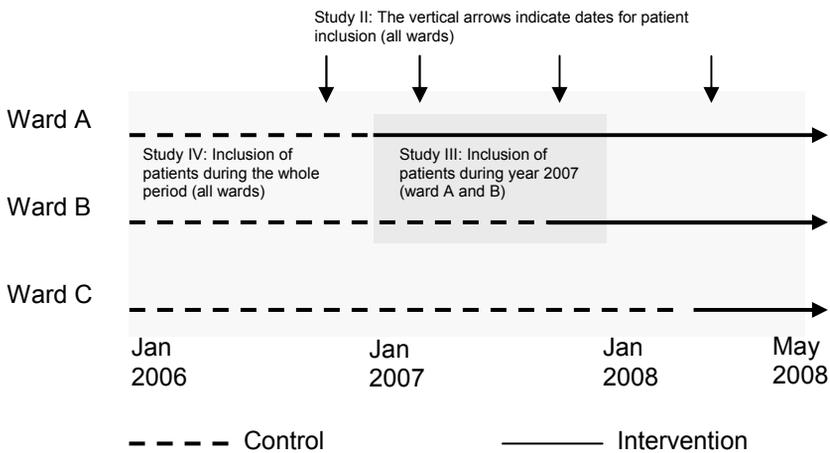
- drugs that required therapeutic drug monitoring
- less appropriate drug therapy
- interchangeable drugs (according to a regional interchangeable drug list)

- problems with drug handling (e.g. problems with swallowing or inhaling medications, inappropriate crushing of tablets)
- drug interactions
- type of drug or drug dose not adjusted according to liver/renal function
- indication for drug treatment not known
- natural remedy drugs
- untreated indication
- drugs with a high risk for adverse drug reactions

Information sources included the patient's medication list, medical record notes, laboratory values, results from the symptom assessment, medication reconciliation, and interview, and other relevant data. During ward rounds, the DRPs which the pharmacist considered to be the most relevant were discussed within the multiprofessional team (physicians, nurses, carers and paramedics). Based on these discussions, the physicians adjusted the drug therapy as appropriate. Patients were followed up at least twice a week to enable identification of new DRPs and to monitor previously identified problems. All data were documented on the L IMM Medication Review Form (Appendix 2).

## Study design

Patients in study I were admitted to an internal medicine ward (ward A in Figure 2) in the operational sector of emergency care at the University hospital of Lund during 24 May 2002 until 9 May 2003, or to the internal medicine sector at Landskrona hospital during 21 November 2005 until 31 December 2006. All patients included in studies II-IV attended one of three internal medicine wards at the University hospital of Lund during the period 1 January 2006 to 31 May 2008. Recruitment of patients differed between studies, but patient samples overlapped (Figure 2). Figure 2 illustrates the routine implementation of the LIMM-based admission medication reconciliation and inpatient medication review at the wards. Intervention periods comprised all three parts of the LIMM model: medication reconciliation upon admission, inpatient medication review and monitoring, and discharge medication reconciliation, including a medication report and a medication list. Control periods comprised only discharge medication reconciliation.



**Figure 2. Horizontal arrows illustrate the implementation of medication reconciliation at admission and medication review during the hospital stay (the intervention) at three hospital wards. Medication reconciliation at discharge was performed during both control and intervention periods.**

## **Data collection and outcome assessments**

### **Paper I**

Inclusion criteria for patients in this descriptive study were: self-medicating at home, cognitively well functioning according to the ward nurses' judgment, and not abusive.

To interview patients upon admission, a structured medication questionnaire (in latter studies redeveloped and named LIMM Medication Interview Questionnaire) was used by clinical pharmacists. The questionnaire included: a) a form to fill in the patient's home medication list, including specific questions on some drug types; b) five questions about medication management skills; c) questions about indication for each drug; and d) the Morisky four-item scale for measuring adherence to therapy and the BMQ-specific for measuring beliefs about drug therapy. The medication reconciliation process conducted in part 'a' was not as comprehensive as described above, as no information was sought from other healthcare instances. The pharmacist compared the home medication list as stated by the patient with the medication list in the hospital records; differences between the lists were considered medication discrepancies unless it was stated in the medical record that they were intentional changes. The terms medication discrepancies and errors in medication history (i.e. medication errors) were used synonymously. Medication discrepancies were classified by type: drug omitted (the drug had not been registered in the hospital EHR drug list), additional drug (a drug had been erroneously added to the hospital EHR drug list), dosage too high, dosage too low, and wrong dosage form. Results from part a-c of the questionnaire were only reported for the patients from the University hospital of Lund (n=39).

A number of alternative statistical approaches to present results from part d (the Morisky four-item scale and the BMQ-specific), were developed by using data from the entire patient sample in study I; 39 patients from the University hospital of Lund and 76 patients from Landskrona hospital.

### **Paper II**

In a prospective, controlled interventional study, we compared patients receiving complete LIMM-based care (intervention group) with patients receiving only discharge medication reconciliation (control group). Patients who attended one of the study wards on four specific dates were evaluated retrospectively for eligibility for inclusion in the study as illustrated in Figure 2. Patients were included if they were aged 65 years or older, and had been

prescribed at least one drug for regular use. Patients were excluded if they had been staying in the study wards during one of the previous inclusion dates.

Blinded reviewers evaluated the appropriateness of the prescribing by using the MAI on admission and discharge. The MAI [39] includes ten items of appropriateness as described in the 'Introduction' section. Blinded reviewers also assessed the probability that a drug-related problem was the reason for any patient readmitted to hospital or visiting the emergency department within three months of discharge. The cases were classified by using the WHO criteria for causality [53], and a scoring of the contribution of the drug-related problem to the hospital revisit [147].

### **Paper III**

A descriptive study was carried out in two wards using L IMM-based care during year 2007 (Figure 2). A clinical pharmacist identified each patient's most accurate pre-admission medication list by conducting a medication reconciliation process shortly after admission, as described above. The medication discrepancies were classified by type in accordance with the classification in paper I. The judgement of unintentional versus intentional changes in the hospital drug list was more comprehensive in paper III than in paper I, as a second evaluation was performed retrospectively by another pharmacist. Hence, medication discrepancies for which no clinical reason could be identified (unintentional changes) were considered medication history errors.

Occasionally, the medication reconciliation was not conducted within one day after admission to the ward. These cases of delayed medication reconciliation were made use of when evaluating the extent to which standard care identified medication errors in absence of the clinical pharmacist. The risk for errors in patients receiving medication reconciliation by pharmacists after 2-3 days and 4-11 days, respectively, was compared with the risk in patients receiving medication reconciliation within one day.

### **Paper IV**

In a prospective controlled interventional study, patients attending hospital wards after implementation of complete L IMM-based care (intervention group) were compared with patients attending the same wards before implementation of medication reconciliation at admission and inpatient medication review (control group) (Figure 2). All hospitalised patients were included unless they deceased during index hospitalisation, or had been previously included in the study.

The observation period for each patient was six months (184 days) from the day of discharge from index hospitalisation. To track the timing and type of healthcare contacts, a regional healthcare register was used (Skåne healthcare register). The primary outcome measure was time to an emergency department revisit. These visits included emergency department visits with or without subsequent hospital admission. In a combined secondary outcome measure, the time to any event (i.e. emergency department revisits, hospital readmissions and cases of death) was evaluated.

## Statistical analysis

### Paper 1

A number of alternative ways to analyse results from the Morisky four-item scale for adherence and the BMQ-specific were developed, all taking into account that the scales have ordered verbal categories. It was suggested that only one way of analysis is chosen for each scale when used in clinical practice. That decision should be based on how discriminating one would like the scale to be, or the relative importance of the different items in the scale for the current patient or group of patients. In patients with many prescribed drugs and/or several co-morbid diseases, it is not convenient to assess adherence and beliefs for all drugs collectively. Rather, the Morisky scale and BMQ-specific should be applied for drugs for one disease or condition at a time. A patient case (fictive patient) is used below to illustrate how the different statistical approaches described in paper I can be applied in practice. For each scale, two alternative ways to present results will be explained.

A 69-year-old man (Mr M) with chronic obstructive pulmonary disease (COPD) and angina pectoris is submitted to hospital because of shortness of breath and fever. When admitted to the ward the patient was prescribed nine drugs for regular use and two drugs as needed. He knew the indication for all his drugs and said he had no problems with the practical handling of drugs at home. He was prescribed the following drugs: ipratropium bromide inhalation (Atrovent®), salbutamol inhalation (Ventolin®), fluticasone/salmeterol inhalation (Seretide®), betamethasone (Betapred®), theophylline (Theo-Dur®), doxycycline (Doxyferm®), isosorbide mononitrate (Imdur®), low-dose acetylsalicylic acid (Trombyl®), glyceryl trinitrate spray (Glytrin®) when needed, and oxazepam (Oxascand®) when needed. The clinical pharmacist decided to focus on Mr M's drugs against COPD when using the questionnaires about adherence and beliefs. Mr M's answers to the Morisky four-item scale and the BMQ-specific are shown in Tables 4 and 5. After answering the questions he also talked about his worries about adverse drug reactions, especially those concerning the use of betamethasone.

**Table 4. Morisky four-item scale.**

a	Do you ever forget to take your medicine for your lung disease?	Yes	
b	Are you careless at times about taking your medicine?		No
c	When you feel better, do you sometimes stop taking your medicine?		No
d	Sometimes if you feel worse when you take your medicine, do you stop taking it?	Yes	

**Table 5. Beliefs about Medicines Questionnaire-specific, comprising five statements about necessity (white) and five statements about concerns (grey).**

	Your views about medicines prescribed for your lung disease	Strongly agree	Agree	Un-certain	Disagree	Strongly disagree
1	My health, at present, depends on my medicines.		x			
2	Having to take medicines worries me.		x			
3	My life would be impossible without my medicines.		x			
4	Without my medicines I would be very ill.			x		
5	I sometimes worry about long-term effects of my medicines.		x			
6	My medicines are a mystery to me.					x
7	My health in the future will depend on my medicines.	x				
8	My medicines disrupt my life.				x	
9	I sometimes worry about becoming too dependent on my medicines.	x				
10	My medicines protect me from becoming worse.		x			

*Morisky four-item scale – uni-dimensional with unequally important items*

Let us suggest that we consider the item ‘stop when better’ the most important, the item ‘stop when worse’ the second most important, and the items ‘forgetfulness’ and ‘carelessness’ the least important for this treatment. The Morisky four-item scale is a two-point scale with the global score A for non-adherence and B for adherence; it can be analysed in different ways depending on how discriminating one would like it to be. If only patients answering ‘Yes’ to the most important question ‘Do you stop when feeling better?’ are considered to be non-adherent, our patient would be considered as adherent (global score B). If patients either answering ‘Yes’ to the most important questions *or* to two other questions are considered non-adherent; our patient would get the global score for non-adherence (global score A).

*BMQ-specific – Multi-dimensional with equally important items*

If the items within each subscale (necessity and concern) are considered equally important, it is convenient to use the median of the items to describe each subscale. The medians on the necessity subscale and the concerns subscale are then combined into a global score. In Mr M’s case, the median answer would be ‘agree’ for both subscales. Depending on how discriminating one would like the scale to be, the number of possible global scores can vary. If using the five-categories median global scale, our patient would receive a global score of C, which represents the group of patients with as much perceived concern as necessity about their medications (\* in Figure 3).

Another alternative is to regard the most negative belief expressed by the patient within one subscale to represent that subscale. The patient in our case strongly agreed to the statement ‘I sometimes worry about becoming too dependent on my medicines’. The overall score for the subscale of concern will then be ‘strongly agree’. It would have been so also if the patient ‘strongly disagreed’ with the four remaining items. In other words, it is sufficient that a patient worries about one aspect of his/hers medication use to be categorised as having concerns about medications. ‘Uncertain’ was, the most negative expressed belief by Mr M on the necessity subscale. A global score can then be created by combining ‘strongly agree’ on the concern subscale with ‘uncertain’ on the necessity subscale; the patient will receive the global score B which represents the group of patients with the second most strongly perceived concerns (§ in Figure 3).

## Necessity

Strongly agree	E		D	C *	
Agree					
Uncertain	D		C	B §	
Disagree	C		B	A	
Strongly disagree					
	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree

**Concern**

**Figure 3. Global scores (A to E) of the BMQ-specific.** \* denotes the global score of Mr M when using the median global scale. § denotes the global score when using the most negative belief global scale.

## Paper II

### *Poisson regression*

When counting occurrences of an event, the response variable is typically a whole number [148]. In such cases, it is appropriate to base the regression analysis on the Poisson distribution rather than the normal distribution [148]. In paper II, the difference between groups in the number of drugs with inappropriate ratings at discharge was analysed by Poisson regression. We assumed that the number of inappropriate drugs at discharge was dependent of the ‘exposure’ of inappropriate drugs at admission. Therefore, the number of inappropriate drugs at admission was used as an offset in the model and the result was presented as a percental decrease between admission and discharge.

### *Chi-square test for trend*

When comparing proportions among groups that have an ordering, such as in the case of drug-related readmissions in paper II (certain, probable, possible and unlikely), one should make use of the ordering to increase the power of the statistical analysis [148]. The Chi-square test for trend tests whether the proportion of subjects in one group increases in successively better outcome categories [149].

## **Paper III**

### *Logistic regression*

If the outcome variable of interest is the presence or absence of some condition (e.g. 'no' and 'yes') logistic regression is used. In paper III, multivariable logistic regression analysis was conducted with the response variable 'presence of medication error'. In logistic regression, the results are presented as odds ratio (OR).

### *Multiple imputation*

In case some data are missing in a data set, there are a number of alternative ways to handle the situation. Patients with missing data can be excluded, but deletion of cases will bias results if the remaining cases are not representative of the entire sample [150]. Another alternative is to replace the missing values with the same value for all patients. However, that method reduces the variance of the variable and diminishes relationship with other variables [150]. Hence, it is recommended to use another method, such as multiple imputation. In multiple imputation, missing values for any variable are predicted using existing values from other variables [151].

## **Paper IV**

### *Time-to-event analysis*

Survival analysis (or more generally time-to event analysis) is an analysis of the time taken for some event to occur [148]. If the period of observation was cut off before the event of interest occurred, we call the survival time for that individual 'censored' [148]. One of the advantages with the method is that it not only takes proper allowances for those observations that are censored, but also makes use of the information from these subjects up to the time they are censored [148].

### *Cox proportional hazards regression*

Survival curves in two groups can be compared by using Cox proportional hazards regression. The method is considered 'semi-parametric', in that no particular type of distribution is assumed for the survival times, but a strong assumption is made that the effects of the different variables on survival are constant over time (proportional hazard) [148]. A hazard is the rate at which events happen. The Cox regression model yields hazard ratios (HR), i.e. the proportion of the hazard in one group relative to that in the other group.

## **Ethics**

The studies in this thesis were evaluated by a regional Ethical Review Board which did not consider a formal ethical approval to be necessary for study I, II and III, and had no objections to these studies. Study IV was approved by the Ethical Review Board. The participants' confidentiality was guaranteed by de-identification and coding of print outs from the healthcare records and register data. Data on paper or on file was securely stored in locked cabinets and password protected computers, respectively. We presented limited demographic data in the papers to minimise the risk for identification of single individuals. Inclusion in the study was judged to be associated with very low risks for harm. Therefore, the benefits of the studies were judged to outweigh the risks.

## Results

### Knowledge, adherence and beliefs about medicines (paper I)

Out of 39 respondents, 13 (33%) had at least one medication for which he/she was not able to specify the indication. Among the 115 respondents answering the Morisky four-item scale, 30% admitted ‘forgetfulness’ as the reason for non-adherence, followed by ‘stop when feeling worse’ (12%), ‘carelessness’ (5%) and ‘stop when feeling better’ (4%). Thirty-four percent reported unintentional non-adherence, 17% reported intentional non-adherence and 10% of patients reported both intentional and unintentional non-adherence. When results from the BMQ-specific were presented using the five-categories median global scale, patients were distributed over global scores A to E as seen in Figure 4. Most patients (54%) agreed to the statements about necessity and disagreed to the statements about concerns. However, 20 patients (17%) agreed to both the statements concerning necessity and concerns; that is, expressed feelings of necessity as well as worries about drug treatment (Figure 4).

#### Necessity

Strongly agree	E (62)		D (10)		C (20)	
Agree						
Uncertain	D (13)		C (0)		B (5)	
Disagree	C (4)		B (0)		A (1)	
Strongly disagree						
	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree	
	<b>Concern</b>					

**Figure 4. The five categories median global scale of BMQ-specific.**

Global score (numbers of patients), n=115. Calculations are based on the median of the sub-scales concern and necessity. The global score ‘A’ represents the group of patients with the most strongly perceived concern and with the least perceived necessity, while scores further down the alphabetic row represents less and less perceived concern or/and more and more perceived necessity.

## Errors in medication history (papers I and III)

In paper I (n=39), the proportion of patients with at least one error in their medication history was 62% (95% confidence interval [CI] 45–77%). In the subsequent, larger study in 670 patients (paper III), the clinical pharmacists identified medication discrepancies for 420 of 670 patients (63%; 95% CI 59–66%). Of the 1136 identified medication discrepancies, 672 (59%) were classified as medication history errors and these errors affected 47% (95% CI 43–51%) of the patients. In both studies, the most common type of error was omission of a drug in the hospital EHR drug list. Overall, 93% of the medication history errors resulted in a correction of the EHR drug list (paper III).

As shown in Table 6, higher number of drugs at admission ( $p < 0.0001$ ), and the patient living in their own home without any care services ( $p = 0.042$ ) were predictors for medication errors at admission (paper III). The results further indicated that standard care by non-pharmacist ward staff had partly corrected the errors in affected patients by four days after admission, but a considerable proportion of the errors made in the initial EHR medication history at admission remained undetected by standard care (OR for medication errors detected by pharmacists' medication reconciliation carried out on days 4-11 compared with days 0-1 = 0.52; 95% CI 0.30–0.91).

**Table 6. Statistically significant predictors of errors in the medication history at admission to hospital.**

Odds ratios were derived from a multivariable logistic regression model.

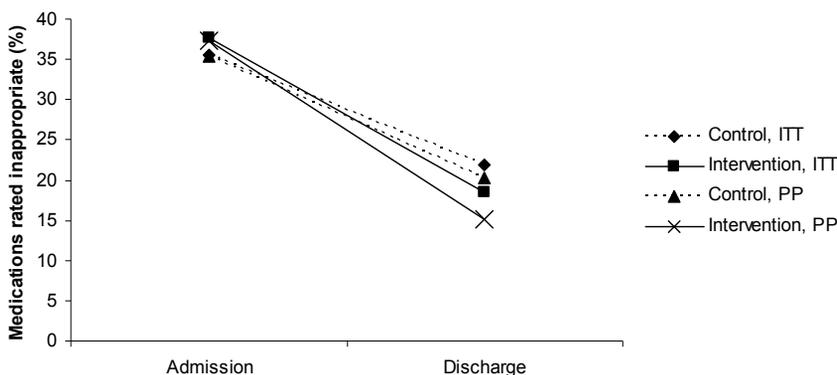
Potential predictors		Odds ratio (95% CI)
Number of drugs at admission	For each 1-drug increase	1.10 (1.06–1.14)*
Type of care service before admission	Care home	Reference
	Own home with community care services	1.08 (0.67–1.75)
	Own home, no care service	1.58 (1.02–2.45)*
Days until medication reconciliation		
Number of days until the pharmacist's medication reconciliation	0-1 days	Reference
	2-3 days	0.85 (0.59–1.23)
	4-11 days	0.52 (0.30–0.91)*

\*  $p < 0.05$

## Medication appropriateness (paper II)

In paper II, 109 intervention patients and 101 control patients were included. There was a significantly greater decrease in the number of inappropriate drugs in the intervention group than in the control group for both the intention-to-treat population (ITT) (51% [95% CI 43–58%] versus 39% [95% CI 30–48%],  $p=0.0446$ ) and the per-protocol (PP) population (60% [95% CI 51–67%] vs 44% [95% CI 34–52 %],  $p=0.0106$ ) (Figure 5).

The MAI item ‘expense’ received the most inappropriate ratings in both control and intervention patients, followed by ‘indication’ and ‘duration’. When the indication was rated as inappropriate, both expense and duration also received an inappropriate rating, according to the MAI instructions. In the intervention group, there were improvements in all MAI criteria except ‘effectiveness’ and ‘correct directions’. In the control group, there was an improvement for six of the ten criteria.



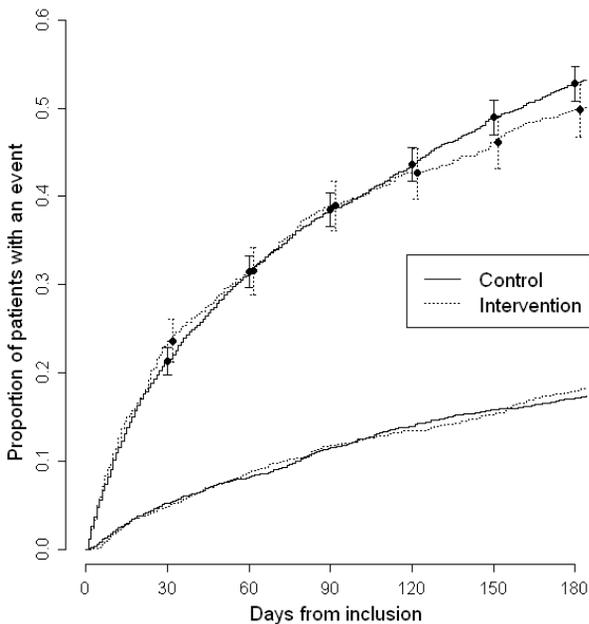
**Figure 5. Medications rated as inappropriate at admission and discharge.**

The intention-to-treat (ITT) analysis included all 210 patients; the per protocol (PP) analysis included 176 patients, and excluded those who died during hospital stay and intervention patients who did not receive the complete intervention.

## Hospital revisits (papers II and IV)

In paper II, drug-related hospital readmissions within three months were more common among intervention patients than in control patients. Revisits to hospital that were judged as 'possibly, probably or certainly drug-related' were reported in 6 of 109 patients in the intervention group compared with 12 of 101 patients in the control group ( $p=0.0469$ , Chi-square test for trend).

In total, 3974 (1216 intervention and 2758 control) evaluable patients were included in study IV. No impact of medication reconciliation and review on the time to an emergency department revisit (HR, 0.95; 95% CI, 0.86-1.04) was demonstrated (Figure 6). In the intervention group, 594 patients (48.8%) visited the emergency department, compared with 1416 (51.3%) control patients. Neither did the intervention appear to have any impact on event-free survival (HR, 0.96; 95% CI, 0.88-1.04). In total, 716 intervention (58.9%) and 1688 (61.2%) control patients experienced any event (emergency department visit, hospitalisation or death).



**Figure 6. Accumulated proportion of patients with an emergency department visit (upper curves) and proportion of deceased patients (lower curves) over six months' follow-up during 2006 to 2008**

## **Discussion**

This thesis demonstrated that patients admitted to hospital are at high risk for being affected by medication errors and there is a high potential to improve their drug therapy. Errors in medication history at hospital admission were experienced by almost half of the patients; unintended omissions of medications from the hospital medication list were most common. By reducing medication history errors and improving medication appropriateness, clinical pharmacy services within a multiprofessional healthcare team improved the quality and safety of patients' drug therapy. Unscheduled drug-related hospital revisits were also reduced. The latter finding needs to be interpreted with caution, though, due to the small number of patients. The intervention had no measurable impact on all-cause emergency department revisits, rehospitalisations, or death.

Since drug-related morbidity is common and may cause patient suffering and extra costs, identifying, solving and preventing drug-related problems is beneficial to both patients and society. Increasing the appropriateness of prescribing and reducing DRPs are of high priority within healthcare [152, 153]. This thesis adds to the evidence that LMM-based patient care in hospital offers a positive contribution. The LMM-model describes a systematic approach to individualising and optimising drug treatment in elderly inpatients. The processes for medication reconciliation and review are systematic, and aided by structured forms and detailed guidelines; thus, they should be easy to be reproduced by others. Furthermore, a large majority of the recommendations from the pharmacist are accepted and implemented by the physicians, which suggests that the process is efficient.

### **Errors in medication history**

In studies I and III, a high rate of errors in medication history in patients admitted to internal medicine wards was found. However, the error rate was higher in study I (62%) than in study III (47%). This might partly be explained by the different data collection methods. In study III, the medication reconciliation process was more comprehensive and the classification of unintentional discrepancies was verified by retrospective evaluation of the EHR notes by a second pharmacist. Moreover, the studies were conducted in different years, and it is possible that the general situation had improved between 2003 and 2007. Finally, characteristics of included patients differed between the studies. In study I, only patients self-medicating at home and cognitively well functioning were included; in study III, all

admitted patients were included. In conclusion, the result from study III is likely to better reflect the true rate of errors in medication history in our study wards. Study III is, to our knowledge, the largest study performed in Sweden and among the largest ones also by international measures which strengthens the representativeness of the results.

The only predictor for errors in medication history upon admission to hospital likely to be of value in clinical practice was an increasing number of prescribed drugs. This finding suggests that there is limited potential for predicting which patients are at highest risk of experiencing errors in their medication history. However, there are a number of possible predictors of errors in medication which were not included in our analysis, e.g. certain 'high-risk' drugs or many outpatient visits during the previous year. If future studies will show that 'high-risk' patients can be identified in clinical practice, it will enable better resource allocation, as interventions to prevent medication errors can be directed towards the relevant groups.

In concordance with the results in studies I and III, other studies have reported high rates of errors in medication histories [60, 66, 98]. However, some variation between countries in rates of errors is expected; Unroe et al. [154] reported a lower rate of error than we did, whereas others have found higher rates of error in medication histories at hospital admission [63, 155]. Besides different healthcare organizations and routines, different definitions of medication discrepancies and errors, and variability in methods of data collection could explain the differences between studies [156, 157]. This wide variation in methods and definitions implies that it is very difficult to compare different studies and draw any conclusions about similarities or differences between settings or organisations [65].

Errors in medication history might result in clinical consequences although this was not studied in this thesis. However, a recent study that was based on a random sample of the study patients in study III, evaluated clinical significance of pharmacists' recommendations [158]. Out of 70 recommendations, two physicians independently ranked 59% as somewhat significant, 23% as significant and 10% as very significant [158]. Retrospective evaluation of clinical significance is valuable from the perspective of the efficiency of the reconciliation process, and also a measure of the potential impact on patient outcomes. Another measure of the efficiency of pharmacists' medication reconciliation is the physicians' acceptance of the pharmacists' recommended changes to drug therapy. In study III, 94% of the recommendations from the pharmacist concerning errors in medication history were accepted and implemented by the physicians, which suggests that the process was efficient.

Clearly, there is a need for medication reconciliation initiatives. However, comparative studies of different approaches to admission medication reconciliation will be needed to reveal which approach is most effective from a clinical and economic perspective.

## **Adherence and beliefs about medicines**

In study I, 40% of the patients reported that they had been non-adherent at times. This is in accordance with previous research [77]. It would have been valuable to collect more information about patients' non-adherence, e.g. which drugs that had been involved, the reasons for non-adherence and how frequently it happened. However, the main objective was not to measure prevalence of non-adherence. Rather, we wanted to use two questionnaires (Morisky four-item scale and BMQ-specific) in clinical practice and suggest alternative ways of analysing the results. Consequently, paper I was focusing on graphical presentation and statistical analysis of results from the questionnaires regarding adherence and beliefs. The analysis was strongly influenced by previous research applying similar analysis to other instruments [159-161]. The statistical approach reported in paper I has several advantages; graphical presentation is often easy to understand and provide an interpretable global score for each individual that can be used in longitudinal studies, as well as in clinical practice. The approach also takes into account the ordinal level of measurement, where response categories represent verbal statements rather than numerical values. The disadvantages include lack of comparability with other studies and insufficient knowledge of the methods among other researchers [161].

The experience of using the Morisky four-item scale and the BMQ-specific in clinical practice in internal hospital wards demonstrates that rather few patients are capable of filling out the BMQ-specific. The instrument is not very well suited for elderly patients with several co-morbid diseases and frequently incipient dementia. Also, there is a need to train pharmacists about the best counselling techniques to be used when patients report negative beliefs and non-adherence. In an ongoing pilot project, the BMQ-specific and the eight-item Morisky Medication Adherence Scale [84] (a further development of the four-item scale) are being used in a hospital outpatient department. In addition, a clinical pharmacist performs counselling sessions based on motivational interviewing technique.

## **Medication appropriateness and hospital revisits**

Studies II and IV evaluated the impact of LIMM-based medication reconciliation and review on patient outcomes. Study II showed that medication reconciliation and review reduced the number of inappropriate drugs taken by patients. In addition, there were fewer unscheduled drug-related revisits to hospital among intervention patients than among control patients. In agreement with the results in paper II, implementation of the LIMM model in another hospital also reduced the number of drugs with at least one inappropriate MAI rating [146]. Other studies on pharmaceutical care, integrated medicines management or other collaborative approaches in hospitalised patients have also shown improvements in the appropriateness of medications (i.e. decrease in MAI scores) [45, 116, 146, 162]. Inappropriate medication therapy may result in adverse drug events [163, 164], or lower HRQoL [165, 166]. Moreover, there are reports of a higher risk for hospitalisation and death among patients with inappropriate medications [164, 167-169]. However, to establish conclusive causal relationships between inappropriate drugs and clinical outcomes, more evidence is needed [16, 18]. In study IV, no impact of the intervention on overall emergency department revisits, hospital readmissions, or primary care visits was demonstrated. However, appropriate prescribing remains essential and patient benefits may include symptomatic wellbeing and improved HRQoL rather than reductions of hospital visits.

When comparing the results of the studies in this thesis with those of similar studies, a number of key elements regarding study design, inclusion criteria, and outcome assessments need to be considered. Table 7 outlines a selection of studies which are similar to studies II and IV to enable comparison.

**Table 7. A selection of studies examining the impact of clinical pharmacy services on the appropriateness of medication and hospital visits.**

Studies	Design, setting and patients	Interventions	Outcomes
Scullin et al. [121]	RCT in Northern Ireland (n=762) Included if: ≥4 drugs, a high-risk drug, antidepressants if ≥65 years old, hospitalisation within last 6 months, or intravenous antibiotics day 1	Admission medication reconciliation including patient interview Medication review	Reduced length of hospital stay Fewer readmissions Increased time to readmission
Burnett et al. [162]	Discharge medication reconciliation including counselling Medication report to GP	Improved appropriateness of prescribing	
Scullin et al. [170]	Naturalistic experiment (n=833); 84 control patients Included if: Similar to above	Same as above [121]	Reduced length of hospital stay No effect on number of readmissions or time to readmission
Gillespie et al. [120]	RCT in Sweden (n=400) Internal medicine wards	Admission medication reconciliation including patient interview Medication review	Fewer ED visits, total visits to hospital, and drug-related readmissions No effect on number of patients readmitted or number of readmissions
Gillespie, U. [171]	Patients ≥80 years with acute admissions	Discharge medication reconciliation including counselling Medication report and unsolved DRPs sent to GP Telephone follow-up at 2 months	Improved appropriateness of prescribing
Bladh et al. [172]	RCT in Sweden (n=400) Internal medicine wards	Medication review Discharge medication reconciliation including counselling	ITT-analysis: no effects PP-analysis: improved global health, no effect in HRQoL
Wallerstedt et al. [173]	Patients included if capable of assessing HRQoL (29% of admitted patients were included)	Medication report sent to GP and given to patient.	Reduced number of inappropriate drugs Found no impact on hospitalisations
Hellström et al. 2011 (paper II)	Quasi-experimental (n=210) Internal medicine wards Included if ≥65 years old, ≥1 drug	Admission medication reconciliation including patient interview Medication review	Improved appropriateness of prescribing Fewer drug-related readmissions
Hellström et al. 2012 (paper IV)	Design and setting same as above (n=3974)	Same as in paper II above	Found no impact on time to ED revisit, or rehospitalisation

DRP, drug-related problem; ED, emergency department; GP, general practitioner; HRQoL, health-related quality of life; ITT, intention-to-treat; PP, per protocol; RCT, randomised controlled trial.

Inclusion criteria differed between the studies (Table 7). It is likely that the patients included in the studies by Gillespie et al. [120, 171] and Scullin et al. [121, 170] were at higher risk for adverse drug events than patients in the study by Bladh et al. [172] and our patients. Also, the intensity of the intervention differed: only Gillespie et al. [120] did a follow-up after discharge; Bladh et al. [172] conducted no admission medication reconciliation; and in our studies a discharge medication reconciliation was undertaken in all the study wards, during both control and intervention periods. The discharge medication reconciliation (medication report and medication list) in studies II and IV was conducted by the physicians and the benefit of this procedure had already been demonstrated [143, 144].

To summarise the studies outlined in Table 7, all interventions improved the appropriateness of prescribing [162, 171, 172] (paper II). The intervention in paper II and the intervention by Gillespie et al. [120], reduced the number of drug-related readmissions, but the proportion of control patients experiencing a drug-related revisit to hospital was lower in study II than in the study by Gillespie et al. [120]. The two studies which reported an impact on all-cause hospital readmissions were those with the most comprehensive intervention [120, 121]; furthermore, they included mainly high-risk patients [120, 121]. In study II, no difference in overall rate of hospital revisits could be demonstrated, although among patients revisiting hospital, fewer intervention patients did so due to a drug-related problem. Study IV was based on the hypothesis that the impact on drug-related revisits as seen in study II, would have an impact on all-cause unscheduled hospital visits in a larger patient sample. The fact that we saw no impact on all-cause hospital revisits might be explained by shortcomings of our intervention (e.g. ineffective intervention, or discharge medication reconciliation in both groups), or the ITT analysis (approximately two thirds of intervention patients receiving intervention in study IV).

Interventions that reduce subsequent hospital revisits are likely to be highly cost-effective [120]. Wallerstedt et al. found no reductions in hospital revisits and consequently, their cost-effectiveness analysis demonstrated a high cost per quality-adjusted life year (QALY) gained [173]. To be able to compare cost-effectiveness between different types of interventions, generic measures such as the cost per life year gained or the cost per QALY gained is preferable [174]. Such measures have not been used in most pharmaco-economic evaluations of clinical pharmacy interventions, and the evaluations also suffer from other methodological limitations [174, 175]. Therefore, the study by Wallerstedt et al. [173] is a positive contribution due to their thorough health economic evaluation, but the studied intervention had a number of limitations which might explain the lack of cost-effectiveness. A health economic model

to study the cost-utility of the L IMM-model (including medication reconciliation at admission and discharge and medication review) showed that savings of SEK 3791 (at 2009 prices) and a gain of 0.005 QALYs could be expected if unplanned drug-related readmissions were reduced from 13% to 6% (based on results from study II) [176]. Sensitivity analysis showed that cost savings might range between SEK 1148 and SEK 3903, and the QALY gained between 0.001 and 0.005 [176].

## **Methodological considerations**

One limitation of the intervention studies in this thesis (papers II and IV) was their non-randomised design. The research study was nested within a quality improvement project conducted in the hospital. In addition, the team approach of the intervention was very important and the staff was taught about pharmacotherapy and DRPs. Therefore, it was not possible to randomise participants at a patient level. Instead, the intervention was introduced in a staggered fashion. The staggered introduction of the intervention offered advantages over a simple before-and-after design because the threat of a secular trend (i.e. a change of the outcome over time as a general development independent of the intervention) was reduced.

When using outcomes that partly rely on subjective judgment, it is important to take measures against potential assessment bias [18]. The use of assessors blinded to group allocation, validated criteria and specific instructions will increase the reliability of the results [18]. We took all these steps to increase the reliability of the classification of medication errors, medication appropriateness and drug-related hospital revisits. However, independent review by different individuals or groups of individuals would have enabled reliability calculations which would have strengthened our reviewing process.

In study II, we chose the MAI for assessment of appropriateness because the index is among the best validated measures [19]. MAI has shown very good intra-rater reliability, moderate inter-rater reliability, and good face and content validity [39, 177-184] (Appendix 3). As the agreement within raters (i.e. at repeated evaluations) has been shown to be high, we chose to use only one MAI assessor. In order not to overestimate the results in study II, we used the most conservative parameters possible (i.e. MAI scores from the blinded assessment, results from the ITT population, and 'baseline observation carried forward' for missing data). However, we also analysed the results of the PP population and found larger effects on MAI. In study IV, we only had data on the ITT population, which possibly lead to a dilution of the effect.

The reviewers evaluating the drug-related revisits to hospital (paper II) were chosen to provide various backgrounds and expert knowledge in order to minimize the risk of misclassifying the revisits. In addition, they used checklists for detecting DRPs and two different explicit criteria to classify the cases [53, 147]. Data on healthcare visits collected from healthcare registers (as in paper IV) can be regarded as an objective measure. However, quality of register data may influence the results. Strengths of the Skåne healthcare register data include the very comprehensive coverage of healthcare consultations [185]; thus, it is likely that the data on the number of healthcare contacts and the type of setting (i.e. emergency department, primary care or hospitalisation) were reliable. However, the data on the type of healthcare contacts within each setting were possibly less reliable and registry data did not allow us to discriminate between different types of visits, e.g. acute or non-acute primary care visits.

## **Practical implications and future studies**

Problems related to inappropriate prescribing and inappropriate use of drugs must be reduced. Most likely, complex interventions conducted in collaboration between different healthcare providers in secondary, primary and community care will be needed. Patient involvement is also important. Methods based on the LIMM-model have been successfully implemented in 19 hospital wards in seven hospitals in the county of Skåne. The team approach as well as the high competence among the clinical pharmacists in the teams are important features of the LIMM-model which probably have contributed to the high acceptance among healthcare personnel and hospital management staff. The systematic and thoroughly described process in the model facilitates the introduction of the model into new hospital wards.

There is a potential for further development of the LIMM-model; patient counselling techniques to improve patients' motivation to adhere to drug treatment are under development. Such counselling should be conducted in hospital as well as primary care settings. Today, the LIMM-model includes effective communication from the hospital setting to primary and community care about changes made to drug therapy and planned follow-up activities. However, there is a potential to improve the quality of prescribing and medication use even more if a broader range of pharmaceutical care issues would be documented and communicated to the next level of care in a structured manner. Issues that would be valuable to communicate to other health care providers include potential or unsolved DRPs, such as adherence problems and monitoring needs. Because written information might not be effective when communicating information about DRPs between different healthcare providers [186], the means for communication need to be carefully considered. Also, safer ways of monitoring the effectiveness of medications and signs of adverse drug reactions in individual patients need to be developed. Patients feeling safe about their medication use are probably more likely to consider the benefits of their medicine to outweigh the risks, resulting in improved adherence to therapy. Probably, additional resources will be needed within primary care to enable closer follow-up of drug therapy; currently a modified LIMM-model for use in primary care is under development and evaluation.

One of the major shortcomings in the Swedish healthcare system is the lack of continuity of care. It is of uttermost importance that the transfer of information between healthcare settings, as well as between healthcare and the patient, is improved in order to improve medication safety as well as patient safety in a larger perspective. Appropriate use of health information

technology (IT) has large potential to improve the situation. Well-designed IT-systems must be supplemented with healthcare personnel taking responsibility for patients' drug-related needs and with involvement of patients in their medication management. For example, IT-initiatives in combination with patient interviews might be the way forward for effective medication reconciliation processes. The L IMM model will need to be adapted to future changes in the IT structure in healthcare. Initiatives such as a national database which all physicians can use for prescribing medications have the potential to improve continuity of care in terms of medication therapy. Hopefully, some of the efforts can be redirected from the 'technical activities', such as correction of medication history errors, to patient related activities such as counselling and follow-up of drug effects. Future studies should examine the impact of the L IMM model on humanistic outcomes, such as HRQoL and also study patients' attitudes towards the model. Multicenter studies would improve generalisability of the results.

## Summary and conclusions

Patients admitted to hospital are at high risk for experiencing medication errors and there is a high potential to improve their drug therapy. By reducing medication history errors and improving medication appropriateness, clinical pharmacy services within a multiprofessional healthcare team improved the quality and safety of patients' drug therapy. The effect of routine implementation of medication reconciliation and review on healthcare visits will need further evaluation; the results from this thesis suggest that drug-related hospital revisits could be reduced.

- The use of a structured medication questionnaire to interview patients upon admission to hospital enabled identification of medication history errors and other problems related to drug use. Different statistical approaches to present results from data on adherence (Morisky four-item scale) and beliefs about medicines (BMQ-specific) could be used depending on the aim of the assessment as well as the patient characteristics (paper I).
- Admission medication reconciliation and inpatient medication review reduced the number of inappropriate medications, and decreased the rate of unscheduled drug-related revisits to hospital (paper II).
- At admission to hospital medication history errors were common; 47% of the patients experienced at least one error. The most prevalent error was the erroneous omission of a drug from the hospital medication list. A high number of pre-admission drugs increased the risk for medication history errors (paper III).
- No impact of routine implementation of medication reconciliation and review on patients' time to a subsequent all-cause emergency department visit, readmission or death was demonstrated (paper IV).

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# Appendix







## Appendix 2. L IMM Medication Review Form

### Patient details

Ward	Bed	Name	Sex	Date of birth	Age	Admission date	Admission date ward	Discharge date	Apodos* <input type="radio"/> No <input type="radio"/> Yes	Version		
Present complaint(s) (information from emergency ward / other ward):						Transferred from ward:		Type of residence (e.g. own home, nursing home)				
<b>Relevant medical history</b> Year   Diagnose						<b>Relevant medication history</b>					<b>Hypersensitivity or allergy</b>	

\*Apodos is a multi-dose system with machine-packed medicines in small, fully labeled plastic bags, used in outpatient settings.

### Hospital care progress

Please indicate if the information is from ward rounds or from the medical record

Date	Information from medical record or from ward round discussions	Date	Information from medical record or from ward round discussions

## Appendix 2. L IMM Medication Review Form

### Identified drug related problems (DRP)

Score out DRPs which are no longer relevant; date and sign.

### Suggested and implemented actions

Date Sign	Potential and actual DRPs	Suggested action (pharmacist's suggestions)	Discussed w. physician Date/ Sign	Implemented actions (by physician or pharmacist)				
	Medications requiring therapeutic drug monitoring							
	Inappropriate medications							
	Improper handling of medications (e.g. crushing, splitting, inhaling)							
	Clinically relevant drug-drug interactions							
	Medication or dose not adapted to patient characteristics (e.g. renal or liver function)							
	Unnecessary drug treatment Indication for a specific drug treatment missing							
	<table border="0" style="width: 100%;"> <tr> <td style="width: 25%;">Short course medication</td> <td style="width: 25%;">Started</td> <td style="width: 25%;">Recommended length of treatment</td> <td style="width: 25%;">Stopped</td> </tr> </table>	Short course medication	Started	Recommended length of treatment	Stopped			
Short course medication	Started	Recommended length of treatment	Stopped					





### Appendix 3. Studies evaluating the reliability of the Medication Appropriateness Index

Patients	Methods	Reliability results
<p>[39, 177] 20 elderly men from the US Veteran affairs internal medicine clinic Age: &gt;65 years Number of drugs: &gt;5</p>	<p>1) Independent blinded MAI assessments by one clinical pharmacist and one internist-geriatrician at baseline and after 2-4 months in ten patients [39] 2) Independent blinded assessments by two clinical pharmacists in a second sample of ten patients at baseline [39, 177] Available information: abstract from the medical chart including: a problem list, the previous two years of medication use, outpatient and inpatient physician notes, and lab and diagnostic test results</p>	<p>Inter-rater agreement: 1) Kappa: Range, 0.71-0.96. For drugs overall, 0.83 Ppos: 0.94-1.0, median 0.99 and overall 0.88 Pneg: 0.75-0.97, median 0.92 and overall 0.95 2) Kappa: 0.51-0.81; overall 0.59 Ppos: 0.90-0.99; overall 0.76 Pneg: 0.60-0.88; overall 0.93 Summated score: Intraclass correlation coefficient, 0.74; perfect agreement for 59% of medications Intra-rater agreement: 1) Kappa: 0.71-0.96; overall 0.92 Ppos 0.96-1.0; overall 0.94 Pneg: 0.75-0.97; overall 0.98 2) Summated score: Perfect agreement for 71% of cases</p>
<p>[178] 16 patients (113 medications) in a geriatric ward Mean age 79.6; 69% female; in average 6.2 drugs</p>	<p>Independent assessment by one pharmacist and one geriatrician Available information: patient chart including data from medical record, patient interview, contact with GP or pharmacist</p>	<p>Inter-rater agreement Kappa: Between 0.09 (drug-drug interact) and 0.78 (duration) but 1 for duplication; overall 0.74 Ppos: 0.89-1.0; overall 0.87 Pneg: 0.2-0.81 but duplication 1.0; overall 0.87</p>
<p>[179] 25 patients (236 drugs), ≥85 years admitted to hospital</p>	<p>Independent assessment by three pharmacy clinicians and a geriatric physician Data was prospectively collected: demographic, medical and laboratory information MAI was modified to be used in acute care</p>	<p>Inter-rater agreement Kappa ≥50% between the pharmacy clinicians in indication, effectiveness, dosage, directions, duplication, cost and overall drug appropriateness Kappa ≥50% between the geriatrician and the pharmacy clinicians in indication, effectiveness and overall drug appropriateness Disagreement in drug interactions, duration, duplication and cost</p>

Patients	Methods	Reliability results
[180] 15 elderly patients (81 medications) in a residential nursing home In average 5 drugs	Independent assessment by three pairs of reviewers (clinical pharmacists) Available information: a profile prepared by investigating pharmacist by combining medical record with complete prescription record and pharmaceutical record over 3 years	<u>Inter-rater agreement</u> Kappa: Between 0,36 (effectiveness) and 0,55 (drug-drug interactions) but duplication was 1 Ppos: Between 0,79 (correct directions) and 1 (duplication) Pneg: Between 0,47 (effectiveness) and 0,6 (duration) but duplication 1 Agreement overall: 85% to 100% <u>Intra-rater agreement</u> Kappa: Between 0,85 and 1. Ppos between 0,98 and 1; Pneg: Between 0,86 and 1 Agreement overall: 96-100%
[181]	Independent assessments by two raters. Information available was community pharmacist-collected medication histories. Modified MAI	<u>Inter-rater agreement</u> Kappa was >0.75 for indication and effectiveness, but 0.41-0.66 for the remaining criteria
[182]	Independent assessments by two clinical pharmacists. Assessments at baseline, 4 months and 5 months (reassessments of 4 months data) One item added that measured underuse (need of drug) Available information: medical diagnoses from GP and medication lists from pharmacy record with complete medication histories from patient interview	<u>Intra-rater agreement:</u> Kappa: 0.38 – 0.62 Ppos: 0.27-0.94; Pneg: 0.41-0.66 <u>Inter-rater agreement:</u> Kappa: 0.01 – 0.44 Ppos: 0.0 – 0.82 Pneg: 0.0 – 0.83 No significant differences in MAI mean overall score Problems with missing data and variability

### Appendix 3. Studies evaluating the reliability of the Medication Appropriateness Index

	Patients	Methods	Reliability results
[183]	30 patients (211 drugs), for inter-group reliability 10 patients for intra-group reliability Primary care setting Mean age 78.5 years; 83.3% women; in average 7.0 drugs	Independent assessment by two pairs of reviewers; group 1: two clinical pharmacologists, group 2: one clinical pharmacologist + one clinical pharmacist. At baseline and 2 two years later Available information from GP: Indication for use, drugs previously used and reasons for change, follow-up method, time of start of treatment and expected withdrawal, results from the latest follow-ups, the dose and instructions given to the patients	<u>Inter-rater agreement</u> Kappa: 0.21-0.74; overall 0.50 Ppos: 0.82-0.99; overall 0.97 Pneg: 0.20-0.76; overall 0.54 <u>Intra-group agreement:</u> Kappa: 0.26 for drug-disease interactions; 0.64-0.88 for the remaining items (missing value for correct directions and drug-drug interactions); overall 0.71 Ppos: 0.94-1.00; overall 0.98 Pneg: 0.29-1.00; overall 0.73 Highly heterogeneous data quality was a limitation
[184]	10 community-dwelling elderly (65 drugs) Mean age 72.1 years; 40% women; in average 6.5 drugs	Independent assessment by two clinical pharmacists. Modified MAI for use with less comprehensive clinical information Available information: Medical history, sociodemographic data, vital signs and lab values, drug concentrations, procedures and test results	<u>Inter-rater agreement:</u> Kappa: 0.64 Ppos: 0.9-1.0; overall 0.78 Pneg: 0.47-1.0; overall 0.86 <i>For summated MAI-score</i> Intraclass correlation coefficient: 0.8 No difference in summated MAI-score

GP, General Practitioner; MAI, Medication Appropriateness Index; Ppos, proportion of positive agreements; Pneg, proportion of negative agreement

