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**Title:** Clinical rules in hospital pharmacy practice to prevent adverse drug events  
**Issue Date:** 2014-05-06
Part I

Introduction
General introduction
Adverse drug events (ADEs) refer to any injury resulting from the use of a drug [1,2]. ADEs can be due to a medication error (intrinsic harm) or an adverse drug reaction (ADR) (extrinsic harm) [3-5]. Worldwide many patients suffer from drug related problems such as ADEs. Indeed, the report “To Err is Human” by the Institute of Medicine shows that a considerable number of people die each year in hospitals partially due to medication related harm [6]. In addition, drugs are the leading cause of adverse events in the Medical Practice Study [7]. Since then, ADEs have been a subject of intense research.

A literature review by Krahenbuhl-Melcher et al. conclude that overall in about 6% of hospitalized patients ADEs occur, with a wide range among the different studies (0.17–65%), and that approximately 50% are considered preventable [8]. The wide range can partly be explained by the different ADE detection methods that are used in studies, such as voluntary report of ADEs, chart review or computer based monitoring systems to detect ADEs [9,10]. ADEs in hospitalized patient do lead to extra costs and prolonged length of stay in the hospital [11-13].

Also in The Netherlands some data is available about the incidents frequency of ADEs. Van der Hooft et al. investigated ADR-related hospitalizations and found that in 2001 1.83% and in 2003 5.1% of acute hospital admissions are ADR related [14,15]. Leendertse et al. shows in their HARM study that of almost 13000 unplanned admissions in the hospital 714 (5.6%) are medication related, and that almost half of these admissions are potentially preventable [16]. More recently, a prospective chart review shows that more than half of the patients admitted to the hospitals are experiencing harm of ADEs, of which most are non-serious, non-preventable ADRs [17].

Since a substantial proportion of ADEs can be prevented, it seems logical to focus on the preventive aspect in particular. In fact it is better to prevent than to cure. Different methods to prevent ADEs are [18,19]:

- basic computerized physician order entry (CPOE)
- CPOE with clinical decision support system (CDSS)
- a clinical pharmacist attending on physician rounds or monitoring medication ordering, transcribing and delivery
- robots in drug dispensing
- "smart" intravenous devices
- barcoding of drug and patients
- automated bedside dispensing devices
- intravenous admixture units at patient care unit
- unit based dosing
Obviously, each abovementioned method interacts in a particular part of the drug distribution chain, from prescribing, dispensing to drug use.

Although a multifaceted approach, such as that Silverman et al. [20] have described for their institution seems to be the best option to reduce preventable ADEs, two of these strategies have our special interest, namely:

- CPOE with CDSS
- Clinical pharmacist activities

The review of Krahenbuhl-Melcher et al. shows that medication errors occur at all stages of the medication process but most often at the administration stage and in the drug prescription process (16.5%, range 13–74% of all errors). CPOE may be in particularly helpful to reduce such prescribing errors [8]. Since our institution uses a CPOE already, this intervention of reducing prescribing errors is of our interest. Although no randomized control trials are performed, there are investigations showing that a reduction in ADEs can be reached through the use of CPOE with CDS systems [21-23]. CDS systems can range from basic to more advanced systems. Basic CDS systems, for example, include basic dosing guidance or drug-drug interaction checking. In contrast, more advanced CDS systems can include dosing support for renal insufficiency and guidance for medication-related laboratory testing [24]. These advanced CDSS use clinical rules, algorithms, and can search for data available in electronic form, such as medication orders, patient characteristics and laboratory values [25]. A Dutch study shows that implementation of a CPOE with basic CDSS reduces certain types of medication errors (such as dosing errors and administrative and procedural errors) but a direct effect on actual patient harm was not demonstrated [26].

Hospital pharmacist participation on ward rounds is common in many hospitals and has been proven to prevent errors, to lower drug costs and to reduce ADEs in for example intensive care and general medicine units [27,28]. Limited human resources may restrict pharmacist participation on ward round teams in all of the medical units of a hospital, necessitating selection of patients at risk of ADEs [19]. Since we have a special interest in clinical pharmacist activities, but we have a limited capacity, we choose to focus on hospital pharmacist interventions guided by alerts from CPOE with CDSS.

At our institution, the site where we perform our studies, Leiden University Medical Center, a CPOE with basic CDSS is in use since 2003, as one of the first University Medical Centers in The Netherlands. This system gives basic drug-drug interaction and drug-dosing alerts and can in that way prevent some medication errors [29]. Our hypothesis is that the use of a more advanced CDSS incorporating clinical rules can better identify patients at risk of
ADEs. In addition, hospital pharmacists can interfere to prevent ADEs and, as such, improve medication safety. We choose to combine our two strategies of interest to prevent ADEs: CDSS for selecting patients at risk of ADEs and hospital pharmacist intervention focused on the specific patient at risk instead of participation on ward rounds.

The aim of this thesis is 1) to develop a CDSS with clinical rules to use in the hospital pharmacy to select patients with potential ADEs and 2) to investigate the ability of this system to select these patients at risk of ADEs and finally 3) to investigate if these potential ADEs can be prevented by interventions by the hospital pharmacist. All of these studies focus on the hospitalized patient.

This thesis starts with a comprehensive review of the literature in which an overview is presented of methods described to prevent ADEs (chapter 2).

The next chapter, chapter 3, describes the development of the CDSS with clinical rules aimed to identify patients at risk of ADEs. The system is called Adverse Drug Event Alerting System (ADEAS). Besides the development of the system and the definition of the first set of clinical rules, the validation of the system and a proof of principle test are described.

In chapter 4 and 5 the newly developed ADEAS is compared with other methods to select patients at risk of ADEs. Chapter 4 describes the retrospective and prospective comparison of ADEAS with the conventional medication surveillance, using a basic CDSS in the existing CPOE. In chapter 5, a limited set of clinical rules from ADEAS and a basic CDSS within CPOE is compared with manual pharmacist medication review.

Chapter 6 investigates the extent in which ADEAS based interventions by the hospital pharmacist can prevent ADEs in the elderly patient with polypharmacy. This study is conducted on 5 hospital wards and ADEs are scored by chart review.

The use of ADEAS with clinical rules in daily hospital pharmacy practice is evaluated in chapter 7. This chapter also gives an overview of the rule effectiveness and positive predictive value of the clinical rules incorporated in ADEAS.

Finally, in chapter 8, the development of ADEAS and the clinical rules, and the ability of the system to select patients at risk of potential ADEs and the ability to prevent these ADEs is discussed and put in perspective. This chapter also describes our ideas for future use of clinical rules in hospital practice to select risk patients, to prevent ADEs and ultimately to make drug use more safe for our patients.
References


