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COMPUTERIZED PROVIDER ORDER ENTRY AND PATIENT SAFETY

Experiences from an Iranian Teaching Hospital

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To my father who wished to

see this book and is always

in my heart

ABSTRACT

Background: Medication dosing errors may have grave consequences for neonatal patients. Computerized Physician Order Entry (CPOE) with dosing decision support functionalities has been effective in reducing these errors. However, the adoption rate is low. Physicians' resistance has been identified as a significant barrier. To reduce this resistance, the system should be designed in close collaboration with the users and reflect their needs. Some hospitals have used nurses as champions to reduce physicians' resistance. However, implementation of CPOE in middle- and low-income countries is more challenging because of several factors, including restrictions in budgets and human resources. Therefore, a careful design based on the users' requirements and contextual factors may increase the success rate in these contexts.

Objectives: To design and implement CPOE with dosing decision support functionalities in an Iranian teaching hospital and evaluate its effect on patient safety. Then tailor the system based on users' perception and compare the two implemented systems in terms of users' satisfaction and effect on patient safety.

Methods: Semi-structured interviews were used to gather prescribers' opinions on CPOE. On-looker observations were used to model the traditional prescription system. As an indicator of patient safety, medication dosing errors were evaluated in a neonatal ward in three periods: Traditional prescription system, physician order entry (POE) without decision support system (DSS), and POE with DSS. Explanations were then added and alerts appeared in every erroneous order, and the effect on dosing errors was compared with the previous period. Afterwards, the order entry was left to the nurses (NOE) but physicians verified the orders and received the warnings. Users' perceptions about POE and NOE were gathered using semi-structured interviews. POE and NOE with DSS were also compared for their effect on medication dosing errors.

Results: The traditional prescription system in Iran is hierarchical and physicians do not interact with the computer. However, in our study, physicians agreed to perform the order entry to be able to receive the warnings themselves. Prescribers prioritized dosing errors above other types of errors. Therefore, neonatal ward was selected as the relevant implementation unit. The rate of non-intercepted medication dosing errors was 53% in the traditional prescription system, which was not significantly different after the implementation of POE without DSS. However, after adding DSS to the POE, a significant reduction to 34% was observed ($P<.001$). Adding explanations to alerts and showing them in each erroneous order could further reduce the errors to 14% ($P<.001$). Implementation of NOE resulted in more satisfaction among nurses and physicians. They believed that in Iran, NOE was more transferable to the other hospitals than POE. Non-intercepted medication dosing errors were reduced from 14% in the last period of POE to 9% in NOE ($P<.001$).

Conclusions: On Iranian neonatal wards, POE without DSS has no apparent advantage over the traditional prescription system. However, together with DSS, POE can significantly reduce dosing errors. Despite the significance, in the hierarchical and physician-centred context of Iran, NOE seems to be a more viable prospect. This order entry method can increase care providers' satisfaction, and together with a dosing DSS it is as effective as or even more effective than POE in reducing dosing errors.

Keywords: Medical Order Entry Systems; Decision Support Systems, Clinical; Adverse Effects; Medication Errors; Infant, Newborn; Patient Safety; Iran,

LIST OF PUBLICATIONS

I. Kazemi A, Ellenius J, Tofighi S, Salehi A, Eghbalian F, Fors UG. CPOE in Iran - a viable prospect? Physicians' opinions on using CPOE in an Iranian teaching hospital. Int J Med Inform. 2009 Mar;78(3):199-207.

II. Kazemi A, Ellenius J, Pourasghar F, Tofighi S, Salehi A, Amanati A, Fors UG. The effect of computerized physician order entry and decision support system on medication errors in the neonatal ward: Experiences from an Iranian teaching hospital. Journal of medical systems. 2009. DOI:10.1007/s10916-009-9338-x.

III. Kazemi A, Fors UG, Tofighi S, Pezeshki N, Ellenius J. Care providers' perceptions of two strategies for implementing a computerized provider order entry system in an Iranian neonatal ward. Submitted 2009

IV. Kazemi A, Fors UG, Tofighi S, Tessma MK, Ellenius J. Physician Order Entry or Nurse Order Entry? Comparison of two implementation strategies for a computerized order entry system aiming at reducing dosing medication errors in a neonatal ward in Iran. Submitted 2009

CONTENTS

LIST OF ABBREVIATIONS

ADE	Adverse Drug Event
BSA	Body Surface Area
CAD	Computer Assisted Diagnosis
CDSS	Clinical Decision Support System
CPOE	Computerized Physician Order Entry and Computerized Provider Order Entry
DDI	Drug-Drug Interaction
DSS	Decision Support System
DSS1	Primary configuration of the DSS: The warnings appeared in the first-time orders and change of the dosing criteria, and provided no explanation
DSS2	Secondary configuration of the DSS: The warnings appeared at each erroneous order and provided an explanation
GFR	Glomerular Filtration rate
HIS	Hospital Information System
ICT	Information and Communication Technology
ICU	Intensive Care Unit
IT	Information Technology
MIS	Management Information System
NICU	Neonatal Intensive Care Unit
NOE	Nurse Order Entry
PBMAC	Paper-Based Medication Administration Chart
POE	Physician Order Entry
RR	Rate Ratio
TAKFA (Farsi)	Developing the use of information and communication technology (English translation)
TAKFAB (Farsi)	Developing the use of information and communication technology in healthcare (English translation)

1 PROLOGUE

I am a medical doctor. During my medical studies, I successfully used computer technology to design and program Computer Assisted Diagnostic (CAD) systems. After graduation in 2000 and upon the completion of my compulsory foundation year in 2001, I began work at Hamadan Medical University in north-west Iran and started a centre at the university called the Management Information System (MIS) Centre in order to implement integrated information systems into the health service in Hamadan. The centre was given the responsibility of finding an integrated information system for all the university hospitals in Hamadan. In Iran, medical universities run the public healthcare in each province [1]. In this role, they supervise the public hospitals and the MIS Centre could make a central decision as to which system should be implemented in the affiliated hospitals. I visited most of the hospitals in Iran where integrated information systems had been successfully implemented and were still in use. However, none of these systems could address clinical issues.

When I spoke with the university authorities, they all agreed that the final target of the information system should be the improvement of the quality of care and patient safety at the hospital. Therefore, we considered this issue in the mutual contract with the local company that took the responsibility for developing the hospital information system.

After I was accepted as a PhD student in 2004, I selected this subject as my PhD thesis and the university authorities agreed to support the project financially. I wanted to find an implementation model for the clinical information system that could include contextual factors, and then evaluate the effect of the implemented system on patient safety.

2 INTRODUCTION

In 2000, the High Council of Informatics took on the responsibility for implementing a plan to develop the use of information and communication technology (ICT) in Iran [2]. The Farsi acronym for the plan is TAKFA. From 2001 to 2005, the Government of the Islamic Republic of Iran allocated between 1 and 2% of the entire annual public budget to information technology (IT). Since then IT has become one of the most important strategic approaches toward improving the quality of public services [3, 4]. A leading council at the Ministry of Health and Medical Education, called "TAKFAB leading council" (B stands for "Behdasht" which means "health" in Farsi) supervised the TAKFA projects in healthcare [5]. The development of ICT-related projects in healthcare and improving the quality of care through the use of ICT was one of their most important strategic plans [6]. At each medical university, there was a TAKFAB committee which decided on the distribution of the allocated resources for ICT-related projects [5].

Following the allocation of the ICT budget in the Iranian health service in 2002, many public hospitals in Iran started to implement hospital information systems [7]. A hospital information system (HIS) is a comprehensive, integrated information system designed to manage the administrative, financial and clinical information of a hospital [8]. Unfortunately, most of the implemented HIS in the Iranian hospitals were only used for financial and administrative purposes and could not address clinical needs. However, in Hamadan, a province in north-west Iran, the university administration wished to improve the quality of care and patient safety using these systems in addition to being able to accurately calculate patient bills and hospital revenue.

The Centre for Management Information Systems (MIS) at Hamadan Medical University was given the responsibility for finding an appropriate solution. In a literature review, Computerized Physician Order Entry (CPOE) was identified as such a solution. A CPOE system is part of a hospital information system that enables physicians to enter the orders directly into the computer. Such systems may also provide real-time clinical decision support [9]. However, in order to implement CPOE, an order-entry based HIS would have to be designed. In an order-entry based HIS, the physician's order is the centre of all activities. The system can provide relevant clinical information at the time of order entry. Therefore, a local IT company in Hamadan (Sayan Rayan Co. Ltd.) was commissioned to create an order-entry based HIS. This product was given the name Sayan-HIS.

Sayan-HIS was successfully implemented in all university affiliated hospitals in Hamadan between 2003 and 2005. However, the system was only used for administrative and financial purposes. In 2005, the MIS centre decided to use the system to improve clinical processes and reduce medication errors on the wards. This thesis mainly deals with the needs assessment, design, implementation, and evaluation of this clinical component.

3 BACKGROUND

3.1 ADVERSE DRUG EVENTS AND MEDICATION ERRORS

Adverse drug events (ADE) are common causes of injury and death among hospitalized patients, and increased costs and prolonged hospital stays can be attributed to them [10]. Many preventable ADEs occur due to medication errors [11]. According to a report by the Institute of Medicine in 2000, about 7000 deaths per year and even more injuries in the USA are directly related to medication errors [12]. According to another study, the mortality rate from drug-induced diseases in hospitalized patients varies from 2% to 12% [13].

In many studies, medication errors were introduced as a surrogate marker for the actual adverse drug events [14, 15]. Based on a previous study, about 7 in 100 medication errors have the potential to cause harm to patients [16]. However, in general, only 1 in 100 medication errors will result in injury. Nevertheless, some of the medication errors including medication dosing errors have a higher potential to harm patients than other types of medication errors [16]. In some studies, this group of medication errors is referred to as "potential adverse drug events" [14, 15, 17], which is identified as one of the patient safety indicators [18].

3.2 MEDICATION ERRORS AMONG CHILDREN AND NEONATES

Medication errors are common among all age groups [15]. However, children are at higher risk from medication errors because of weight-based dosing, lower tolerance to a dosing error, and limitations in communicating with health providers to explain the adverse event [19]. In a study, around half of the surveyed physicians were unable to correctly convert drug doses from a percentage concentration to a more conventional unit of concentration [20] despite the fact that miscalculation of dosage may have fatal consequences for children [21].

The problem becomes even more significant in neonatal wards and Neonatal Intensive Care Units (NICUs) where the patients are more susceptible to medication errors because of their unique issues [22, 23]. Neonates are extensively exposed to multiple medications in neonatal wards or NICUs despite of their small body mass [23]. During hospitalization, their weight and renal function may change frequently [22]. These changes demand frequent adjustments of prescriptions and administered dosages, which increase the risk of medication errors and potential adverse drug events [24, 25].

Potential adverse drug events occur three times more often in newborns than in adults [15]. Most errors happen at the prescribing stage, and dosing errors are the most prevalent type of medication errors among hospitalized neonates [15]. Antibiotics are among the most frequently involved drug groups [15, 26]. Ten-fold and greater prescription and administration dosing errors have been repeatedly reported in these patients [21, 26, 27]. Severe adverse events have been reported due to dose miscalculation of the prescribed

anticonvulsants [28]. Therefore, strategies to prevent dosing errors of antibiotics and anticonvulsants in neonates should be prioritized.

3.3 COMPUTERIZED PHYSICIAN ORDER ENTRY AND DECISION SUPPORT SYSTEMS

In recent years, expectations that clinical decision support systems might provide important clinical knowledge at the moment of prescription and reduce the number of medication errors have gained greater acceptance [29].

In 1998, Bates et al. reported that a Computerized Physician Order Entry (CPOE) system had reduced the incidence of non-intercepted serious medication errors by 55% in the USA [14]. This study has been frequently cited in other research papers as evidence of the power of CPOE in reducing severe medication errors. In addition to this investigation, several studies in different places in the world have confirmed the effect of CPOE with decision support functionalities in reducing different types of medication errors [17, 30-32]. Despite these positive views, there are studies that have identified the negative effects of CPOE in facilitating certain types of medication errors or in increasing the mortality rate [33-37]. However, these positive and negative results are not necessarily contradictory but they are difficult to compare because of different design and implementation methods [38].

In addition to prescription and administration errors, CPOE systems have been successful in reducing transcription errors. Different studies have reported a significant reduction in or even elimination of transcription errors following direct order entry by physicians and exclusion of intermediate operators [39, 40].

3.4 CPOE IN NEONATAL SETTINGS

Despite many studies on CPOE and Clinical Decision Support Systems (CDSS) in adults and paediatric patients, little researches has been performed in the neonatal setting. It is probably difficult to implement CDSS in neonatal settings because of their specific requirements and unique issues [22, 23]. However, the few studies that have been conducted in this setting show that the implementation of CPOE with decision support functionalities is effective in reducing medication *dosing* errors [30]. Gard et al. [41] reported elimination of self-reported antibiotic dose calculation errors in an NICU following the implementation of a computer-generated antimicrobial dose calculator. Cordero et al. [42] found that Gentamicin dose calculation error among very low birth-weight neonates was eradicated after the implementation of CPOE. Considering that dosing errors are the most prevalent type of medication errors in the neonatal setting, the results of these studies demonstrate that CPOE and CDSS can significantly improve medication safety among hospitalized neonates.

3.5 CPOE ADOPTION IN HOSPITALS

Despite these promising results, recent investigations show that even in developed countries only a minority of hospitals have successfully implemented CPOE and are still using it. The results of a research project in the USA, the leading country in the number of

2

published papers in this area [31], demonstrate that despite an extensive national effort, only 6% of the hospitals are using CPOE [43]. Different investigations show different results based on the methods used. Ashishk et al. [44] reported the CPOE implementation rate in the USA to be as high as 17%. In another research project that compared seven high-income countries, Aarts et. al. [45] reported the CPOE adoption rate in US hospitals to be as high as 15%. In their research, the situation in the Netherlands was a bit better (about 20%) but it was much worse in other countries they compared. The adoption rate in the U.K. was about 2%. In France and Germany as well as in Australia, only a few hospitals could successfully adopt CPOE systems. Surprisingly, in Switzerland only one hospital was reported to have CPOE. It is important to mention that their investigation method was based on a literature review not on surveys in different countries. This can be biased by the number of available publications, publication language, affiliation of the authors (the Netherlands), etc. However, it shows the variety of adoption sites based on the publications from these countries. The situation in paediatric hospitals is not much better. Based on research by Teufel et al. in 2009 [43], the adoption rate in US paediatric hospitals is about 23%. These results demonstrate that the adoption rate is still low.

3.6   RESISTANCE TO CPOE

Among several causes, high implementation costs, physician resistance, and user frustration were found to be the most significant barriers to the successful adoption of these systems [46-48].

The CPOE project at the Brigham and Women's Hospital (BWH) in the USA has cost approximately 11.8 million US dollars over eleven years, a third of which was spent in the first year of implementation [46]. After 6 years of implementation, a net benefit was obtained and after 7.5 years, a financial benefit occurred in the operating budget of the hospital. Despite this long-term financial benefit, many hospitals, even in the high-income countries, find it difficult to afford these costs.

Resistance toward CPOE is common among physicians, specialists, and sub-specialists in many hospitals in developed countries [49]. Studies in different countries demonstrate that the introduction of electronic health records represents a substantial change in doctors' workflow, and imposes a greater burden on them [47, 49, 50].

One aspect that can increase physicians' resistance is the time consumed by care providers for the order entry. In general, physicians are sceptical toward technologies that can reduce their attention on their patients [36]. For many physicians, using time-consuming technologies like CPOE is a win-lose game where the institution gains benefits but the physician loses clinical efficiency [51]. When they spend more of their time on order entry, they have less time to spend with their patients. Therefore, strategies that can reduce the order entry time are important for the system designers.

3.7 STRATEGIES TO REDUCE PHYSICIANS' RESISTANCE

3.7.1 Proper Needs assessment and user-centred design

According to software engineering standards, requirement elicitation and analysis are essential primary steps in any information system development and should focus on the users' views [52]. Therefore, the better the understanding we have regarding users' needs and points of view, the less resistance will occur among them [53]. Studies have shown that it is difficult to adopt systems that physicians do not like to work with [47]. Indeed, physicians' acceptance and their collaboration in the design process have been recognized as key factors of successful implementation of CPOE systems [54].

The user interface design can play an important role in reducing the time spent on order entry and increasing user acceptance. Using pre-constructed order sets and drop-down menus can increase the accuracy of the selected items and reduce the time spent on typing orders [55]. In the study by Sard et al., a quick prescription list with dosing decision support capabilities reduced medication dosing errors among paediatric patients from 31 to 14 errors per 100 orders [56].

In addition, the similarity of electronic prescription system user interfaces with the sheets of previously used paper-based system can increase the system's acceptability among physicians. The comparison of cooperation models in both situations shows that users tend to adopt a distributed decision-making paradigm in the paper-based situation, while many CPOE systems support a centralized decision-making process [57].

The ease of use is another important factor that can reduce physician's resistance. Unfortunately, many of the CPOE systems are not designed to address usability issues [58]. They are hard to use, hard to learn, and they often generate user frustration and eventual abandonment [59]. In many cases care providers are mandated to perform the order entry which might lead to an increased coordination load on them, and create opportunities for new sources of errors [59].

To summarize, physicians are sceptical about the usability and user simplicity of many implemented CPOE systems. The successful adoption, to great extent, is dependent on the designed model, training, and adaptation of the implemented system to the context. Although worldwide commercial systems may have better engineering technology, home grown systems are better customized to the specific context [60].

3.7.2 The role of DSS design in improving compliance among physicians

A well-designed CPOE might support physicians' clinical decision-making by automatically calculating an appropriate dosage, recommending the drug administration route, calculating drug volume, and reporting possible interactions [61, 62]. Unfortunately, compliance of physicians with the recommendations is low. Many drug-drug interaction and dosing alerts are overridden. van der Sejs et al. [63] have reported a list of overridden alerts in different studies. Drug-drug interactions (DDI) were more often overridden than dose alerts. Different reasons can contribute to the increase in overridden alerts. In many

cases, physicians perceive the alerts to be clinically unimportant or irrelevant [64]. In addition, in many systems DDI alerts are not classified based on their severity, which may reduce the compliance of prescribers with the recommendations [65]. However, even with such a classification there is no guarantee that alerts will be thoroughly reviewed and safely ignored [63, 65, 66]. The situation is probably better in dosing errors since the safe margins are clearer than for interactions. Especially, fewer high-level overdose alerts are overridden [63]. In a study by Nightingale et al. [67], the rate of overridden warnings for high-level dosing error was 27% while for low-level it was 53%. This shows the importance of the specificity of dosing alerts [63]. Despite this fact, based on previous reports, between 20-90% of the dosing errors are ignored [67, 68].

One of the important factors that can affect physicians' acceptance with the displayed alert is the availability of relevant explanations for the appeared warning. Previous studies have stated that non-interruptive drug information should be available with the alert [69, 70]. The information can be shown on the same interface with the alert or a different popup menu [70]. However, long explanations can cause frustration and increase the number of overridden alerts. Therefore, it is important to only display essential and relevant information as the explanation.

The frequency of alerts is another important factor that can affect the override rate. Previous studies have mentioned that frequent alerts might result in users' frustration and withdrawal of cooperation [63, 66]. A highly sensitive alert, set to appear for all possible interactions, will disturb the prescriber and most of the alerts will be overridden[63]. The danger is when a severe alert occurs in-between these mild alerts and the prescriber ignores the alert unintentionally [66]. In some programs, severe errors appear in a different colour or with a different interface to notify the prescriber [71]. Therefore, setting the frequency of alert has an important effect on both prescribers' satisfaction and medication safety.

3.7.3 Nurses are the champions
Some studies have focused on nurses as a strategy to overcome resistance [72, 73]. As nurses, unlike many physicians, often have a positive attitude toward information technology, their involvement in the implementation and adoption of clinical information systems can stimulate a constructive climate and reduce resistance [73]. Even in the hospitals that have successfully implemented the physician order entry method, some orders are still entered into the computer by nurses or other non-physician care providers [54]. Many researchers are now using CPOE as an abbreviation for computerized *provider* order entry in order to include nurses and other non-physician care providers within the CPOE boundary [74-76].

3.7.4 Teamwork
Teamwork has been identified as one of the important factors that can increase the success rate of CPOE implementation. Nowadays, more and more hospitals in the western countries are trying to redefine traditional borders between doctors and nurses by creating a closer collaboration between them in all clinical activities [77, 78]. This teamwork should

also include pharmacists. Previous studies in developed countries have shown a 60% to 80% reduction in medication errors following the active participation of a senior clinical pharmacist in the clinical rounds [79, 80].

3.8 CPOE IN DEVELOPING COUNTRIES

Implementation of computerized physician order entry in low- or middle-income countries is even more challenging because of the financial as well as human resource constraints. Few studies have been conducted to assess essential requirements for the implementation of CPOE in middle-income countries, including the Middle East. To the best of our knowledge, before this thesis, no study had evaluated the effect of CPOE on patient safety in this region. Among these countries, the Government of the Islamic Republic of Iran has, in its strategic cooperation plan with the World Health Organization (WHO), committed itself to extending the use of information technology and evidence-based decision-making in the health sector [81].

3.9 ADE AND MEDICATION ERRORS IN IRAN

Iran is a middle-income country in the Middle East with almost 70 million inhabitants [82]. In a study conducted by Gholami and Shalviri [83], the rate of adverse drug events was reported to be as high as 16.8%. The severity of 9.8% of the ADEs was identified as mild, 86.3% as moderate, 1% as severe, and 2.9% as lethal. The length of hospitalization increased with the severity of the ADEs. Preventable ADEs were more severe than those that were non-preventable. They noticed that about half of the adverse events could have been prevented if dose, interval and choice of the prescribed drugs had been appropriate and proper laboratory tests had been performed.

In another study, the researchers reported that medication-related problems in Iran were responsible for 11.5% of admissions, and that 92% of them were either preventable or probably preventable [84].

A third study on the elderly population of Iran revealed that 27.6% of them were prescribed at least one inappropriate medication per visit and that 10% of the prescribed orders contained at least one drug-drug interaction [85].

In a fourth investigation in a main teaching hospital in Iran, researchers reported that more than half of the reviewed prescription charts contained transcription errors. Dosing transcription errors contributed to 18% of the total errors (9% of the prescribed medications) [86].

In another research project, conducted in a general ICU in Iran, the rate of preparation and administration errors was reported to be as high as 9.4%. About one-third of the errors had occurred in the preparation, and the rest in the administration process.

6

The results of these studies demonstrate that Iranian healthcare has the same problems as the other countries in the world regarding medication errors, and may benefit from CPOE and decision support systems.

3.10 COMPUTERIZED PHYSICIAN ORDER ENTRY IN IRAN

To the best of our knowledge at the time of this study, there was no implemented CPOE system in Iranian hospitals. Paper-based medical records were used as the primary source of all medical information [87], and physicians were not responsible for any computerized registrations of inpatients. In Iran, medical faculty members are specialists who have treatment, teaching, and research responsibilities. Overcrowding of patients, involvement in therapeutic activities, and constraints on time have forced these physicians to spend more of their time on treatment activities and less on educational and research activities [88, 89]. Therefore, to convince these busy physicians to change their daily habits and spend time on order entry is a challenge.

In addition, at the time of this study, there was no Iranian commercial on-line decision support available, which could inform physicians before they administer a drug. All monitoring and feedback was produced a couple of weeks or months after medication administration. Although this type of feedback has its own value in increasing the knowledge of prescribers, the patient could already have been exposed to potential harm following the medication error.

3.11 INFORMATION TECHNOLOGY AND HOSPITAL INFORMATION SYSTEM IN IRANIAN HOSPITALS

The public hospitals in Iran have financial autonomy [90]. Doctors, nurses and hospital administrators are all public-sector employees and their salaries are paid for by the Government. Any other costs should be paid for from revenue generated by the hospitals themselves [91, 92]. In Iran, hospitals generate revenue through a fee-for-service system, where the tariff is annually set by the Government. According to official data, health insurance coverage in Iran is about 92% (2009) [93]. Hospitals are therefore financially dependent on insurers. The low health service tariffs and delays in payment by insurers have made it very difficult for the hospitals to renew their equipment [94].

ICT projects for both software and hardware should also be paid for from hospital revenue, with the result that they can seldom afford them [94]. Accordingly, many Iranian hospitals do not have a specific IT item in their annual budget.

Following the allocation of the specific public budget for ICT projects in 2002 (TAKFAB), many university hospitals in Iran signed contracts with local ICT companies for developing and implementing hospital information systems. Most of these HIS are not order-entry based. In these systems, all clinical activities like medication administration and clinical service delivery are registered on the computer after they have been performed for the patient and the information system has no control over them. If any medical error occurs

during the data entry process, the system normally cannot prevent or intercept the possible harm to the patient by correcting the erroneous prescription or raising alerts. The main focus of such systems is to calculate patient bills and service delivery costs.

In contrast, in an order-entry based HIS, the physician's order is the centre of all activities in the hospital. The system can suggest the appropriate actions based on the entered orders. It can automatically recognize the target hospital department for the requested services. It can also provide relevant clinical information and alerts at the time of order entry by checking for dosing errors and drug-drug interactions. In these systems, the order is entered once, and until the order is active, the computer can suggest the exact time and dosage for medication administration. In addition, it can estimate the need of medication for the following day and the day after and so on. To the best of our knowledge, Sayan-HIS is the only order-entry based HIS available in Iran.

3.11.1 HIS in Hamadan University Hospitals

Hamadan is a province in the north-west Iran, with 1,700,000 inhabitants. Sayan-HIS (Sayan Rayan, Co. Ltd, Hamadan, Iran) is a commercial patient-centred hospital information system that was implemented in 2005 and has been in use ever since in all fifteen university hospitals in Hamadan. It is a client-server application and uses MS-SQL server 2005 as its database management system on the server side. The client side is programmed using Delphi 7 programming language. Users interact with the system in a local area network and through desktop computers installed at the workstations. The system includes an administrative as well as a clinical information system. The administrative information system handles patient billing and insurance company interface as well as providing various reports for the financial controllers and management.

The clinical information system of Sayan-HIS includes functionalities for order entry. When the physician's order is entered into the computer, the prescription system delivers the requested order for medications, lab tests, and imaging to their relevant target hospital departments at the appropriate time.

Before the start of this study, the system could limit the selection of drugs and their possible pharmaceutical forms (vial, ampoule, tablet, etc.) through drop-down menus and pre-constructed orders (See Appendix, Figures App 1 and App 2). A minimum and maximum dose reminder was also available. This alert was to some extent useful for adults but not for neonates whose dose might vary up to tenfold for the same drug because of the weight-based dose calculation.

3.12 STUDY RATIONALE

Medication dosing errors are the most prevalent type of medication errors among neonates [15]. Dosing errors may have fatal consequences for neonates because of their small body mass, weight based dosing, exposure to several drugs in NICU, and frequent change in weight and renal function during hospitalization [22, 23]. Therefore, strategies to prevent dosing errors among neonates should be prioritized.

8

The few studies in neonatal settings demonstrate that CPOE could substantially reduce dosing errors or even eliminate them [30, 41, 42]. Despite the significant results, the CPOE adoption rate is low [44, 45]. Even in the USA, less than one fourth of children's hospitals could successfully adopt CPOE [43]. One of the most important reasons for this failure was physicians' resistance to performing order entry.

Different hospitals have used different strategies to overcome physician resistance. Some hospitals have mandated physicians to enter orders. However, studies have shown that it is difficult to adopt systems that physicians do not like working with or perceive as time-consuming [47]. Therefore, usability issues and user-centred design play an important role in the system's acceptability among physicians [52, 53]. Prior to system development, their expectations and concerns should be gathered and paid close attention to during the development phase [54]. Other hospitals have used nurses as champions to reduce physicians' resistance [72, 73]. Unlike many physicians, nurses often have a positive attitude towards the information technology [73].

However, all of the CPOE studies were conducted in high-income countries [31]. Among the middle-income countries, the Islamic Republic of Iran has decided to extend the use of ICT in healthcare to improve the quality of care [2, 3, 81]. Prior studies have shown that medication errors and adverse drug events are important problems for the Iranian healthcare system [34, 83-86]. Therefore, Iran may benefit from the implementation of CPOE with dose decision support functionalities. However, implementation of CPOE in middle- and low-income countries is more challenging than in high-income countries because of several restrictions including limitations in budget and human resources. Therefore, finding an appropriate implementation model that can address contextual factors may warrant the successful adoption of the system. However, the more important question is whether the successful adoption can improve patient safety in that context.

4 RESEARCH QUESTIONS, AIM, AND OBJECTIVES

4.1 RESEARCH QUESTIONS

Is CPOE a viable prospect in Iran? If yes, to what extent? If no, what is the most feasible and sustainable computerized order-entry model in this context? What are the advantages and disadvantages of the new model in contrast to CPOE?

4.2 AIM

The aim of this thesis work is to find an appropriate model for adopting computerized provider order entry with clinical decision support functionalities in Iran, and evaluate the effect of the implemented model on patient safety.

4.3 SPECIFIC OBJECTIVES

1- Study the traditional prescription system and the obstacles and opportunities to design and implement computerized physician order entry with decision support functionalities in a teaching hospital in Iran (situational analysis and needs assessment) (Study I).

2- Study the effect of *physician* order entry and decision support system on medication errors on a ward that is more relevant to emerging type(s) of medication error (selection of the type of medication error that should be investigated and consequently the target ward is based on the results of Study I) (Study II).

3- Study care providers' views on the advantages and disadvantages of a sustainable computerized order entry model in contrast to the initial CPOE model (satisfaction, advantages, disadvantages and transferability to other clinical settings) (Study III).

4- Study the advantages and disadvantages of the new computerized order entry model in contrast to the initial CPOE model in terms of reducing medication errors and increasing physicians' compliance with the system's recommendations (Study IV).

5 METHODS

5.1 GENERAL SETTING

This study was carried out in two Iranian tertiary care teaching hospitals in Hamadan, Iran. In 2005, there were five teaching hospitals in Hamadan. These hospitals were, Ekbatan, Mobasher Kashani, Sina, Fatemieh, and Imam Khomeini. Ekabatan was the largest of these hospitals in 2005. However, in 2006, the clinical wards of Mobasher Kashani and Imam Khomeini moved to a new building and formed Besat Hospital. In spring 2007, a majority of the clinical wards of the Ekbatan Hospital were also integrated into the Besat Hospital, and Ekbatan became the centre for cardiology and internal medicine. Since 2007, Besat has been the largest public hospital in Hamadan.

5.2 STUDY OVERVIEW

In this thesis, by conducting observations in the clinical wards and interviews with prescribers, the traditional prescription system was analyzed. Semi-structured interviews were performed to identify physicians' needs and their concerns about implementing a computerized physician order entry system at the hospital. This qualitative study formed Study I (Figure 1, iteration 1).

Based on the results of this study, the strict physician order entry (POE) method was designed, implemented, and tested on the neonatal ward. In Study II, POE was evaluated in terms of reducing medication dosing errors (Figure 1, iteration 1).

Based on the interviews with the involved care providers, we noticed a high resistance to POE method. To improve the order entry workflow, a new model was designed in close collaboration with the involved care providers to meet their requirements. In the new order entry method, nurses performed the order entry in a similar way to the *traditional prescription system*. However, this time physicians verified the correctness of data entry and countersigned the electronic order. This method was called NOE (nurse order entry). At the end of the NOE period, the involved care providers were interviewed for a second time. They were asked to compare the advantages and disadvantages of POE and NOE. This investigation together with the related observations in the POE and NOE periods formed Study III (Figure 1, iterations 2 and 3).

To examine whether the NOE method was as effective as POE in reducing non-intercepted medication dosing errors, Study IV was conducted. The four studies together make up this thesis (Figure 1, iterations 1 and 2).

As we mentioned above, in two periods, one before POE implementation and the other one after the change from POE to the new order entry method, nurses performed the order entry. In order to easily distinguish between the two periods, in this thesis, we will refer to the first nurse order entry period as "traditional prescription system" (since it existed before the start of this project) and to the latter period as "nurse order entry" (NOE) period.
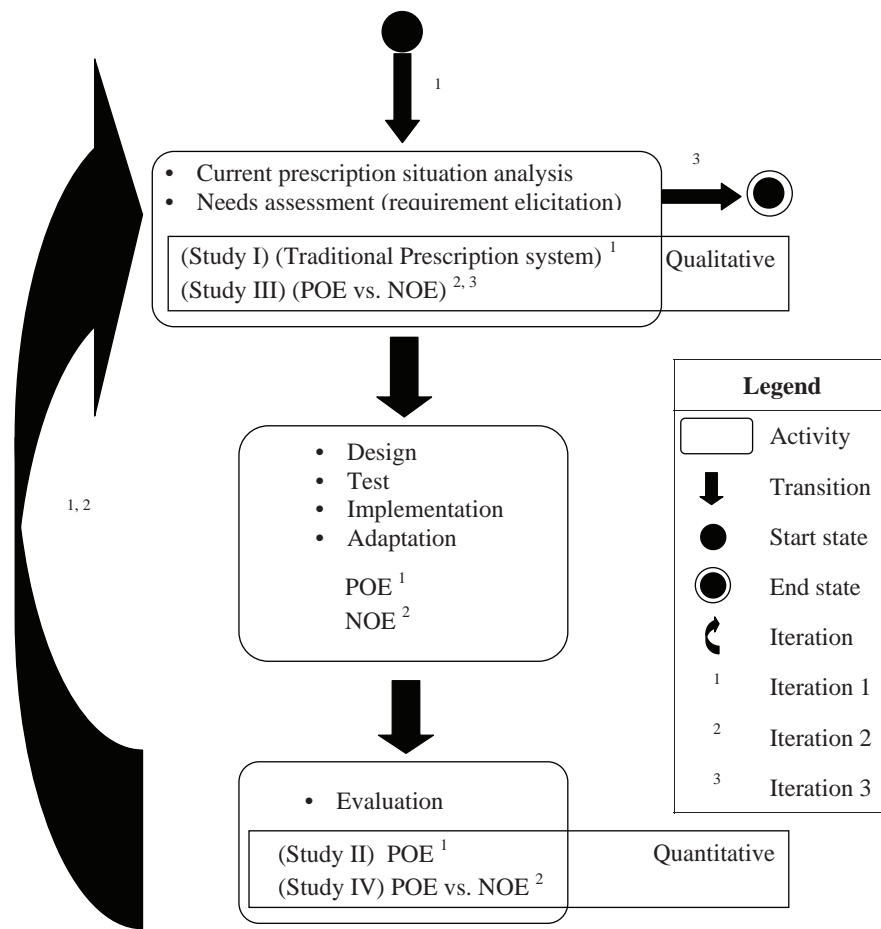
Figure 1. Schematic view of the research Project. It is divided into four studies (UML activity diagram). Note that of the three existing iterations in this model, two are completed but the third iteration exits the loop after fulfilling the first activity. Iterations are appointed to the related activities with superscript numbers.

5.3 STUDY I

5.3.1 Setting

Ekbatan is a 234-bed teaching hospital in the capital city of Hamadan. In 2005, the active clinical wards included Surgery, Internal medicine (Gastroenterology and Nephrology), Urology, Cardio-vascular, Emergency, CCU, Transplantation, and Paediatrics. The paediatric department consisted of: a paediatric ward, NICU and neonatal ward, paediatric ICU, and chemotherapy unit.

5.3.2 Investigation methods

Before designing or implementing any CPOE system, we tried to understand on-going prescription patterns and assess the prescribers' expectations of these systems. Therefore, on-looker observations were performed on different wards at the Ekbatan hospital. To explore physicians' opinions on the subject, semi-structured interviews were conducted with different groups of prescribers. To create interview guideline, focus group discussions were carried out with a group of experts.

5.3.3 Observations

Forty sessions of on-looker observations were performed on different wards at Ekbatan Hospital practising internal medicine, urology, paediatrics, neonatology, and cardiology. Observations were conducted between December 2006 and January 2007. The average observation time per session was about 2 hours. Fourteen observations were performed in the morning shifts (8 a.m. to 2 p.m.) and others during the afternoon and night shifts. Observations took place in different shifts because the activities were different. For example, a majority of the clinical rounds occurred in the mornings and specialists participated in these activities. I had worked for one year at Ekbatan Hospital during my internship and was familiar with the hospital.

During the observations, I focused on the role of senior and junior physicians and nurses in the prescription process and tried to understand their interactions.

5.3.4 Focus group discussions to develop interview guideline

In order to select focus group participants, all full-time faculty members and senior residents at Ekbatan Hospital were invited to a meeting. These people were considered to be the most knowledgeable prescribers available in the hospital. I explained the subject to them and based on their interest and critical views and their willingness to participate in the discussions, eight of them were selected. I tried to select those people who were from different specialties and had different views on the subject in order to capture multiple realities (maximum variation purposive sampling [95]).

These eight experts were, 1- a faculty member in cardiology, 2- the director of the hospital (who is a faculty member in nuclear medicine), 3- a sub-specialist in children's infectious diseases (who is a faculty member of the paediatric department), 4- a sub-specialist in paediatric gastroenterology (who is also a faculty member of the paediatric department), 5- the head of the surgery department, 6- a faculty member of the urology department, 7- the head of the pharmacology department, 8- and the chief resident of paediatrics at the hospital. Six sessions were conducted with these eight experts and the guideline was developed through the discussions. I moderated all sessions.

5.3.5 Semi-structured interviews

In order to select interviewees, the hospital chancellor invited all prescribers at the hospital to a one-day workshop. Prescribers were from different specialities and different levels (sub-specialists, specialists, residents, and interns). I explained the aim of the project and demonstrated how the order entry was performed in the HIS system. Since at that time the system did not have a dosing decision support system, Epocrates Rx (Free version) (http://www.epocrates.com, accessed on 18 March 2008) was used as a prototype to simulate order entry by physicians and medication error warnings by the system.

The interviewees were selected based on their willingness and their ability to share different perspectives on the subject (maximum variation purposive sampling [95]).

Before the start of each interview session, the aim of interviews and the ongoing order-entry system as well as the meaning of CPOE and CDSS were explained to the interviewees in order to make sure that all of them had the same understanding of the issue at the beginning of the interview session. Finally, twenty prescribers were invited. All except one cardiologist willingly accepted to participate. Of these, twelve were specialists or sub-specialists in different disciplines (cardiology, internal medicine, paediatrics, surgery and urology), three were residents, and four were interns.

The interviews mainly focused on four concepts: ordering behaviours; attitude toward medication errors; computers and employing them in daily practice; and finally prerequisites, advantages and obstacles of implementing a medication error prevention system at the hospital. A digital recorder was used to record all interviews. I personally interviewed all the interviewees. The interviews were held in Persian (Farsi) which is my first language. I transcribed all interviews verbatim. During transcription, the identity of the informants was removed to guarantee their confidentiality.

The analysis method was inductive thematic analysis [95]. Meaning units were condensed and primary codes were extracted using content analysis. Codes with similar meaning were put into the same category. All meaning units were translated into English, my co-investigators checked the coding process, and categories were discussed.
The results of the semi-structured interviews and the observations were used to present a graphical model of the present prescription workflow. The model was introduced to the hospital care providers in different group meetings at the hospital and they confirmed its correctness with minor changes. Most importantly, the physicians also identified transitions within this model having a higher possibility of errors (asterisks in Figure 6).

5.4 DEVELOPMENT AND EVALUATION OF CPOE

5.4.1 Setting of Studies II, III, and IV

Based on the results from Study I, a neonatal ward was selected as the most relevant ward to implement Computerized Provider Order Entry (CPOE). Since the neonatal ward of Ekbatan Hospital had moved to Besat, the neonatal ward in Besat Hospital was selected as the implementation unit. Besat is a 400-bed tertiary-care referral teaching hospital in Hamadan. Besat's neonatal ward is a 17-bed clinical ward that includes two NICU beds.

5.4.2 Development and evaluation of POE, DSS, and NOE

Development and implementation of CPOE in this thesis work was gradual and in some stages based on the results of the previous period. The design and programming of POE and DSS started in February 2007. However, the actual evaluation of POE started in late July 2007. We had a 6-week adaptation period between June and July 2007 before we started the investigation of POE. The design, programming, and testing of the dosing DSS started in February 2007 and were completed before June 2007 (Figure 2). However, the evaluation of the DSS started in October 2007. The evaluation stages of this work can be divided into five periods between May 2007 and Sep 2008. Each of the evaluation periods was about 2.5 months. The five periods and their relation with Studies II, III, and IV are shown in Figure 2.

Data collection of the electronic orders and the electronic medication administration chart was performed automatically in the system's database in each period (Figure 2). Data collection of paper-based medication administration chart (PBMAC) of the traditional prescription system was performed during the POE period and for the POE period was performed after July 2008. Data collection of paper-based orders of the NOE period was performed after the NOE period (Figure 2). The analysis started in December 2007.
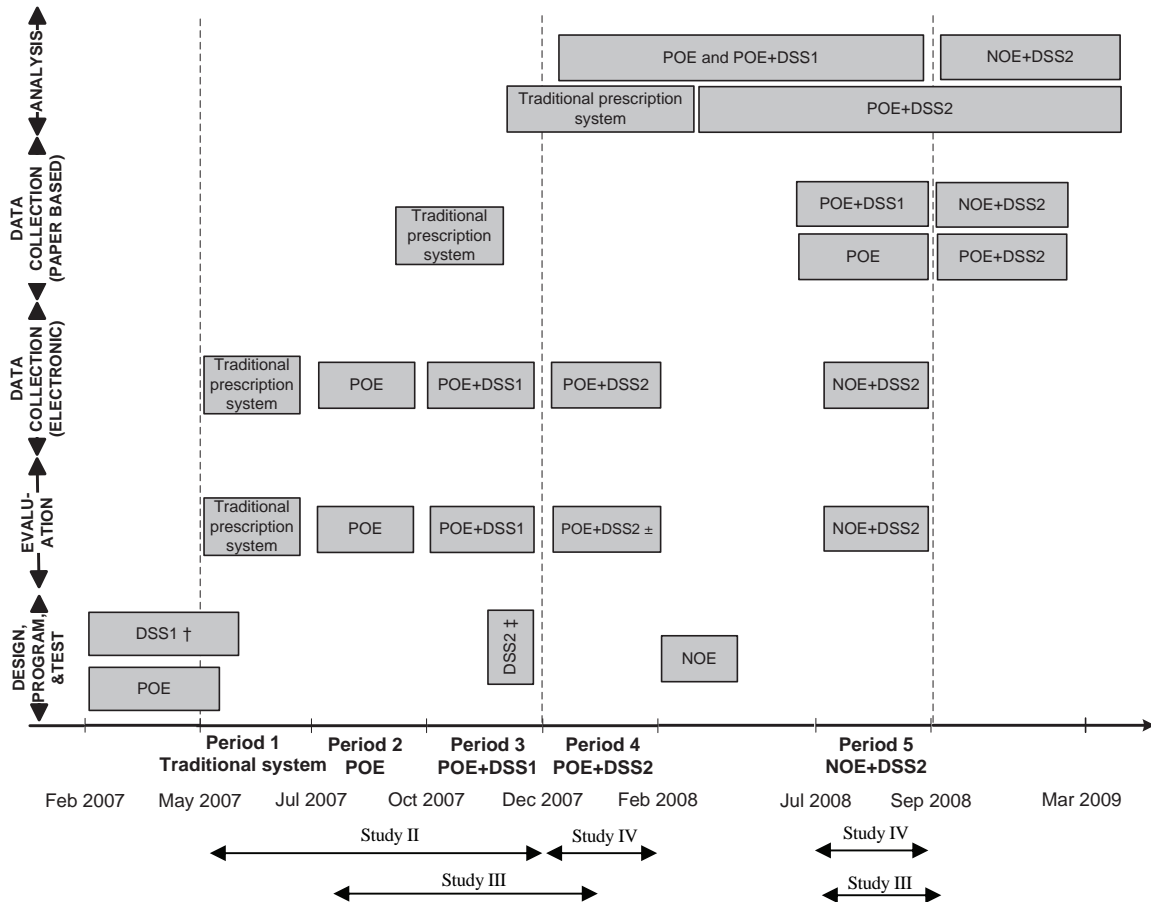
DSS, Decision Support System; POE, Physician Order Entry, NOE Nurse Order Entry followed by physician confirmation

† Warnings appeared at the first-time order and change of the dosing criteria, and provided no explanation

‡ An explanation was developed and added to the warning which could explain the reason that the alert appeared for

± Warnings appeared at each erroneous order and provided an explanation

Figure 2. Development and evaluation of DSS, POE, and NOE on the neonatal ward of Besat Hospital.

5.4.3 Dosing Decision Support System (dosing DSS)

Before POE implementation, a knowledge base was created by using the local guidelines of best practice based on the paediatric reference books that were approved by the National Board of Paediatrics in Iran [96-98]. The knowledge base was completed for all routine antibiotics and anticonvulsants, based on the patient's clinical diagnosis, age, weight, gestational age, and glomerular filtration rate (GFR). Three neonatal sub-specialists reviewed the knowledge base and approved its compliance with the original guidelines. A

computer function was developed to calculate GFR for neonates based on the patient's creatinine clearance, body surface area (BSA), age, and gestational age. A paediatric nephrologist tested the functionality of the GFR calculator, reviewed its compliance with the references [99, 100], and approved it. All prescribers were informed that they had to comply with the mentioned guidelines while setting the dose and frequency of medications.

At the time of order entry, a rule-based dosing DSS examined the dose and frequency of each prescribed medication, based on the abovementioned references. It requested the prescription system to provide detailed information required for retrieving relevant dose and frequency ranges from the knowledge base (Figure 3). According to the calculated GFR, the renal function evaluator component determined whether the dose should be adjusted, and to what extent. Based on all above information, the clinical inference component calculated the patient specific appropriate dose and frequency, and compared the results with the prescribed dose and frequency. If this was not within the normal range, the DSS informed the prescriber about the appropriate dose and/or frequency by demonstrating a warning message that asked for correction. The prescriber was, however, allowed to ignore it. If the prescriber accepted the correction, the order was updated based on the DSS recommendation. Prescribers' response to the warning, was recorded in an error registration table. Detailed information on decision flow is shown in Figure 4.
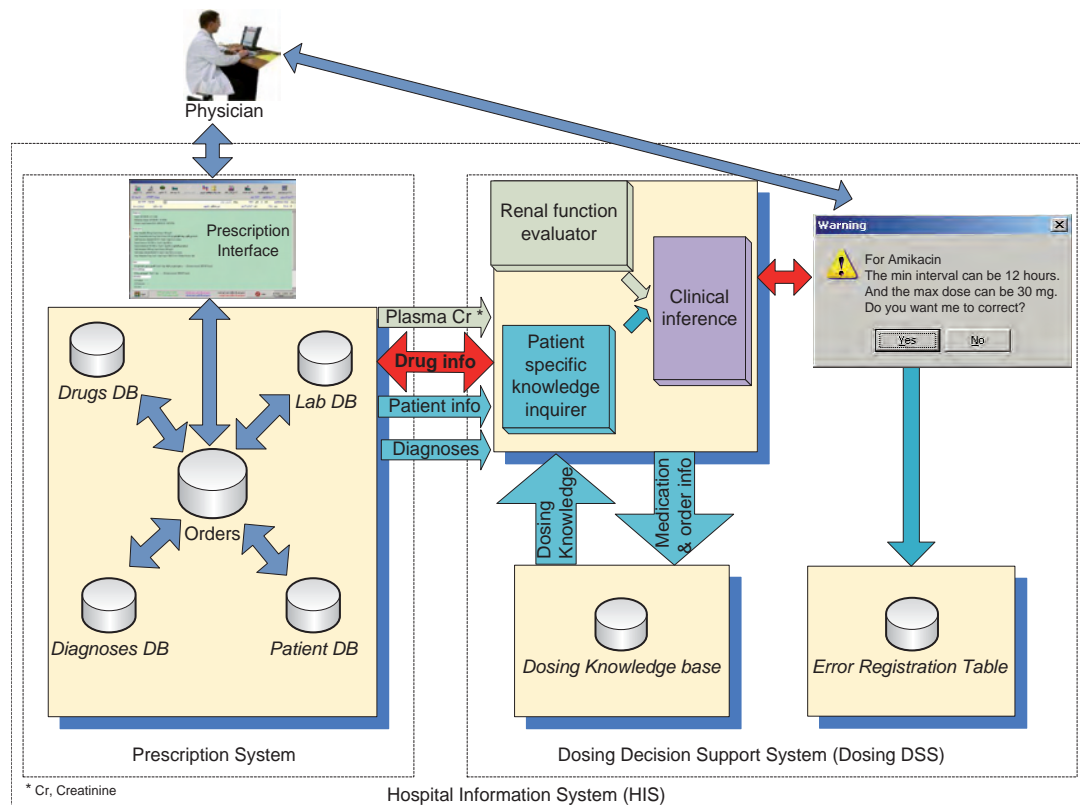

Figure 3. Schematic view of the dosing DSS architecture, and its interactions with the prescription system in the physician order entry method.
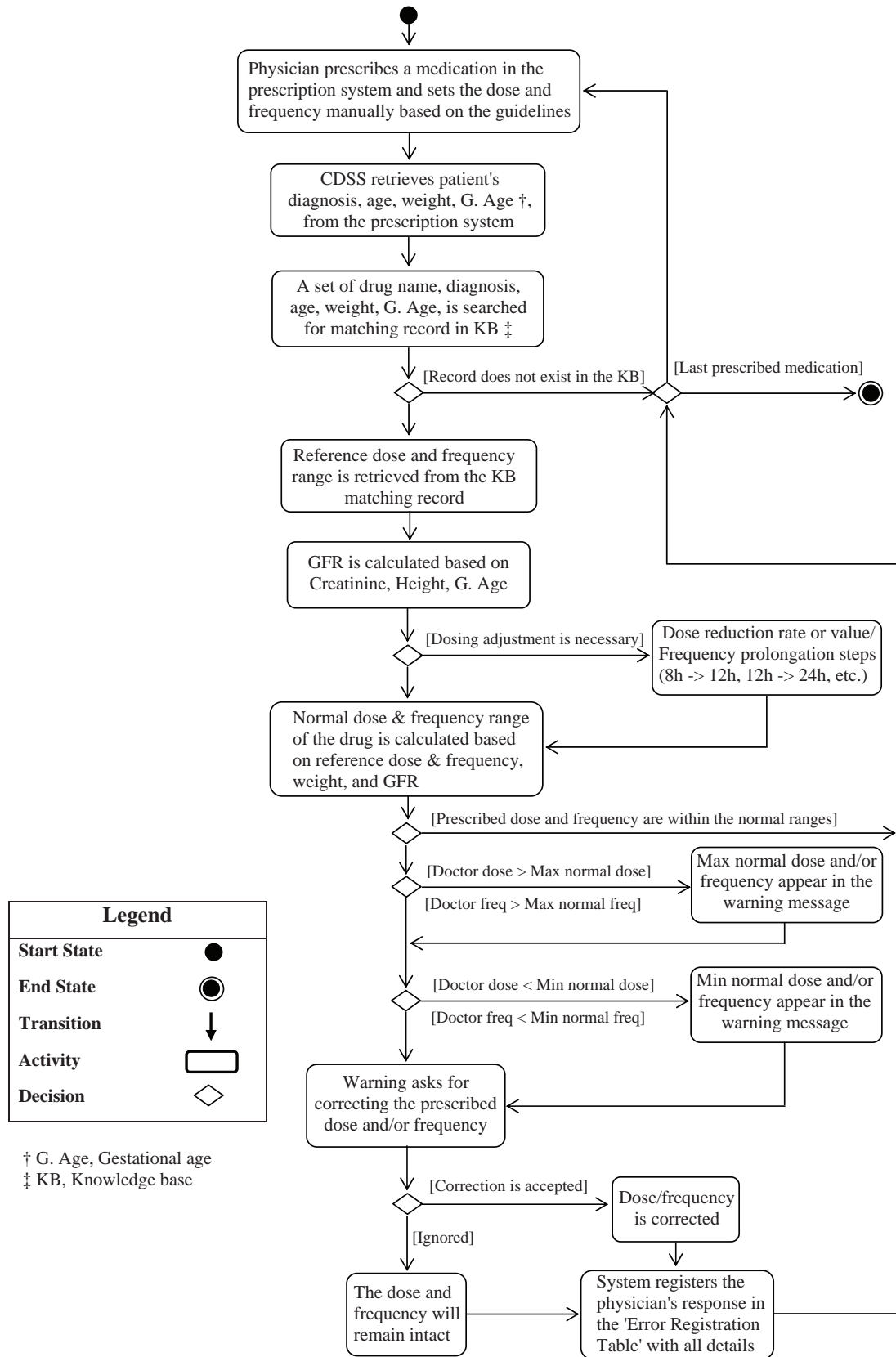
Figure 4. Dosing decision support system workflow (UML activity diagram)

5.4.4 Evaluation periods and their characteristics

Characteristics of the five evaluation periods are concluded in Table 1. A detailed description of each period is presented after the table.

Table 1. CPOE evaluation periods on the neonatal ward of Besat Hospital

	Period 1 May - Jul 2007	Period 2 Jul - Oct 2007	Period 3 Oct – Dec 2007	Period 4 Dec 07 - Feb 08	Period 5 July - Sep 2008
Intervention	No intervention	POE	POE+DSS1 †	POE+DSS2 ‡	NOE+DSS2
Order entry	Nurses	Physicians	Physicians	Physicians	Nurses
Verification and countersignature	N/A	Nurses	Nurses	Nurses	Physicians
Dosing DSS functionality	N/A	N/A	Warnings	Warnings with explanation	Warnings with explanation
Warnings displayed at	N/A	N/A	Order entry	Order entry	Countersignature
Documentation	HWO	E-Prints	E-Prints	E-prints	HWO and E-prints
Transcription to	Computer + Cardex + PBMAC	Cardex + PBMAC	Cardex + PBMAC	Cardex + PBMAC	Computer + Cardex + PBMAC
Review process	EO+EMAC + HWO + PBMAC	EO + EMAC + PBMAC	EO+EMAC + PBMAC + ERT	EO+EMAC + PBMAC + ERT	EO+EMAC + HWO + PBMAC+ERT

POE, Physician Order Entry; DSS, Decision Support System; HWO, Hand-Written Orders; E-Prints, Electronic Prints (of prescriptions); PBMAC, Paper-Based Medication Administration Chart; HWO, Hand-written Orders; EO, Electronic Orders; EMAC, Electronic Medication Administration Chart; ERT, Error Registration Table; N/A, Not Available

† The warnings appeared at the time of an erroneous new prescription or change of the dosing criteria, and provided no explanation

‡ The warnings appeared at each erroneous order and provided an explanation

5.4.4.1 Period 1 – Traditional prescription system

On the neonatal ward, residents were responsible for calculating the appropriate dose and frequency of the prescribed medications and registering them on the paper-based order sheets. In Period 1, nurses transcribed prescription orders to the computer and physicians did not interact with the computer system (Table 1 and Figure 5). The main reason for this order entry was to calculate patients' bills. Nurses also transcribed prescribed medications from paper-based orders to paper-based nursing Cardex that was used for drug preparation. After administration, the delivered dose and administration time were registered in the PBMAC.

During this period, together with a colleague, we conducted group and private training sessions for the residents to teach them how to use the prescription system. Residents could also obtain access to a demo version of the system for further training.

5.4.4.2 Period 2 – Physician Order Entry (POE)

In Period 2, physician order entry was introduced as a separate period to evaluate the role of physicians' data entry without the assistance of the computer-generated warnings in reducing or increasing dose and/or frequency medication errors. At the beginning of this period, paediatric residents took responsibility for entering all the details of the prescription orders into the computer (Table 1). However, when a resident had completed the electronic registration of an order, a nurse checked and electronically countersigned the order to verify it to reduce possible data entry errors (Figure 5). This verification was designed to reduce the likelihood of typing errors and selecting incorrect drugs from the drop-down menus. A further design consideration was to remind physicians about obvious dosing errors.

In this period, transcription of paper-based orders to the computer was eliminated but transcription to the Cardex and paper-based nursing reports were continued (asterisks (*) in the middle workflow of Figure 5). Because Iranian law does not permit electronic signatures, each electronic order was printed and saved in the patient's medical file after countersignature [101] (Table 1).

To evaluate the non-intercepted medication errors in Periods 1 and 2, patients' order books were reviewed to complete missing information on weight, height, gestational age, and the clinical diagnosis in the HIS and medication errors were assessed retrospectively (Table 1).

5.4.4.3 Period 3 – Physician Order Entry and dosing DSS providing warnings (POE+DSS1)

In Period 3, residents continued to enter prescriptions into the computer and nurses verified and countersigned each physician-entered electronic order in the computer (Table 1). In this period, nurses' verifications were mainly used to remind physicians about obvious dosing errors of those medications that were not included in the knowledge base because the warning messages became functional and informed physicians following a dose or frequency medication error of the included medications (Figure 2). If the prescriber

ignored a warning, the next warning would appear when one of the decision criteria (diagnosis, age, weight, GFR, etc.) was changed in the renewed order or a new erroneous dose and/or frequency was set for that medication (DSS1 in Figure 2).

In this period, when a resident complained about a warning that was perceived by him /her as being inappropriate, I asked him/her to explain how did he/she calculate the dose and frequency for that medication. Away from the resident, I then reviewed the system's calculation method and compared the two approaches. The aim was to explore the reasons for the ignored warnings and the possible causes of medication errors without influencing the prescriber. At the end of Period 3, the results of these investigations were categorized into main causes of errors (presented in the result section).

5.4.4.4   Period 4 –Physician Order Entry with new DSS functionalities (POE+DSS2)

In this period, order entry, verification, and documentation were continued in the same way as in Periods 2 and 3 (Table 1).

Two changes were made in the functionality of the DSS in this period.
1- The ignored warnings appeared each time the order was renewed with an erroneous dose and/or frequency or when a new erroneous dosage was prescribed.
2- An explanation was added to the warning's interface, which explained the reason that the warning appeared for. The explanations were created based on the findings in Period 3 (main causes of errors).
The DSS with the new functionalities was called DSS2 (Figure 2).

5.4.4.5   Period 5 - Nurse Order Entry followed by Physician verification and countersignature (NOE+DSS2)

In Period 5, the care providers of Period 4 switched their roles in order entry and countersignature, vis-à-vis (Table 1 and Figure 5). Resident physicians wrote the initial orders on the prescription papers and delivered them to the nurses who subsequently entered them into the computer with all details. Residents then verified and countersigned the orders electronically. The warning's interface and its functionality were similar to Period 4. However, in this model, warnings appeared when the physician countersigned the electronic order. Therefore, the warnings still appeared to the physicians but not to the nurses (Figure 5). The reason for this strategy was to give the physician the option of deciding whether to change the original dose or keep it the same. The new model was designed in close collaboration with the physicians and nurses involved in the project in order to address their needs

After the physician's verification and countersignature, the electronic prescription was printed and if a complied warning had led to the change of dose or frequency, both the nursing Cardex and patient file were updated (Figure 5). In this period, both electronic print-outs and hand-written prescription papers were saved in the patient's file (Table 1).
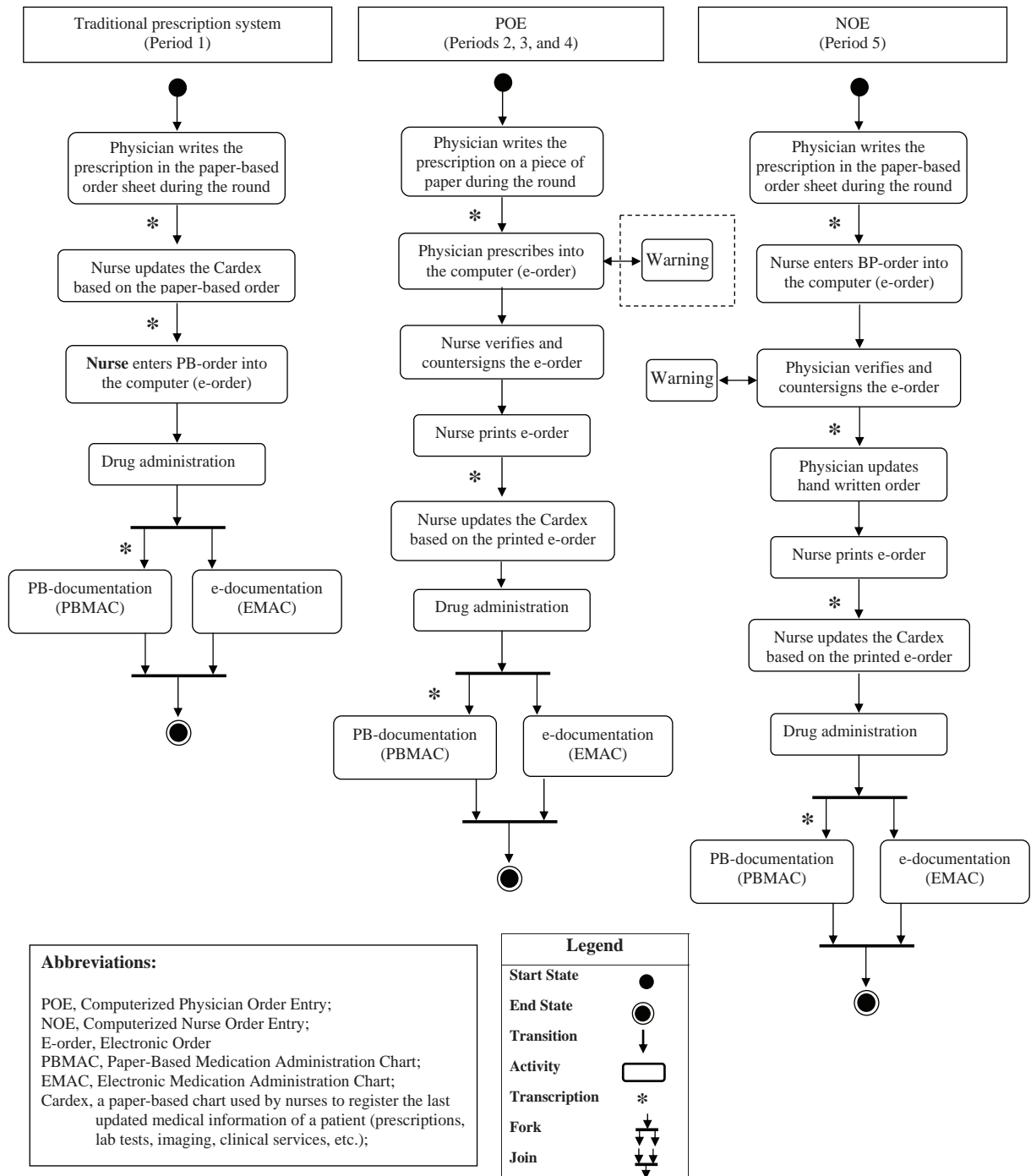
20

Figure 5. Medication prescription and administration workflow in the traditional prescription system, POE, and NOE on the neonatal ward of Besat Hospital. Note that the warnings in the POE method did not appear in Period 2.

5.5   STUDY II

Evaluation of the first three periods constituted the study II (Figure 2).

5.5.1   Inclusion criteria and study population

All neonates who received antibiotics for infectious diseases or anticonvulsants for seizure in the study period were included in the study. For the included patients, all orders that led to the administration of antibiotics and/or anticonvulsants were included.

5.5.2   Definition of medication errors

In this study, we investigated prescription and transcription errors, but not the administration errors. Among different prescription parameters, dose and frequency were selected because they are the most common source of prescription errors in the neonatal setting [15, 26].

Normal ranges of doses and intervals of the selected medications were calculated according to the local guidelines of best practice using the mentioned published references [96-100]. Therefore, over- or under-dosages and curtailed or prolonged intervals were considered as medication errors. Those medication errors that were prevented before they reached patients were categorized as intercepted and those that reached patients were categorized as non-intercepted medication errors.

A prescription error was defined as a medication that was prescribed with an erroneous dose or frequency by the physician. Prescription errors could occur at the time of selecting the reference dose, calculating the patient-specific dose, and registering dose in the order book. A transcription error was defined as a medication that was registered with an erroneous dose in the PBMAC while the prescribed order was correct. The other types of dose transcription errors such as delayed or omitted doses were not included in this study.

5.5.3   Measuring medication errors

A prescribed medication that resulted in at least one administration over the measured 24 hours was defined as a *medication-day*. Therefore, even if the prescribed medication was repeated in several renewed orders on the same day, it was considered as one medication-day. When the dose and frequency of the prescribed medication was correct in all orders of the same day, it was considered as one correct medication-day otherwise it was counted as one erroneous medication-day.

Medication-day was used as the primary unit of analysis. Medication-days account for both the number of concurrent medications used for one patient and the duration for which a medication is continued. In order to make sure that the obtained differences are not adversely affected by the error measurement unit and to be able to compare the results with similar studies, in addition to *medication-day*, the rate of non-intercepted medication errors was calculated using three other measurement units. These three measurement units were:

Patient-day: one day of hospitalization for a patient who received medication therapy on that day. If all medications in all prescribed orders on the same day were correct, it was perceived as one correct patient-day, otherwise as erroneous.

Order: a collection of prescribed medications, lab tests, imaging, etc. written by a physician for a patient during or after a visit. If all prescribed medications in the same order were correct, it was perceived as one correct order, otherwise as erroneous.

Ordered medication: a medication prescribed in an order. If the prescribed medication was correct, it was perceived as one correct ordered medication, otherwise as erroneous.

Each measurement unit has advantages as well as disadvantages and different studies have used different measurement units. These will be discussed under the methodological considerations in section 7.5.

5.5.4 Data collection and review process

Physicians' responses to the warnings were stored in a table together with the erroneous as well as corrected doses and frequencies (Figure 3). It was hence possible to detect those medications that were initially incorrect but were intercepted by the warnings. In addition to that, I reviewed all relevant paper-based medical documents and electronic patient records. This included hand-written orders, electronic orders, and paper-based and electronic medication administration charts (Table 1).

By triangulating different sources of data, we could detect those medications that were prescribed erroneously and were not intercepted by the warnings but were intercepted by physicians or nurses before they were administered to the neonates. In this case, the electronic order was registered with an erroneous dose but the PBMAC was registered with the correct dose. Those medications that were prescribed erroneously and were registered in the PBMAC with the erroneous dose were considered as non-intercepted prescription errors. Those medications that were prescribed with a correct dosage but were registered in the PBMAC with an erroneous dose or frequency were considered as non-intercepted transcription errors. This type of error could happen because of the frequent transcriptions between paper-based and electronic orders, orders and nursing Cardex, or Cardex and PBMAC.

5.6 EXTENSION OF STUDY II

In order to investigate the role of DSS design in reduction of medication errors and increase of physicians' compliance with the system's recommendations, we in an extension to Study II, compared Period 3 (POE+DSS1) and Period 4 (POE+DSS2).

Since the warnings appeared more frequently in the follow-up orders of Period 4 than they did in the follow-up orders of Period 3, we also performed a subgroup analysis and divided the orders into first-time and follow-up orders to account for this difference. The warnings were also divided into first-time and follow-up.

A first-time ordered medication was defined as a medication that was prescribed for the first time in an order for a patient and resulted in an administration.

A follow-up ordered medication was defined as a medication that was continued from the previous order with the same or different dosage and resulted in an administration.

5.6.1 Inclusion criteria and study population
The same as Study II

5.6.2 Definition of medication errors
The same as Study II

5.6.3 Measuring medication errors
The same as Study II.

5.6.4 Data collection and review process
The same as Study II.

5.7 STUDY III

5.7.1 Investigation methods
Non-participant observations were performed in order to understand POE and NOE workflows [95]. Semi-structured interviews were conducted with the involved care providers to explore their perceptions of the advantages and disadvantages of POE and NOE.

5.7.2 Observations
To identify POE and NOE workflows, I attended at least three times a week on the neonatal ward during the study period and observed care providers and their interactions with the system and with each other. Overall observation time was about 200 hours and the average time per session was about 1.5 hours.

Observations were performed between July and December 2007 in the POE period, and between July and October 2008 in the NOE period (Figure 2). The observations took place at different working hours during the day- and night-shifts. The focus of the observations was mainly on the role of different actors, including senior and junior physicians and nurses during the clinical rounds and order entry activities.

The results of the observations were used to generate graphical models of POE and NOE workflows (Figure 7). The involved care providers verified the correctness of the designed models in October 2008.

5.7.3 Semi-structured interviews

Two series of semi-structured interviews were conducted with all 19 care-providers who were involved in both POE and NOE. Participants were eight paediatric residents, eight nurses, and three specialists. The initial interviews were conducted between December 2007 and January 2008 while POE was ongoing on the neonatal ward (Figure 2). The follow-up interviews with the same interviewees were carried out between September and October 2008 while NOE was ongoing on that ward (Figure 2). Interviews took on average 40-50 minutes to conduct.

Interviews mostly focused on: patient benefit and harm following the implementation of the DSS and each of the order entry methods; educational climate in the two methods; possibilities and obstacles of each order entry method in terms of responsibility, feasibility, complications, required skills, spent time, redundancy, and transferability; and the effect of each method on care providers' interactions with themselves and with patients.

I moderated all interview sessions and recorded them using a digital voice recorder. The interviews were held in Persian (the native language of both the interviewees and the interviewer) and were transcribed verbatim in Persian. The analytical method was inductive thematic analysis [95]. Meaning units were condensed and assigned primary codes using content analysis. Codes with similar meaning were put into the same category. Meaning units were translated into English. The investigators discussed primary categories and reached agreement on the final categories.

5.8 STUDY IV

The comparison of POE+DSS2 (Period 4) and NOE+DSS2 (Period 5) in terms of medication dosing errors and physicians' compliance with the system's recommendations constituted Study IV (Figure 2).

5.8.1 Inclusion criteria and study population

The same as Study II

5.8.2 Definition of medication errors

The same as Study II

5.8.3 Measuring medication errors

The same as Study II

5.8.4 Data collection and review process

The same as Study II.

5.9 STATISTICS

Descriptive statistical analysis was carried out to determine the median for numerical variables and the percentages for categorical variables. The median [25th percentile, 75th percentile] non-intercepted error per patient and the median for age on admission, gestational age and length of hospital stay were computed. A two-tailed Chi-square test was performed for non-ordinal qualitative variables to find statistically significant differences in the proportion of medication errors, complied, and ignored warnings between different periods [102]. The non-parametric Mann-Whitney test was employed to determine differences in the median non-intercepted error per patient between evaluation periods, when there was remarkable deviation from normality. Rates of non-intercepted dosing errors were reported per order, per ordered medication, per medication-day, and patient-day. Error rate differences between different periods were calculated using $r = |\text{Initial period error rate - Final period error rate}|$ formula. Rate ratio (RR) was defined as the rate of errors in the successor period divided by the rate of errors in the predecessor period. RR < 1 indicates that the later intervention has a "protective effect", and RR > 1 demonstrates that the later intervention has an "incremental effect" on medication errors. RR = 1 shows that that the later intervention has "no incremental or protective effect" on medication errors. Confidence intervals for the ratios were determined under the assumption that the number of events per 100 patient-days followed a Poisson distribution. Miettinen's test-based approximation was used to calculate the confidence interval for the rate ratios [103]. The level of statistical significance was specified at 0.05. Statistical analyses were performed by using SPSS version 17.

EPI Info version 6.0 was used to calculate Chi Square for trend Mantel extension test [104] to examine any increasing or decreasing linear trend for medication errors between a sequence of periods.

5.10 ETHICAL CONSIDERATIONS

The National Ethical Committee at the Ministry of Health and Medical Education of Iran gave the ethical permission for the studies in this thesis work in 2005 (registration Number: P/391). Participation in the study was voluntary, and participants could withdraw at any time. Participants were informed of their rights. A verbal informed consent was tape-recorded before the start of each interview. When analysing, patient documentation was de-identified to guarantee confidentiality.

6 RESULTS

Traditional prescription system vs. Physician Order Entry

The results of the qualitative approach toward the traditional prescription system and physician order entry were concluded in Study I, and the results of the quantitative approach were concluded in Study II and its extension.

6.1 STUDY I

Based on the interviews and observations, three themes emerged as: the traditional prescription process at the hospital; opinion of the physicians on the traditional prescription system; and finally, opinion of the physicians on a possible future migration to CPOE and using clinical decision support systems.

6.1.1 Traditional prescription process at the hospital

The prescription process before the introduction of POE is shown in Figure 6. The process started when the physician in charge took the patient's history, performed physical examinations, and reviewed available medical documents, including progress notes, laboratory findings, and imaging. These data sources guided the physician(s) to a set of differential diagnoses or a definitive diagnosis, which helped the prescriber(s) to select appropriate treatment for the patient.

The prescriber then registered medical records on paper. At the time of this study physicians did not interact with the HIS system. The nurse then read the paper-based prescription and registered the new prescriptions into the HIS. In Iran, nurses have no authority to prescribe, or to change prescriptions. Following the data entry, the system reminded the nurse of the accurate drug administration time. The nurse administered medications and registered their delivery into the HIS. Pharmacists had no influence on prescription, administration or control of the dose and frequency. The HIS system accumulated the next 24h medication needs of the ward and delivered the sum of each needed medication to the pharmacy. After receiving all requested medications in a basket, the nurses prepared ready-to-administer doses on the ward.

6.1.2 Opinion of the physicians on the traditional prescription system

In Figure 6, an asterisk (*) identifies a transition with higher probability of medication errors. The findings in this theme were categorized into there groups: decision-making, transcription, and overconfidence errors.

6.1.2.1 Decision making errors

All interviewees (19 out of 19) believed that, in Iran while prescribing drugs, doctors often rely on their memory and rarely look for dosages or intervals in their references. Physicians with less experience on the subject, and particularly interns, may easily make erroneous decisions and the patient may suffer from such mistakes.
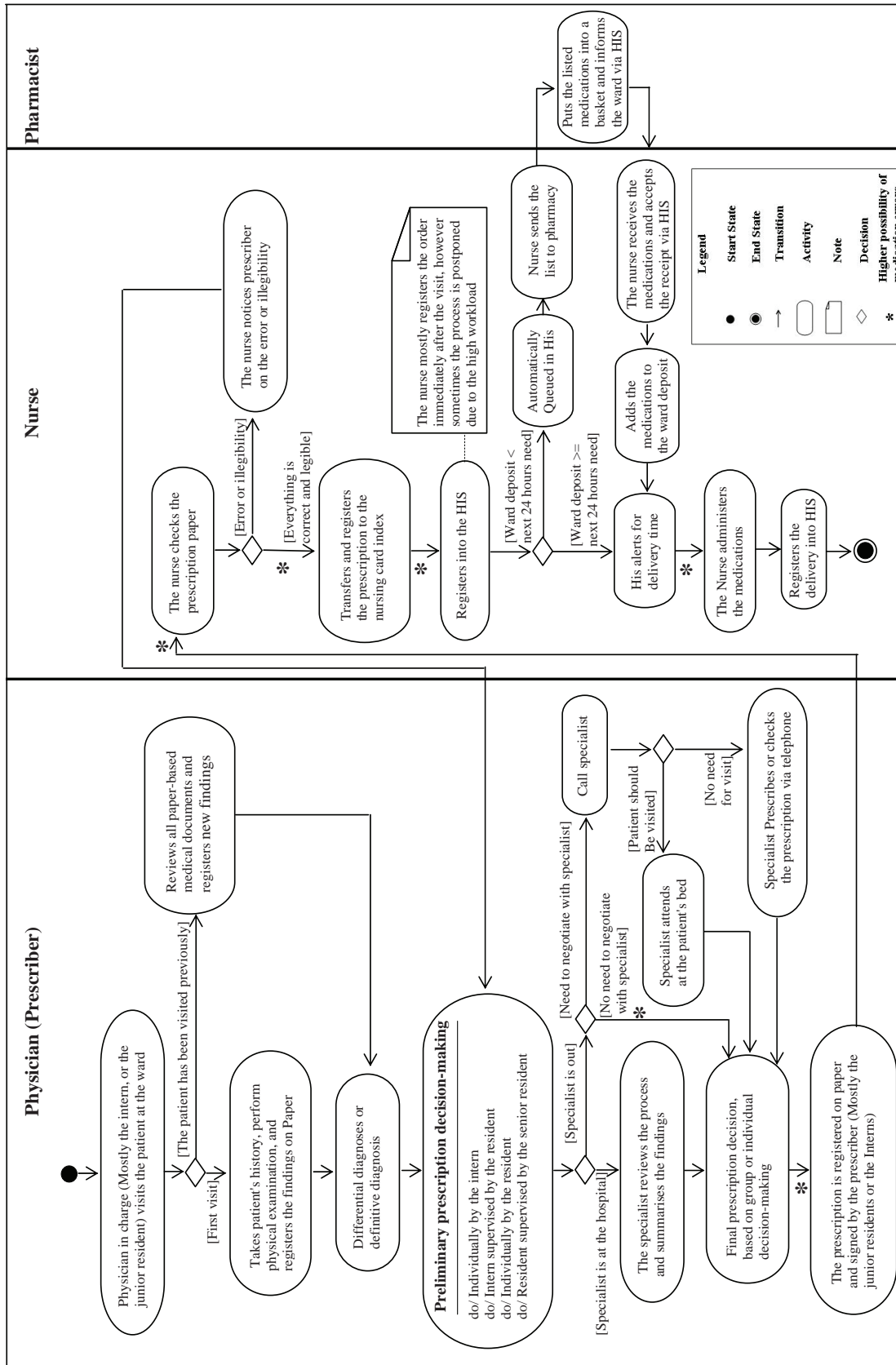
Figure 6. The traditional prescription process at Ekbatan Hospital (UML Activity Diagram).

6.1.2.2 Transcription errors

Physicians believed that multiple transfers from one sheet to another might lead to transcription errors. The probability will increase when several groups of prescribers, such as specialists, residents and interns with more or less illegible handwriting are involved in the registration process and nurses and operators with different clinical insight transcribe them.

6.1.2.3 Overconfidence errors

In our study, none of the interviewees had previously received any feedback on their possible medication errors. When asked to rate themselves, most of them (16 out of 19) believed that they did not make critical and frequent mistakes while prescribing.

6.1.3 Opinion of the physicians on a possible future migration to CPOE and using clinical decision support systems

Physicians believed that in the Iranian healthcare context, there were several issues that could help or hinder the introduction of CPOE. Accordingly, we categorized physicians' opinions into two general groups: *expected benefits* and *perceived obstacles* while employing a CPOE system.

6.1.3.1 Expected benefits

The expected benefits were further grouped into three specific categories: confidentiality issues, reduction of medication errors, and educational benefits.

6.1.3.1.1 Confidentiality issues

Physicians liked to receive feedback on their practice but did not like their errors to be disclosed to the nurses. They preferred to enter their prescriptions by themselves to receive the feedback directly. This is a typical reply:

> *"It is much better to give the feedback to the prescriber. In that case, the **physician will cooperate better** and **will show less resistance**. Also if the new medication or the changed dosage is also incorrect, the prescriber will receive the feedback immediately".*

6.1.3.1.2 Reduction of medication errors

In our study, all interviewees believed that physicians committed mistakes and errors. They mentioned that dose and interval calculation are more important sources for medication errors in comparison with selection of drugs, because drug selection is based on the prescriber's knowledge but regulating dose and interval is based on memory and accurate calculation.

6.1.3.1.3 *Educational benefits*

All interviewees believed that they did not have sufficient academic training on prescription methods, and that they had learned from each other at the hospital. This lack of training was expressed by one physician as:

> *"We did some research which showed that only 1 out of 403 prescriptions (for outpatients) had applied all the 17 different mandatory rules of prescribing".*

They believed that by using pre-constructed orders and standardized prescribing formats, new prescribers and trainees could use the system as a self-learning and educational programme.

6.1.3.2 Perceived obstacles

Findings in this general category were grouped into four specific sub-categories: high costs; social and context-specific barriers; a time-consuming system will fail; and problems with technical support.

6.1.3.2.1 *High costs*

Interviewees believed that since Iran is a middle-income country and hospitals are economically autonomous, it would probably be difficult for the hospital to afford the relatively high costs of the project from its self-generated revenue.

6.1.3.2.2 *Social and context specific barriers*

One third of interviewees were concerned about the future of advanced computer technology in Iran, since it is mostly produced by American companies. Their concern relates to the current trade embargo imposed on Iran by the USA regarding the purchase of advanced technologies.

They also mentioned that the social expectation is that physicians should be able to fulfil their job everywhere in the country. One of the specialists stated:

> *"With the traditional paper-based prescription system by using the light of a candle and a piece of paper in a poor rural area, it is still possible to prescribe drugs and save lives. But what if the physician becomes totally high-tech dependent and loses the clinical proficiency? Is it possible to afford these technologies everywhere in Iran?"*

Another social expectation from doctors is to have everything in their memory, without having to refer to book at any stage during the care episode.

6.1.3.2.3 *A time-consuming system will fail*

Interviewees mentioned that the most important threat to the continuation of a CPOE system is the time spent for data entry. Physicians will get frustrated and will quit if they have to type many things into the computer, especially in the early stages. Shortcuts, menus, pre-constructed order sets, as well as close collaboration with prescribers while designing the system were mentioned as possible solutions to this problem.

6.1.3.2.4 Problems with technical support

Since most of the HIS in Iran are locally developed by small companies with limited resources, interviewees were concerned about the future support and maintenance of the system.

Because of the abovementioned obstacles, our interviewees suggested a pilot study on one ward before trying CPOE on all wards in the hospital to find appropriate solutions to these obstacles and determine whether the benefits outweigh the costs.

6.2 BASELINE CHARACTERISTICS OF THE FIVE EVALUATION PERIODS

Based on the above results, the neonatal ward at Besat Hospital was selected as the implementation unit. During the five study periods, 399 neonates met the inclusion criteria and were included in the study (Table 2). There were no significant differences in sex, and gestational age between the five periods. The average age on admission was about 3 to 7 days. The median length of hospital stay of the included patients was about 7 to 9 days.

In Period 2, 69 orders belonging to 8 patients who met the inclusion criteria, but for whom the orders were entered by the nurses, were excluded from the study. The reason was that the aim of this period was to investigate the effect of *physicians'* order entry.

Table 2. Distribution and characteristics of the included patients, orders, and medications in the five evaluation periods

	Period 1 Traditional	Period 2 POE w/o DSS*	Period 3 POE+DSS1	Period 4 POE+DSS2	Period 5 NOE+DSS2
Patients †	96	83	79	69	89
Male / female	47 / 49	43 / 40	42 / 37	35/ 34	41 / 48
Median age on admission (days)	5	3	6	7	5
Median gestational age (weeks)	38	38	38	38	38
Orders	1248	1080	878	972	978
Ordered medications	2728	2350	2059	2357	2297
Patient-days ‡	735	686	576	601	648
Medication days §	1688	1489	1331	1466	1492
Median length of hospital stay (days)	6.8	6.8	6.6	9.1	6.7

* w/o: without

† Two included patients in Period 2, 8 in Period 3, and 7 in Period 4 had been admitted in the previous period but had stayed on the ward in the next Period.

‡ The number of days that included patients received antibiotics or anticonvulsants

§ The number of days that included medications were continued for the included patients

6.3   STUDY II

In this study, we compared the first three periods to evaluate the effect of POE, and DSS on medication errors.

6.3.1   Prescription and transcription errors

Most of the non-intercepted medication errors occurred during the *prescription* stage (Table 3). The rate of *transcription errors* was not significantly different in the first three periods. Before intervention (Period 1), the total rate of non-intercepted medication errors was about 53%. Introducing POE *without* DSS in Period 2 *did not* significantly decrease or increase non-intercepted medication errors. However, after the introduction of the dose and frequency DSS in Period 3, the rate of non-intercepted medication errors was reduced to 34% (19% reduction compared to Period 1) (*P* <.001).

Table 3. Distribution of non-intercepted prescription and transcription dosing errors in the three periods

Error type	Period 1 Traditional $n = 1688$	Period 2 POE w/o DSS* $n = 1489$	Period 3 POE+DSS1 $n = 1331$	*P* value Period 1&2	*P* value Period 2&3
Prescription	876 (51.9) †	749 (50.3)	442 (33.2)	0.4	<.001
Transcription	15 (0.9)	16 (1.1)	15 (1.1)	0.6	0.5
Total	891 (52.8)	765 (51.4)	457 (34.3)	0.4	<.001

* w/o: without

† Numbers in parentheses represent the percentages of crude numbers divided by *n* (*n* is the number of medication days in Table 2).

6.3.2   Non-intercepted medication errors

In Table 3, the significant difference in non-intercepted medication errors between Period 2 and Period 3 was achieved using the medication-day method. To strengthen the accuracy of the obtained result, in Table 4, in addition to medication-day, patient-day, order, and ordered medications respectively were used as the measurement unit to compare the rate and rate ratios of non-intercepted medication dosing errors between Period 2 and Period 3. All methods showed a highly significant reduction of this type of medication errors from Period 2 to Period 3. The rate difference between Period 2 and Period 3 in different measurement methods were close to each other. The highest rate difference was seen when calculated according to orders (18.6%) (rate ratio 0.73; 95% CI 0.67, 0.78; *P*<.001), and the lowest when using the patient-day method (16.7%) (rate ratio 0.75; 95% CI 0.69, 0.83; *P*<.001). Indeed, when dosing DSS was introduced in the existing POE in Period 3, a significant reduction occurred in the rate of non-intercepted medication dosing errors based on all four calculation methods.

Table 4. Rates and rate ratios of non-intercepted medication dosing errors in Period 2 and Period 3 using different measurements

Measurement unit	Period 2 POE without DSS *errors*/*n* (%)	Period 3 POE+DSS1 *errors*/*n* (%)	RR † (95% CI ‡)
Orders	748/1080 (69.3)	445/878 (50.7)	0.73 (0.67, 0.78) ***
Ordered medications	1165/2350 (49.6)	661/2059 (32.1)	0.65 (0.60, 0.70) ***
Medication-days	765/1489 (51.4)	457/1331 (34.3)	0.67 (0.61, 0.73) ***
Patient-days	477/686 (69.5)	304/576 (52.8)	0.75 (0.69, 0.83) ***

*** $P < .001$ † Rate ratio   ‡ Confidence Interval

§ *errors* is the number of errors. *n* is the total number of measurement units in Table 2.

Numbers in parentheses are percentages of errors and are calculated as *errors*/*n**100.

The median non-intercepted error per patient was 5.5 in Period 1 (25th percentile 2 and 75th percentile 11) and 6 in Period 2 (25th percentile 2 and 75th percentile 10), which was not significantly different between the two periods. However, it was significantly reduced to 2 in Period 3 (25th percentile 0 and 75th percentile 7.5) (P=.01).

While only 21% (20/96) of the patients in Period 1 and 18% (15/83) in Period 2 were error-free, the rate was significantly increased to 35% in Period 3 (28/79) (P=.01).

In Period 3, Physicians complied with 53 warnings while ignoring 108 (33% compliance rate).

6.3.3 Severity of overdose errors

The maximum registered dose in Period 1 was 500% of the normal dose (one case) and in Period 2 was 375% (2 cases). Two-fold or greater dosing errors happened in about 13% of the overdosed medications in both Period 1 and 2 (χ^2=.001, P=0.98). These severe errors contributed to 16% of the overdoses in Period 3. However, the difference with Period 2 was still non-significant (χ^2=1.4, P=0.23). In Period 3, the maximum registered dose was 365% of the normal dose (1 case).

6.3.4 Main causes of errors

Based on personal discussions with prescribers to find specific reasons for the errors and ignored warnings, five main causes were identified: medication-diagnosis mismatch, dose adjustment difficulties, ignoring the new age-group, selecting a "neighbouring cell", and miscalculations.

6.3.4.1 Medication-diagnosis mismatch

Sometimes antibiotics were prescribed for an inappropriate diagnosis. For example, a meningitis dose was prescribed for a less severe infectious disease.

6.3.4.2 Dose adjustment difficulties

Residents seemed to have problems in correctly interpreting the GFR and detecting renal impairment. The situation became more complicated when the prescriber had to recalculate the dosage based on every new plasma creatinine result.

6.3.4.3 Ignoring the new age group

Based on the previously mentioned table used for calculating the antibiotic dosages (see Appendix, Table App. 1), the frequency and/or dose should have changed for most of the antibiotics when the age of the hospitalized patient changed from 7 to 8 days. Interviews and personal discussions revealed that prescribers had rarely applied the necessary change.

6.3.4.4 Selecting a "neighbouring cell"

In order to select the appropriate dose and frequency in the mentioned antibiotic guideline table (Appendix, Table App. 1), residents had to find the appropriate age and weight group for the selected medication based on the diagnosis. Sometimes they calculated the dose and frequency based on a wrong "neighbouring cell", probably because of visual mistakes, or by choosing the inappropriate diagnosis, age or weight group.

6.3.4.5 Miscalculations

Miscalculations occurred frequently. During the shifts, three residents were responsible for all paediatric patients in the paediatric intensive care unit, the neonatal ward, the two general paediatric wards, and the emergency ward of the hospital. They were busy, under stress, and could easily make mistakes while calculating dose and frequency.

6.4 EXTENSION OF STUDY II

As we mentioned in the methods section, the major difference between Period 3 and Period 4 was in the design of the DSS. Here we have compared these two periods in terms of non-intercepted medication errors and compliance of the prescribers with the warnings.

6.4.1 Intercepted and non-intercepted medication errors

The rate of dosing errors that were intercepted by the warnings and the rate of non-intercepted errors significantly reduced from Period 3 to Period 4. The rate of errors that were intercepted by care providers did not significantly change from Period 3 to Period 4. However, the latter type had a small share in the total number of errors in both periods. Therefore, the total number of dosing errors was also significantly reduced from Period 3 to Period 4 (rate ratio 0.51; 95% CI 0.46, 0.57; $P<.001$).

Further analysis showed that the number of dosing errors prevented by care providers was 6 in Period 1 and 14 in Period 2. Indeed, the rate of this type of intercepted errors was not significantly different between the traditional prescription system and POE.

Table 5. Intercepted and non-intercepted medication dosing errors and their rate ratios in Periods 3 and 4

Type of medication error	Period 3 POE+DSS1 (*n=2059)*	Period 4 POE+DSS2 (*n=2357)*	RR † (95% CI ‡)
Intercepted by the warnings	48 (2.3)	106 (4.5)	1.93 (1.38, 2.70) ***
Intercepted by care providers ±	6 (0.3)	12 (0.5)	1.74 (0.66, 4.65)
Non-intercepted	661 (22.2)	301 (12.8)	0.40 (0.35, 0.45) ***
Total	715 (24.8)	419 (17.8)	0.51 (0.46, 0.57) ***

*** $P < .001$ † Rate ratio ‡ Confidence Interval

§ Numbers in parentheses are percentages of errors and are calculated as *errors*/*n**100

± Includes errors intercepted by nurses or physicians after the prescription stage and before administration.

Table 6 depicts different measurements employed to calculate the rate and rate ratios of non-intercepted medication errors in Period 3 in contrast to Period 4. All methods showed a highly significant reduction in medication errors from Period 3 to Period 4. However, the highest rate difference was seen when calculated according to patient-days (28.3%) (rate ratio 0.46; 95% CI 0.39, 0.54; $P<.001$), and the lowest when using the ordered medications method (19.3%) (rate ratio 0.40; 95% CI 0.35, 0.45; $P<.001$). Indeed, Period 4 showed a greater reduction effect on medication dosing errors in contrast to Period 3, in all four calculation methods.

Table 6. Rates and rate ratios of non-intercepted medication dosing errors in Period 3 and Period 4 using different measurements

Measurement unit	Period 3 POE+DSS1 *errors*/*n* (%) §	Period 4 POE+DSS2 *errors*/*n* (%)	RR † (95% CI ‡)
Orders	445/878 (50.7)	221/972 (22.7)	0.45 (0.39, 0.51) ***
Ordered medications	661/2059 (32.1)	301/2357 (12.8)	0.40 (0.35, 0.45) ***
Medication-days	457/1331 (34.3)	211/1466 (14.4)	0.42 (0.36, 0.48) ***
Patient-days	304/576 (52.8)	147/601 (24.5)	0.46 (0.39, 0.54) ***

*** $P < .001$ † Rate ratio ‡ Confidence Interval

§ *errors* is the number of errors. *n* is the total number of measurement units in Table 2. Numbers in parentheses are percentages of errors and are calculated as *errors*/*n**100.

In period 3, the median non-intercepted error per patient was 2 (25th percentile 0 and 75th percentile 7.5) and in Period 4 was also 2 (25th percentile 0 and 75th percentile 5). Indeed, the median was equal in the two periods but the inter-quartile range (75th percentile - 25th percentile) was lower in Period 4 (7.5 in Period 3 and 5 in Period 4). The percentage of error-free patients was 35% (28/79) in Period 3 and 38% (26/69) in Period 4.

6.4.2 Severity of overdose errors

The maximum registered dose in Period 4 was 280% of the normal dose (one case). Two-fold or greater dosing errors happened in about 25% (16 / 49) of the overdosed medications in Period 4. However, the difference was not statistically significant with Period 3 (χ^2=2.79, P=0.09). Indeed, two-fold or greater dosing errors were not significantly different before and after the implementation of the physician order entry method.

6.4.3 Prescription and transcription errors

The rate of prescription errors significantly decreased from 31.3% in Period 3 to 10.3% in Period 4 (rate ratio 0.33; 95% CI 0.29, 0.38; P<.001) while transcription errors even showed a significant increase from 0.8% in Period 3 to 2.5% in Period 4 (rate ratio 3.22; 95% CI 1.86, 5.58; P<.001) (Table 7). However, in both Period 3 and 4, the majority of non-intercepted errors occurred in the prescription phase and less in the transcription (98% in Period 3 and 80% in the Period 4).

Table 7. Non-intercepted prescription and transcription dosing errors in the ordered medications of Period 3 and Period 4 and their rate ratios

Error type	Period 3 POE+DSS1 (n=2059)	Period 4 POE+DSS2 (n=2357)	RR † (95% CI ‡)
Prescription errors	645 (31.3) §	242 (10.3)	0.33 (0.29, 0.38) ***
Transcription errors	16 (0.8)	59 (2.5)	3.22 (1.86, 5.58) ***

*** P < .001   † Rate ratio   ‡ Confidence Interval

§ Numbers in parentheses are percentages of errors and are calculated as *errors/n*100.

As we explained in the method section, the difference in DSS design in Periods 3 and 4 could potentially have affected the follow-up orders. In order to test this hypothesis we also performed a subgroup analysis.

6.4.4 Non-intercepted medication dosing errors in first-time and follow-up orders in Periods 3 and 4

After dividing orders into first-time and follow-up orders, a highly significant reduction was seen in the number of erroneous medications in the follow-up orders (rate ratio 0.38; 95% CI 0.33, 0.43; P<.001) (Table 8). There were no significant differences between

errors in the first-time orders in Period 3 and Period 4. In both periods, more than 90% of the orders were prescribed in the follow-up orders.

Table 8. Distribution of non-intercepted medication dosing errors in first-time and follow-up orders in Periods 3 and 4

Order type	Period 3 POE+DSS1	Period 4 POE+DSS2	RR † (95% CI ‡)
First-time orders §	38/176 (21.6) ††	30/177 (16.9)	0.79 (0.51, 1.20)
Follow-up orders ‡‡	623/1883 (33.1)	271/2180 (12.4)	0.38 (0.33, 0.43) ***

*** *P* < .001 † Rate ratio ‡ Confidence Interval

§ A first-time order is the first order in which a medication has been prescribed in.

†† Numbers in parentheses are percentages of errors

‡‡ Follow-up orders are the orders that are prescribed after the first-time order

6.4.5 Medication errors intercepted by the warnings in first-time and follow-up orders in Periods 3 and 4

We also performed the subgroup analysis for the first-time and follow-up orders of those medication errors that were intercepted by the warnings (Table 9). A highly significant increase was seen in the number of intercepted medication errors in the follow-up orders (rate ratio 0.38; 95% CI 0.33, 0.43; *P*<.001), while there were no significant differences between this type of error in the first-time orders of Period 3 and Period 4.

Table 9. Distribution of medication errors that were intercepted by the warnings in first-time and follow-up orders in Periods 3 and 4

Order type	Period 3 POE+DSS1	Period 4 POE+DSS2	RR † (95% CI ‡)
First-time orders §	39/176 (22.2) ††	37/177 (20.9)	0.94 (0.63, 1.04)
Follow-up orders ‡‡	9/1883 (0.5)	69/2180 (3.2)	6.62 (3.32, 13.23) ***

*** *P* < .001 † Rate ratio ‡ Confidence Interval

§ A first-time order is the first order in which a medication has been prescribed.

†† Numbers in parentheses are percentages of errors

‡‡ Follow-up orders are the orders that are prescribed after the first-time order

6.4.6 Compliance with the warnings

Compliance of prescribers with the warnings that appeared in the first-time orders was not significantly different between the two periods (Table 10). However, the rate of complied warnings in the follow-up orders in Period 4 was significantly higher than in Period 3 (12% in Period 3 and 39% in Period 4).

Table 10. Distribution of the warnings in first-time and follow-up orders in Periods 3 and 4

Order type	Period 3 POE+DSS1	Period 4 POE+DSS2	*P* value †
First-time			
Complied	43 (57%)	38 (66%)	0.3
Ignored	32 (43%)	20 (34%)	
Total	75 (100%)	58 (100%)	
Follow-up			
Complied	10 (12%)	98 (39%)	<.001
Ignored	76 (88%)	156 (62%)	
Total	86 (100%)	254 (100%)	

†Chi-square test was employed to detect significant differences between Period 3 and Period 4.

Physician Order Entry vs. Nurse Order Entry

The *qualitative* approach toward POE and NOE were summarized in Study III, and the *quantitative* approach toward POE and NOE with decision support functionalities (Periods 4 and 5) were summarized in Study IV.

6.5 STUDY III

The results of the observations in Period 2, 3, 4, and 5 were used to model POE and NOE workflows on the neonatal ward. Indeed, the important similarity between Period 2, 3, and 4 was the physician order entry. However, in this study and in Study IV, whenever we speak about the DSS functionality of POE, we basically mean the DSS in Period 4 (DSS2), which had the most optimized functionality between the three POE periods and the frequency of appearance and the interface was similar to NOE in Period 5 (NOE+DSS2). Figure 7 demonstrates the two workflows. There are some differences between the two workflows, for example, in POE, the prescriber could enter the order directly into the computer while in NOE, the physician was to write the order in the order sheet and the nurse would then enter that it into the computer. In POE, the DSS assessed prescribed medications at the time of order entry while in NOE it was assessed when the physician countersigned the order. Therefore, in both methods the warnings appeared to the physician. After the countersignature, in both POE and NOE methods, the order was printed and archived in the patient's file and the nurse updated the information of the paper-based Cardex based on the electronic order. This Cardex was used to record the last updated information on the patient's prescriptions. In NOE, the physician was to correct the hand-written prescription after correcting the electronic order. Therefore, in contrast to POE, NOE posed one to two additional transcription activities based on whether POE was performed at the patient's bed or at the nursing station (Asterisks (*) in Figure 7).

Figure 7. Two computerized order entry methods implemented on the neonatal ward of Besat (UML activity diagram).
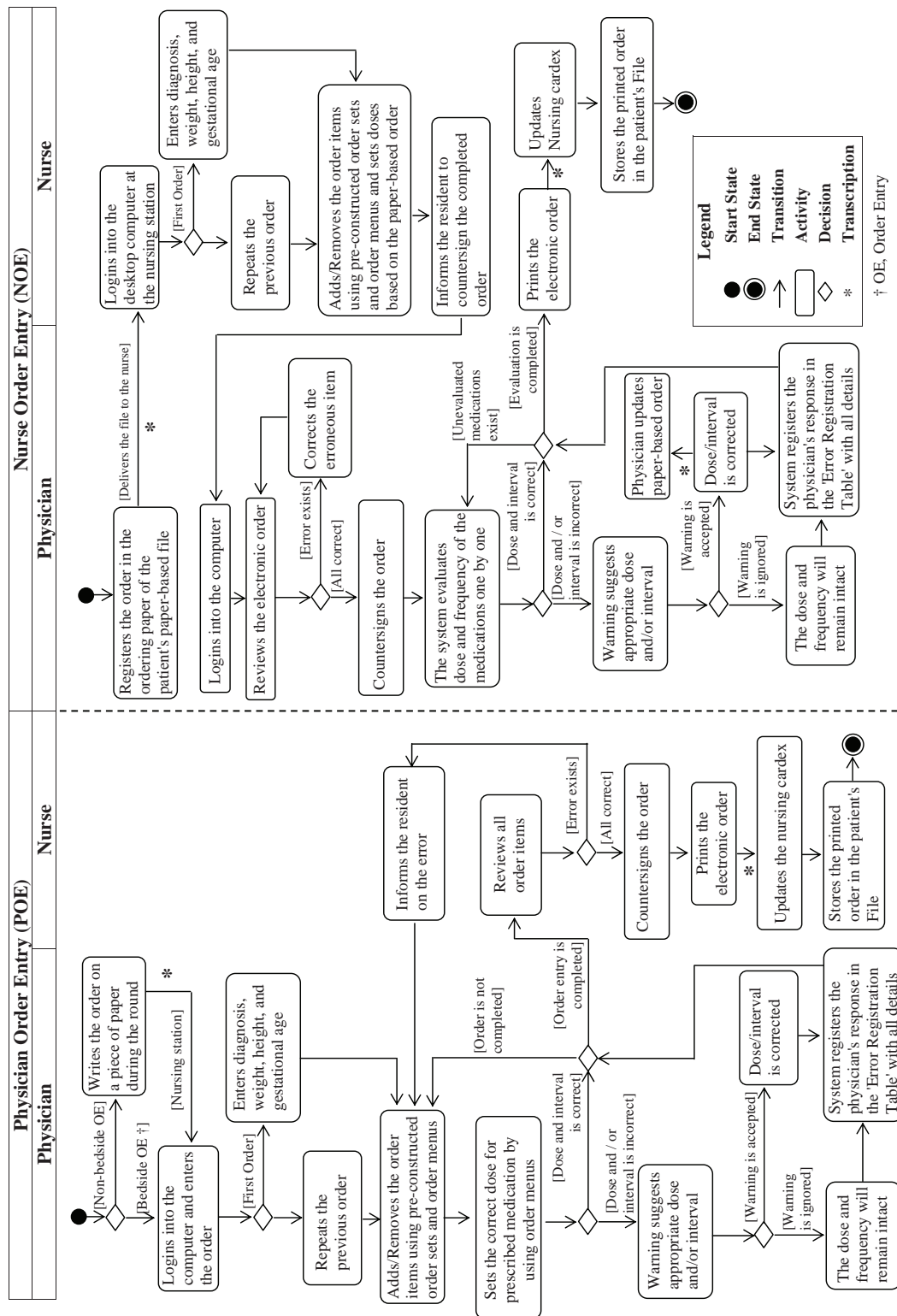
The analysis of interviews yielded five categories: 1-patient safety, 2- education, 3-registration and documentation, 4- inter-professional collaboration and communication, and 5- transferability.

In these categories whenever it was possible, we compared POE and NOE methods.

6.5.1 Patient safety

The interviewees believed that some aspects of the system could improve patient safety while some other aspects might even threaten it.

6.5.1.1 Advantages

6.5.1.1.1 Reduction of medication errors

All interviewees mentioned that the warnings had led to a reduction in medication errors and improvement in patient safety in both POE and NOE methods.

6.5.1.1.2 Remote order entry

Interviewees found the possibility to enter orders from any department at the hospital or even outside the hospital fascinating. However, they had contradictory opinions about enabling this possibility for interns and residents. Those who were against it, believed that residents might underestimate life-threatening situations and put the orders remotely without visiting the patient. However, those who supported this possibility mentioned that residents would only use the remote order entry for minor changes. They believed that the possibility would increase residents' satisfaction with the POE method because they could enter minor changes from another ward while they were busy attending to an emergency case during a hectic shift.

6.5.1.2 Disadvantages

6.5.1.2.1 Computer-centred vs. patient-centred climate

Residents believed that POE could reduce their attention to critical patients, and nurses thought that NOE could postpone the care delivery to them, both of which could cause harm to the patient.

6.5.1.2.2 Facilitating medication errors

Residents mentioned that during the POE period, prescribers were often overconfident in the capabilities of the knowledge base, and paid less attention to their prescribed dosages, expecting the DSS to correct them. However, since the DSS provided alerts for a limited number of drugs, the likelihood of prescription errors could even increase for those medications that were not included in the knowledge base.

Interviewees also mentioned that bedside order entry could put extra pressure on the user and result in several mistakes. One of the residents explained his experience as:

> *"It is so stressful. You have to visit the patient, answer the professor's questions, and at the same time perform the order entry. When you start the order entry, the entire*

group will follow your data entry and you feel pressure on yourself. You can't focus on the data entry and will make mistakes!"

6.5.2 Education

6.5.2.1   Advantages
All but one resident believed that POE could improve their knowledge of dose calculation criteria. Some believed that pre-constructed orders could educate them by providing a list of relevant prescriptions for each diagnosis. All interviewees expressed that the design of the DSS did not make the prescribers dependent on the computer but gave them an opportunity to learn. One of the residents expressed this belief as:

> *"If the system provides the correct dose as a default value, you will not become aware of your faults and you may even become dependent. But when you calculate it by yourself and a warning comes up, then you will search for the reason and will try not to make the same mistake again."*

6.5.2.2   Disadvantages
The interviewed physicians believed that the educational effects of the system were limited and only of interest in the first two to three months of the residency program. This did not, according to them, justify the time and attention to detail needed to perform data entry.

All residents complained that because of POE they could not attend in routine conferences and journal clubs on the ward. In addition, the average time spent on clinical rounds and regular educational activities was reduced following the POE.

The secondary interviews revealed that NOE had solved these problems, although it had deprived them from the educational advantages of the system. Physicians proposed that junior residents might start with POE for educational purposes but should switch to NOE after a few months. Nurses also complained that NOE had no specific educational incentive for them.

6.5.3 Registration and documentation

6.5.3.1   Advantages

6.5.3.1.1 Less redundancy
Interviewees mentioned that POE, especially at the bedside, had eliminated handwritten prescriptions, and accordingly less transcriptions were required. In contrast, NOE had even increased the number of transcriptions and had led to more redundancy. However, they believed that the thorough documentation of initial and revised doses in the NOE period might be good for legal reasons and for future reviews.

6.5.3.1.2 Legible and well-structured orders

Nurses mentioned that POE had helped them to receive legible and well-structured print-outs of the order sheets. However, after the introduction of NOE, the nurses had to work with the handwritten orders again.

6.5.3.1.3 Prevention of unintended continuation of drugs

In the handwritten orders, all the repeated medications were replaced with a 'RPO' (Repeat Previous Order) in the renewed order. After the implementation of POE, repeated medications were also printed on the order sheets each time the order was renewed. Both residents and nurses believed that if they could see a written list of the ongoing prescriptions, it could prevent unintended continuation of the discontinued medications in the follow-up orders, an error that could easily occur in the paper-based orders before the start of POE. In the NOE period, since the focus was shifted again to the paper-based orders, they believed that the risk could increase

6.5.3.2 Disadvantages

6.5.3.2.1 Time-consuming order entry

The time spent on order entry was mentioned as the most important barrier to POE during the shifts. Residents mentioned that their order entry speed might have increased over time but it was still two to three times slower than using pen and paper. The observer occasionally witnessed that, in the POE period, order entry was interrupted several times because the resident was asked to visit patients on the other wards. Most of the nurses believed that POE had not reduced the time they spent with the system because they had to verify and correct the orders that had been entered by physicians.

However, both nurses and physicians mentioned that NOE had reduced the overall time that physicians spent with the system. Since nurses were not interrupted as much as residents, they could focus better on performing order entry. However, the residents were still sometimes postponing verification of the entered orders. Nurses complained that residents did not prioritize medication errors, and management made no serious objection to their prioritizations.

6.5.3.2.2 Huge medical files

The interviewees complained about the bulk of the added order print-outs in the POE period, which had reduced readability and increased costs. During the NOE period, this was even worse, because both handwritten and printed orders were stored in the patient's file.

6.5.4 Inter-professional collaboration and communication

During the POE period, residents were reluctant to disclose their prescription errors to nurses. Interviews during the NOE period revealed that physicians had gradually become less sensitive about error disclosure. I observed that, over time, nurses had accepted the errors as something that could happen to anybody, and not as a sign of the physician's incompetence. They corrected their Cardex without blaming, backbiting or making fun of

the residents. One of the specialists believed that NOE had the potential to change the working environment from a competitive to a collaborative one.

Five nurses believed that tension between nurses and physicians was reduced after the implementation of DSS because nobody could deny his/her mistakes. Two of the nurses mentioned that they had more problems with junior doctors who wanted to show their power and knowledge. Despite the advantages, four residents and one nurse mentioned that POE had reduced verbal communication between physicians and nurses.

6.5.5 Transferability
Six residents, two specialists, and all nurses believed that NOE method had a greater chance of being successfully implemented on other wards because the nurses there were already performing primary data entry. They also believed that it is easier to convince physicians to verify electronic orders rather than asking them to enter all prescription lines. However, they also mentioned that the success of physician order entry depends on several factors, including the scientific and educational gains, ease of order entry, strong leadership, and sufficient time. All interviewees believed that in the present context of Iran, expecting the order entry from nurses or non-physician personnel is more realistic than requesting it from physicians.

6.6 STUDY IV
Based on the results from Study III, both physicians and nurses were more satisfied with NOE than with POE. In this study, we have compared POE+DSS2 and NOE+DSS2 (Period 4 and 5) in terms of medication errors and physician compliance.

6.6.1 Intercepted and non-intercepted medication dosing errors
As Table 11 shows, the total rate of errors was reduced to an equal extent during both Period 4 and 5. However, as the rate of errors intercepted by warnings increased from 4.5% in POE+DSS2 to 8.1% in NOE+DSS2 period (rate ratio 1.80, 95% CI 1.43, 2.27; $P<.001$), the rate of non-intercepted errors dropped from 12.8% to 7.6% respectively (rate ratio 0.60, 95% CI .50, .71; $P<.001$). Most of the intercepted dosing errors were caught by warnings at the prescription stage. Only a few errors were subsequently detected and intercepted by the nurses or physicians before they were administered to patients. The number of errors intercepted by care providers was not significantly different between the two periods.

The total number of warnings was 312 in the POE+DSS2 period and 339 in the NOE+DSS2 period. Complied warnings significantly increased from 44% (136/312) in POE+DSS2 to 68% (232/339) in NOE+DSS2 ($P<.001$).

Table 11. Intercepted and non-intercepted medication dosing errors and their rate ratio in POE and NOE

Type of medication error	Period 4 POE+DSS2 (*n=2357*)	Period 5 NOE+DSS2 (*n=2297*)	RR † (95% CI ‡)
Intercepted by warnings	106 (4.5) §	186 (8.1)	1.80 (1.43, 2.27) ***
Intercepted by care providers ±	12 (0.5)	11 (0.5)	0.94 (0.42, 2.13)
Non-intercepted	301 (12.8)	175 (7.6)	0.60 (0.50, 0.71) ***
Total	419 (17.8)	372 (16.2)	0.91 (0.8, 1.03)

*** *P* < .001   † Rate ratio   ‡ Confidence Interval

§ Numbers in parentheses are percentages of errors and are calculated as *errors*/*n**100

± Includes errors intercepted by nurses or physicians after the prescription stage but before administration.

Table 12 depicts different measurements employed to calculate the rate and rate ratios of non-intercepted medication errors following the implementation of NOE+DSS2 in contrast to the POE+DSS2 period. All measurement methods showed a highly significant reduction in medication errors between the POE+DSS2 and NOE+DSS2 periods. However, the highest rate difference was seen when calculated according to patient-days (9.5%) (rate ratio 0.61; 95% CI 0.49, 0.77; *P*<.001), and the lowest when using the ordered medications method (5.2%) (rate ratio 0.60; 95% CI 0.50, 0.71; *P*<.001). NOE+DSS2 showed a greater reduction effect on medication errors using all four calculation methods.

Table 12. Rates and rate ratios of non-intercepted medication errors in POE and NOE using different measurements

Measurement unit	Period 4 POE+DSS2 *errors*/*n* (%) §	Period 5 NOE+DSS2 *errors*/*n* (%)	RR † (95% CI ‡)
Orders	221/972 (22.7)	142/978 (14.5)	0.64 (0.53, 0.77) ***
Ordered medications	301/2357 (12.8)	175/2297 (7.6)	0.60 (0.50, 0.71) ***
Medication-days	211/1466 (14.4)	129/1492 (8.6)	0.60 (0.49, 0.74) ***
Patient-days	147/601 (24.5)	97/648 (15.0)	0.61 (0.49, 0.77) ***

*** *P* < .001   † Rate ratio   ‡ Confidence Interval

§ *errors* is the number of errors. *n* is the total number of measurement units in Table 2.

Numbers in parentheses are percentages of errors and are calculated as *errors*/*n**100.

The median non-intercepted error per patient reduced from 2 (25th percentile 0 and 75th percentile 5) in POE+DSS2 period to 0 (25th percentile 0 and 75th percentile 2) in NOE+DSS2 period (*P*=.005). While in Period 4 about 38% (26/69) of the patients were error-free, in Period 5, about 53% (47/89) of them did not experience any dosing errors (the rate difference was 15%).

6.6.2 Severity of overdose errors

The maximum registered overdose was 280% of the normal dose in Period 4 and about 215% in the Period 5. Two-fold or greater dosing errors occurred in about 25% (16 / 65) of the overdosed medications in Period 4 while it was significantly reduced to about 7% (5 / 67) in Period 5 (χ^2=7.1, *P*=0.008).

6.6.3 Non-intercepted prescription and transcription errors

The rate of prescription errors significantly decreased from 10.3% in POE+DSS2 to 4.6% in NOE+DSS2 period (rate ratio 0.45; 95% CI 0.36, 0.56; *P*<.001) (Table 13). Transcription errors even showed a negligible increase from 2.5% in POE+DSS2 to 3% in NOE+DSS2. However, in both periods, the majority of non-intercepted errors occurred in the prescription phase and less in the transcription phase (80% in the POE+DSS2 and 60% in the NOE+DSS2).

Table 13. Non-intercepted prescription and transcription errors in the ordered medications of POE and NOE and their rate ratio

Error type	Period 4 POE+DSS2 *(n=2357)*	Period 5 NOE+DSS2 *(n=2297)*	RR † (95% CI ‡)
Prescription errors	242 (10.3) §	106 (4.6)	0.45 (0.36, 0.56) ***
Transcription errors	59 (2.5)	69 (3.0)	1.20 (0.85, 1.69)

*** *P* < .001   † Rate ratio   ‡ Confidence Interval
§ Numbers in parentheses are percentages of errors and are calculated as *errors/n*100.

Indeed, as the rate of non-intercepted prescription dosing errors reduced from more than 50% in the traditional prescription system (Period 1) to less than 5% in the NOE period (Period 5), the rate of non-intercepted transcription dosing errors increased from less than 1% in the traditional prescription system to 3% in the NOE period. This change of pattern increased the share of transcription errors in the total rate of dosing errors from 2% in the traditional prescription system to about 40% in the NOE period.

6.6.4 Distribution of errors in different prescription and transcription stages

While many prescription errors occurred because the prescriber set an erroneous dose at the time of prescription, some others occurred when one or more of the dose decision criteria (age, weight, GFR, etc.) had changed since the last visit but the prescriber failed to change the prescribed order and repeated the previously ordered dose and frequency (Table 14). Both types of prescription errors showed a significant linear decreasing trend from Period 3 to Period 5.

In the NOE+DSS2 period, many transcription errors occurred when the electronic order was updated following a complied warning, but the paper-based order was not updated or was updated with a different dose or frequency. This error did not happen in the POE+DSS1 and POE+DSS2 periods since handwritten orders were eliminated in the POE method. The rate of errors that occurred following incorrect registration of the paper-based medication administration chart, while the electronic medication administration chart was correct, did not significantly differ between the three periods. The rate of errors that occurred because of failing to update the paper-based Cardex was approximately the same during Periods 4 and 5. However, this type of transcription error did not occur during Period 3. The total non-intercepted dosing errors also showed a significant linear decreasing trend from Period 3 to Period 5.

Table 14. Distribution of non-intercepted medication errors in different registration steps of POE and NOE periods

Reasons for dose and frequency errors	P/T ±	Period 3 POE+DSS1 (n=2059)	Period 4 POE+DSS2 (n=2357)	Period 5 NOE+DSS2 (n=2297)	RR † (95% CI ‡) Period 3 and 4	RR (95% CI) Period 4 and 5	Chi² For Linear trend
Ordered dosage was initially incorrect	P	501 (24.3) §	163 (6.9)	70 (3.0)	0.28 (0.24, 0.33) ***	0.44 (0.34, 0.58) ***	493 ***
Order continued with the previous dose despite the change in dosing criteria	P	144 (7.0)	79 (3.4)	36 (1.5)	0.48 (0.37, 0.63) ***	0.47 (0.32, 0.69) ***	85 ***
PB-order inconsistent with E-order	T	0 (0.0)	0 (0.0)	22 (1.0)	N/A	N/A ***	N/A ††
PBMAC inconsistent with EMAC ‡‡	T	16 (0.8)	24 (1.0)	13 (0.6)	1.31 (0.70, 2.46)	0.56 (0.28, 1.09)	0.7 ¶
Prescribed order changed but still the previous dose administered (Cardex was not updated)	T	0 (0.0)	35 (1.5)	34 (1.5)	N/A ***	1.00 (0.62, 1.59)	N/A
Total		661 (32.1)	301 (12.8)	175 (7.6)	0.40 (0.35, 0.45) ***	0.60 (0.50, 0.71) ***	452 ***

*** $P<.001$ ¶ $P=0.4$ † Rate ratio   ‡ Confidence Interval

± P/T: Prescription or Transcription error

§ Numbers in parentheses are percentages of errors and are calculated as *errors/n*100

†† Odds ratio can not be calculated (zero denominator) therefore, *P* value for trend can not be calculated

‡‡ PBMAC, paper-based medication administration chart; EMAC, electronic medication administration chart

7 DISCUSSION

Traditional prescription system vs. Physician Order Entry

The analysis of the traditional prescription system and the needs assessment for the physician order entry are discussed under the subheading 'Study I', and the quantitative comparison of the two systems are discussed under the 'Study II'.

7.1 STUDY I

To successfully implement a CPOE system, a proper analysis of the current situation and a comprehensive assessment of the needs are necessary. The results of the first study give us a better idea of the traditional prescription system and the existing relationship between the care providers and patients in Iranian hospitals. It also provides useful information on how physicians look at computerized technology in healthcare, what their expectations of clinical decision support systems are, and what concerns they have about computerized order entry.

Reviewing the prescription workflow and the interviews demonstrate that the interactions inside Iranian teaching hospitals comply with a hierarchical top-down, physician-centred model, where the attending physicians, who are faculty members, are at the top, with residents and interns below them, and nurses at the bottom of this pyramid. This is probably one of the most important reasons why senior physicians do not appreciate receiving comments on their failures from junior staff and are afraid of any system that leads to disclosure of their mistakes to junior physicians and nurses. The relationship between care providers and patients in many Iranian hospitals [105] is probably different from some European or American hospitals, in which a patient centred collaborative model has been introduced on the wards, and physicians and nurses have become part of a team, on an equal footing and aimed at providing better care for patients through collaboration [77]. However, even in western countries, a hierarchical structure still exists in many hospitals [78].

The hierarchical model may also explain physicians' overconfidence in an environment where there is little or no feedback from the base of pyramid to its peak. We should also be aware of the importance of displaying knowledge to junior staff and to patients by having all dosage information in one's head and writing the order without consulting reference books in front of the patient. In the 1970s and 1980s, this was perceived as a global problem and it was hoped that the introduction of IT solutions in the health sector would lessen sensitivity among patients [106]. In time, however, these concerns were gradually reduced in developed countries and now the physician has little hesitation in consulting a reference book for the appropriate dosages and drug interactions in front of the patient. It seems that Iran is now in a transition period in this respect.

In addition to these context-specific concerns, some issues are common all around the world. The high costs of implementation have been an important concern even in the USA

[46]. However, the problem becomes even more prominent for middle- and low-income countries, where hospitals have more financial concerns. In Iran, hospital autonomy and limited budgets hinder investment in information technology and the renewal of IT equipment [94]. Accordingly, the results of a CPOE project in Iran should go a long way towards convincing policy makers to shift the limited available resources to these types of interventions.

Another worldwide concern with CPOE is the time spent on order entry by physicians. In general, many physicians are not interested in spending more of their time with computers [36, 47, 51]. In many studies, the time spent on data entry has been identified as one of the most important barriers to the implementation and continuation of CPOE systems [47, 107]. In our study, to reduce the time spent on order entry, the interviewees suggested using pre-constructed orders and drop-down menus, which is also mentioned as a solution in other studies [55, 56].

Technical support of the system is a third worldwide concern [29, 36, 108]. The issue is specifically important regarding CPOE because a delay in prescription can cause harm to the patient. Therefore, 24-hour immediate support for both hardware and software is crucial for the continuation of these systems. The problem becomes even more prominent when we consider the US sanction on Iran which prevents the country from receiving any technical support for computer technology [109].

Understanding the factors that could facilitate or hinder implementation helped us to design a computerized order entry system that was more acceptable to physicians in this specific context. The design included both the order entry and decision support user interfaces. During the design, we used some of the interviewees' suggestions, such as using drop-down menus and pre-constructed orders sets. The first study also helped us to prioritize dosing errors and to find a target ward based on this prioritization.

In many systems in developed countries, DSS provides the correct dose as a default value [42, 110]. However, in our system, DSS provided information after the physician had made a mistake in calculating the appropriate dose. The reason for this was that, in the first study, the attending physicians were worried that their residents would become computer-dependant, while these systems were not available in other areas of Iran. The design in our study may have advantages as well as disadvantages. One of the advantages is that it gives the prescriber the opportunity to actively learn from his/her mistake. The other advantage is that, in the NOE+DSS2 period (Period 5), the prescribers could still receive dosing feedback themselves while nurses entered the orders. If the system provided the recommended doses as default values, it would not be possible to give first-hand dosing feedback to physicians when nurses entered the orders into the computer. However, giving the feedback after the physician has made the final decision may increase prescriber resistance and result in more overridden warnings. Nevertheless, when the dose is suggested as a default value, many physicians will choose the easier way and will comply with the recommended dose.

In order to quantitatively compare the traditional prescription system and POE, and to evaluate the effect of DSS design on reduction of medication dosing errors, Study II and the extension of this study were carried out.

7.2   STUDY II (INCLUDING THE EXTENSION)

In the quantitative studies, we have mostly focused on the non-intercepted medication dosing errors as a type of error that is very likely to result in adverse drug events [14, 15, 17]. However, this type of medication error may occur in the prescription or transcription stages. We discuss both types of errors in detail below.

7.2.1 Prescription dosing errors

7.2.1.1   Period 1- Traditional prescription system

The rate of non-intercepted prescription dosing errors in the traditional prescription system (Period 1) of our study was much higher than in similar studies in developed countries. Several reasons can contribute to this. For example, the absence of a clinical pharmacist on clinical rounds can be considered an important reason because his/her presence could prevent many potential errors in previous studies [79, 80]. In addition, based on the prescription workflow presented in the first study, the hospital pharmacist has no control over the dispensed medication. The automatic drug request by the HIS has eliminated their responsibility to actively check every ordered prescription before sending them to the ward.

Another possible reason is the complexity of dose calculation on the neonatal ward. Previous studies in the USA have revealed that between 30 and 40% of the dosages calculated by paediatric residents were erroneous [111]. These calculation errors had no correlation with grade, knowledge, or commitment of the studied residents to recheck their prescribed dosages.

In addition to the abovementioned reasons, the measurement unit used to calculate medication errors, the data collection method, and the review process can significantly affect the results. We will discuss these factors later under a separate heading (methodological considerations) in more details.

Though tenfold and greater dosing errors are common in the neonatal setting [21, 26, 27], in our study, the maximum registered dose was five times the normal dose. However, most of these several-fold errors occur during the preparation and administration processes, which our investigation did not included [21].

7.2.1.2   Period 2- POE without DSS

The introduction of POE without dosing decision support functionalities did not significantly change the rate and severity of prescription errors. The obtained result is in line with two previous studies by Shulman et al. [110] and Potts et al. [112]. In both studies the absence of a dosing DSS in the CPOE system is mentioned as the most important

reason for the non-significant change of dosing errors following the CPOE adoption. In the study by Shulman et al., quick prescription and selection of drug dosages from drop-down menus by prescribers was mentioned as another factor contributing to medication errors. In other studies, the introduction of POE without a dosing DSS had even increased the rate of calculation errors [36, 37].

In Period 2 of our study, resident physicians instead of nurses made the order entry. Since the residents calculated the dosages *prior* to the order entry, giving them the responsibility for order entry could not improve the accuracy of dose calculation. Indeed, it could even contribute to an increase in typing errors since the residents were new to order entry whereas the nurses had been doing it for a long time. However, it seems that training beforehand, access to a demo version of the system, and more importantly double-checking by nurses helped the residents to keep their typing mistakes to a minimum.

7.2.1.3 Period 3- POE with DSS providing warnings without explanation that appeared in first-time orders and change of dosing criteria

The introduction of dosing decision support functionalities to the existing POE system resulted in a significant reduction in prescription dosing errors. Previous articles in the neonatal setting have also obtained the same results [41, 42, 113]. This reduction highlights the value of introducing dosing DSS on neonatal wards that wish to improve their quality of care but cannot increase the number of care providers because of financial or other constraints.

Despite the significant decrease, dosing errors were not eliminated as they were in the study by Cordero et al. [42]. However, in the latter study, a clinical pharmacist attended the clinical rounds. Their system also suggested a default dose for the investigated antibiotic (Gentamicin). In our study, we provided the warnings after the prescription calculation. Therefore, when the prescriber could not understand the reason for the alert, he/she would override the alert. This can probably explain the low physician compliance in POE+DSS1 period (33%). However, the obtained result is similar to a previous study by Killela et al. [70] on paediatric patients. In their study around 33% of the dose and frequency alerts were accepted by the physicians despite the fact that non-interruptive drug information was available in the alert as an explanation for the appeared warning.

The investigation about the causes of errors and the ignored warnings demonstrated that it was difficult for residents to correctly calculate the dosages in complicated situations like renal insufficiency. In such cases, prescribers preferred to ignore the warnings. Therefore, one of the deficiencies of the DSS design in Period 3 was the lack of an explanation of the cause of error in the DSS alert interface. The difficulties of dose calculation in the neonatal setting and the importance of explanations for the displayed warnings have been emphasized in other studies [22-25, 63, 111].

If the prescriber erroneously ignored a warning in the first order, the next alert would come up when dosing decision criteria were changed or a new dosage was set. In this case, an error could be repeated in the follow-up orders if a new or the same prescriber was just repeating the previous dosage without recalculating it. Legally, physicians must check the dosages every time they want to repeat the previous order. However, in reality physicians sometimes just rely on the previous prescriber and do not check the doses themselves. In such situations, an erroneously ignored warning can lead to several repeated non-intercepted errors when the warning does not appear in every erroneous order. Therefore, another improvement in the design could have been the increase of frequency of alerts in the follow-up orders. However, many studies have reported that frequent alerts can lead to user frustration and system abandonment [63, 66].

7.2.1.4 Period 4- POE with DSS providing warnings with explanations that appeared in all erroneous warnings

In order to investigate the role of the new DSS design on the users' compliance and medication dosing errors, we compared Period 3 and Period 4.

In Period 4, the rate of non-intercepted errors dropped by 76% in contrast to Period 1 (before POE), which is in line with the study performed by Myers et al. [113].

As we expected, the main effect of this design was on the follow-up orders, which resulted in a dramatic reduction of non-intercepted prescription errors in this type of order. However, the median non-intercepted error per patient was not different, the reason being that the first-time orders were not significantly affected. However, since errors were caught in the earlier stages in follow-up orders, the inter-quartile range in Period 4 was lower than Period 3.

Prescriber compliance with the system's recommendations showed a similar pattern with non-intercepted prescription errors, where there was no significant difference in first time orders but a significant increase in follow-up orders. This result is in contrast to many studies in developed countries, where a higher frequency of alerts led to an increase in overridden warnings [63, 66]. One explanation for the obtained result is that in addition to the increase in the frequency of alerts, we had simultaneously added explanations to the warnings. We can say that, in Period 4, the combination of frequent alerts and explanations resulted in better compliance among physicians with the system's recommendations in follow-up orders. This improved compliance increased the rate of intercepted errors in the follow-up orders of Period 4, which led to a further reduction in non-intercepted dosing errors in this group. The role of explanations in increasing compliance among prescribers has been studied previously [63, 114].

Care providers intercepted only a small number of dosing errors. This could happen when the physician wanted to sign the printed order or when the nurse wanted to update the nursing Cardex. The rate of this type of intercepted errors was not significantly different between the first four periods. This shows that care providers, despite their expertise, did

not substantially intercept dosing errors on the studied neonatal ward and dosing DSS played an important role in this respect. Many studies support this idea [14, 27, 41, 42, 111]. It also demonstrates the importance of dosing DSS in this context.

7.2.2 Transcription dosing errors

Transcription errors showed an unexpected increasing pattern during the first four periods of this study.

7.2.2.1 Period 1 (Traditional prescription system)

In Period 1, most of the dosing errors occurred in the prescription stage and few in the transcription stage. This is in line with the study performed by Kaushal et al. [15]. The rate of transcription errors in their study was about 0.6% and in Period 1 of our study about 1%. In their study, most of the dosing errors occurred in the prescription stage and less in the transcription stage, which is also similar to our results. However, in their study, 10% of the errors occurred in the transcription stage but in Period 1 of our study it was only about 2%. The reason is the huge number of prescription errors in Period 1 of our study, which reduced the share of transcription errors in the total rate of medication dosing errors.

However, the rate of transcription dosing errors in the study by Fahimi et al. [86] was nine times more than in our study. Unfortunately, they did not discuss the reasons in detail. In their investigated hospital, they had a HIS already in place. They have mentioned that some prescription requests were sent to the pharmacy through the system and some by other means. However, they have not mentioned that how the second group were transferred and how many transcriptions were performed before they reached the pharmacy. In addition, they had a different definition for transcription errors than us and considered any deviation from the prescribed dose to be a transcription error. Since they did not investigate prescription errors, it is possible that a drug was prescribed with an incorrect dose (prescription error) but was corrected during the transcription stage. However, in their calculation method, this intercepted prescription error was considered as a transcription error. In addition, they used the direct observation method for data collection, which seems rigorous but has no apparent advantage over chart review when it comes to detecting transcription errors and is more effective on detecting *administration* errors [115].

7.2.2.2 Period 2 (POE without DSS)

While the introduction of CPOE and elimination of handwritten orders led to a substantial reduction of transcription errors in many studies [110, 116], in our study, following the implementation of POE in Period 2, there was no significant difference in the rate of transcription errors compared to Period 1. A possible explanation is that a reduction in transcription errors requires a reduction in transcription activities and simplification of the prescription workflow. As we observe in Figure 5, the number of transcription activities was not reduced from Period 1 to Period 2 and 3 (asterisks in Figure 5) and the workflow was not simplified. One reason is that Iranian law does not allow the withdrawal of paper-based medical documents including order sheets [101]. Therefore, the introduction of

electronic patient records and CPOE systems will result in different duplications. In our study, the nurses had to write their traditional paper-based charts in addition to the electronic charts. The electronic orders had to be printed and signed by physicians. In case of any change in the order, the print-out and signature had to be repeated. Electronic orders should be printed immediately after the order entry and could not be printed at the time of discharge since the physicians and nurses had to have access to the latest prescribed orders during clinical rounds. This could create confusion in the documentation, when several versions of the same order were printed. It could also result in bulky medical documents, since each order had to be printed on a separate sheet.

7.2.2.3 Period 3- POE with DSS providing warnings without explanation that appeared in first-time orders and change of dosing criteria

The introduction of dosing DSS in Period 3 did not significantly influence the number of transcription errors. Based on Figure 5, the number of transcription activities did not change from Period 2 to Period 3. The results strengthen the idea that a reduction in transcription errors is more dependent on a reduction in transcription activities in the prescription workflow and simplification of the prescription workflow, and not on the introduction of a dosing DSS. In this study, we did not have any reminder or DSS for transcription errors.

7.2.2.4 Period 4- POE with DSS providing warnings with explanations that appeared in all erroneous warnings

Surprisingly the change of DSS functionality in Period 4 resulted in a significant increase in transcription errors. In a superficial evaluation, it seems that this result contradicts our previous explanation that transcription errors are related to the number of transcription activities and complexity of the prescription workflow. However, a deeper evaluation indicates that the design of DSS in POE+DSS2 period (Period 4) resulted in more transcription activities in the follow-up orders than the DSS design in POE+DSS1 period (Period 3). Following a change in a follow-up order, the nursing Cardex should be updated. In Period 4, warnings appeared in every erroneous follow-up order. Table 10 shows that the residents complied with many of these warnings, which resulted in a further reduction in prescription errors. However, this higher compliance required additional transcription activities by nurses to update their Cardex. Table 14 clearly shows that the major difference between the transcription errors in Periods 3 and 4 occurred when the prescriber changed the dose in the electronic order but the nurse forgot to update her Cardex and continued the previous dosage.

Despite the significant reduction in non-intercepted medication errors in Period 3 (POE+DSS1) and especially in Period 4 (POE+DSS2), residents were mostly reluctant to continue with the system after 6 months of full implementation. As we mentioned in the method section, a new implementation strategy was introduced in a close collaboration with the care providers involved. This new strategy involved nurses entering the orders with all details and physicians verifying and countersigning them, receiving the warnings and correcting the dosages at the time of countersignature (NOE+DSS2). We compare the

two order entry methods (POE and NOE with same decision support system) below, both from the user perspective (qualitative) and in terms of effect on medication errors (quantitative).

Physician Order Entry vs. Nurse Order Entry

Qualitative aspects of POE and NOE were investigated by inquiring about care providers' perceptions and by means of observations (Study III). Quantitative aspects were studied by evaluating medication dosing errors and physician compliance with warnings (Study IV).

7.3 STUDY III

In both periods, physicians could directly receive the warnings and change the dosages based on the recommendations. In this respect, all care providers were satisfied with both systems at the same level. A quantitative study should answer which method is more capable of reducing dosing errors and increasing patient safety among neonates. However, from the care providers' perspective, each method had some benefits as well as some drawbacks.

7.3.1 POE

One of the major advantages of POE over NOE was the ability to reduce transcription and transfer activities. Direct order entry by prescribers could eliminate the transcription of paper-based orders to the computer by nurses and professional operators. Bedside order entry could also eliminate paper-based orders. Remote order entry could also reduce orders by telephone and the need to be present on the ward to make minor changes to the orders. In some hospitals in developed countries, these facilities had increased physicians' satisfaction [117]. However, in our study these facilities had some drawbacks. Direct order entry by prescribers was time-consuming and stressful for residents. Bedside order entry had increased prescribers' stress and thus increased the risk of typing errors. Remote order entry could reduce physician-patient contact and adversely affect patient safety. This problems was also mentioned by some Australian care providers in a previous study [118]. However, despite all the disadvantages, legibility of the printed orders in the POE method was an important benefit, which is in line with the findings of previous studies in developed countries [76].

Educational benefits were another incentive encouraging prescribers to continue with order entry. Using DSS may favour POE by reducing the onus on prescribers to memorize all clinical details. However, the limited information provided by the system could not satisfy the residents for a long period. It could also deprive them from their regular education activities like conferences and rounds. This problem seems to be experienced in other contexts in the West and has been addressed in a previous study by Knight et al. [107]. They suggested wide-scope, evidenced-based, relevant, and frequently updated information to encourage physicians to continue with the system.

The major problem with POE was the time needed for order entry by residents. This was even a concern from the first study. Despite all the facilities, such as drop-down menus and

pre-constructed orders, residents could not be convinced to continue with the method after 6 months of order entry. The problem is more significant for those practitioners who have high workloads [47]. Solving this problem via recruiting new physicians is often challenging for the management due to, for example, financial constraints or bureaucratic issues, as was the case in the setting of our study. Therefore, residents had to perform order entry in addition to all their other duties. This was a major reason for their resistance. It seems that without strong leadership support on the national level, it is difficult to implement POE in Iranian hospitals [119]. Even with such support, there is no guarantee that physicians will widely accept POE. For example, in the USA, only a minority of hospitals have successfully implemented CPOE despite national support [43].

7.3.2 NOE

The major benefit of NOE was the significantly smaller amount of time residents needed to spend on order entry and their consequent enthusiasm for continuing with the system. They could focus on their regular educational activities while at the same time having the possibility to interact with the system and reduce their dosing errors.

When physicians are reluctant to enter orders, NOE becomes an alternative method. Nurses often have more positive views than physicians towards technology, and may act as champions to reduce physician resistance [72, 73, 120]. When nurses are involved in decision-making or order entry, they feel respected and will try to help physicians instead of blaming them and highlighting their lack of competence at working with computers. American hospitals that have initiated a collaborative climate between physicians and nurses have been more successful in using CPOE [77, 78].

Despite the positive aspects, NOE leads to significant redundancy and may increase the risk of transcription errors. When employing NOE, prescribers may also verify the order and correct an erroneous dose *after* the first or even the second administered dose, potentially causing harm to the patient. However, since the implemented POE also led to considerable redundancy, the results should be compared using quantitative methods.

In general, using non-physician medical professionals has several disadvantages. In spite of these disadvantages, their positive attitude favours NOE in hospitals that are facing strong resistance from physicians to performing order entry. As our interviewees stated, NOE seems to be more sustainable in Iranian hospitals than the POE method. However, user satisfaction is only one of the important dimensions.

7.4 STUDY IV

The primary aim of the quantitative evaluation was to assess whether NOE with dosing DSS was as effective as POE with the same dosing DSS in reducing non-intercepted medication dosing errors and increasing physician compliance with the warnings or not. Therefore, we compared Period 4 (POE+DSS2) with Period 5 (NOE+DSS2) because the DSS functionality was the same in the two periods. For ease of use, we will refer to these two periods as POE and NOE.

Surprisingly the results showed that NOE was even more effective than POE in reducing non-intercepted medication dosing errors. Interception of prescription errors played a substantial role in this reduction.

7.4.1 Prescription dosing errors

Prescribers complied with a higher rate of warnings in NOE than in POE. This higher compliance intercepted a greater number of medication dosing errors in the NOE period. The result was a significant reduction in the rate of non-intercepted *prescription* dosing errors. Other studies have also reported that decision support systems can reduce *prescription* errors if prescribers comply with the system's recommendations [31, 116].

In both periods, prescription errors contributed to the majority of non-intercepted errors. The significant reduction in prescription errors and the constant rate of transcription errors from POE to NOE led to a significant reduction in the overall rate of non-intercepted medication dosing errors.

We must mention that in Period 5 (NOE+DSS2), similar to the former four periods, only a few dosing errors were caught by care providers. Indeed the role of care providers in intercepting dosing errors was negligible in all five periods. This is in line with our previous findings that the reduction in errors in this context is more attributable to warnings not to care providers. As mentioned before, in most Iranian hospitals, pharmacists and clinical pharmacologists do not participate in clinical rounds and the pharmacy does not prepare ready-to-administer doses. Ward nurses are responsible for preparing them. In Iranian hospitals, nurses shoulder many responsibilities, probably as a result of the abovementioned hierarchical system that exists among healthcare personnel in Iranian hospitals. Hospital managers mostly burden nurses with tasks that physicians or pharmacists object to, because nurses are at the bottom of the hierarchy. Medical data entry is one such task. In Iranian hospitals, there is little legal or administrative incentive for physicians to record medical data electronically [121]. Therefore, strategies like NOE requiring less data entry by physicians may increase their compliance and result in a more sustainable implementation of a computerized provider order entry system.

In addition, several other reasons can be discussed as possible explanations for the increase in compliance in the NOE method. One explanation is that in the strict physician order entry method, prescribers mostly focused on data entry rather than on the warnings. Sometimes they were ignoring warnings unintentionally or because of the frustration and stress they suffered following a prolonged data entry session. In previous studies, prolonged data entry and user frustrations have been important causes of the failure of order entry among physicians [47]. However, in the nurse order entry method, physicians could just focus on their prescription errors and warnings. This could increase their attention to the displayed warnings and result in better compliance.

It is also possible that the new collaborative environment in the NOE period created more positive views on the advantages of using dosing alerts, which resulted in higher compliance among physicians with the system recommendations. Nowadays, hospitals in western countries are trying to eliminate the existing hierarchical system and encouraging a collaborative environment between different group of care providers to improve the quality of care [77, 78]. It seems that, in countries like Iran, where a hierarchical and physician-centred atmosphere exists in clinical settings, it is important for successful implementation of CPOE systems that managers and policy makers change the environment to a more collaborative and patient-centred one.

In previous studies, computerized *physician* order entry was introduced as an effective order entry method [14, 17, 122]. In the first study, our interviewees, who had little or no previous experience of order entry, believed that physicians should enter the orders themselves. However, when they started to perform the order entry, the method did not seem to be practically viable in that context. However, the NOE method was designed in close collaboration with those care providers who were practically involved in order entry and reflected their experiences. This reveals the importance of a user-centred design and obtaining feedback from actual users. As other studies have emphasized, *user* acceptance and collaboration in the development process are key factors in the successful implementation of computerized order entry systems [54].

It is also possible that double-checking of the prescribed orders by responsible physicians in the NOE period reduced the errors, independent of the DSS warnings. In the NOE model, prescribers had to check transcribed orders before signing them. This enabled physicians to double-check what they had already prescribed, before they received any warning. However, previous studies have shown that dosing calculation errors are not correlated with the commitment of the prescriber to double-checking the prescribed order [111].

7.4.2 Transcription dosing errors
In our study, the increase of transcription errors from the POE to the NOE period was non-significant. Considering the explanation we had, the workflow of NOE in Period 5 seems to be more complex than the workflow of POE in Period 4. Therefore, the rate of transcription errors in the NOE period should be higher than in the POE period. However, the implemented POE in our study required redundant recordings and documentations because prescribers were legally obliged to print and save the electronic order in paper format and change the printed sheet if the order was changed. Therefore, POE has no apparent advantage to NOE in such a context in terms of transcription errors. In the USA and some European countries, where computerized order-entry has reduced paperwork, POE has become a powerful tool to prevent transcription errors [39, 110, 116, 123].

In our study despite the non-significant difference in the overall rate of transcription errors, there are certain types of these errors that could be eliminated by POE. When a physician directly inputs orders into the computer and prints them out, there will be no room for

discrepancy between the electronic and paper-based order. In contrast, when using NOE, the physician has to write a paper-based order and sign it for the nurses so that they can enter them into the computer. Since this paper is a legal document, the resident must also update the paper-based order in the event of him/her accepting a warning, and negligence may result in non-intercepted errors as happened in our study. Transcription errors in other stages were not significantly different between POE (Period 4) and NOE (Period 5), because after the prescription stage, the transcription and administration workflows are the same in both periods.

As highlighted by care providers in our study, paperwork in Iranian hospitals has dominated clinical care and the computerized systems have created lots of redundant registrations and documentations, which is mostly due to the legal requirements. However, it seems that in order to reduce transcription errors in Iran, prescription workflow should be simplified and paper work should be limited, which requires some legal amendments. This can save time, reduce costs, increase care providers' satisfaction, and result in higher acceptance among them. However, adapting Iranian law to the demands of the digitalized world is a challenge. Future studies should test our explanation as a hypothesis.

7.5 METHODOLOGICAL CONSIDERATIONS

In this investigation, six measurement units were employed to calculate the rate of non-intercepted dosing errors. Four of the measurement units account for the duration of treatment. Therefore, in these four methods, the length of hospital stay and the duration of treatment cannot adversely affect the rate of errors. The four measurements consist of patient-day, medication-day, order, and ordered-medication. The two other measurement units are median non-intercepted error per patient and error-free patients.

Different studies have used different measurement units, which may affect the results [32, 124]. In our study, for example, measuring errors based on patient-days may show the rate of non-intercepted medication dosing errors to be twice the ordered-medication method for the same population. Therefore, the absolute rate of errors does not necessarily indicate the extent of problem with medication errors. The important criterion is the difference in dosing errors between the two periods with the same measurement method.

Each of the measurement units has advantages as well as disadvantages.
Each *patient-day* represents one day of medical treatment. It can therefore correctly show the number of days that the patient was error-free. However, this method cannot account for the number of erroneous medications on the same day. For example, a patient who is prescribed one antibiotic with an incorrect dose will have one patient-day dosing error and a patient that is prescribed three antibiotics simultaneously, but only one of them has an incorrect dose, will also have one patient-day dosing error on the same day.

Medication-day can account for both the duration and the number of simultaneous medications. In this method, in the above example, the first case will have one medication-day dosing error while the second case will have three medication-day dosing errors. This

method gives a good estimate of the extent of errors when the average number of orders per day varies between the periods. However, this method is not a direct representative of the impact of errors on the patient because the target of the measurement unit is medication and not the patient. In addition, several erroneous orders on the same day will be treated as one erroneous medication-day.

Reporting the errors per *order* can solve the latter problem. However, when the average number of orders per day varies between the compared periods, the results can have significant bias. In addition, since the measurement unit is the order and not the patient, it has the same problem as the medication-day method.

Calculating dosing errors based on *ordered-medications* can account for the duration and the number of concurrent medications on the same day and even the same order. However, since the measurement unit is medication and not the patient, it has the same problem as the medication-day and order methods.

Median non-intercepted error per patient is another measurement method that we used in this work. As we have used the median and not the mean, skewness in the distribution of population cannot adversely affect the measurement. Since the unit is the patient, it can truly represent the impact of error on the patient. However, there are two problems with this measurement unit. The first problem occurs when more than 50% of the patients in both periods are error-free (for example in one period this figure is 61% and in the other period is 91%). In this situation, this measurement unit cannot show any difference between the two periods (both will be zero). In order to solve this problem, the rate of error-free patients should always be reported along with the median non-intercepted error per patient.

The other problem is when the median is equal but one of the compared methods can reduce variation in the number of non-intercepted error per patient, more than the other method. In this situation, the inter-quartile range should be reported. The example is the difference between Period 3 (POE+DSS1) and Period 4 (POE+DSS2) in our study. Despite the significant effect of DSS design on the follow-up orders of Period 4, which reduced the overall number of errors in this type of order, since the first-time orders were not affected by the new design, the median non-intercepted error per patient in both cases was equal. However, the inter-quartile range was lower in Period 4 indicating the reduction of variation in the number of non-intercepted error per patient following the implementation of DSS2.

The sixth measurement unit that we used was the number and rate of *error-free patients*. As we discussed, this measurement unit can complement the median non-intercepted error per patient. However, it only shows the rate of patients who have not experienced any error and does not say anything about patients who have suffered from errors.

In addition to the error calculation method, the data collection method and review process can affect the error rate [32]. Studies like the one by Simpson et al. [80], which are based on the critical or spontaneous reports, can detect only a fraction of medication errors [115]. Therefore, their reported rate of error is very low.

Chart reviews, especially when they are coupled with voluntary reports like the study conducted by Kaushal et al. [15], can detect a higher proportion of prescription errors. The error rate in this study was 5.5 per 100 orders. Direct observation is appropriate for detecting administration errors [115], though it is prone to biases like the Hawthorne effect [125]. Further on, studies like Cordero et al. [42] that have reviewed handwritten and electronic medical records, have detected a higher rate of medication error. They have reported the error rate to be as high as 13 per 100 orders. In our investigation, we reviewed both the handwritten and electronic medical records of orders and nursing charts in all periods. As a comparison, the rate of non-intercepted dosing errors in our study was reduced from 69 per 100 orders in Period 2 to 51 per 100 orders in Period 3 and to 23 per 100 orders in Period 4, and finally to 15 per 100 orders in Period 5 (about 79% reduction).

In summary, methods for calculating and reporting medication errors in the neonatal setting are diverse and the results are difficult to compare.

7.6 LIMITATIONS

7.6.1 Qualitative studies

As expected in a qualitative study, it is not possible to *statistically* generalize the findings [95]. However, we have used several techniques to increase the *trustworthiness* of the obtained results [95]. We tried to increase the transferability [95] of the findings by giving a detailed description of the context, and its similarities and differences with other studies. In addition, triangulation of methods, data, and investigators further strengthens the credibility of our findings [126]. In the first study, we used maximum variation sampling technique to obtain as many different views as possible [95]. However, in the third study, to the best of our knowledge, POE was only implemented on the neonatal ward of Besat Hospital. Therefore, we could only interview all care providers on this ward who had experienced both POE and NOE.

7.6.2 Quantitative studies

Different limitations could be discussed in this thesis work. The study was performed in a neonatal setting, and therefore, the results may not be generalizable to adults.

We selected the patient group over time because we could not divide patients into two groups and set a control group in the neonatal ward. Implementation of medical order entry systems will impose a systemic change on the prescription flow on the ward. Moreover, we could not form a control group from the other wards of the hospital since the guidelines and dose calculation criteria were very different between the neonatal and other wards.

Since the residents were still in training, their knowledge would be expected to increase over time. This can be a competing explanation of the findings, though previous studies have reported that dose calculation skill among paediatric residents is not related to their experience, grade, level of training, or commitment to recheck their calculated doses [27, 111].

Residents might have gained more trust in the decision support's functionality over time. That could lead to higher compliance among prescribers over time and can well explain the obtained results. This increase of trust could happen because of the positive experiences of prescribers or other care providers with the system over time, and sharing those experiences with the others. It could also happen because general attention to patient safety gradually increased among caregivers. However, the influence of these environmental factors is expected following positive experiences with decision support systems.

Additionally, the care providers knew that they were being studied. Therefore, they might have improved their performance in the study period, which could lead to the Hawthorne effect [125]. This can affect the results. For example in Study IV, the residents knew that one of the purposes of the project was to find the appropriate implementation method to extend to other wards of the hospital. It is possible that residents performed better in the NOE period to convince the hospital and university authorities to continue this method and not return to POE. An attempt by nurses to do the opposite could also explain the high rate of transcription errors in the NOE period. However, we could not find any evidence supporting such attempts. In addition, residents knew from the first study period that their errors would be investigated but the reduction of dosing errors did not happen in Period 2 but occurred after the introduction of DSS in Period 3.

8 CONCLUSIONS

Care providers' relationship in the traditional prescription system was hierarchical and physician-centred. Iranian physicians had context-specific as well as general concerns that should be taken into consideration when designing the system. Despite the concerns, physicians believed that they would perform the order entry if the system could reduce their dosing errors and they could receive the warnings themselves. This shows that one of their motivations for performing the order entry was to keep their medical errors undisclosed.

The implementation of strict physician order entry without DSS functionalities did not reduce non-intercepted dosing errors on the neonatal ward. However, after adding dosing decision support functionalities to the existing POE, a significant reduction in the rate of dosing errors occurred. This demonstrates the importance of a dosing DSS in the neonatal context for reducing non-intercepted dosing errors and increasing patient safety.

By adding explanations to the existing warnings and increasing the frequency of alerts, a further reduction happened in the rate of non-intercept dosing errors, which demonstrates the importance of DSS design in the interception of these errors.

In Iranian healthcare, there are little or no legal or financial incentives to motivate physicians to perform order entry. In this context, despite the significant effect of the POE with DSS functionalities in intercepting dosing medication errors, strict physician order entry does not seem to be a viable prospect because physicians are busy and resistant to order entry. However, a new computerized order entry model based on nurse order entry and physician verification and countersignature can increase care provider satisfaction and result in successful implementation of the system in this context. The new order entry method is as effective as or even more effective than the strict physician order entry method in intercepting dosing errors and reducing the rate and severity of non-intercepted medication dosing errors among neonates.

In sum, in order to successfully adopt a CPOE system, the selection of order entry method and the design of DSS should be performed in close collaboration with the care providers and with consideration for the limitations in the local context.

9 SUGGESTIONS FOR POLICY MAKERS, AUTHORITIES, CARE PROVIDERS, AND REASERCHERS IN IRAN

9.1 NATIONAL OR MINISTRY LEVEL
- Disseminate the results of this research at ministry level to encourage policy makers to invest in technologies that can improve patient safety in hospitals
- Recognize electronic medical documents (digital recordings) as legal documents
- Provide financial incentives for e-prescription by insurers
- Incorporate e-prescription and e-documentation into regular medical education
- Encourage implementation of order-entry based HIS at hospitals
- Prioritize integration of clinical information systems into hospital information systems in the IT strategic plan of the Ministry of Health and Medical Education
- Approve a specific budget for the implementation of CPOE and clinical decision support systems in all Iranian hospitals.

9.2 UNIVERSITY OR HOSPITAL LEVEL
- Set up a patient safety committee at hospitals. Members should preferably include managers, doctors, nurses, and pharmacologists
- Change the Sayan-HIS workflow for drug request and delivery from 'per ward request' to 'per individual request'
- Request the hospital pharmacist to actively control each prescription request before delivering it
- Involve clinical pharmacologists in the clinical rounds
- Implement the system on other neonatal wards and comparison of the results

9.3 WARD LEVEL
- Increase the clinical authority of nurses to get them more involved in clinical decision-making
- Create a more collaborative environment between physicians and nurses by introducing common tasks for which both groups have the same expertise Information technology is one example of such a task
- Investigate the long-term health outcomes of CPOE, e.g. mortality rate
- Encourage physicians to use dosing decision support systems by sharing the results of this research with them

9.4 SUGGESTIONS FOR FUTURE RESEARCH
- Implement the system on other neonatal wards and comparison of the results
- Investigate the long-term health outcomes of CPOE, e.g. mortality rate
- Investigate the cost effectiveness of POE and NOE
- Investigate the effect of a clinical pharmacologist who actively participates on the clinical rounds on reduction of medication errors and adverse drug events
- Design and implement a new order entry model with less transcription activities and a simplified workflow, and test the explanations we had for reduction in transcription errors as a hypothesis. Our explanation was "reduction in transcription errors requires a reduction in transcription activities and simplification of the prescription workflow."

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66

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12 APPENDIX

Table App 1. Suggested Dosage Schedules for Antibiotics Used in Newborns (Adopted from Nelson Textbook of Pediatrics, 18th edition, 2007).

		DOSAGE (MG/KG) AND INTERVAL OF ADMINISTRATION				
		Weight < 1200 g*	Weight 1200 - 2000 g		Weight > 2000 g	
ANTIBIOTIC	ROUTE	Age 0-4 wk	Age 0-7 Days	Age > 7 Days	Age 0-7 Days	Age > 7 Days
Amikacin[†] (SDD)	IV, IM	7.5 q12h	7.5 q12h	7.5 q8h	10 q12h	10 q8h
Amikacin[†] (ODD)	IV, IM	18 q48h	16 q36h	15 q24h	15 q24h	15 q24h
Ampicillin	IV, IM					
Meningitis		50 q12h	50 q12h	50 q8h	50 q8h	50 q6h
Other infections		25 q12h	25 q12h	25 q8h	25 q8h	25 q6h
Aztreonam	IV, IM	30 q12h	30 q12h	30 q8h	30 q8h	30 q6h
Cefazolin	IV, IM	20 q12h	20 q12h	20 q12h	20 q12h	20 q8h
Cefepime	IV, IM	50 q12h	50 q12h	50 q8h	50 q12h	50 q8h
Cefotaxime	IV, IM	50 q12h	50 q12h	50 q8h	50 q12h	50 q8h
Ceftazidime	IV, IM	50 q12h	50 q12h	50 q8h	50 q8h	50 q8h
Ceftriaxone	IV, IM	50 q24h	50 q24h	50 q24h	50 q24h	75 q24h
Cephalothin	IV	20 q12h	20 q12h	20 q8h	20 q8h	20 q6h
Chloramphenicol[†]	IV, PO	25 q24h	25 q24h	25 q24h	25 q24h	25 q12h
Ciprofloxacin[§]	IV			10-20 q24h		20-30 q12h
Clindamycin	IV, IM, PO	5 q12h	5 q12h	5 q8h	5 q8h	5 q6h
Erythromycin	PO	10 q12h	10 q12h	10 q8h	10 q12h	10 q8h
Gentamicin[†] (SDD)	IV, IM	2.5 q18h	2.5 q12h	2.5 q8h	2.5 q12h	2.5 q8h
Gentamicin[†] (ODD)	IV, IM	5 q48h	4 q36h	4 q24h	4 q24h	4 q24h
Imipenem	IV, IM		20 q12h	20 q12h	20 q12h	20 q8h
Linezolid	IV		10 q12h	10 q8h	10 q12h	10 q8h
Methicillin	IV, IM					
Meningitis		50 q12h	50 q12h	50 q8h	50 q8h	50 q6h
Other infections		25 q12h	25 q12h	25 q8h	25 q8h	25 q6h
Metronidazole[‡]	IV, PO	7.5 q48h	7.5 q24h	7.5 q12h	7.5 q12h	15 q12h
Mezlocillin	IV, IM	75 q12h	75 q12h	75 q8h	75 q12h	75 q8h
Meropenem**	IV, IM		20 q12h	20 q12h	20 q12h	20 q8h
Nafcillin	IV	25 q12h	25 q12h	25 q8h	25 q8h	37.5 q6h
Netilmicin[†] (SDD)	IV, IM	2.5 q18h	2.5 q12h	2.5 q8h	2.5 q12h	2.5 q8h
Netilmicin (ODD)				Same as for gentamicin		
Oxacillin	IV, IM	25 q12h	25 q12h	25 q8h	25 q8h	37.5 q6h
Penicillin G (units)	IV					
Meningitis		50,000 q12h	50,000 q12h	50,000 q8h	50,000 q8h	50,000 q6h
Other infections		25,000 q12h	25,000 q12h	25,000 q8h	25,000 q8h	25,000 q6h
Penicillin benzathine (units)	IM		50,000 (one dose)	50,000 (one dose)	50,000 (one dose)	50,000 (one dose)
Penicillin procaine (units)	IM		50,000 q24h	50,000 q24h	50,000 q24h	50,000 q24h
Piperacillin	IV, IM		50-75 q12h	50-75 q8h	50-75 q8h	50-75 q6h
Peperacillin/tazobactam				Same as for piperacillin		
Rifampin	PO, IV		10 q24h	10 q24h	10 q24h	10 q24h
Ticarcillin	IV, IM	75 q12h	75 q12h	75 q8h	75 q8h	75 q6h
Ticarcillin-clavulanate				Same as for ticarcillin		
Tobramycin[†] (SDD)	IV, IM	2.5 q18h	2 q12h	2 q8h	2 q12h	2 q8h
Tobramycin (ODD)				Same as for gentamicin		
Vancomycin	IV	15 q24h	10 q12h	10 q12h	10 q8h	10 q8h

* Data from Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr infact Dis J* 1990;9:111.

[†] Adjustments of further dosing intervals should be based on aminoglycoside half-lives calculated after serum peak and trough concentrations measurements.

[§] Doses suggested based on anecdotal clinical experience.

[‡] A loading intravenous dose of 15 mg/kg followed 24 hours later (term infants) and 48 hours later (preterm infants) by 7.5mg/kg every 12 hours has been suggested by other investigators.

** Dosages of meropenem suggested are the same as those of imipenem.

IM, intramuscular; IV, intravenous; ODD, once- daily dosing; PO, oral; SDD, standard daily dosing.

Adapted from Sáez-Liorens X, McCraken GH, Jr: Clinical Pharmacology of Antibacterial Agents, In Remington JS, Klein JO, Wilson CB, Baker CJ (editors) *Infectious Diseases of the Fetus and Newborn Infant*, 6th edition. Philadelphia, Elsevier, 2005.
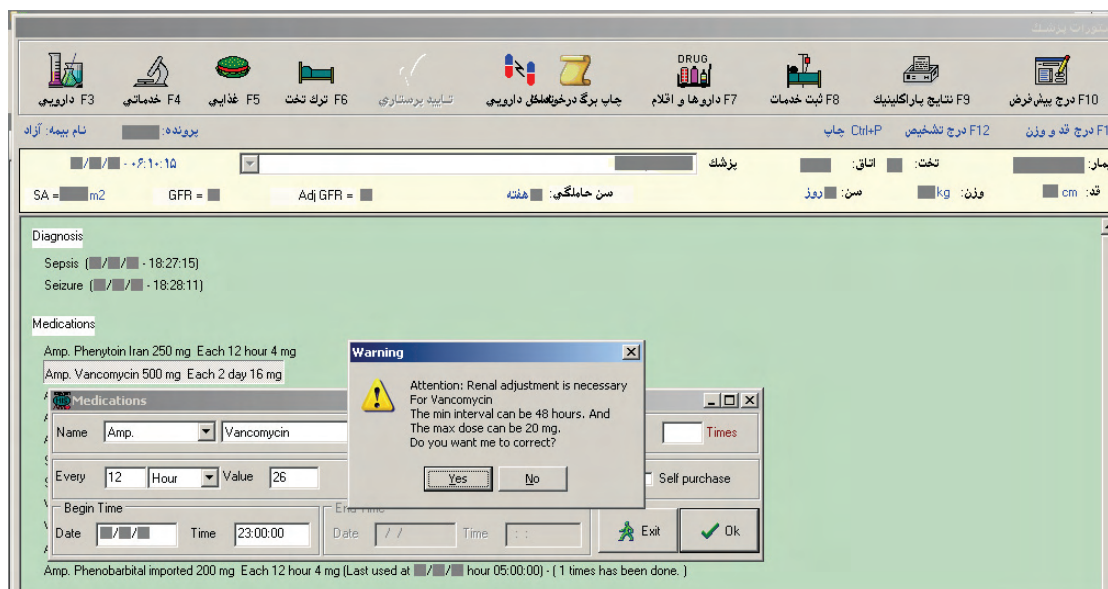
Figure App 1. The medication prescription menu and the dosing warning interface in the order interface of Sayan-HIS in Period 4 (POE+DSS2). In Period 3 (POE+DSS1), the explanation in the fist line of the warning did not appear. Dates, names, and other identifiers are removed.

Figure App 2. The user interface of a pre-constructed order set in Sayan-HIS in NOE+DSS2 period. Dates, names, and other identifiers are removed.