NOTE TO USERS

uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

uOttawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Michael David Saginur
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Epidemiology)
GRADE / DEGREE

Department of Epidemiology and Community Medicine
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Technologies to improve medication safety in hospitals : a study of their effectiveness and use in Canada

TITRE DE LA THÈSE / TITLE OF THESIS

Ian Graham
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

George Wells
CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

Ineke Neutel

Carl van Walraven

Gary W. Slater
LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES /
DEAN OF THE FACULTY OF GRADUATE AND POSTDOCORAL STUDIES

Technologies to improve medication safety in hospitals: a study of their effectiveness and use in Canada.

by

Michael David Saginur, BSc

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the MSc degree in Epidemiology

University of Ottawa

Date: September 9, 2005

Your file Votre référence
ISBN: 0-494-11400-2
Our file Notre référence
ISBN: 0-494-11400-2

Abstract

Introduction
Adverse drug events (ADEs) caused by medication errors occur regularly in hospitals.

Research questions

How effective are in-hospital drug-distribution technologies at improving medication safety? How prevalent are such technologies in Canada's acute-care hospitals?

Methods

A systematic review synthesized publications from 1985 to 2002 about the effectiveness of inpatient drug-distribution technologies. A cross-sectional survey of pharmacy directors at Canada's 100 largest acute-care hospitals described technology use, plans for change, and pharmacy-directors' attitudes to technology use and medication error.

Results

The systematic review categorized 154 technology comparisons into 23 technology groupings. The evidence consistently favoured the new technologies but its strength was limited. The survey response rate was 78%. Clinical pharmacy services, computerized decision support for pharmacists, and unit-dose system were common; bar-coding and computerized physician order entry were not.

Conclusion
This thesis offers a unique compilation of evidence to guide decision-makers in their uptake of technologies intended to improve medication safety.

Acknowledgements

First of all, I thank my family for all its support.

My thesis committee was terrific: it was a privilege to have their guidance. Dr. Graham, Dr. Wells, and Dr. Forster contributed to all aspects of the thesis. They taught me a lot.

Ian Graham was great. He oversaw the design and implementation of the survey, provided input throughout, and kept me on track. Alan Forster's content expertise was crucial, and he was excellent about providing input. George Wells provided crucial content expertise; earlier, he suggested doing the survey, and prior to the thesis project had significantly enhanced my education in epidemiology.

I thank Michel Boucher, Andrea Fisher, Janet Joyce, and the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) as an organization. Michel Boucher and Andrea Fisher supervised me at CCOHTA. Andrea Fisher introduced me to CCOHTA's systematic review. Michel Boucher provided expertise in French and in pharmacy, provided input into the survey questionnaire, and answered some pharmacy directors' phone calls. Janet Joyce helped me search for published surveys similar to the thesis survey, and helped me understand CCOHTA's literature search. I thank CCOHTA as an organization for its literature review, financial and material support.

List of Acronyms and Short Forms Used in the Thesis

Ab	Antibiotic
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AE	Adverse Event
AHRQ	Agency for Health Research and Quality
APTT	Activated Partial Thromboplastin Time
CABG	Coronary Artery Bypass Graft
CDSS	Clinical/ Computerized Decision Support System
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CCT	Controlled Clinical Trial
CHA	Canadian Healthcare Association
CHF	Congestive Heart Failure
CHO	Carbohydrate
CI	Confidence Interval
CPOE	Computerized Physician Order Entry
CS	Controlled Substance
CQI	Continuous Quality Improvement
D/C	Discharge
DVT	Deep Vein Thrombosis
e MAR	Electronic Medication administration Record
FDA	Food and Drug Administration
FMA	Failure Mode Analysis
FTE	Full Time Equivalent
GI	Gastro-Intestinal
GP	General Practitioner
HTA	Health Technology Assessment
Hr	Hour
HMPS	Harvard Medical Practice Study
ICU	Intensive Care Unit
IHI	Institute for Healthcare Improvement
INR	International Normalized Ratio
IQR	Inter Quartile Range
ITT	Intention To Treat
IV	Intravenous
MAR	Medication administration Record
NA	Not available
NICU	Neonatal Intensive Care Unit
NSAID	Non Steroidal Anti Inflammatory Drug
OR	Odds Ratio
PE	Pulmonary Embolism
Pt	Patient
POE	Physician Order Entry
PR, PTR	Prothrombin Ratio
QI	Quality Improvement
R	Range (in tables)
RCA	Root Cause Analysis
RCT	Randomized Controlled Trial
RD	Risk Difference

RR	Relative Risk
Rx	Prescription
RN	Registered Nurse
SAM	Self-administered Medication
SD	Standard Deviation
TDM	Total Drug Monitoring
TPN	Total Parenteral Nutrition
VA	Veterans Affairs
VAS	Visual Analogue Scale
Vs	Versus
Xs	Excess
1^0, 2^0	Primary, secondary

Table of Contents

List of Tables.
Systematic Review

List of Figures

1. Chapter 1: Introduction and Objectives

1.1 Introduction

Medication errors and their consequent adverse drug events are a serious problem in hospital care. They endanger patients and add to health-system costs.

In "setting a vision for quality in health care," The Romanow Report declared that "the health care system itself is now being recognized as a major cause of illness, death and added costs because of errors, infections, the adverse effects of medications, the under-use of effective interventions and the provision of unnecessary or inappropriate care."[1]Likewise, the United States Institute of Medicine identified "Medication management—preventing medication errors and overuse of antibiotics" as a priority area for quality-improvement in American health care.[2] Although the emphasis on professional responsibility is a well-established paradigm of error prevention in hospital practice, "there is virtual unanimity among patient safety experts that a focus on systemic change will be far more productive than an emphasis on finding and punishing poor performers."[3]

This thesis evaluates the effectiveness of drug distribution technologies and system changes in the prevention of medication errors and adverse drug events. It also investigates the use of such technologies in Canada, and compares technology use to the evidence gathered about the effectiveness of the technologies in error prevention.

1.2 Definitions

Medication errors are failures to administer the correct medication to the right patient at an appropriate dose, route, and time[4;5] while the medication is in the control of the health care professional, patient, or consumer.[6] Medication errors may result from errors in drug ordering, transcribing, dispensing, administering, or monitoring.[7;8] Many errors have little ability to harm a patient. For example, if an anti-hypertensive medication is given one hour late, it is technically an error, but the risk of harm is very low. Other errors in drug administration could have significant consequences. For example, a 10-fold overdose of a narcotic analgesic will likely adversely affect the patient.

Adverse events are adverse patient outcomes caused by medical care. *Adverse drug events (ADEs)* are the subset of adverse events that are causally linked to drug use.[9] ADE is a more inclusive term than *adverse drug reaction (ADR)*. The term *ADE* encompasses the *ADR*, which the WHO defines as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function"[10]; however, an *ADE* could also be an adverse event related to inappropriate drug use. If an *ADE* results from a medication error, it is called a *preventable ADE*.[11;12]

Potential ADEs are cases in which a medication error could have caused harm but did not, either because the error was identified and rectified before it reached the patient, or because of good fortune.[13]

1.3 The Problem

1.3.1 Aggregate Impact of Medication Errors and Preventable Adverse Drug Events

Large population-based adverse-event studies provide most of the information about the effects of medical errors on hospitalized patients. A large Canadian population-based chart review suggests that 185 000 adult, non-obstetric, non-psychiatric hospital admissions annually are associated with adverse events, of which 70 000 are potentially preventable, and 16 000 are potentially preventable deaths.[14] Baker *et al*'s study[14] employed a two-stage chart review process in which nurses and physicians sequentially reviewed medical charts to determine a) whether the patient experienced an adverse outcome, and b) whether the cause of the observed adverse outcome was medical treatment. The study randomly selected 4 hospitals (1 teaching, 1 large and 2 small community) from each of 5 provinces, then randomly selected patient records from each hospital.

In the Canadian study,[14] drugs and fluids accounted for 24% of adverse events, making them the second most common class of adverse event (after surgical). Likewise, in the Harvard Medical Practice study (the model for the Baker study), ADEs accounted for 19% of all adverse events[15]: 45% of drug-related adverse events were considered preventable,[12] and 14% resulted in serious disability. Comparable ADE rates have been observed in other large retrospective chart reviews.[16-18] This Canadian estimate suggests that almost 0.8% of adult, non-obstetric, non-psychiatric hospital admissions are associated with preventable ADEs, or almost 20,000 per year:

[0.8% preventable ADE/pt = (7.5%AE/pt) (24% ADE/AE) (45% preventable ADE/ADE)]

The study by Baker *et al*[14] and others like them probably overlooked adverse drug events that went undocumented. Studies that employ more intensive observation have observed much higher ADE rates. For example, using a combination of stimulated incident-reporting and almost-daily chart review, Bates *et al* found in-hospital ADEs in 6.5% of admissions, of which 28% were judged preventable: i.e., preventable ADEs in 1.8% of patients.[19] Using pharmacist surveillance in a Canadian hospital, Forster et al found a rate of 2.6 preventable ADEs per 100 patient days (versus 1.1 per 100 patient-days in the above-quoted study by Bates).

1.3.2 Predictors of ADEs and Medication Errors

Patterns are emerging in the distribution of medication error and preventable ADEs, which may inform technology diffusion and certainly inform technology assessments (e.g., comparability and generalizability). Studies have described several patient-level risk factors. Increased patient age[14;15;20;21] and disease severity[17;21;21-27] increase the risk of experiencing harm due to a medication

error: variation in the volume of drug use offers at least a partial explanation.[25] Children may experience a greater risk of potential ADEs.[7]

Few studies have evaluated system factors predictive of ADEs; however, teaching hospitals seem associated with more adverse events (AEs)[14;23], and Intensive Care Units (ICUs) with more preventable AEs (as cited above in the relation to disease severity)[22;25]. With regard to error rates, underlying temporal patterns in medication error may exist,[28-30] as well as patterns of confusion of similar drug names.[31] Lighting may even play a role.[32]

1.4 The Cost of Adverse Drug Events

ADEs are not only harmful to patients' health: they are expensive for the health-care system. The cost of adverse drug events has been modeled in three large (>500 bed) teaching hospitals in the United States (US). Hospitalization costs attributed to the average ADE ranged from US$2013 (1997 dollars)[33] to US$2595 (1998 dollars),[27] depending on the type of ADE (e.g., itching, US$677, versus bleeding, US$6702),[33] and the level of acuity of care (e.g., intensive care versus general).[27;33;34]

1.5 Situating Medication Errors in Drug Distribution

Many technologies have been proposed to prevent medication error. This study defines technology as any intervention which can be introduced at the ward or hospital level, to prevent medication errors. A breakdown of the relationships of different types of error to ADEs provides a useful context for the assessment of different technologies' potential to prevent different types of ADEs. This is important because the technologies target errors and ADEs very differently, and because many evaluations measure only process variables as opposed to clinical outcomes.

Technologies intended to prevent medication error affect different steps of the medication cycle, adapted from "Prescription for Change"[35]:

The Medication Cycle

1. Assess therapeutic need
2. Issue medication order
3. Process order
4. Transport order to pharmacy
5. Process order in pharmacy
6. Transport medication to patient
7. Administer drug

Errors may occur at any stage in the medication cycle. It is worth noting that the assessment of therapeutic need assumes a prior diagnosis, which this thesis does not question or consider. The major stages of medication delivery associated with error are medication

a) ordering (prescription), (a stage which debatably includes order transcription)

b) dispensing; and

c) administration.

Of the preventable and potential ADEs observed in a sample of medication orders from 11 medical and surgical units, half (49%) originated at the ordering stage; 11% at the transcription stage; 14% at the dispensing stage, and 26% in the administration stage.[19] Among ordering errors with the potential for adverse patient effects, the majority (59%) relate to knowledge and the application of knowledge regarding drug therapy and patient factors that affect drug therapy; whereas use of calculations, decimal points, rate-expression factors, and drug nomenclature factors explain about a third (31%) of prescription errors.[4]

In his book on *Human Error*,[36] James Reason distinguished two types of human error: skill-based slips and lapses, and mistakes. Slips and lapses are errors in carrying out an intended plan in real time and space.[36] Mistakes are errors in planning: in identifying a goal, and choosing a process to achieve that goal. Mistakes may be "rule-based" or "knowledge-based": rule-based mistakes involve "familiar problems in which solutions are governed by stored rules," whereas knowledge-based mistakes involve new problems which require conscious analysis of stored knowledge.[36]

Applying the *Human Error* framework to medication delivery, it appears that about half of "serious' errors related to preventable and potential ADEs originate from organisational slips and lapses (in transcription, dispensing and administration), but a large minority are mistakes (in prescription), many of which appear to be knowledge-based mistakes.

1.6 Research Questions

The thesis research questions are as follows.

- What is the evidence for the effectiveness of hospital-based technologies in the prevention of medication errors, preventable ADEs, all-cause ADEs, and potential ADEs?
- How often are such technologies used in Canada's acute-care hospitals?
- How does the use correspond to the evidence of effectiveness?

1.7 Drug-distribution Technologies Designed to Improve Medication Safety

Table 1 presents the drug-distribution technologies evaluated in the systematic review, in broad groupings: prescribing and order-communication systems, dispensing ("processing" of the order) systems, administration systems, and "Other." What follows is an introduction to each of the technologies which this thesis addresses.

1.7.1 Prescribing and Order Communication Systems

Computerized Physician Order Entry (CPOE) involves physicians entering medication orders directly into a computer system. The advantages include order legibility, the potential to guide

physician drug choice and dosing through the use of menus and forcing functions for selection of drug, dose, route, and frequency; the ability to inform physician prescribing with Computerized/ Clinical Decision Support Systems; and the ability to link physician orders to electronic medication profiles, eliminating the frequent need for re-transcription. Inconvenience to physicians, non-compliance, and (as with any automated process) catastrophic failures are potential disadvantages; acquisition and maintenance costs are others.

Table 1: Technologies in Systematic Review

Technology Grouping	Examples
Prescribing and order communication systems	Computerized Physician Order Entry (CPOE) Computerized/Clinical Decision Support Systems (CDSS) Clinical pharmacy services Pharmacokinetic dosing Nomograms Computerized pumps Standard drug protocols Physician education and new prescription forms Electronic Medication Administration Records (e-MARs) and profiles Verbal orders
Verification of order communication	Bar-coding Double-check protocols
Dispensing systems (for "processing" of the order)	Bed-proximal drug dispensing & storage Unit-dosing, traditional pharmacy, ward-stock . Decentralized (satellite) pharmacy systems. Automated dispensing
Administration	Bar-coding Drug administration models (primary vs. functional, RN vs. unlicensed, etc)
Other Interventions	Highly automated systems (bar-code, eMAR, etc) Self-administered medication (SAM) Unique Multidimensional Quality Improvement (CQI) programs Failure Mode Analysis (FMA), Root Cause Analysis (RCA)

Clinical Decision Support Systems or Computerized Decision Support Systems (CDSS) for physician or pharmacist order entry automatically and routinely applies a set of rules to screen out inappropriate drug orders. These checks may suggest corollary orders, or screen out contra-indicated drug combinations, potential drug overdoses or under-doses, orders for drugs to which the patient is allergic, and drug-lab-value abnormalities. The decision support system may provide the clinician with an on-line source of clinical information, or formulae for dose calculations [*n.b.*, Patient-specific CDSS designed for specific pharmacokinetic drug dosing was considered in a special class: pharmacokinetic monitoring (below)]. Potential disadvantages are that CDSS may be systematically

wrong, decrease time spent with patients, encourage non-adherence, and decrease incentives for independent clinician evaluation.

Decentralized inpatient clinical pharmacists work on the ward, interacting directly with patients and other healthcare professionals to enhance the design, implementation, and monitoring of patients' therapeutic plans. The pharmacists may apply their expertise broadly: e.g., in counselling at the patient's bedside, at interdisciplinary rounds, and at medical rounds. Pharmacists may also lead the monitoring of specific drug protocols: e.g., anticoagulant- and antibiotic-monitoring programs, and pharmacokinetic monitoring programs. The pharmacists may choose from two broad care philosophies: clinical pharmacy, in which pharmacists supply physicians with drug information and help choose doses, and routes of administration; and pharmaceutical care, in which pharmacists broadly identify drug-related problems and undertake the responsibility to prevent or resolve them.[37] Other than the salary costs, potential problems include increased complexity of care processes increasing the potential for miscommunication and loss of coordination.

Pharmacokinetic dosing involves the application of a specific pharmacokinetic model to determine patient-specific dosing of a given drug. Potential disadvantages are analogous to broader forms of CDSS (which were described earlier): e.g., systematic error, non-adherence, and less independent clinician evaluation of dosing. *Computerized pumps* may apply pharmacokinetic dosing principles directly in setting drug infusion rates. For the purpose of this review, computerized or programmed *pharmacokinetic dosing* protocols were distinguished from *nomograms* and other *standard protocols* for drug therapy which involve the application of specific rules without computerization or other calculation aids.

Physician training may enlighten ignorance or promote adherence to accepted prescribing standards. *New ("prescriber-friendly") prescription forms* may promote the latter as well. The cons of training are that its effects may be short-term, and poorly conceived education may constitute a distraction or diminish morale.

A *computerized medication profile*, or *computerized Medication Administration Record (MAR)* allows for remote and multiple access of a given patient's list of drugs. In many hospitals, the pharmacy maintains a medication profiles separately from nursing which keeps MARs. Computerization may facilitate the integration of the two to improve order communication; however, issues around data access and modification are important to resolve.

Verbal orders may disrupt pharmacy work processes and do not create automatic records; however, they offer a potential for direct human feedback regarding each prescription.

1.7.2 Verification of Order Communication

Bar-coding may facilitate drug verification. Bar-coding applied to a medication package may facilitate the verification of a medication's appropriateness during the *dispensing* and *administration* stages. During drug *administration*, bar-coding of the patient (e.g., wristband) may help verify the appropriateness of the medication to the patient.

Double-check protocols are another way to verify the appropriateness of medication distribution. Although they reduce the potential for individual mistakes, they may be time-consuming and disrupt work processes.

1.7.3 Dispensing Systems (for "processing" of the order)

A unit-dose system distributes drugs in short-term, unit-of-use packages that are ready to be administered by the nurse from a patient-specific bin, labelled with the drug name and dose (e.g., for 24 hours). Unit-dosing eliminates the need for a nurse to select a medication from the floor stock or from the patient specific bottle (as in Individual Prescription): a pharmacist, pharmacy technician, or automated dispensing device performs the task instead.

Automated dispensing devices package and label drugs in unit-of-use packages, based on computerized medication profiles. Two examples include the Baxter ATC-212, which usually is located centrally at the pharmacy, and the Pyxis Medstation Rx, which is designed to dispense medication directly to nurses, peripherally, at the "point of use." The machines' intent is to prevent dispensing errors and decrease the human resource requirements of dispensing.
Alternatives to central unit-dosing are Traditional pharmacy and Ward-stock pharmacy (these alternatives may co-exist at the same bed). Traditional pharmacies dispense containers of medication (e.g., vials, bottles) which were ordered for the patient. The containers are labelled with the patient's name, the drug name, the dispensed quantity, and directions for use. In acute-care hospitals, a three-day cycle is typical. Most wards have some ward-stock, which involves nurses or other non-pharmacists in the hospital ward performing pharmacy functions: a) storing drugs in bulk in a common floor stock; b) manually selecting drugs from bulk storage; and c) distributing drugs to patients.

A satellite pharmacy is a subunit of the hospital pharmacy which is physically separated from the central pharmacy, which usually serves a specific ward. Potential advantages include timeliness and pharmacist specialization (i.e., familiarity with local needs); potential disadvantages relate to the complexity of managing satellite pharmacies.

1.7.4 Drug Administration and Managerial Models

A variety of models exist for drug administration: e.g., self-administered medication (SAM), and primary versus functional models. In the primary model, nurses are responsible for their own

patients, whereas a functional model designates a medication administration nurse for the period of the shift. Drug administration may be carried out by one or two registered nurses or specialized technicians; the remainder of the division of nurse-supervised labour may be altered as well.

1.7.5 Other Interventions

Multi-faceted combinations of technologies were often evaluated. Integrated, *highly automated* combinations of technologies may potentially perform differently from single-technology interventions (e.g., integrated eMARs, bar-coding, CPOE, and CDSS together). Finally, multi-faceted interventions are based on prior in-depth analyses like *Failure Mode Analysis* (FMA) or *Root Cause Analysis* (RCA). Failure mode analysis involves involves identifying errors that may happen before they happen, and assessing the likely consequences of those errors,[38] whereas root cause analysis involves the retrospective identification and assessment of factors which may have contributed to important events.[39] These may conceivably have different results from standard *multi-faceted* or *continuous quality improvement* interventions. The *Continuous Quality Improvement (CQI)* approach involves problem assessment, collective intervention, and evaluation.

Altered *resident work schedules* balance provider fatigue against the need for continuous patient care. Finally, *pharmacy-based intravenous (IV) admixture services* transfer the preparation of IV admixtures into the pharmacy, potentially providing a cleaner environment and personnel more skilled in IV admixture preparation.

1.8 Medication Error and ADE Detection

An important issue in studies' assessments of the above technologies and in the perception of medication error is the issue of error detection and measurement.

In addition to varying outcome definitions, heterogeneous methods of outcome-ascertainment may account for significant inter-site and inter-observer variation. In one study which compared different methods of error-detection using a common set of doses (n=2556), the four different methods of error detection led to widely diverging administration error estimates through: incident report, 0.04%; chart review, 0.7%; direct observation of administration compared with the patient's chart, 11.7%; and a blinded comparison of the research pharmacist's administration record to the pharmacy's copy of orders, 17.9%.[40] The insensitivity and potential variability in the sensitivity of measures such as incident reporting is a major limitation of studies that use such measures.[41]

In addition to problems with detection, limitations with the measurement of the impact of medication errors relate to the resolution of cause and effect. In reviewing the causes of adverse drug events, observers' hindsight bias may exaggerate what other people should have anticipated *a priori*, and the impact of the medication error.[36;42] On the other hand, prospective monitoring of processes at risk of error may overlook many mistakes which may be detected only once their effects are made

manifest, through patient follow-up[36]; also, the significance of errors to patient outcomes is only reasonably inferred through follow-up of patient outcomes.

In assessing the significance of medication errors, one difficulty is that different modes of ascertainment capture different types of error. For example, pharmacist surveillance reveals more order errors and fewer transcription and administration errors.[43] A major difficulty is the fact that many errors are intercepted at later stages in the cycle.[22;44] Only a small proportion, perhaps 1%, of errors that occur in medication delivery cause observable harm to patients.[22;45] Thus, not all errors are relevant to patient outcomes, and it is important to note the type of medication error under consideration, as well as its mode of ascertainment.

1.9 Thesis Format and Objectives

This thesis is concerned with the evaluation of different 'drug distribution technologies' (interventions, section 1.7) as they concern rates of medication errors and adverse drug events (outcome, section 1.3). This thesis comprises two studies: a systematic review and a survey. The systematic review answered the question, "What is the evidence for the effectiveness of hospital-based interventions in the prevention of medication errors, preventable ADEs, all-cause ADEs, and potential ADEs?" The survey answered the question, "How often are such technologies used in Canada's acute-care hospitals?"

Following the introduction to medication error in Chapter 1, Chapter 2 presents the systematic review, Chapter 3 presents the survey, and Chapter 4 discusses how the evidence of effectiveness corresponds with technology use. The specific objectives are as follows.

Systematic review

To assess the effectiveness of any hospital-based intervention (excluding clinical practice guidelines) in the prevention of

1. medication errors (primary outcome).
2. preventable ADEs and all-cause ADEs (secondary outcome).
3. potential ADEs (tertiary outcome).

Survey

1. To measure the prevalence of the use of technologies included in the systematic review, in Canadian acute-care hospitals.
2. To identify the same hospitals' plans for changes in the intensity of technology use.
3. To identify potential determinants of technology use in those hospitals: namely, hospital size, budget per bed, attitudes to the level of technology use, and perceptions of medication error.

By presenting the evidence of technologies' effectiveness with the evidence of their use, the thesis informs the way that Canadian hospitals use technologies which may be related to the rate of

medication errors and ADEs in hospitals. The identification of possible determinants of technology use may help to tailor efforts to promote evidence-based use of error-preventing technologies.

2. Systematic Review

2.1 Introduction

In Canada, a large population-based chart review suggests that, every year, 185 000 adult, non-obstetric, non-psychiatric hospital admissions are associated with adverse events (AEs), of which 70 000 are potentially preventable, and 16 000 are potentially preventable deaths.[14] In Canada, drugs and fluids accounted for 24% of adverse events, making them the second most common class of adverse event (after surgical). About half of drug-related adverse events are preventable.[12] The above-mentioned AE rate and proportion of AEs related to drugs are comparable with what has been observed in other similarly conducted studies.[16-18]

Increasingly, it is felt that patients' frequent exposure to preventable adverse drug events (ADEs)[14;19] is a property of the health-care system which can only be mitigated through system change.[2;3] Several recent high-profile position papers call for the increased use of technologies intended to prevent medication errors, while acknowledging the poorly established epidemiological evidence of the technologies' effectiveness in preventing medication errors and ADEs, and acknowledging the technologies' immaturity.[46-50] In spite of uncertain evidence, health-care managers have responded often with enthusiasm for these technologies[51]: e.g., the FDA has mandated the use of bar-coding for most prescription drugs and on certain over-the-counter drugs.[52]

In 2001, the Agency for Health Research and Quality (AHRQ) commissioned 40 authors at 11 institutions to review in 6 months a representative sample of "patient safety" practices, which were reviewed by a 4-person editorial board.[3] The AHRQ reported substantial gaps in the evidence base regarding technologies intended to improve patient safety: for example, computerized physician order entry (CPOE) with computerized decision support systems (CDSS), and control over antibiotic use and venous thromboembolism prophylaxis. The AHRQ presented its report as a template for extensions on their work. Later literature reviews have assessed specific technologies, such as computer-based decision-support systems.[53;54;55] Although these later reviews applied systematic methodologies, they addressed specific questions without globally assessing the variety of options open to those attempting to prevent hospital medication errors.

The goal of this chapter is to evaluate the effectiveness of technologies intended to prevent medication errors and ADEs. In comparison to existing, focused reviews, this review offers technology assessments which have greater internal consistency, and are better able to account for the multidimensional aspect of many technological interventions.

2.2 Systematic Review Objectives

To assess the effectiveness of any hospital-based intervention (excluding clinical practice guidelines) in the prevention of

1. medication errors (primary outcome);
2. preventable ADEs and all-cause ADEs (secondary outcome);
3. potential ADEs (tertiary outcome).

2.3 Methods

Appendix AG summarizes the contribution of the Candian Coordinating Office for Health Technology Assessment (CCOHTA) to this thesis.

2.3.1 Literature Search

A librarian (BA, MLS), a nurse (RN, MSN, MSc), and two pharmacists (both BSc, MSc) designed an electronic literature search to identify primary intervention studies of in-hospital medication errors or adverse drug events: see Table 2 for more detail. The librarian used Dialog OneSearch to search MEDLINE®, CANCERLIT®, TOXFILE®, EMBASE®, and BIOSIS Previews®, and Pharmaceutical News Index®. The librarian searched CINAHL first with CINAHL*direct*®, and later with Ovid. The CD-ROM version of The Cochrane Library was also searched (2002 issue). Appendix A describes in full the Dialog OneSearch search strategy used to search MEDLINE®, CANCERLIT®, and TOXFILE®.

Table 2: electronic literature search strategy (last updated: Nov 2002)

#	Search Component	Example Terms
1	An outcome of medication errors or any type of adverse drug event: all-cause, preventable, or potential	(explode medication errors) OR (medication adverse effect) . . .
2	A hospital setting	[(explode: hospital departments) OR . . . OR (hospices). (MeSH)].
3	a medication-error prevention technology, defined broadly	(explode medication systems) OR (explode hospital information systems) OR . . .)
4	essentially any study design	(clinical trial) OR . . . (review literature) OR . . . (case control studies) . . .
AND		
5	A publication date no earlier than 1985	

To find grey literature,[56] the librarian searched broadly on the Internet, and specifically reviewed the websites of potentially relevant organizations (e.g., the Canadian Medical Society, Health Canada, and the CCOHTA's HTA Checklist of websites, which includes members of the International Network of Agencies for Health Technology Assessment). Additional specialized databases were searched: e.g., at the University of York NHS Centre for Reviews and Effectiveness. Experts were also contacted. The bibliographies of primary studies and major reviews (most

importantly, the AHRQ report[3]), through June 30, 2003, were reviewed with a CCOHTA research officer (MB).

2.3.2 Study Selection Criteria

Following the CCOHTA protocol for medication errors in hospitals (Appendix B), two CCOHTA researchers (MB, AF, KG) and I selected studies independently; differences were resolved by a third reviewer. Included were studies of any intervention (other than clinical practice guidelines, a decision taken by CCOHTA), of any comparative study design, which measured medication errors, preventable ADEs, all-cause ADEs, or potential ADEs in the hospital setting (including rehab and long-term care but not nursing homes or homes with assisted living). Language was not a reason for exclusion.

2.3.3 Data Extraction of Primary Studies

Data was extracted about each study's design, setting, population, intervention, follow-up periods, (relevant) outcome definitions, methods of ascertainment, and general threats to validity. In a 10-study pilot, we (MS, AF, MB) found that our data extraction of study characteristics was comparable; I extracted the other studies independently. The data extraction tool is given in Appendix D. Translators familiar with medical terminology translated studies not published in English or French.

Medication errors were the primary outcome. Preventable and all-cause ADEs were secondary outcomes, and potential ADEs were a tertiary outcome.

2.3.4 Statistical Analysis

Kappa was used to measure inter-rater agreement in the selection of potentially relevant studies (see Appendix C: kappa calculation).[57] Where possible, 95% confidence intervals were generated around study-specific estimates of relative risks (RRs) and risk differences (RDs), mostly using standard formulae.[58] StatXact5 generated exact 95% confidence intervals for ratios of Poisson rates and for risk differences and risk ratios of sparsely populated binomial proportions. Study results were extracted as reported. No events were imputed, nor were cluster-randomized controlled trials re-analyzed to account for their clustering of allocations.

Pre-specified subgroup analyses addressed technology and study design; pre-specified sensitivity analyses concerned population (e.g., pediatric or adult), outcome (e.g., error ascertainment method), and length of follow-up (see Appendix E1: pre-specified analyses). These sub-analyses required refinement over the course of the review: for example, the continuous quality improvement (CQI) studies were divided according to the primary changes that they imposed on the drug-distribution process.

When appropriate, the relative risks and risk differences of similar studies were combined using the random-effects models in Review Manager 4.2.[59] We chose to use random-effects models instead of any fixed-effects models for two reasons. We chose random-effects for the sake of consistency, and to overcome the anticipated limitations of the fixed-effect model's assumption of a common effect in the face of anticipated variation: variation between interventions; between baseline error rates and error types[23]; between lengths of follow-up; and between modes of outcome ascertainment.[40] Review Manager 4.2 was also used to assess the heterogeneity of study results. In assessing the statistical heterogeneity of study results considered for combination, a p-value of 0.10 was used as a threshold for the significance of the statistical test for heterogeneity[60]; the I^2 statistic was also used to quantitatively gauge heterogeneity of study results, but not as a threshold test for meta-analysis.[61] The I^2 statistic is intended to describe the proportion of the overall variation among studies that is due to heterogeneity rather than chance: it lies between 0% and 100%. Specifically,

$$I^2 = \text{MAX}\ [0,\ 100\% \times (Q - df)/\ Q]$$

where Q is Cochran's heterogeneity statistic (a weighted sum of the squared differences of each study's estimate from the overall meta-analytic estimate, for which a chi-squared distribution is assumed) and df the degrees of freedom.

Among similar RCTs, evidence of publication bias was assessed using inverted funnel plots: no such methods were used with observational studies.

2.3.5 Data synthesis

The final summary table involved a summary of technology classifications, vote counts, levels of evidence, and study results (relative risks and risk differences). The summary table focuses on technologies' main effects, not on differences within technology groupings which are presented in the technology-specific summaries. Vote counts represent counts of the overall direction of each study's results: as "pro"-technology (i.e., less harm occurred with technology use); "con" (against the technology: i.e., more harm occurred with technology use); or "neutral" ("no effect"). A "pro" or a "con" vote did not require a demonstration of statistical significance: the avoidance of statistical significance as a threshold for counting votes limited confounding of study results with data reporting and analysis.

This review used an Oxford Centre's scheme of establishing levels of evidence, assigning the same grade to poor-quality ecological studies as to poor-quality cohort studies.[62] For each technology the evidence of benefit of technology versus no technology was assessed by assigning "grades of recommendation" according to the Oxford scale: the highest available level of evidence was indicated to the reader as well. Table 3 (below) summarizes the grades, whereas Appendix E2 presents them in detail.

Table 3: Oxford Evidence Grading System

A	consistent level 1 studies (mostly RCTs);
B	consistent level 2 or 3 studies (mostly cohort and ecological studies), or extrapolations from level 1 studies (mostly RCTs);
C	level 4 studies (mostly poor-quality cohort and ecological studies) or extrapolations from level 2 or 3 studies
D	level 5 evidence (expert opinion or bench research) or troublingly inconsistent or inconclusive studies of any level.

The Oxford scheme was chosen over the Canadian Task Force's evidence ranking because the Oxford scheme offered more guidance in describing levels of evidence from observational studies, and in suggesting a grade of recommendation based on that evidence.[62]

2.4 Results

2.4.1 Literature Search: Number of Studies Identified and Selected

The summarized results of the literature screen are in Table 4. The electronic literature search identified 2029 citations, of which 89 were finally included; non-electronic searching identified 46 articles that were finally included. The Kappa score for independent inter-rater agreement regarding the inclusion of full-text articles retrieved was 0.54 (95% CI=0.47, 0.61).

Table 4: Literature Search: Number of Studies Identified and Selected

ARTICLE FLOW	Electronic Search	Non-Electronic Search	All Articles
Possibly relevant articles identified	2029	Na	
Full-text reviewed	317	75	392
Exclusions	*228*	*29*	*257*
Included	89	46	135

The most common reasons for exclusions of full-text articles (n=257) were: no outcome of interest (n=73); no intervention (n=68); no primary data (n=54); not hospital patient population (n=25); no comparative data (n=18); comparison of ADE-monitoring systems (n=13); other (n=6).

The 135 articles provided 154 relevant technology or system comparisons (less than 5 studies were counted twice in separate technology categories). Table 5 presents the number of technology comparisons per technology, stratified by study design. The intention of this table is to offer a general sense of how the various technologies have been studied.

Table 5: Number of Technology Comparisons, by Study Design

	Article Number				
Technology or system	Total	Pre/post or other time-series	Cohort or CCT[A]	RCT[B]	Cross - over
Computerized Physician Order Entry (CPOE) alone	3	2	1		
Computerized Decision Support System +/- CPOE	23	22	1		
Pharmacokinetic dosing	15	2	3	10	
Clinical pharmacist	16	9	5	2	
Nomograms	9	7	1	1	
Computer pumps	4		1	3	
Drug-specific protocols	10	10			
Physician training or order forms	10	10			
Verbal orders	2	2			
Double-check	7	7			
Decentralized pharmacy	4	2	1		1
Unit-dose	5	2	3		
Bed-proximal dispensing	3	1	2		
Automated dispensing	6	5	1		
E-medication profile	4	4			
Bar-code	2	1	1		
Highly automated systems[C]	4	4			
Self-administration	2	1	1		
Drug administration models[D]	7	4	2	1	
Continuous Quality Improvement or multi-faceted	12	12			
Failure Mode or Root Cause Analysis	2	2			
Unique (e.g., resident work schedule)	4	4			
Total	*154*	*113*	*23*	*17*	*1*

[A]CCT: controlled clinical trial
[B] RCT: randomized controlled trial
[C] e.g., e-medication profile, bar-code, automated dispensing...
[D] e.g., primary vs. functional

The studied comparisons were generally derived from large teaching hospitals, in the United States (75%), Europe (14%), Canada (5%), Oceania (5%), and Israel (1%). Of the comparisons, 113 (73%) studied a time-series, including 100 pre/post studies (60%), 8 time-series studies (5%), and 5 repeated pre/post studies (3%). There were 22 cohort studies (14%) and 1 controlled clinical trial, CCT (1%). The 17 randomized controlled trials, RCTs (11%), included 3 that were randomized at the ward- or physician-level but analyzed at the patient level. One study could only be analyzed as a cross-over study (1%).

What follows is a series of technology-specific evidence summaries. For each technology grouping, there is a reminder of the technology definition, followed by a summary of study characteristics (complete study details can be found in Appendices F to AE), followed by a summary of study findings about comparisons of risks of medication error and adverse drug events (complete study-specific summaries are in Appendix AF: a table or tables of study-by-study descriptions followed by a summary table).

With one exception, the summaries of study characteristics begin by enumerating the designs of the relevant studies. If applicable, the descriptions are subdivided by technology subclass (as suggested by the method of analysis). As well, if applicable, the studies are subdivided according to outcome type, namely: drug error, preventable and all-cause adverse drug events, and potential adverse drug events. If subdivided, the study designs within the subgroup are enumerated again. Finally, the nature of the technology comparisons and outcome measurements is described.

Each section about the risk of medication error and adverse drug events presents each study's quantitative findings, couched within the details of the study context. A summary table (or tables) augments each technology-specific summary of study findings. Each table provides the following information: study identifier; technology comparison; outcome; relative risk (RR) versus control, with a 95% confidence interval if calculable; risk difference (RD) versus control, with a 95% confidence interval if calculable. While the technology-specific comparisons consider differences among applications of the different technologies, the final summary presents a simplified analysis of the technologies' "main effects" (i.e., technology versus no technology).

The detailed tables of study characteristics are presented in the appendices, along with a glossary.

2.4.2 Computerized Physician Order Entry (CPOE) without Computerized Decision Support : the Evidence

Computerized Physician Order Entry (CPOE) involves physicians entering medication orders directly into a computer system. The advantages include order legibility, the potential to guide physician drug choice and dosing through the use of menus and forcing functions for selection of drug, dose, route, and frequency; the ability to inform physician prescribing with computerized Clinical Decision Support Systems; and the ability to link physician orders to electronic medication profiles, eliminating the frequent need for re-transcription. Inconvenience to physicians, non-compliance, and (as with any automated process) catastrophic failures are potential disadvantages; acquisition and maintenance costs are others.

Study Characteristics (n=3, Appendix F[63-66])

Three studies evaluated CPOE alone: a cohort study[63] a pre/post study,[64;65] and an interrupted time-series study.[66] The cohort study identified order-entry errors: it compared direct physician order entry against errors in unit clerk entry of physicians' written orders, through routine pharmacist review and incident report. This latter comparison was independent of the study's objective of assessing the relative verbal-order error rate (the "verbal" comparison was placed in the verbal-order section). The pre/post study compared the incidence of pharmacist order clarifications in a system of hand-written orders, against a new system of CPOE with pick-lists and some fill-in orders. The time-

series study assessed the incidence of miscellaneous medication errors, ascertained through an unknown method, before and after CPOE implementation: CPOE followed sequentially after education and forced allergy listing.

Computerized Physician Order Entry (CPOE) without Computerized Decision Support: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 6a, 6b)

The cohort study of typed CPOE found 0.2 fewer order errors per 100 CPOE orders (95% CI:-0.5, 0.06) than per 100 written orders, a relative reduction of 26%; however, the study was confounded by prescriber type. Error rates in this study were higher among attending physicians, who were over-represented in the hand-written group. The order-error rates among attending physicians and among residents were similar in the CPOE -order and written-order groups. The study observed no adverse events due to order transmission errors.

The pre/post study analysis of fill-in CPOE extrapolated the error rate of hand-written orders written in the first 15 days of CPOE to the entire 6-month CPOE observation period.[64;65] Orders through the computerized pick-list were statistically significantly less error-prone than hand-written prescriptions (2.3% versus 0.7%): the difference in errors came from missing information (-0.4%) and incorrect information, excluding wrong dose, frequency, and route (-1%). The small number of typed, fill-in prescriptions were much more error-prone (7.1%), while the hand-written prescriptions in the first two weeks of the "post" period had an error rate somewhat lower than in the "pre" period (1.6%). The modeled overall risk difference with fill-in CPOE was 1.2 fewer order errors per 100 orders, for an odds ratio of 0.48 (95% CI: 0.31, 0.73). The study's selective extrapolation introduces more than random error: time-dependent effects may include, on the one hand, a decay of compliance or attention to detail, or, on the other hand, an intervention-favourable learning curve.

Finally, the time-series study found 1 fewer medication error per patient-day, a 22% reduction (CI unavailable). The time series showed an increase in errors during implementation (mean RR=1.1).[66] This result is more uncertain due to previous technology introductions, the lack of confidence intervals, and the indeterminate error-detection methods.

Although the results of the three studies of CPOE tend to support the new technology, the above-mentioned study limitations make the evidence supporting CPOE's effectiveness inconclusive. Specifically, the evidence does not suggest that the error rate in fill-in prescriptions is lower than the error rate in hand-written prescriptions.[63-66] Although prescriptions from a pick-list seem less error-prone than other written or typed orders, there is little evidence from comparisons of whole CPOE systems to support an effect of CPOE on the overall error rate.[64-66]

2.4.3 Computerized Decision Support System (CDSS) with or without Computerized Physician Order Entry (CPOE): the Evidence

Clinical Decision Support System (CDSS) for physician (CPOE) or pharmacist order entry automatically and routinely applies a set of rules to screen out inappropriate drug orders. These checks may suggest corollary orders, or screen out contra-indicated drug combinations, potential drug overdoses or under-doses, orders for drugs to which the patient is allergic, and drug-lab-value abnormalities. The decision support system may provide the clinician with an on-line source of clinical information, or formulae for dose calculations [*n.b.*, Patient-specific CDSS designed for specific pharmacokinetic drug dosing was considered in a special class: pharmacokinetic monitoring (below)]. Potential disadvantages are that CDSS may be systematically wrong, decrease time spent with patients, encourage non-adherence, and decrease incentives for independent clinician evaluation.

Study Characteristics *(n=23, Appendix G* [34;67-89]*)*

There were 20 CDSS evaluations. The study designs were as follows: 16 pre/post, 3 repeated pre/post, 3 time-series, and a cohort. 13 evaluated CDSS alone, whereas 7 evaluated the combination of CDSS and CPOE. 11 studies were from 2 sites: 8 from the LDS hospital in Salt Lake City, and 3 from the Brigham and Women's Hospital in Boston. All but a single study of CDSS alerts was locally customized.[83] There were also three multidimensional interventions that appeared to be centred around CDSS. All but one study of CDSS occurred in teaching hospitals. The studies assessed both medication errors and adverse drug events. The studies assessed CDSS and CPOE for broadly defined order errors; CDSS for renally adjusted dosing; CDSS for heparin prescribing, CDSS for anti-infective management; CDSS for cisapride and digoxin; and CDSS for total parenteral nutrition (TPN) and other dispensing calculations.

Five studies by four investigators assessed CPOE + CDSS for all types of orders: 4 pre/post studies and 1 interrupted time-series.[67;68] The two by the same investigator at the Brigham & Women's prospectively measured ADEs[67-69]; one of the two studies measured errors at the point of drug administration.[67;68] The studies were funded by the American Society of Health-system Pharmacists [69] and the Risk Management Foundation.[67] The three other broad CDSS + CPOE studies measured prescription errors retrospectively: through a record review,[70] an undefined method,[71] and incident report.[72]

There were two database assessments of CDSS for renally adjusted dosing: one of Brigham & Women's modified CDSS+CPOE which assessed dose errors, [73] and one of CDSS alerts which monitored patients' renal impairment.[74] Both were repeated pre/post studies.

A repeated pre/post study of CDSS for heparin prescribing counted diagnoses of pulmonary emboli and deep vein thrombosis and prescriptions that disagreed with local guidelines.[75]

Eight studies of CDSS for anti-infective management were conducted at the LDS hospital, a private, 520-bed teaching hospital.[34;76-82] There were seven pre/post studies and one interrupted time-series.[79] Together, they formed essentially a single interrupted time-series study (thus their results are described altogether). Outcome ascertainment was through record review. The interventions included CDSS reminders to stop antibiotic prophylaxis,[79] CDSS standing orders for antibiotic prophylaxis,[79] stand-alone CDSS for antibiotic-prescribing consults,[78;79] CDSS for pharmacist order checks,[77;81] and CDSS linked to CPOE .[76;77] In addition to the studies that reported on errors and antibiotic-associated ADEs, one study which spanned several of the above-described interventions[76;78;79;81] reported on overall antibiotic associated mortality.[34]

Four other drug-specific studies of CDSS systems assessed the systems' effects on dangerous cisapride interactions,[83] toxic digoxin reactions,[85] and TPN errors [87;88] The comparison of cisapride interactions came from an National Library of Medicine -funded evaluation of a broadly customized version of a commercial CDSS (note: cisapride is not used now).[83] The assessment of toxic digoxin reactions also noted the pre/post association with medication errors, identified through undeclared methods.[85] The TPN studies compared computer- to hand-calculation using order review: one used different standards of comparison,[87] while the other did not declare its standard.[88]

Finally, one time-series study and two pre/post studies assessed multidimensional interventions that appeared to be centred around CDSS.[84;86;89] The time-series study assessed CDSS which indicated the correct heparin infusion rate and a change in the standard heparin concentration, using incident report.[86] The pre/post studies were related to clinical pharmacy,[84] and double-check protocols.[89] The former intervention involved CDSS plus a clinical pharmacist 1 day per week and was evaluated through pharmacists' record review.[84] The latter intervention involved pharmacists calculating appropriate antimicrobial doses using a spreadsheet, as well as nurse and physician verification.[89]

2.4.3 Computerized Decision Support System (CDSS) with or without Computerized Physician Order Entry: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 7a-f)

The results summary deviates from the general structure of results summaries. It begins with the LDS hospital's anti-infective management program, which introduces the wide range of potential CDSS implementations, and accounts for the relationships between the many related LDS studies (which in a sense may be viewed as a complex, single study). What follows is a discussion of the results beyond the LDS hospital.

Anti-infective management at the LDS Hospital (Table 7a)

The LDS studies are record reviews of errors prevented through electronic-record-based CDSS. The LDS hospital's first interventions in 1985 involved a year of CDSS-suggested stop-order

stamps[79] and a year of CDSS-suggested, charted reminder stickers[80] to end excessive prophylaxis[80] and initiate prophylaxis appropriately.[79] Both the interventions were associated with fewer errors. With the stop reminders, there were 6 fewer excess doses per surgical patient still hospitalized after 48 hours, a statistically significant risk difference (RD) of 36%. With the prophylactic reminders, there was a -18% risk difference in prophylactic doses omitted or administered at the wrong-time, a difference which largely disappeared when the program was discontinued.[79]

The introduction and re-introduction of CDSS-determined prophylactic standing orders were associated with even fewer wrong-time or omission errors: statistically significant decreases of 34 and 17 fewer per 100 doses (RRs of 0.11 and 0.15). Errors increased five times with the interim CDSS discontinuation.[79]

LDS implemented CDSS in 1990 to prevent drug-allergy and administration errors, then observed 0.039 fewer ADEs per 100 patients, a (statistically significant) 85% relative reduction.[81] Following a later modification in 1995, excess doses of vancomycin, gentamicin, cefazolin, and cefuroxime occurred in 6.5 per 100 fewer patients (95% CI: 0.08, -0.05), and 0.61 fewer ADEs were observed per 100 patients who received these drugs.[82]

The LDS implemented CPOE + CDSS for anti-infectives in 12 ICU beds in 1994, and hospital-wide by 1995. Following implementation, the ICU study found 16 fewer susceptibility mismatches, 6.4 fewer drug-allergy alerts, and 20 fewer excess dose-alerts per 100 patients (each $p<0.01$): 1.7 fewer anti-infective ADEs per 100 patients overall (a 70% relative reduction). The non-ICU CPOE+ CDSS study found 1.2 fewer preventable ADEs per 100 patients, a 97% decrease (in the same year, retrospective chart review found a antibiotic-associated ADE rate of 19%).[77] Overall-antibiotic-associated ADEs decreased by 0.25 per patient in 89 vs. 88, and 0.33 per patient in 94 vs. 88. Overall antibiotic-associated mortality decreased 1% (RR=0.73, 95% CI: na).[34;79]

Computerized Decision Support System (CDSS) with or without Computerized Physician Order Entry (CPOE), not LDS-hospital focused: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 7b-f)

This section first discusses the technology's effect on medication errors, then on ADEs.

Among all the hospitals which implemented CPOE + CDSS, seven studies found decreases in prescription errors (table 7b).[67;70-73;75;76] Two studies evaluated prescription errors broadly; they found relative decreases of 83% and 50%,[71;72] similar to the 88% overall decrease in non-missed dose errors.[67] The former two studies had RDs of -0.12 per patient-day through record review and -0.0026 per patient-day through incident report,[72] whereas the Brigham and Women's study of missed-dose errors found a final decrease of -1.15 non-missed-dose errors per patient-day.[67]

The studies observed relatively larger decreases in prescription errors with more targeted interventions and more narrowly defined populations and outcomes. Automated record reviews found that with CPOE+CDSS, excess doses declined by 12 per 100 doses of low-risk drugs,[70] and 20 per 100 antibiotic orders (using LDS's CDSS for antibiotics)[76]; wrong dosages of renally cleared drugs decreased by 21 per 100 orders after the CPOE + CDSS was tuned for renal function.[73]

One study, the interrupted time-series, observed increases in missed-dose errors with the sequentially developed CPOE+CDSS: overall increases of 0.5, 0.2, and 1.4 missed doses per 100 orders following each new intervention.[67]

CDSS alerts were all associated with fewer errors (table 7c): significantly fewer cisapride errors (RR=0.3),[83] fewer prescriptions errors overall (RR=0.87),[85] and shorter excess-dose periods (relative means of 0.39 and 0.62).[82;83] Interestingly, the one commercial system was associated with a relatively small relative error reduction of 13% (CI na).[85] As with the LDS studies, the absolute risk differences were smaller without CPOE.

CDSS for dispensing calculations was associated with large and statistically significant error reductions in the methodologically limited studies of TPN calculation errors (table 7d): -12 and -54 (including -8 major) ordering errors per order.[87;88] Two pre/post studies which used incident report and an undeclared method did not detect any intervention-specific calculation errors with CDSS plus a clinical pharmacist one day per week, or with an added double-check protocol.[86;89]

In short, with the exception of insensitive studies, all the interventions were ultimately associated with reduced error rates; however, the studies were very heterogeneous, and estimated error reductions varied substantially.

Ten studies assessed ADEs (preventable, all-cause, and potential) in relation to CDSS implementation (table 7e). Three studies assessed a CDSS +CPOE application at the Brigham and Women's Hospital: two assessed a broad CPOE + CDSS application versus none,[69;82] and a third study assessed renally adjusted dosing for the CPOE+CDSS.[74] The other studies assessed bleeds and thrombi with CPOE+CDSS for heparin use,[75] antibiotic-associated ADEs with CPOE+CDSS and with anti-infective CDSS alone,[81;82] cisapride-associated ADEs in a broad CDSS system,[83] and toxic reactions to digoxin.[85] The first Brigham and Women's implementation study was published in 1999 as the second of four time points.[67] After implementing the first CPOE + CDSS, the rate of preventable ADEs per patient-day doubled (RR=2.0, 95% CI: 0.67, 6.9), increasing by 2.8 per 1000 patient-days. Then, the same investigator implemented CPOE+CDSS at another ward, and found 17% fewer preventable ADEs (p=0.37), a risk decrease of 0.8 per 1000 patient-days; he published the results in 1998 (a year earlier than his earlier negative study).[69] Finally, the investigator returned to the ward where his CPOE + CDSS system had been associated with increased preventable ADEs and

made interventions associated with decreases in preventable ADEs: -1.8 and -1.9 preventable ADEs per 1000 patients (versus baseline), neither difference being statistically significant.[67] Over time, the risk differences versus baseline were 2.8, -0.8, -1.8, and -1.9 preventable ADEs per 1000 patient-days; the trend was unclear with all-cause ADEs.[67;69]

As stated earlier, CPOE + CDSS for anti-infectives decreased ADEs by 1.7 and 1.2 per 100 patients after the implementation of CPOE + CDSS at the LDS.[76;77] CDSS alerts for antibiotics (LDS again) were associated with large relative decreases in ADEs observed but small absolute differences: -0.039 per 100 patients overall and -0.61 per 100 patients on one of four specifically targeted antibiotics. Serious renal impairment developed in 4.1 per 100 fewer patients receiving nephrotoxic drugs

The other, specific CDSS systems were associated with less important absolute risk differences for ADEs: -0.037 per 100 surgical patients with CDSS for anticoagulation, -0.02 per patient treated with cisapride (the 90% fewer toxic reactions to digoxin seemed like data dredging as the intervention was broad while the outcome was surprisingly narrow[85]).

To summarize (table 7f), most of the CDSS studies were self-evaluations of locally customized technologies. The seven studies that consistently found decreases in prescription errors support the contention that CDSS + CPOE will prevent the prescription errors that the evaluators intend to prevent. The broadly oriented CDSS + CPOE studies from Brigham and Women's distinguished themselves through their ADE ascertainment mechanisms which appeared not so dependent on the intervention, and through the magnitude of the decrease that they observed: the most dramatic being 0.8 and 1.9 fewer per 1000 patient-days (neither statistically significant).[67;69] The developer's less publicized and underemphasized early negative results are a reminder of the threat of publication bias which runs through this entire review (although there are other competing explanations such as temporal variation, and an institutional learning curve).

The LDS anti-infective management system involved a serious, long-term institutional commitment to technology development, reflected in substantially decreased rates of anti-infective ADEs. Unfortunately, a basic limitation of the LDS studies is that they are record reviews of errors prevented through record reviews: a standard that favours itself.

The risk differences suggest potentially substantial benefits with sophisticated CPOE + CDSS for anti-infective management: a 97% relative decrease of -1.2 preventable ADEs per 100 patients[77] (although recall that in the same year a chart review found a baseline risk of 19%). Implementation of routine CDSS standing orders for surgical prophylaxis also was associated with substantially fewer omissions and wrong-time errors than following charted CDSS reminder stickers: in the ballpark of one for every 3 to 5 surgical patients.[79] The error reduction with the LDS antibiotic

consultant was much smaller (RR=0.88, RD=-0.034/pt, not statistically significant). CDSS alerts for clinical pharmacists prevented much smaller numbers of ADEs, both at the LDS at other sites. Finally, CDSS appears to be potentially very helpful as a calculation support tool (RRs of 0 and 0.18 with TPN,[87;88] and 0 with cointerventions[86;89]), although the evidence is not particularly robust.

2.4.4 Pharmacokinetic dosing: the Evidence

Pharmacokinetic dosing involves the application of a specific pharmacokinetic model to calculate patient-specific dosing of a given drug. Potential disadvantages are analogous to broader forms of CDSS (which were described earlier): e.g., systematic error, non-adherence, and less independent clinician evaluation of dosing.

Study Characteristics (n=15, Appendix H, [90-104])

Fifteen studies evaluated pharmacokinetic dosing: 10 RCTs, 1 CCT, 2 observational cohorts, and 2 pre/post studies. All the studies were specific to a drug or drug class. 8 studies assessed the achievement of therapeutic drug concentrations, 6 assessed adverse drug events, and 4 assessed blood-clotting times. Five studies were of aminoglycosides (3 RCTs, 1 cohort, and 1 pre/post), one of vancomycin (cohort), five of theophylline or aminophylline (3 RCT, 1 CCT, 1 pre/post), one of heparin (RCT), and three of warfarin (RCTs). Two aminoglycoside studies occurred in the same New Zealand hospital with one investigator in common [91;92] The Eli-Lilly funded ICU study used a nomogram comparator,[92] whereas the non-ICU study used guided physician dosing,[91] in order to achieve target drug concentrations after a few days. Two other aminoglycoside studies used "normal practice" controls: they assessed the proportion achieving therapeutic drug concentrations at different times[93] and nephrotoxicity (the latter excluding protocol violations).[90] Finally, a study of adherence to pharmacokinetic dosing recommendations compared the incidence of nephrotoxicity and measures of non-therapeutic drug concentrations in patients whose doctors complied with all the recommendations, versus the patients whose doctors had complied with less than 100%.[94]

The vancomycin cohort study allocated patients according to physician preference and counted instances of renal insufficiency; the kinetic group providers were aware of the study while the non-kinetic group providers were not.[101]

Theophylline and aminophylline are seldom used now. Four kinetic-dosing studies examined the achievement of therapeutic drug levels.[96-99] An RCT, a CCT, and a pre/post study compared kinetic dosing to normal practice; the other RCT compared kinetic to guided dosing and excluded protocol violations.[100]

The heparin RCT compared kinetic dosing to a nomogram (not weight-based) with respect to bleeds, adverse clinical events, and proportions of therapeutic clotting times.[95]

There were two studies of specific pharmacist order review (see table 9c). One of the warfarin studies compared kinetic dosing to standard dosing practice.[102] The other two compared kinetic dosing to standard dosing practice[103;104]: one had two kinetic arms[103] (funding: American Society of Hospital Pharmacist[103], Regional Health Authority[104]). All used a variety of lab indicators of hemodynamic risk; three counted bleeds and two counted thrombi.

Pharmacokinetic Dosing: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 8a-c)

The three studies of achieving therapeutic aminoglycoside concentration showed statistically significant benefits. The decreased occurrence of a non-therapeutic peak concentration was statistically significant in both of the New Zealand RCTs.[91;92] The RD was -0.44 per patient in the non-ICU study (95% CI of RD=-0.73, -0.16; RR=0.50), and -77 per patient in the ICU study (95% CI of RD:-0.93, -0.41); RR=0.08): these results are significantly different ($Chi^2 = 3.26$ ($P = 0.07$), $I^2 = 69\%$). After a few intervening pilot interventions, the pre/post study found it took less time to achieve a therapeutic concentration and that fewer patients experiences possible nephrotoxicity (RRs of 0.60 and 0.24)[93] The fourth aminoglycoside study showed a statistically insignificant decrease in aminoglycoside-associated nephrotoxicity, which was probably an overestimate since it excluded patients whose dose recommendation was not implemented within 48 hours.[90]

In the cohort study of vancomycin dosing, the physician's patient allocation resulted in unbalanced groups: for example, the intervention group had fewer diabetics (2% vs. 16%) and concomitant aminoglycoside users (15% vs. 24%), both of which are risk factors for nephrotoxicity. It found an RD of 17% fewer patients experiencing related renal insufficiency (95% CI=-30%, -4%), a relative decrease of 72%; however, due to likely bias, the significance of this result is unclear.[101]

With regard to theophylline, the two RCTs found a statistically insignificant trend toward decreases in the occurrence of a non-therapeutic concentration[96;99]: a combined RD of -9% of patients (95% CI:-24%, +6%; $Chi^2 = 0.02$ ($P = 0.88$), $I^2 = 0\%$), a 33% relative decrease. The study of cardiac arrhythmias was neutral: RD=0 (95% CI: -0.16, 0.15).[98] Another study showed more nausea in the kinetic group: RD=0.04 (95% CI: -0.09, 0.18).[100]

The RCT of pharmacokinetic heparin dosing versus the non-weight-based nomogram found no clear difference in the number of non-therapeutic clotting tests (activated partial thromboplastin time ratios, or APTTRs).[95] However, there was a significant elimination of "adverse clinical events" per patient (RD=-0.23/pt; 95% CI: -0.39, -0.07), and a similar rate of bleeds (RD=0.01, 95% CI: -0.14, 0.16).

The three RCTs of pharmacokinetic warfarin dosing found non-statistically significant trends toward fewer failures to stabilize the PR or dose,[102-104] fewer bleeds [102;104], and more thromboemboli.[102;104]: see Table 8b for details.

Studies also observed decreased time to stabilization, one by a day (CI na) and one by two days (p=0.01).[103;104]

With the exception of the pre/post study[93] and a warfarin RCT,[104] study conditions appeared more carefully controlled than is normal: in fact, two studies excluded protocol violations.[90;100] All of the studies showed benefit in terms of attaining targeted therapeutic dose ranges and anticoagulation ranges. The pharmacokinetic interventions tended to show benefit with regard to any sort of adverse event. Table 8c presents the relevant meta-analyses.

The primary meta-analysis was performed on the four RCTs of AEs that did not explicitly exclude protocol violations[95;96;102;104]: it found a relative risk of 0.56 (95% CI: 0.20, 160), which was equivalent to 5 fewer adverse events per 100 patients (95% CI: -0.14, 0.04). The secondary meta-analyses that included the studies which excluded protocol violations estimated a higher but comparable RR and RD (both still statistically insignificant). [90;95;96;100;102;104] The two observational studies had point estimates that suggested greater decreases in AEs with kinetic dosing; however, their confounding makes their estimates less reliable.

To summarize (table 8d), the studies of pharmacokinetic dosing were mostly small RCTs with tightly controlled interventions, outcome measures that focused on expected benefits, and limited reporting on losses to follow-up. They demonstrated improvements in the attainment of desired drug concentrations, and a statistically insignificant trend toward fewer adverse events. The one (pre/post) study that evaluated a system-level intervention had analogous results. The technology can have limited only applicability, as the interventions are for drugs that are unique in requiring specific dosing and monitoring.

2.4.5 Clinical Pharmacist: the Evidence

Clinical pharmacists work on the ward, interacting directly with patients and other healthcare professionals to enhance the design, implementation, and monitoring of patients' therapeutic plans. The pharmacists may apply their expertise broadly: e.g., in counselling at the patient's bedside, at interdisciplinary rounds, and at medical rounds. Pharmacists may also lead the monitoring of specific drug protocols: e.g., anticoagulant- and antibiotic-monitoring programs, and pharmacokinetic monitoring programs. The pharmacists may choose from two broad care philosophies: clinical pharmacy, in which pharmacists supply physicians with drug information and help choose doses, and routes of administration; and pharmaceutical care, in which pharmacists broadly identify drug-related

problems and undertake the responsibility to prevent or resolve them.[37] Other than the salary costs, potential problems include increased complexity of care processes increasing the potential for miscommunication and loss of coordination.

Study Characteristics (n=17, Appendix I [69;84;105-118])

Seventeen studies assessed clinical pharmacists: ten pre/post, five cohort, and two randomized studies. Of the ten non-specifically oriented studies, four investigated ADEs, and six investigated errors. Six studies were drug-class specific, including four that investigated warfarin dosing.

Four studies reviewed charts to follow-up on ADEs that occurred with and without a broadly expanded clinical role for the pharmacist[69;105;106;111]: an 8-group RCT,[69] two cohorts,[105;106] and a pre/post study.[111] The ward-level RCT prospectively elicited additional ADE reporting from staff to assess a "team" intervention, which primarily made the pharmacist more available on the ward, and additionally involved supporting dilution and drip-rate calculations, and adding a nurse-pharmacy log: a validity-related weakness is potential measurement instability due to the recent implementation of CDSS plus CPOE.[69]

A pretest-posttest control group study added 0.5 full-time-equivalents (FTE) of an experienced senior clinical pharmacist for a 17-bed ICU[105]; the other cohort study added 2 clinical pharmacists for 30 patients.[106] Finally the fourth pre/post study assessed one FTE clinical pharmacist for 28 beds by reviewing charts of patients who received drugs commonly used to treat ADRs.[111]

Three cohort[108;110;112] and three pre/post[84;107;109] studies reviewed records to identify errors with and without an expanded role for the clinical pharmacist. A cohort[108] and two pre/post studies[84;109] of adding a clinical pharmacist measured errors broadly. One study counted excess doses where the change in the pharmacist's duties included, among other things, optimizing doses of renally eliminated drugs following serum-creatinine determinations.[107] A cohort study measured recorded drug discrepancies with and without pharmacists comparing the GP's drug history with the admission drug history and educating patients.[110] One cohort study was unique in comparing the nature of pharmacist interventions with two surgeons (analogous to "errors prevented"): the pharmacist with one surgeon took medication histories and made recommendations, whereas the other simply reviewed the chart.[112]

Finally, seven studies were drug or class-specific. Three pre/post studies assessed bleeds and thrombi where pharmacists had a defined role in warfarin management.[114-116] Interestingly, two used retrospective methods pre-intervention and prospective methods post-intervention.[114;115] A Canadian RCT assessed errors with and without pharmacist recommendation about the misuse of the then-recently unrestricted drug cefotaxime,[117] and a pre/post study assessed the dosing of hypnotics.[118]

Finally, a cohort study[113] and a pre/post study[119] assessed a pharmacist-managed warfarin use which also employed pharmacist-managed heparin nomograms. The associated adverse events did not fit neatly into either the clinical pharmacy or the nomogram category, which follows after clinical pharmacy.

Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 9a-e)

All five studies which evaluated errors found decreases with an increased clinical pharmacist role (table 9a): two results were statistically significant.[107;110] The two studies which evaluated errors broadly found relative decreases of 38% and 50%: in one, 0.5 fewer discrepancies in the records per patient (*n.b.*, using broad and unclear error definitions). Going from 0.2 to 1.0 FTE of clinical pharmacist on 53 beds was associated with 1.8 fewer prescription errors per 100 doses (RR=0.89, CI na). With a clinical pharmacist who adjusted renally eliminated doses, there were 71% fewer excess doses per renally eliminated dose (RD=-0.48/dose). Finally, there were 0.48 fewer drug discrepancies per drug on discharge when the clinical pharmacist resolved differences between the GP record and the admission history.[110]

The RCT found 6 fewer prescription errors per 100 doses with the pharmacist reviewing the newly broadened use of cefotaxime; also, 8% of control patients were excluded because of the risk of no pharmacist intervention.[117] The quality improvement (QI) study of pharmacist review of hypnotic orders found that they were eliminated.[118]

Finally, related to error but unique (and not tabled) is a study of pharmacist interventions which found that, compared to a pharmacist who reviewed the drug chart for errors with one surgeon, a pharmacist who took the medication history, and charted recommendations for another surgeon more often changed the drug as opposed to the dose, and was graded as making more significant interventions (RD of +15% for a "significant" or "very significant" intervention).[112]

The Clinical Pharmacist and the Risk of Adverse Drug Events

Three of the four studies of clinical pharmacists found decreases in ADEs. The three studies that measured preventable ADEs found a statistically significant decrease of -1.0 per 100 patient-days in the ICU,[105] a borderline statistically insignificant -2.1 per 100 patient-days in the general medical ward,[106] and a statistically insignificant increase of 0.9 per 100 patient-days in a mix of general and intensive-care wards.[69] Supporting the validity of the decrease in preventable ADEs in the ICU were the larger decrease in all-cause ADEs (-3.2 per 100 patient-days), and a small increase in ADEs in the concurrent control (RR=1.3)[105]; the patient comparability in the study of general medicine wards seemed also very good.[106] The final study of pharmaceutical care found a smaller (statistically significant) decrease in ADEs of -0.052 per patient which reflected its narrower outcome definition. The study which showed an increase in ADEs differed from the other three in a variety of ways,

including its larger sample size, its randomization of wards, its above-mentioned sources of potential measurement instability, and the fact that it merely changed the pharmacist's responsibility without adding clinical pharmacist FTE.[69]

Three pre/post studies of pharmacists' warfarin management counted bleeds and thrombi.[114-116] None of the studies was statistically significant, but there was a trend towards fewer in-hospital bleeds (-0.08, -0.03, and +0.02 per 100 patients) and fewer in-hospital thrombi (-0.03, +0.0075 per 100 patients). The study which followed up on patients longer also found a trend fewer bleeds (-0.05/patient) and thrombi (-0.03/patient).

In the pharmacy-managed heparin nomograms and warfarin protocols, [113;119] the adverse-event data were uncertain and variable. In the pre/post study, the bleeding-risk difference was positive but not at all significant: RD=1/100 patients, OR=1.4 (95% CI: 0.2-12.5). Conversely, in the cohort study there were fewer bleeds (RD=-0.04; 95% CI: -0.14, 0.03) but more thrombi (RD=0.02; 95% CI: -0.06, 0.11) Interventional patients in the cohort study were more likely to have a therapeutic INR at discharge: RD=-0.13 (95% CI: -0.34, 0.07).

In summary, the studies that added clinical pharmacist FTEs were associated with consistent decreases in error rates (particularly prescription errors rates), and relatively large absolute decreases in ADE rates. Study validity is a concern with them: theoretically in terms of their selection of pharmacists (the "experienced senior pharmacist") and the lack of pharmacist-blinding to the assessment; and quantitatively evidenced by some atypically high recommendation-acceptance rates. Likewise, the results of studies of pharmacy-managed anticoagulation were variable but tended toward large benefits with the interventions. The main caveat with these is the easily identifiable study limitations, such as the comparison of prospective to retrospective data collection, and inclusion of vascular patients in only one group.

2.4.6 Nomograms, the Evidence

A nomogram consists of three lines, each representing a correlated variable, where the relationship between variables is described by a straight line drawn through the three lines: i.e., the recommended dose is suggested by two correlated variables: e.g., a patient's weight. The purpose of a nomogram is to individualize dosing based on patient-specific factors: e.g., a patient's weight.

Study Characteristics (n=8, Appendix J,[113;119-125])

The eight nomogram studies dealt with heparin dosing. There were seven pre/post studies and an RCT. The two studies of pharmacy-managed heparin protocols which also assessed warfarin protocols were managed by clinical pharmacists: thus, their warfarin-associated elements were discussed in the clinical pharmacy section, although their adverse-event data is also presented in the tables in this section.[113;119]

Seven pre/post studies compared weight-based nomograms to empirical dosing (n=1),[120] weight-independent nomograms to empirical dosing (n=3),[119;121;122] and weight-based nomograms to weight-independent nomograms (n=2).[123;124] One weight-independent heparin nomogram also included a warfarin protocol.[119] One RCT which did not conceal allocations compared weight-based to weight-independent nomograms.[125] Finally, a cohort study compared a weight-based heparin nomogram and which also involved warfarin dosing to normal physician management.[113]

Heparin indications were both non-specific[119;122-124] and specific to deep vein thromboses (DVTs) or pulmonary emboli (PEs).[121;125] Studies took place in the mid-80s to the mid-90s.

All the pre/post studies employed retrospective chart review, with the exception of one that used daily chart review.[121] One used retrospective data collection pre, and prospective data collection post.[122] Other clear pre/post study limitations include generalizability in the comparison of weight-based and non-weight-based nomograms that excluded protocol violations,[124] and internal validity in two studies of weight-based versus empirical dosing.[120;123]

Two pre/post studies assessed standard nomograms with regard to the proportion of non-therapeutic APTTRs: per test[121] and per hour.[119] Two studies compared nomogram dosing (one weight-based, one not) to empirical dosing in terms of the proportion of patients achieving a therapeutic APTT at 24[122;123] and 48 hours.[122] Three pre/post studies assessed time-to-therapeutic APTT in nomogram vs. empiric dosing: 1 weight-based nomogram[120] and 2 not.[121;122] The RCT of weight-based versus non-weight-based nomograms measured these latter two outcomes as well (proportion with therapeutic APTT and time-to-therapeutic APTT).[125] One pre/post study and the RCT observed bleeds and thrombi with weight-based dosing versus empiric[120] and weight-independent dosing.[125]

Nomograms: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 10a-b)

With nomogram use, patients spent less time with non-therapeutic APTTs (RR of 0.84, RD of -9%)[119] and had fewer lab tests with non-therapeutic APTTs (RRs of 0.63 and 0.89, RDs of -14% and -6%).[113;121] In two pre/post studies with limited internal validity, nomograms were associated with statistically significantly fewer patients not achieving a therapeutic APTT at 24 and 48 hours. For example, at 24 hours, the estimated risk differences were as follows: with the weight-based nomogram, 44 fewer patients per 100 (95% CI: -64, -23, RR=0.16); with the weight-independent nomogram, 28 fewer patients per 100 (95% CI of RD: -47, -10; RR=0.55). The cohort-study results at 24 hours were complementary but less dramatic, with an RD of -0.04 and an RR of 0.67. Weight-based nomograms were particularly efficacious: in direct comparison to weight-independent nomograms (estimated relative risks of 0.67 and 0.63, and risk differences of -0.20/pt and -0.21/pt, and 24 and 48 hours, respectively), and in the non-head-to-head comparison of the pre/post studies

quoted above.[122;123] The two weight-independent nomograms found an meta-analyzed average of a 32-hour decrease in time to therapeutic APTT (95% CI:-40, -23, Chi = 0.04, (p=0.85), $I^2 = 0$). The weight-dependent decreases were 23 hours (95% CI: -42, -19) in the pre/post study and -1.7 hours (p=0.14) in the cohort study, to absolute time-to-therapeutic APTTs that were similar. The direct comparison found it took 12 fewer hours to reach a therapeutic dose (P<0.001 with Kaplan Meier). The pre/post study found 3 fewer bleeds per 100 patients (95% CI: -10, 5) and 7 fewer thrombi (95% CI: -16, 2) with the weight-based nomogram compared to empiric dosing; however, in addition to the statistical uncertainty, the patient populations were very different. Likewise, the RCT observed 3 fewer bleeds and 20 fewer thrombi per 100 patients, but the groups were unbalanced, so the comparison is not very meaningful.[125]

In summary (table 10b), the evidence for the superiority of nomograms over empiric dosing was consistently favourable, but of low quality: many studies' internal validity was limited. Statistically significant improvements were observed in terms of achieving a therapeutic APTT at 24 and 48 hours, and in terms of time-to-therapeutic APTT. The studies also presented statistically uncertain trends toward decreases in bleeds and thrombi. Based on the results, heparin nomograms appear likely to improve the achievement of therapeutic APTTs; however, the adverse event data itself is limited in suggesting a benefit to nomogram use. It is difficult to apply these studies to the use of drugs other than heparin.

2.4.7 Computerized Pumps, the Evidence

The computerized pumps in this review applied pharmacokinetic principles to set drug-infusion rates directly.

Study Characteristics (n=4, Appendix K, [126-129])

There were four studies of computerized pumps, all for perioperative use. There were three RCTs and a prospective cohort study. Two monitored hemodynamic parameters during CABG, with fentanyl[126] and midozolam[127] dosing assistance. One study, post-cardiovascular surgery, measured blood-pressure control with computer-assisted fentanyl and midazolam dosing.[128] Finally, one monitored pain control post-orthopedic surgery, with computer-assisted alfentanil dosing compared to patient-controlled morphine.[129] There was one RCT in each of the three categories, plus the cohort. Follow-up was short: up to 32 hours long. The studies were small: with 10, [126;129] 12, [127] 20 and 40[128] patients randomized per study arm.

Computerized Pumps: Risk of Potential Adverse Drug Events and Adverse Drug Events (see Appendix AF, Tables 11a-b)

Compared with patient-controlled administration of morphine, computer-controlled alfentanil administration decreased time spent with pain [visual analogue scale (VAS)>3.0] by an average of 175 minutes (95% CI: -310, -29), a 44% reduction. Nausea and vomiting were unchanged (RR=1), while urinary retention decreased by 49% (95% CI: 0.1, 1.9).

The computerized blood pressure monitor decreased the mean difference from the target blood pressure (70-80mg) by statistically significant amounts in each of the four hours following cardiac surgery: in hour 1, -9.5 mm Hg; in hour 2, -8.4; in hour 3, -8.1; and in hour 4, -2.8.

The cardiac surgery study of assisted fentanyl dosing found trends toward fewer hypotensive and hypertensive episodes with computer-assistance, particularly with the variable, physician-adjusted drug concentration set point; however, the results were not statistically significant. The investigators in the cardiac surgery study of assisted midazolam and fentanyl dosing felt that they found no important difference in mean arterial pressures or heart rates.

To summarize (table 11b), the computer-assisted dosing studies were small, unique efficacy studies in the perioperative setting: the study did not address safety with widespread use. One study favoured computer-assisted dosing in terms of pain control; however, a major difference between the interventions was the use of alfentanil as opposed to morphine.[129] Collectively, the three other perioperative studies were variable, but suggested potential improvements in hemodynamic control.[126-128] One study suggested improved post-operative blood-pressure and heart-rate control.[128] Intra-operative blood-pressure control seemed comparable in one study,[127] and potentially improved, though not statistically significant different with the variable set-point, computer-assisted fentanyl dosing.[126]

2.4.8 Standard, Hospital drug-specific Protocols: the Evidence

Standard protocols for drug distribution involve the application of a specific set of rules without computerization to minimize procedural variations.

Study Characteristics (n=10, Appendix L, [118;130-135])

Ten pre/post studies (one of which included time-series data[132;133]) described the results of implementing standard hospital drug protocols: for heparin,[130] narcotics,[130] chemotherapy,[130;131] insulin, [118;130-133] TPN, [135] and patient-controlled analgesia.[134] Most of the protocols seemed targeted hospital-wide. The heparin protocol reported the time to therapeutic coagulation range and the proportion of pharmacy order interventions.[130] One chemo protocol reported on medication errors[131]; the other chemo and narcotic protocols reported associated ADEs.[130] The insulin protocols reported hypoglycemic episodes,[130] potential errors,[118] errors related to insulin,[131] and hypoglycemic episodes and potential errors combined[132;133] The patient-controlled analgesia study reported on related

incidents, and the TPN study reported on TPN form errors. The TPN study tabulated errors prospectively[135]; the seven other studies either used incident report[132-134] or did not declare their methods[118;130] Of 21 potentially relevant system changes evaluated inside the 40-hospital Institute for Healthcare Improvement (IHI) collaboration, four protocols (one for heparin, one for narcotics, one for chemotherapy , and one for insulin) represented four of the eight reported successes.[130]

Hospital drug-specific protocols: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 12a-b)

All eight studies showed protective associations, but their statistical uncertainties were not calculable (table 12a). Of the IHI studies, the heparin protocol claimed a 16-hour decrease in mean time to therapeutic PTT (a 70% reduction) along with a 32% absolute decrease in pharmacist order interventions. The narcotic and insulin protocol each claimed about 10 fewer related ADEs per month (88% and 62% reductions), while the chemo protocols reported 85% fewer errors and 50% fewer ADEs: both had error-reporting limitations.[130] The insulin protocols reported 10 fewer hypoglycemic episodes per month (as above),[130] one fewer insulin error per patient-day,[131] the elimination of 4.4 "potential errors" per patient,[118] and 2.7 fewer insulin errors and hypoglycemic events per 100 unreported units[132;133]: the latter decline in insulin errors and hypoglycemic episodes seemed to stabilize over time at the new lower level). Patient-controlled analgesia incidents declined by 3.2 per 100 days (relative risk reduction=44%),[134] and TPN-form errors per patient declined by 0.82 per patient (relative risk reduction=88%), consistently across categories (infusion rate, %lipid/%glucose, % amino acid, electrolytes, trace elements & vitamins, heparin).[135]

The greatest absolute differences were seen in the IHI collaboration's protocols for heparin, narcotics, chemotherapy, and insulin. Although the IHI's heparin study results were similar to the nomogram studies, the IHI collaboration's results were particularly susceptible to bias: publication bias internally and in their hierarchical reported structure (with subordinates reporting study results to their managers). The TPN study was also very positive: its intervention prevented many errors of unclear significance.

To summarize (table 12b), the consistently favourable direction of these studies' results supports the value of drug protocols. However, in all of the studies data collection was suspect, none included probabilistic analyses, all used pre/post designs, and all the studies of ADEs (and some of the error studies) openly focused on reporting the most successful trials: the process of evidence-gathering appears inadequate.

2.4.9 Physician Education and Order Forms: the Evidence

Physician training and new order forms are intended to promote adherence to prescribing standards. The cons of training are that its effects may be short-term, and poorly conceived education may constitute a distraction or diminish morale.

Study Characteristics (n=10, Appedices M-O [118;130;136-143])

Ten pre/post studies evaluated non-electronic interventions related to physician ordering: i.e., prescription-writing and order forms. Investigators' outcome of interest was prescription quality. Of the seven studies that targeted all orders, four evaluated education alone,[130;136;138;143] two evaluated the combination of education with new prescription forms,[140;141] and one evaluated the phased implementation of education first, and then a new form.[139]

The three specialized interventions targeted nonsteroidal anti-inflammatory drugs (NSAIDs) with education, and chemotherapy with new forms[118] and education.[142] They were not particularly informative but seemed more meaningful lumped with ordering behaviour than with miscellaneous quality improvement. The study of the implementation of a chemotherapy order form, facilitation of information-sharing, and clarification of nurse and pharmacist responsibility was vague in its methods, and came from a list of QI "successes" but used a form like the Gardulf study[140] and an error definition like Thorn.[139] The study of education for the prevention of NSAID-related prescription errors seemed to aim for a reduction in overall use by emphasizing NSAID-related AEs.[142] Finally, a study evaluated the training of junior doctors about IV drugs. The characteristics of the three groups of studies are presented separately, beginning with the physician education studies.

Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 13a-d)

Four of five studies showed improvements in prescription writing, of which two were statistically significant (table 13a). One of the studies simply reported that eight of twelve error elements improved and two deteriorated.[138] Two studies seemed similar enough to meta-analyse with regard to order illegibility[136;137]: their combined RD was 11 fewer illegible orders per 100 orders [95% CI: -0.12, -0.10; $Chi^2 = 0.57$ ($P = 0.45$), $I^2 = 0\%$]. The studies' relative risks of 0.36 and 0 were too heterogeneous to combine ($P < 0.00001$, $I^2 = 95.7\%$).[136;137]; however, both the risk differences and relative risks are qualitatively similar to a third (somewhat questionable) study's point estimates of the decreased risk of an illegible or non-standard order, which observed an RD of -0.13 per 100 prescriptions, and an RR of 0.35.

One study of incomplete orders found a decrease with education[137] whereas two had unclear results.[136;139] With respect to wrong-patient and wrong-dose errors the studies found no differences but were underpowered.

Physician education and New Prescription Form: Risk of Medication Error

As shown in table 13b, all three studies showed trends toward fewer missing or illegible elements in prescriptions. One study was not internally valid in terms of its patient selection, its error-definitions, or its error ascertainment methods[141] which left two useful studies. One study of a new prescription form and education found a consistent trend toward less missing information (with 2/4 differences individually statistically significant).[139] Another which additionally involved new legislation found an overall trend toward less missing or illegible information: in 3 different pre/post samples, -36/100 orders, +4/ 100 orders, -20/ 100 orders. An attempt to meta-analyze these samples was unsuccessful: $P(< 0.00001)$, $I^2 = 98.7\%$, and 98.0%, respectively.

Specialized Physician Education or Forms: Risk of Medication Error (table 13c)

The vague QI study of the implementation of a chemotherapy order form, education, etc reported an elimination of potential errors per chemotherapy order: an RD of 1.7 fewer potential errors per order.[118] The result could be impressive if it were explained in greater detail: how it was derived and what was observed. The study of education about NSAIDs results in fewer errors overall: 6 fewer per 100 patients (95% CI: -21/100, 9/100).[142] There was no difference in violations (more serious errors); the difference was composed by the reduction in the rate of inadequacies.

Finally, the study of training junior doctors presented uncertain results: it claimed it started with 6 errors per year and ended with 3 per year, but indirectly reported an overall rate of 8.2 per year. The reporting suggests a problem: e.g., that temporal variation swamped the pre/post observation; that the change in incident reporting form affected reporting; or that there was a mistake in the report.

Overall (table 13d), four of five studies of physician education suggested that physician education may improve order quality. Two suggest potential decreases of twelve illegible orders per 100 prescriptions (with RRs of 0, 0.35, and 0.36). There was no clear effect on incomplete orders. The two useful studies (see above) of combined education and order form change suggest a decrease in missing information with improved order sheet. It is unclear to what degree these changes affect medication delivery to patients, although presumably they are significant sources of the problem with roughly 1% of prescriptions being unclear at the time of administration.[144]

2.4.10 Verbal Orders: the Evidence

Verbally transmitted orders may disrupt pharmacy work processes and do not create a paper trail but allow for direct order feedback.

Study Characteristics (n=2, Appendix P[63;118])

Two studies evaluated the accuracy of verbal orders: a pre/post study and a cohort study.[63;118] One compared order errors in verbal orders to nurses with orders written and, separately, with orders

typed.[63] These verbal orders were allowed only in restricted situations.[63] The other study officially restricted verbal orders to registered nurses: i.e., not clerical personnel.[118]

Verbal orders, Risk of Medication Error (see Appendix AF, Tables 14a-b)

In their restricted situations of use, verbal orders to nurses had fewer errors than written (RD=-0.6/100) or typed orders (-0.3/100).[63] This may be a function of an inherent clarity of verbal orders, nurse order correction and clarification, or selection bias due to restriction of verbal orders to certain situations. The study of prohibiting telephone orders to clerical personnel found "no difference": no power calculations were reported. The study results (presented in table 14b) do not prove the superiority or inferiority of verbal orders.

2.4.11 Double-check: the Evidence

Extra checks can screen out errors at any stage of drug distribution: they were applied here in the sense of screening for slips and lapses, as the CDSS, nomogram, pharmacokinetic, and clinical pharmacy studies addressed mistakes. Although extra checks reduce the potential for individual mistakes, they may be time-consuming disrupt work processes, or even create a sense of complacency.

Study Characteristics (n=7, Appendices Q, R[132;133;143;145-149])

The seven pre/post studies (including one time-series study) evaluated checks on the drug distribution process. Three of the five single-intervention studies used incident report to assess a second check in pharmacy on all drugs dispensed[143]; a move from a double- to a single-check by nurses of drugs to be administered[145]; and a triple-verification system for chemotherapy alterations.[146] Another physically compared drawer fill to fill-lists to compare technician and pharmacist checks on dispensing.[147] The fifth assessed the formal medication reconciliation by doctors and nurses, one of just two pilot studies reported of ten implemented.[132;133]

Two multi-faceted intervention studies also involved extra checks. One incorporated a technician check on order entry while also adding special delivery bins, and halving the allowable order-entry time per person per day.[148] The other was described above with the studies of the electronic medication profile: it involved pharmacist order verification and use of a computer-edited list to dispense drugs.[149]

Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 15a, b)

All 7 studies reported fewer errors with their new interventions (table 15a). The differences in two of the three dispensing assessments that physically ascertained dispensing errors were statistically significant. One such assessment was unimodal.[147] The trained and selected technicians outperformed pharmacists routinely checking doses dispensed. They allowed 0.2 fewer dose-errors per 100 doses (95% CI: -0.26, -0.13), a 50% relative reduction, and made 0.023 fewer potentially

serious errors in verification per 100 doses (RR=0.51, 95% CI: 0.23, 1.04), in a sample in which the technicians prevented 21% fewer total errors but prevented the same number of potentially serious errors.[147]

Three other unimodal assessments used incident reports, observed few events, and are particularly susceptible to changes in voluntary reporting. The mandatory double-check in pharmacy and new incident-report form were associated with one less incident report per 3 months: a 40% relative decrease (CI na).[143] Likewise, the triple-check chemo form was associated with 1 fewer incident report per month (RR=0.10, CI na).[146] Compared to the prior nurse double-check, the new single check was associated with one fewer incident report per 7 months plus an unreported number of errors related to the double-check of 8 drug classes (e.g., drugs requiring calculations).[145]

The formal medication reconciliation study tracked the rate of potential ADEs and ADEs starting while implementing admission order reconciliation, and continuing through the implementation of discharge medication reconciliation and formal registered nurse and pharmacist signing. The rate of errors (potential ADEs and ADEs) appeared stable during the four weeks of January when the intervention was being implemented, then declined about 50% three weeks later, eventually to a mean of 70% lower than the month of admission drug reconciliation (-57% overall: the sample size was not reported). There was no decline in charted errors after discharge reconciliation, which makes sense, since there was no follow-up post discharge.[132;133]

The study of added technician checks, less pharmacist order entry per day, and special delivery bins found 41% fewer dispensing discrepancies and 17% fewer missing-dose phone calls (CIs na).

Finally, as reported above, the study of the extra pharmacist check and creation of a computerized list for drug dispensing found a significant benefit in dispensing accuracy: 4.5 fewer dispensing errors per 100 doses dispensed (95% CI of RD: -4.9, -4.1. RR=0.33), with especially fewer omissions (-2.8/100) and excess doses (-1.4/100). Unfortunately the study evaluation favoured computerization through its reference point for dispensing errors: post-computerization, the computerized medication record, versus pre-intervention, the photocopy of the original prescription. Data loss and other order transcription errors account for at least some of the benefit claimed for computerization of the record.

The firm conclusion from these studies of checks on drug distribution is that newly trained and selected full-time technicians perform dispensing checks better than pharmacists in their normal routine: the difference was not huge (-0.2 per 100 doses).[147] The vagueness about the intervention's timing casts doubt on the otherwise promising decline in errors associated with admission drug reconciliation. [132;133] The evaluations of single interventions observed too few events too poorly to

draw conclusions (table 15a). One of the multifaceted interventions was suggestive of benefit but biased[149]; in both, the contribution of each individual intervention is unclear.

2.4.12 Drug Distribution--Bed-proximal Drug Storage: the Evidence

Bed-proximal drug dispensing involves dispensing drugs closer to the patient's location.

Study characteristics (n=3, Appendix S, [118;150;151])

Two cohort studies and a pre/post study evaluated bed-proximal drug storage and administration errors. There were two American studies[118;150] and an Australian study[151]. Two cohort studies presented quantitative results[150;151]: the pre/post study did not.[118] The Australian cohort used active observation to compare bedside drug storage with "doorside" drug storage: the within-ward comparison seemed good, with similar staff, patients, time, work environmental, and the same pharmacy.[151] Chart review informed the American study which compared "doorside" medication storage to storage in medication carts.[150]

Bed-proximal Drug Distribution: Risk of Medication Error (see Appendix AF, Table 16a, f)

The two cohort studies found error decreases with more bed-proximal drug storage.[150;151] The third study, a pre/post study, found "no difference" (its power and methods of observation are unknown).[118] In the well-designed prospective study, the bed-side drug storage was associated with a large reduction in administration errors compared with door-side storage: -10 per 100 doses (95% CI: -15, 0.1).[151] Compared with storage on a medication cart, doorside medication storage was associated with the elimination of retrospectively identified administration errors of commission: -0.13 per 100 doses (95% CI: -0.57, 1.6). Errors of omission seemed to decrease by about 1 or 2 doses per 100.[150] Of note, the Australian hospital which estimated the 10% decrease in administration errors did not adopt the bedside system since the space was too cramped for nurses.

In summary (table 16f), the most valid -seeming study estimated a relatively large decrease of 10 administration errors per 100 doses; the others were more neutral. No study of bed-proximal dispensing was informative about adverse events: in the bed-side medication study, neither arm involved adverse events that led to medical intervention; the approach to the doorside did not comment at all on ADEs. Space may be an issue in implementing bedside dispensing.

2.4.13 Drug Distribution--Unit-dose systems: the Evidence

Unit-dose systems distribute drugs in short-term, labeled, unit-of-use packages ready to be administered by the nurse from a patient specific bin. Unit-dosing eliminates the need for a nurse to select a medication from the floor stock or from the patient specific bottle (as in individual Prescription): a pharmacist, pharmacy technician, or automated dispensing device performs the task instead.

Study characteristics (n=5, Appendix T [152-155])

The characteristics of the five studies of unit-dosing (two pre/post, three cohort) are presented below. Two pre/post studies[152;153] evaluated administration errors. One counted incident reports with a modified unit-dose system for controlled drugs[152]; the other used disguised observers to compare ward stock to a centralized unit-dosing for all drugs. No study captured ADEs.

The 3 cohort studies involved as co-interventions automated tools to facilitate dispensing.[154-156] They counted deviations from prescriptions: at the dispensing stage in matched psychiatric wards[154] and at the administration stage in international comparisons (US vs. UK[156] and GER vs. UK[155]).

Drug Distribution: Unit-dose vs. Ward-stock. Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 16b, c, f)

All five studies found statistically significantly fewer errors with drugs dispensed as unit doses (table 16b). The 2 pre/post studies of unit-dosing were consistent: meta-analysed, they showed a 39% decrease in administration errors (RR=0.61 (0.47, 0.79), $Chi^2 = 0.05$, df = 1 (P = 0.83)): estimated through direct observation, 1.3 fewer errors per 100 doses, including 2.3 fewer wrong-dose and 2 fewer expired dose errors, and 1 more wrong-time error /100 doses.[153] All six inventory management errors decreased more than 50%: overall, they decreased 71%. The pre/post study of unit-dosing for controlled substances [152] described potential externalities. Concurrent with the decrease in controlled-substance errors was a significant increase in error in the pre-existing unit-dose system for non-controlled substances (RR=1.4 (1.13, 1.7)), which drove an increase in the overall error rate (RR=1.24 (1.02, 1.5)). Finally, of note is that O'Brodovich found qualitatively results with different reporting methods, which adds some uncertainty.[153]

On the whole, the 3 cohort studies of unit-dosing were less useful to this evaluation (table 16c). They found larger, statistically significant error-decreases with unit-dosing: RRs of 0.086, 0.44, and 0.47; RDs/100 doses of -1.3, -3.8, and -2.7. The French study of psychiatric wards found the smallest RR, 0.086, and the smaller RD, -1.3, associated with the dispensing stage: the errors prevented were usually omissions (RD=-0.9) or extra doses (RD=-0.5), normally of intermediate importance (RD=-0.78/100) but often serious (RD of -0.25/100). Unfortunately, the uniqueness of the unit-dosing technology and of the ward-stock comparator limit study generalizability to North America. Internal validity is a major concern in the international comparisons which limits their utility as technology evaluations (the evaluation of the German traditional system was excluded since its error outcome was not comparable[155]).

The evidence for unit-dosing (table 16f) derives support from the consistency of the five studies that evaluated it, the consistency of the two pre/post study results, and the basic

reasonableness of the Canadian pre/post study[153] and the French cohort study (whose RDs were about -1.3 errors per 100 doses: largely wrong doses, wrong times, and omissions). The studies have unique limitations, however: two have poor comparability,[155;156] one questionable generalizability,[154] and another incident reporting.[152]

One study raised questions about potential externalities,[152] a concern in many of the studies that went unaddressed in the majority. It found 3.4 more errors per 100 doses not dispensed through the expanded unit-dose system (95% CI: 0.0120, 0.056); as a result, the overall error rate increased by 2.3 per 100 doses (95% CI: 0.0023, 0.04), in spite of the 9 per 100 decrease among doses switched to unit dosing.

2.4.14 Drug Distribution--Decentralized Pharmacy: the Evidence

A decentralized pharmacy involves core pharmacy drug dispensing functions taking place outside of the central pharmacy. Potential advantages include timeliness and pharmacist specialization (i.e., familiarity with local needs); potential disadvantages relate to the complexity of managing satellite pharmacies.

Study characteristics (n=3, Appendix U[157-159])

The two studies which gathered data on miscellaneous drug errors from whole 300-400 bed hospitals used incident report; the other study of preoperative drug administration in the OR did not declare what it used. There was a retrospective cohort study of a decentralized pharmacy versus centralized unit-dosing; a sparse time-series study of a roving pharmacist compared to traditional, centralized pharmacy services; and study of a pharmacist order review to dispense preoperative drugs from a mobile cart.

Decentralized Services, Risk of Medication Error (see Appendix AF, Table 16d, f)

None of the study results were particularly robust (table 16d). Compared with a centralized pharmacy, a roving pharmacist was associated with 42% fewer incident reports (95% CI: 0.48, 0.70); the absolute reduction is unclear due to the use of incident report. On the one hand, the suggested consistency of non-medication incidents supports this indicator of the study's validity; however, the new system of transcription and checks may conceivably have changed the sensitivity of incident reporting. Compared with a unit-dose system, the error rate with decentralized pharmacy services was unclear. Finally, there was a trend toward pharmacist order review facilitating the delivery of preoperative drugs at the appropriate time.

Drug Distribution, Satellite + Bedside, the Evidence[160]

Finally, there was a cross-over study of administration errors with satellite pharmacy plus bedside dispensing versus ward stock and traditional dispensing.[160] The study used nurse volunteers. See Appendix V for more details of the study characteristics.

The study found a large decrease in administration errors (there is no stand-alone table for this one study). Non-timing administration errors decreased by 8.5 per 100 dose-opportunities (95% CI: -12, -5); the corresponding relative risk was 0.22 (95% CI: 0.12, 0.40). Prevented errors were primarily wrong dose (-3.7%), documentation (-2.4%), and omission (-1.2%) errors. Time in motion studies found that the system was more labour-intensive. The study seems to add support to the evidence for bedside dispensing, and a little for satellite pharmacy, although the unmeasured interaction terms limits the interpretation of this cross-over study.

2.4.15 Drug Distribution--Automated dispensing: the Evidence

Automated dispensing devices package and label drugs in unit-of-use packages, based on computerized medication profiles. Two examples include the Baxter ATC-212, which usually is located centrally at the pharmacy, and the Pyxis Medstation Rx, which is designed to dispense medication directly to nurses, peripherally, at the "point of use." The machines' intent is to prevent dispensing errors and decrease the human resource requirements of dispensing.

Study Characteristics (n=6, Appendix W[66;161-165])

Six studies (5 pre/post, 1 cohort) at five American teaching hospitals evaluated two companies' automated dispensing systems: the Pyxis Medstation Rx and the Baxter ATC212.[66;161-165] Three studies (2 pre/post, 1 cohort) directly measured dispensing errors (cart-filling accuracy).[161-163] Another study addressed dispensing omissions (and overall incidents poorly).[164] The last two studies evaluated overall medication administration accuracy[66;165] All the machines were new. No study disclosed its funding source, except the Beta-test (which implicitly suggested one).[162]

Automated Dispensing: Risk of Medication Error (see Appendix AF, Tables 16e, f)

In all six studies, automated dispensing was associated with decreases in medication errors (none evaluated ADEs): two of the three with calculable 95% CIs were statistically significant (table 16e).

The Baxter and Medstation pre/post evaluations estimated similar dispensing-error reductions: RRs of 0.78 (95% CI of (0.46, 1.3)) and 0.69 (na), and RDs of -0.19/100 doses and -0.28/ 100 doses.[161;162] The Baxter evaluation was the cleaner of the two. "Incorrect strength, right drug" errors accounted for 75% of its RD.[161] The Medstation study had problems. Its comparability rested on the faulty assumption that the Medstation's automated dispensing function is error-free; also, it tested efficacy in ignoring the automated system's manually dispensed doses.[162] The Baxter cohort study estimated the greatest reduction in dispensing error but was the least informative: for it described errors caught routinely (i.e., not passed along) in an efficacy study with a control arm more susceptible to error (as the control involved less familiar, less common drugs).

A direct-observation study of Pyxis in medication administration [165] found a striking reduction in medication administration errors due to errors in dispensing and administration: RR=0.62 (95% CI of RR: 0.48, 0.78); RD=-6.5 / 100 doses (95% CI of RD: -9.7, -3.3); however, the potentially reactive study measure is a confounder. Most of the RD observed through direct observation of administration arose from wrong-time errors (-3.0/100), omissions (-2.0/100), and "other" errors (-1.3/100); "unauthorized drug, extra dose, wrong-dose, rate, or preparation" errors together contributed -0.17/100. One study's review of the nurse's log also found reductions in dispensing omissions per day (an average RR of 0.3 on its two units, or an average of 0.38 fewer per patient-day[164]) and another found a shorter main wait for the first dose.[162]

Two (less error-sensitive) studies of incident reports and unclear methods[66;164] estimated relatively smaller but quantitatively uncertain benefits (the methods of one were particularly problematic[164]).

To summarize (table 16f), one reasonable pre/post study and two biased efficacy studies showed decreases in dispensing errors with automated dispensing, on the order of about 0.2 fewer /100 doses. Three observational studies suggested reductions in administration errors: the estimate which was quantitatively precise, statistically significant, but confounded suggested a large benefit (-6.5 errors/ 100 doses) related mostly to wrong-time and omission errors (which the dispensing studies did not measure).

2.4.16 E-medication profile: the Evidence

Electronic medication record creation and linkage allows for remote and multiple access of a given patient's medication record, potentially preventing erroneous order interpretation, or order handoffs (e.g., transcription). Computerization may facilitate the integration of the two to improve order communication; however, issues around data access and modification are important to resolve.

Study Characteristics (n=4, Appendix X [144;149;166;167])

Four pre/post studies, including one with interrupted time-series data, evaluated the creation and linkage of electronic-medication profiles: three studies evaluated record linkage[144;166;167] and the other an electronic pharmacy medication profile.[149]

The two single-intervention evaluations were American. One counted incident reports of all medication errors which occurred in the 2 years before and after implementing a nurse- and pharmacist-shared computerized MAR.[166] Another was an Ohio University Health System-funded audit of order transcription errors which occurred with and without the linkage of CPOE to the MAR.[167] A British hospital assessed a Medichain-supplied, linked electronic system of CPOE, CDSS, electronic nursing MAR, point-of-use automated dispensing, and bar-coding for administration.[144] Finally, a Spanish study which was also counted under double-check protocols

assessed a computerized MAR in conjunction with an additional pharmacist check on orders.[149] Sampled follow-up periods ranged from 1-12 months, in the early 1990s.

Results (see Appendix AF, Tables 17a, b)

All four studies' interventions were associated with decreases in medication errors (none evaluated ADEs): the three with calculable 95% CIs were all statistically significant (see table 17a).

Two of three studies of electronic record linkage evaluated order communication directly. Both addressed record linkage to CPOE. Both claimed that the linkages eliminated the linkage-related order communication errors.[144;167] Compared to an unlinked manual MAR and CPOE, the linkage of an eMAR to CPOE was associated with the statistically significant elimination of 11.3 per 100 order transcription errors (RR=0, 95% CI: 0, 0.05), including 4.6/100 orders not transcribed and 3.5/100 wrongly transcribed. The major uncertainty specific to this study relates to lack of reporting on the process of the audit of the eMAR. The other study of order communication, company-sponsored, found that CPOE linked to a portable nursing eMAR eliminated the 1% of prescriptions otherwise illegible or unclear in their instructions at the time of administration. These vague prescriptions may result in omissions, wrong-time errors, and other errors of commission.

The third study of record linkage presented incident-reported errors arising out of a shared eMAR. It found fewer errors while using a shared nursing and pharmacy eMAR: RR=0.6, $p<0.0001$. In particular, minor errors seemed to decline: the RR of wrong med dispensed not administered was 0.50, and the RR of wrong time was 0.46, versus an RR of 1 for wrong drug administered and duplicate meds. The time-series data demonstrated a consistent, gradual decrease in the error rate with time.

The fourth study evaluated the pharmacy's creation and use of a computerized list for the purpose of drug dispensing. Besides potentially facilitating the use of the medication profile, the intervention involved an extra occasion for the pharmacist to review the order. The study found a significant benefit in dispensing accuracy: 4.5 fewer dispensing errors per 100 doses dispensed (95% CI: -4.9, -4.1. RR=0.33), with especially fewer omissions (-2.8/100) and excess doses (-1.4/100). Unfortunately, as discussed with regard to double-check protocols, the study evaluation favoured computerization through its reference point for dispensing errors, by assuming zero transcription errors in the computerized group.

In summary (table 17b), two pre/post studies (one with unclear methods[167]) reported significant benefits with regard to order communication: -11.3 /100 transcription orders (statistically significant) and -1% of prescriptions unclear.[144;167] Two others are suggestive of benefits, which were statistically significant but less certain due to study design weaknesses.[149;166]

2.4.17 Bar-coding: the Evidence

Bar-coding adds a verification step for drug dispensing or drug administration. Bar-coding applied to a medication package may facilitate the verification of a medication's appropriateness during the *dispensing* and *administration* stages. During drug *administration*, bar-coding of the patient (e.g., wristband) may help verify the appropriateness of the medication to the patient.

Study Characteristics (n=2, Appendix Y [168;169])

Two American studies assessed the impact of bar-code systems alone: one for drug dispensing,[169] and one for drug administration.[168] The evaluation of bar-coding for drug dispensing (bar-coded unit doses and drug cassettes) checked medication cassettes against the computer medication profile at a satellite pharmacy.[169] The evaluation of bar-coding used incident report pre-intervention, and incident report plus the bar-code system's automatic log post-intervention; thus, the study comparison was unbalanced. Other studies evaluated bar-coding in concert with other technologies and thus were treated as multi-faceted interventions.

Bar-coding, Risk of Medication Error (see Appendix AF, Tables 18a, b)

Bar-coding for dispensing was associated with the elimination of dispensing errors: i.e., the elimination of the 0.38 dispensing errors per 100 doses allowed by the first pharmacist's check (95% CI: -0.46, -0.30).[169] The investigators who used more sensitive error-detection methods in the arm with bar-coding for drug administration observed a non-statistically significant increase in discrepancies per dose: $+2x10^{-5}$ (95% CI: $-3.9 *10^{-5}$, $7.9*10^{-5}$), RR=1.1.

2.4.18 Highly Automated Drug-distribution: the Evidence

Due to alterations in user/machine interfaces, integrated, highly automated drug distribution systems may function differently from single-technology interventions and are discussed here. For example, the functionality of bar-coding for checks on drug administration might change if it is linked directly to CPOE, as opposed to a manually entered pharmacy MAR.

Study Characteristics (n=4, Appendix Z [5;144;170-172])

There were four pre/post studies of installing integrated, highly automated drug-distribution technologies: with eMARs, and bar-coding for drug administration in all four,[5;144;170-172] CPOE in three,[144;170;171] CDSS in three [5;144;170;172] and maybe a fourth,[171] and automated dispensing in one[144] ("maybe" CDSS in one Clinicare study because the other Clinicare system included CDSS and the study reporting is questionable). The element of bar-coding for drug administration is of particular interest due to the absence of comparative evidence assessing bar-coding for drug administration alone.

Almond *et al* came closest to suggesting a funding source: Medichain invited them to test the system and provided constant technical support.[144] The study used direct observation on a medical

ward to identify omissions and instructions unclear at administration (instructions unclear at administration were addressed under "e-medication profile").

The three other studies used incident report, which can be particularly limited in these studies due to their institution of electronically linked records (with fewer checks). The VA hospital study instituted automated dispensing but no CPOE: it evaluated pharmacy and nursing errors.[5;172] The last two studies measured drug errors broadly with "Clinicare by Clinicom": i.e., CPOE, eMAR, and bar-coding for administration, with CDSS mentioned in one[170] but not the other whose co-intervention was hospital downsizing.[171]

Highly Automated Drug Distribution: Risk of Medication Errors (see Appendix AF, Tables 19a, b)

After instituting eMAR, bar-coding for admission, and automated dispensing, there were 5.4 fewer dispensing omissions per dose (95% CI = -7.9, -2.9; RR=0.46). As mentioned with e-medication profiles, the 1% of order illegible or unclear at administration were eliminated (CI na).

The studies of incident reports had varied results. The VA system observed a statistically significant and large relative reduction in errors (RR=0.36; 95% CI=0.27, 0.47); however, the absolute difference was small (RD=-0.014 per 100 doses), nine times smaller than the positive Clinicare study (RD=-0.12/ 100 doses, CI na) but with a similar relative risk (RR=0.29). The Clinicare studies were also contradictory. Whereas the Clinicare study with the interim downsizing found no difference (RR=1, CI na), the aforementioned Clinicare study which mentioned CDSS found a decrease per 1000 doses of 1 deviation from the original prescription, and 1.2 deviations from pharmacy and nursing standards.[170;171] The latter decrease includes 47% fewer transcription errors (potentially attributable to electronically linked records), 43% fewer wrong-time and 52% fewer omissions (potentially attributable to CPOE, nurse eMAR printouts and alerts), and 33% fewer wrong-drug and "no change" in wrong-dose errors (potentially attributable to bar-coding and secondarily CDSS).

The studies also mentioned undesired effects which may be relevant to error. All three implementations mentioned that clinicians found technology use difficult in some way: e.g., in terms of time,[5;144;172] a steep learning curve,[170] less of dosing flexibility, and a loss of doctor-nurse coordination.[173]

To summarize (table 19b), three of four studies suggested benefits with integrated electronic dispensing technologies; one was neutral but limited by its interim downsizing (and reliance on incident report). The Medichain system of linked CPOE, eMAR, bar-coding for admin, and CDSS reported 5.4 fewer dispensing omissions per dose (95% CI = -7.9, -2.9; RR=0.46), and 1% fewer orders illegible or unclear at administration. Collectively, the three other studies suggested likely technology-associated decreases in pharmacy and nursing medication errors by an uncertain amount.

A concern is that clinician's difficulties with technology use may have negative global effects which went unmeasured.

2.4.19 Self Administered Medication (SAM): the Evidence

Patients and their care partners can "self-administer" medication (instead of nurses).

Study Characteristics (n=2, Appendix AA[174;175])

Two American hospital units from '90s provided evaluations of self-medication programs: one, a post-partum unit,[174] and another, a unique Cooperative Care acute-care unit in which a family member or friend lives with the patient.[175] In the pre/post study of the post-partum unit, SAM involved educating capable patients to use a standardized SAM packet, as opposed to ward-stock pharmacy for a variety of medication regimes. In the cohort study of Cooperative Care versus the rest of the acute-care teaching hospital, the SAM intervention involved educating patients and their care partners to administer their medications themselves prior to discharge.

Self-administered Medication: Risk of Medication Error (see Appendix AF, Tables 20a, b)

Both studies' control groups were limited in their comparability, and found reductions in medication errors with SAM. In one study, the "pre" system changed from offering many customized medication plans to a "post" system with a small number of standardized medications.[174] Decreased narcotic use is another confounder, but surveyed women were satisfied.[174] Post-partum SAM was associated with relative risk of oral medication error of 0.25, for a risk difference of -0.11/pt (5/33 vs. 2/53 patients).[174]

In the other study, the self-administration group had one-quarter the number of prescriptions and was selected for its ability to self-medicate; also, the use of incident report may be sensitive to the altered care process.[175] Medication administration by patient and care partner was associated with statistically significantly fewer incident reports per order: a relative risk of 0.76 (95% CI of 0.61, 0.95), or 1 fewer medication incident report per 100 discharges.

Together (table 20b), the studies suggest a potentially smaller risk of medication error with SAM of an uncertain magnitude; however, the studies have serious limitations.

2.4.20 Drug Administration Modifications: the Evidence

Nurse-led drug administration can vary in its use of personnel, level of personnel training, and administration records. For example, nurses can distribute responsibility for drug administration, or allocate the task to specialized drug-administration personnel. Another example is the comparison of registered nurses with nurse technicians.

Study Characteristics (n=7, Appendix AB[118;176-180])

There were 7 single-intervention studies of drug administration[118;176-180]: 4 pre/post studies, 2 cohorts, and a two-group RCT. One paper described a cohort study and a pre/post study to compare

administration-error rates with a designated medication nurse and nurses administering medication for each of their patients.[176] A two-group randomized crossover study compared two nurses administering medication to one single RN: only the period before the crossover was incorporated into this review.[177] A biased cohort study compared unlicensed medication administration technicians' day- and night-time error rate to RNs' nighttime error rate. There was an evaluation of an IV training module.[179] Finally, two studies addressed changes to records of medication administration. A pre/post study addressed special transcription procedures to avoid potential misinterpretation of the MAR.[118] A study early and late in a returned-dose monitoring program counted returned doses.[180]

Drug Administration Modifications: Risk of Medication Error (see Appendix AF, Tables 20a, b)

The studies of alterations to systems of drug administration were inconclusive. Table 20a describes them in greater detail. The cohort study of a designated (primary) medication nurse observed 42% fewer errors with the primary model (RR=0.48, 95% CI: 0.37, 0.63); however, the reliance on incident reports made the RD small (9 fewer administration errors per 10000 doses). Conversely, the pre/post/post study found an initial 130% increase in error during year one with the primary model (95% CI: 40%, 290%), followed by a 10% increase over year 0 during year 2 (95% CI: -40%, +100%); the risk differences were similarly small (5.5 per 10000 doses administered, and 5 per 100 000). The pre/post study may be a more reliable than the cohort study since it used the MAR to identify errors and the cohort study cohorts were very different. Essentially, however, the evidence on primary versus functional models is null. Likewise, the study of adding a second nurse for drug administration found a statistically significant decrease in administration errors, totally driven by instances of "no signature [written on MAR]/drug omitted": a relative risk of 0.67 (95% CI: 0.48, 0.94) and a risk decrease of 0.13 per 100 doses. The insensitive recording methods and potential confounding of records with practice (where a second nurse might record) make these results very limited. With the minimal description of study methods and the sample size unreported, the reported 60% reduction in potential misinterpretations of the MAR with special transcription procedures is also difficult to interpret.[118]

Three studies were somewhat more informative. A cohort study of administration errors with unlicensed personnel found a very small relative risk of errors of omission, 0.094 (95% CI of RR: 0.03, 0.31. RD=-1.0 /100 doses) and wrong time, 0.20 (95% CI of RR: -0.07, -0.6; RD=-0.6/100 doses)[178]; however, the comparison was like night (RN administration time) and day (unlicensed personnel administered day and night, but most drug administration takes place during the day), and confounded by who was associated with the incident reports. The results are promising but warrant further investigation. The IV training module was associated with a gradual decrease in error over

time: omissions dropped, while wrong-dose and other errors remained constant.[179] The cause may have been increased vigilance due to training, as the investigators suggested, but they did not rule out other causes of temporal variation such as decreased sensitivity of incident reporting over time.

Finally, the 64% reduction in dose returns with the returned-dose log was statistically significant, representing 0.7 fewer dose returns per 100 doses (95%CI: -0.8/100, -0.6/100).[180] The overall impact of the intervention is unclear, however, due to uncertainty about the balance of the inferable decreases in dispensing duplications and administration omissions, and the balance of costs of increased personnel time and decreased drug waste: the decrease in dose-returns certainly was much greater than the decrease in administration omissions with the implementation of returned-dose reminders and the overcoming of supply shortages (RR of 0.71, 95% CI: 0.5, 0.9).

To summarize (table 20b), the evidence for preventing administration errors through system modification is inconclusive.

2.4.21 Unique, Miscellaneous, Single Interventions: the Evidence

Some interventions were simply unique and hard to classify.

Study Characteristics (n=4, Appendix AC[181-184])

Four pre/post studies were unique and unexpected. One, which took place during one semester, evaluated a new house-officer schedule with dedicated night teams, in a hospital with low night volume allowing fewer night shifts (10% of admissions from 10pm – 8am).[181] One used incident report to evaluate error-based performance evaluations.[182] One studied a multifaceted change to a "Byzantine" heparin ordering and documentation process,[183] and the last an outsourcing of substandard in-house IV admixture compounding.

Unique Interventions: Risk of Medication Error and Adverse Drug Events (see Appendix AF, Tables 22a, b)

The schedule with dedicated night teams was associated with 4.9 fewer potentially serious physician drug error per 100 patients discharged (95% CI n/a), an RR of 0.71; and 0.37 fewer potentially serious drug errors per discharge drug order (95% CI: -2/100, 0.9). The night team were associated also with a statistically insignificant 1% absolute decrease in in-hospital mortality (95% CI: -6%, 4%), an 18% relative decrease. Potential mediators of improvement included more patients being admitted on short-call (60% vs. 20%), and less acute sleep deprivation (mean sleep post-long call: 4.3 vs. 2.3 hours). Serious potential confounders include the 20% shorter mean LOS (which could be a cause or a consequence), and increased intern and resident experience during the academic term. It is unclear how many prescribing errors actually reached the patients.

The study which emphasized personal responsibility for incident reports of dispensing errors found 14 fewer dispensing errors per month for 964 beds (95% CI na), otherwise expressed as a 70%

decrease. The problem with this study which makes it unconvincing is the likely dependence of measurement sensitivity on the intervention.

Two studies suggested relationships that seem intuitive.[183;184] There was a study of outsourcing the IV admixture compounding service, from a facility that did not meet American Society of Hospital Pharmacist guidelines and experienced space and IV supply shortages, to an external supplier with a contract contingent on the study results; the intervention also involved adding technician reminders to nurses of missed doses.[184] The study found a statistically significant decrease of 1.1 administration omissions per 100 doses (95% CI: -2/100, -0.19/100). The take-home message seems to be that carefully conceived performance-based outsourcing can (in the short-term) outperform substandard local facilities. Finally, a study that did not explain its data collection methods reported that simplification of earlier "Byzantine" heparin-ordering procedures reduced heparin order errors by 73%, or 0.59 per month (95% CI unknown).[183]

2.4.22 Multi-faceted and Continuous Quality Improvement (CQI) Interventions: the Evidence

CQI studies involve a measurement, a collective response to the measurement (generally multi-faceted), and a re-assessment. Multi-faceted interventions involve several system changes that cannot be assessed in isolation.

Study Characteristics (n=12, Appendix AD [22;79;131-133;185-194])

12 studies fell into the multifaceted or CQI framework, primarily by default. The studies in this category were heterogeneous, except that they all used a pre/post or other time-series design. The main strength of these studies was that they appeared to frequently involve whole hospitals[132;133;185-189;191;193;194] as opposed to single wards[190] or sets of patients.[79;192] One study involved 1 intervention,[185] four studies had 3-5 interventions,[190-192] five had 6 or more,[132;133;186;187;189;193;194] and three were unclear about the number of interventions.[22;79;188] Common categories of intervention were automation (n=5),[132;133;187;191-194] education (n=5),[189-191;193;194] and standardization (n=4).[132;133;187-189] Outcome ascertainment was through chart review (n=3),[79;132;133;187;192] incident report (n=3),[22;189;193] variations on self-report (n=3),[185;186;188] pharmacy log review (n=1),[194] and undeclared methods (n=2).[190;191] Three studies were related to multi-hospital collaborations.[132;133;186-188]

Results (see Appendix AF, Table 23a, b)

Of three studies of multi-hospital initiatives, two studies summarized the results of the Institute for Healthcare Improvement (IHI) collaboration.[132;133;186;187] The main report summarized the initiatives of 22 teams in the 27 participating hospitals. The study counted medication errors averted by 17 projects: mostly heparin-related (n=7), or warfarin-related (n=4), but also (1 each) related to chemotherapy, electrolytes, IV administration, IV solutions, medication and allergy

verification, narcotics, and polypharmacy. Relying on the various implementing teams' progress reports to their supervisors, the investigators found that the teams had averted 1513 errors in 13 months (excluding teams which censored error increases), an average of 17 per hospital per month, and a median of 6.5 per month.[186] One of the IHI hospitals reported separately on chart reviews of errors[133] or potential ADEs and ADEs[187] per dose: it found a decrease of 0.52 per 100 doses during a 3-year period of promoting a safety culture with new employees, standardization, automation, and 11 targeted interventions.[132;133;187] Finally, a 13-hospital collaboration reported on the results of a survey given to hospital-participants who had implemented several initiatives, and found that the representatives were statistically significantly less likely to have observed any medication error in the previous week (RD=-0.055, 95% CI = -0.09, -0.022; RR=0.73), and more likely to report that the error did not reach the patient (RD=0.06, 95% CI=0.013, 0.12; RR=1.12).[188]

There were two relatively non-diffuse multidimensional intervention studies. The drug-administration study which introduced new multiskilled (non-professional) workers, and new architecture (including bed-proximal dispensing) to a newly demarcated unit found 3.1 fewer medication errors per month (RR=0.44, CI na), using undeclared error-ascertainment methods.[190] This difference is much smaller than that observed than in single-intervention studies of unlicensed drug-administration personnel [178] bed-proximal dispensing, but given the likely insensitivity of this study's[190] measurement and cointerventions (e.g., new employees), this study sheds very little light.

The study of morphine-treated NICU patients found 2 fewer adverse reactions to morphine reported every 3 months following the introduction of CPOE and CDSS (CI na); sedation assessment forms for nursing; and mandatory endotracheal intubation before ophthalmic cryo-surgery.[192]

There were three studies of hospital-level interventions that only fit within the CQI category: they all involved measurements and responses at some level.[22;79;185] Compared to year 1 of a program of medication-error committee meetings and recommendations, year two of the program saw 47 fewer incident-reported errors, of which 33 were serious and one was an "actual" error—i.e., which reached the patient (CI n/a).[22] The LDS hospital did not explain how it achieved a statistically significant decrease of 35 errors per 100 deep sternal or mediastinal infections. (95% CI=-58/100, -13/100) The last study involved clinical pharmacists attempting to meet their targeted standards for percent-acceptance of their intervention, then analysing and reviewed their success three times: overall, the exercise statistically significantly decreased the chance of their interventions not being rated as preventing a serious error by 9 per 100 interventions (95% CI=-0.15, -0.226; RR=0.90). Also, percent-acceptance of interventions increased.[185]

There were four studies of broad, multidimensional interventions within hospitals.[189;191;193;194] Standardization of medication administration times, education, new drug labels, managerial studies,

and a managerial push to improve delivery times was associated with a 20% relative decrease in incident-reported deviations from charted prescriptions, particularly among wrong-time orders.[189] Automated dispensing, standardization or administration times, reminders, structured communications, new charting documents, and new dispensing areas were associated with a 7 fewer errors in documentation per 100 patient-days (CI n/a).[191]

Last among broad, multidimensional intervention studies are the two of 23 and 22 system changes implemented over (long) 4- and 6-year periods, respectively.[193;194] A major limitation of both of these studies is the lack of clarity of the relative timing of implementation periods and observation periods, which limits the reports' abilities to associate interventions with event rates. The former study, Pfizer-sponsored, found relative rates of 23% fewer prescribing errors and 53% fewer serious prescribing errors in the pharmacy log(CIs n/a).[194] The other study, at Sick Kids (Toronto), analyzed incident reports as a time-series.[193] Between 1992 and 1998, there was a 46% decrease in "actual" incident-reported errors per year (RD=458; CI na). No stable baseline measure was taken, but there was a continuous decrease until about 1995/1996, and then a plateau. Relative risks of errors subdivided by severity were similar; actual plus potential errors among nurses, pharmacist, and physicians all declined (in that order of RDs). The consistency of the decline of several types of errors adds some weight to causal inference.

This heterogeneous group of studies of complex interventions does not lend itself to definitive conclusions, particularly given the studies' methodological limitations (see Tables 23a, b). All the studies showed some benefit: nine in terms of error [22;79;186;188-191;193;194]; one in terms of potential ADEs and ADEs or errors[132;133;187]; one in terms of adverse reactions to morphine,[192]; and one in terms of the clinical significance of pharmacist interventions.[185] One hospital seemed quite successful in the prevention of series errors; however, it was quite vulnerable to threats to validity (e.g., it lacked a stable baseline measure) and it is unclear how one could go about replicating it. [132;133;187] Other broadly oriented intervention studies found appreciable relative benefits but small risk differences, which makes the significance of the results questionable (although promising to many authors). As a default category, the CQI category was too depleted to lend itself to any inferences. None of this set of multifaceted or CQI studies was conducted in a manner that explained the effectiveness of a particular technology or system.

2.4.23 Failure Mode Analysis and Root Cause Analysis: the Evidence

Failure Mode Analysis and Root Cause Analysis are two formal analytic methods which can guide multifaceted interventions. Failure mode analysis involves identifying potential errors in each of a process's steps, assessing the likelihood of those errors, and determining their likely

consequences,[38] whereas root cause analysis involves the retrospective identification and assessment of factors which may have contributed to important events.[39]

Study Characteristics (n=2, Appendix AE [39;195])

Two pre/post studies employed formal analytic methods to guide multifaceted interventions.[39;195] In a study which took place in a 30-bed ward , Failure Mode and effects Analysis (FMA) suggested the following changes: standard medication administration times, the use of medication protocols, removal of unrequired medication from the drug trolley, and provision of a current drug reference.[195] Another study at a large hospital involved root-cause analysis guiding the implementation of 22 system changes: e.g., the availability of a clinical pharmacist, floor-stock limits, computerized weight-based dose checks, and dual dose calculation by nurses.[39] Both studies relied on incident report: to identify errors[195] and to identify "actual," potential, and fatal ADEs.

Results (see Appendix AF, Tables 24a, b)

The study of FMA with administration standardization found 1 fewer error per 100 doses (RR=0.69, CI=n/a).[195] The observed error reduction was largely due to omissions and wrong-time errors, although errors declined consistently across categories (25% relative decrease in non-omission nor wrong-time errors, per day). The study of RCA for ADE prevention found a statistically insignificant decrease in ADEs: 3 fewer per 10000 patient-days, a relative reduction of 60%.[39] The study was prompted by the events of the first month, which, if excluded, yield a relative reduction of 35%, representing 3.8 fewer potential and actual ADEs per year.

These studies' limitations relate to the problems with incident report. For example, in the FMA study the stimulated incident report may have been a reactive measure, and both measurement techniques were clearly insensitive. In the FMA study, the risk difference of 1% per dose may have been large, considering that it was based on incident report, and the relative reduction was appreciable, but it is difficult to extrapolate from relative associations in errors observed to absolute reductions in errors prevented. Likewise, the RCA study involved increasing the availability of clinical pharmacists: if the other 21 system changes were neutral, the clinical pharmacist studies would suggest larger absolute ADE reductions than were observed in the RCA study.[39] To summarize, the studies were too insensitive yet complex to be conclusive, other than to offer a suggestion of a potentially favourable effect.

2.5 Discussion

2.5.1 Final Summary

This review does not simply subdivide the evidence and address it on a technology-by-technology basis. This review takes advantage of its broad scope and internal consistency to globally assess the many technologies available to help prevent medication error and adverse drug events.

To summarize, the limitations of the evidence add uncertainty to recommendations about technology use. Based on the evidence gathered in the review, it seems that the most promising technology for current application is the clinical pharmacist, followed by CDSS for CPOE in advanced applications. The evidence for pharmacokinetic dosing and nomograms is also quite suggestive about avoiding ADEs. The next most promising group of technologies included electronic medication record linkage, bed-side drug dispensing, physician education about prescription-writing, and unit-dose systems—with automated dispensing, CDSS for dispensing calculations, and dedicated night officer teams perhaps a notch below. The technologies with the least promising evidence were as follows: CPOE, computerized pumps, standard drug protocols, verbal orders, self-administration, double-check, decentralized pharmacy, e-medication profile creation, bar-coding, altered drug administration models, and multifaceted interventions guided primarily by the FMA, RCA, and CQI frameworks.

To inform the choice between the technologies, the final data summary table (Table 25) presents information which allows for a comparisons between technologies with regard to the consistency of technology-specific evidence, the grade and level of the evidence, and the magnitude of the observed associations.

Vote-counting should not be the primary analysis for this review (see column 2). The consistency of the favourable evidence is as much a cause for concern as it is a cause for conclusive reassurance, given the threat of publication bias. As only 41% of the comparisons of interventions reported a statistically significant outcome (64/155), most of the evidence falls into a statistically uncertain but intervention-favourable domain.

The level and grade of the evidence was low on the whole (see column 4: level and grade of evidence). On the Oxford scale of recommendations, which runs from A to D, there were no As and the majority did not score higher than a D on any outcome—Ds essentially pointing to an absence of epidemiologic evidence. The order of the technologies in the discussion that follows reflects a general decline in the grade of the evidence supporting the technologies' effectiveness.

All of the technology assessments counted medication errors or potential ADEs. Only CDSS, clinical pharmacists, kinetic dosing, and nomograms offered strongly suggestive evidence

(i.e., not grade D/D) about preventable ADEs or all-cause ADEs (incidentally, those are all the interventions and the only interventions which primarily address prescription errors).
Of these technologies, only CDSS and clinical pharmacists were assessed for broad patient indications. Within the review, the magnitude of the risk differences were greater with clinical pharmacists (-5 per 100 patients; -2, -1, +1 per patient-day) than with CDSS+CPOE (-0.08 and 0.2 per patient-day at Brigham and Women's; -1.2 and -1.7 per 100 patients at LDS); the former also achieved statistical significance, whereas the latter did not. All these ADE evaluations were pre/post studies limited in their generalizability; however, the CPOE+CDSS studies appear somewhat more limited, with their underemphasized early negative results (at the Brigham and Women's) and record-centric evaluations (at the LDS hospital)—discussed in section 2.4.3. A recently published pseudo-randomized trial is notable in that it demonstrated a statistically significant effect on a serious patient outcome[55]: a 3.3% absolute decrease in the rate of patients experiencing deep-veins thromboses or DVTs, among patients automatically flagged as high-risk, without an increase in rates of bleeds or death.[196]. Although potentially limited by contamination and externalities, this study presents strong evidence as to the potential benefit of CDSS. This review agrees with a recently published systematic review which found consistent evidence that CDSS helps prevent the errors that the designers intend to prevent[55]: what seems key is to support appropriate decision-making, and to design efficient systems that do not detract from other dimensions of care.

The studies of dosing-support technologies for various specific indications had results which were of a common order of magnitude. Pharmacokinetic dosing of aminoglycosides, theophylline, (vancomycin,) and anticoagulants, clinical-pharmacist dosing of anticoagulants, and nomogram dosing of anticoagulants saw non-statistically significant trends toward decreases in ADEs on the order of single digits per 100 patients (it is difficult to comment further given the heterogeneity). The pharmacokinetic dosing studies were generally small, efficacy RCTs, whereas the observational studies of clinical pharmacists and nomograms seemed reasonably representative of normal practice.

The other studies that reported differences in ADEs were more limited. There was one more study of CPOE+CDSS for decided heparin prophylaxis which observed 0.04 fewer ADEs per 100 patients (95% CI=-0.5/100, 0.4/100). CDSS alerts for targeted interactions saw large relative decreases (0 & 0.2) but the absolute ADEs reductions per indicated patient were less dramatic (-1.7/100 and -0.04). Some studies from the Institute for Healthcare Improvement collaboration reported large decreases in ADEs (e.g., -10 per 100 patients); however, the reporting structure of subordinate to supervisor, the lack of definition of study methods, and the lack of statistical inference undermine the conclusions of these studies. The FMA/RCA and other multi-faceted studies that

reported ADEs and interventions relied on incident report; thus, they observed very few events and, beyond projecting a favourable direction of results, are not very informative.

The interventions that were associated with reduced preventable and all-cause ADEs were associated with varying decreases in errors and potential ADEs. Clinical pharmacy and CDSS+CPOE both had grade B evidence; as with ADEs, the RDs with clinical pharmacy (-20/patient; -2/order) were lower than with broad CDSS+CPOE (in one study, -1 non-missed dose error per 100 patient-days, while missed-dose errors increased by 1.4 per 100 patient-days; in the other, there were 0.5 fewer non-intercepted potential ADEs per 100 patient-days). Nomograms also had grade B evidence for a shorter time to therapeutic dose (shown), and lower proportions of patients with non-therapeutic clotting times (see "nomograms") for more detail). The kinetic studies were downgraded to a "C" for their lack of generalizability but showed fairly large decreases in potential ADEs: a median mean of -9 per 100 patients (range: -77, -4). Finally, while a customized CDSS alert system was associated with 66% fewer cisapride alerts (95% CI=0.3, 0.4), the one commercial CDSS system evaluated (of alerts) was associated with a relative risk of error of 0.87 (CI n/a, RD n/a).

With one exception, the remaining technologies relied on counting errors to indicate a reduced probability of ADEs: on the Oxford scale, they scored Cs and Ds. More frequent C-level error-preventers were CPOE linkage with the pharmacy MAR, bed-side drug dispensing, and physician education (not obviously different with new forms): their risk differences were, respectively, -11 transcription errors per 100 orders (95% CI(RR)=0, 0.05); -10 dose administration errors per 100 doses (95% CI=-19, -2), and about -11 illegible orders per 100 (2 studies). Also at the C-level were highly automated systems, unit-dose systems, and automated dispensing: their RDs were -5.4 dispensing omissions per 100 doses, -1.3 administration errors per 100 doses, and -0.2 dose dispensing errors per 100 doses (-6.5 dose-administration errors per 100 in a study with a reactive measure).

The D-level technologies were as follows: CPOE, CDSS for dispensing calculations, computerized pumps, drug protocols, verbal orders, self-administration, double-check, decentralized pharmacy, e-medication profile creation, bar-coding, drug-administration models, FMA, RCA, multi-faceted interventions, and the new resident work schedule. The most dramatic error reduction was with CDSS calculations: so dramatic* that the evidence for them is promising in spite of their studies' limitations (*very statistically significant RRs of 0, 0.18; RDs of -12 and -54 per 100 orders). Based on the evidence, possibly promising technologies include standardized drug protocols, decentralized pharmacy for perioperative dispensing, unlicensed specialized drug-administration technicians, and dedicated "night" house officer teams.

The dedicated "night" officer team study was one of two that observed statistically insignificant mortality reductions which were also methodologically limited, but still worth considering. The LDS hospital reported a decrease in antibiotic-associated mortality of 1% of patients (RR=0.7), while the new night teams were associated with an overall decrease of in-hospital mortality of 1% (95% CI=-0.06, 0.04). A recent study of an intervention that randomized interns (but not patients) to a schedule that reduced interns' cross-coverage to increase interns' sleep found that the randomized interns made 17% fewer medication errors (p=0.03) and 27% fewer serious medical errors ($p<0.001$); however, the non-randomized patients died statistically insignificantly more often with less cross coverage (p=0.27): 14.5% vs. 12.7% and rates of preventable ADEs were almost constant (38.6 vs 38.5 per 1000 pt-days, p=0.91). Thus, while sleep-oriented scheduling may be promising, the effect on patients' outcomes is unclear.

Table 25: Final Summary
Note: acronyms presented below the table.

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
CPOE alone	3:0:0	Fill-in, picklist, na	D (4)	3	0.74 (0.5, 1.09) or, stratified, 1 (na); OR=0.48 (0.3, 0.7); 0.8 (na)	-0.22 -1.2 -0.1	Order error /order Order error /order Misc. Error /pt-day
CDSS +/- CPOE	23:0:0	CDSS +CPOE	B (2c)	6	Median 0.27 (Range: 0.14, 0.5; 4 stat. significant)	-0.3 to 115	ADE /pt-day
			C (2c)	1	1.5 (1.3, 1.7)	1.4	Missed-dose error /pt-day
		CDSS alerts	C (2c)	2	0.34 (0.3, 0.4); 0.87 (na)	-6 Na	Cisapride order error /order --
		CDSS (calculation)	D (4)	2 (2)	0 (0, 0.1); 0.18 (0.08, 0.4)	-12, -54	Order error /order
		CDSS+CPOE	C (2c)	2	0.83 (p=0.4); 0.36 (0.04, 2)	-0.08 -0.19	ADE /pt-day
		CDSS+CPOE , antibiotic		2	0.03 (na)-broad 0.3 (0.1,0.8)-ICU	-1.2 -1.7	Antibiotic ADE /pt Antibiotic ADE /pt
		CDSS+CPOE, heparin		1	0.86 (0.1, 5)	-0.04	Heparin ADE /pt
		CDSS alert	C (2c)	2	0 (na) 0.2 (0.1, 0.3)	-1.7 -0.04	Cisapride ADE /pt Digoxin ADE /pt
Kinetic dosing	15:0:0		C (2b)	11 (1)	Median mean=0.63 (Range: 0.1, 0.81)	Median mean: -9 (R:-77,-4)	Potential ADE /pt
			A (1a)^	4 (random)	0.56 (0.2, 1.6)	-5 (-14, 4)	ADE /pt

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
Clinical pharmacist	16:1:0	Broad	B (2c)	3	0.5, Na 0.6, (p almost significant) 0.9 na	 -20 -2	*Rx Error* - *Misc Error* /pt *Rx error* /order
				1	0.2 (0.12, 0.33)	-0.48	Discharge Rx error /order
			B (2c)	4	0.13, (0.016, 1.016) 0.22, (0.02, 1.04) 0.25, (0.04, 0.94) 1.26 (0.83, 1.9)	-5.2 -2.1 -1.0 0.9	Prev or All-cause /pt ADE /pt-day /pt-day /pt-day
		Warfarin	B- (2c)	3	0.2 (0.01, 1.04) 0.37 (0.03, 2.4) 1.4 (0.2, 10)	-8 -3 +2	Bleed /pt
				2	0 (0,7) 1.2 (0.2,7)	-3, +0.8	Thrombus /pt /pt
Nomogram	8:0:0	Heparin	B (2b)	5		Median Mean Difference: -23 (Range: -1.7, -33)	Potential ADE
			B (2b)	3	0.5 (0.1, 3) 0.8 (na) 0 (0, 1.9)	-3 -3 -4	ADE: Bleed /pt /pt /pt
				2	0 (0, 2), 1/0 (0.14, 1/0)	-7 +2	ADE: Thrombus /pt /pt
Computer pumps	4:0:0	Peri-operative use	D (1b-)	3	0.8, (0.3, 2), 0.4 (0.1, 1.6)	 -9.5	hypertensive episode /pt hypotensive episode /pt torr from target@1hr /pt

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference	
Drug protocols	10:0:0	Varied	D (4)	6	Median: 0.26 (range:0,0.59) CI na	Median -82	Error	/pt
		Varied	D (4)	3	0.12 (na) 0.38 (na) 0.50 (na)	-10 -10	ADE	/100 month
Doctor training or order forms	9:0:1	Training	C (2c)	3 (2)	0 (0, 0.04) 0.36 (0.2, 0.8) 0.35 (na)	-11 -11 -13	Rx error: illegible Rx error: illegible Rx error: non-standard	/order
		Training + form	C (2c)	2 (1)	study1: 0.4,1.1,0.8 (0.3,0.5;1,1.2;0.8,0.8) study 2: 0.6, 1.2, (0.1,5,8; 0.2, 7; 0.1, 0.06 0.04,0.3; 0.01, 0.4)	-20 -10	Prescription error: missed or illegible elements	/order
Verbal order	1:0:1		D (4)	2	0.3 (0.2,0.6) "no difference" (na)	-6	Order error	/order
Double check	7:0:0		D (4)	3	0.6 (na) 0.1 (na) 0.8 (na) 0.43 (na)	-0.3 -1 -0.1 -125	dispensing or administration error	/month /month /month /pt
Bed proximal dispensing	2:0:1		C (2c)	3	0.4 (0.2, 0.90) 0,0,1 "no difference"	-10 study's total: -1	Admin errors Admin errors	/dose /dose
Unit dose	5:0:0		C (2c)	3 (2)	Meta-analysis of 2 studies: 0.61 (0.47, 0.79)	-1.3	Admin errors	/dose
Decentralized pharmacy	3:0:1		D (4)	1	0.58 (0.48, 0.7)	-0.09	Admin error	/pt-day
				1	0.51 (na)	-38	Admin error (peri-operative med)	/pt
		+unit-dose	D (4)	1	0.22 (0.1, 0.4)	-8.5	Administration error	/dose

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
Automated dispensing	6:0:0		C (2c)	2 (2)	0.78 (0.46, 1.3) 0.69 (na)	-0.19 -0.28	Dispensing Error /dose Dispensing Error /dose
			C/D (2c/4)	1 (1)	0.62 (0.5, 0.78)	-6.5	Administration error /dose
Electronic medication profile	4:0:0	Linked	C (2c)	1 (1)	0 (0, 0.05)	-11.3	Rx transcription error /order
				1	0 (na)	-1	At admin, Rx unclear /order
		Created	D (4)	1	0.33 (0.29, 0.37)	-4.5	Dispensing error /dose
Bar-code	1:1:0	For Dispensing	D (4)	1	0 (p=0.0000)	-0.38	Dispensing error /dose
		For Administration	D (4)	1	1.1 0.7, 1.7	0.002	Administration error /dose
Highly automated	3:0:1	CPOE, eMAR, bar-code, auto disp	C (2c)	1	0.46 (0.4, 0.6)	-5.4	Dispensing omission /dose
		e-MAR, bar-code, CDSS..	D (4)	3	0.36 (0.3, 0.5) 0.4 (na) 1 (na)	-0.014 -0.22 0	Misc. Error /dose
Meds self-administered	2:0:0		D (4)	2	0.25 (na) 0.76 (0.6, 0.95)	-11 -0.00095	Administration Error /pt
Drug admin models (eg, 1^0 vs functional)	6:1:0	2-nurse drug admin	D (4)	1	0.67 (0.5, 0.94)	-0.13	Administration Error /dose
		Un-liscenced technician	D (4)	1	0.09 (0.03, 0.3) 0.20 (0.1, 0.6)	-1.0 -0.6	Omission Error / dose Wrong-time Error /dose
		IV training	D (4)	1	post, post: 0.9, 0.6 (na)	-2, -9	Misc. Error /100 month
Unique (eg, resident work schedule)	4:0:0		D (4)	1	0.71 (na) 0.76 (0.3,2) 0.82 (0.39, 1.7)	-4.9 / pt -0.4 / order -1 / pt	Rx error at discharge /pt Rx error /order Mortality /pt

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference	
CQI or multi-faceted	12:0:0		D (4)	7	Median 0.67 (Range: 0.33, 0.81, n=7. CIs na)	Median: -2800	Error, various (see technology-table re ADEs)	/month *
Failure mode, Root cause analysis	2:0:0	Root cause analysis	D (4)	1	0.69 (na)	-0.01	Misc. Error	/dose
		Failure-mode analysis	D (4)	1	0.26 (0.02, 1.6)	-0.002	ADE	/pt-day
Total	147:3:4							

*Unit is for risk difference. Other units used as well. ^almost given a "minus" which would have dropped the grade to "D"
ADE. Adverse Drug Event. BP: blood pressure. CI Confidence Interval. CQI Continuous Quality Improvement. CDSS Computerized Decision Support System. CPOE Computerized Physician Order Entry. eMAR electronic Medication Administration Record. ICU Intensive Care Unit. Hep: heparin. HM: hundredths of months. HR: heart rate. IR: Incident Report. OR Odds Ratio. Pt: patient. PD: patient-day. Pot A. : potential ADE. Prev. A: preventable ADE. Pt Patient. R Range. Rx: Prescription.
1^0,2^0 primary, secondary.

This table summarizes the study results, with vote-counts, evidence grades, and a presentation of the magnitude of the observed relative risks and risk differences. The columns with vote counts address the direction of results and the columns which include the relative risks and risk differences address the consistency of the evidence. The column named "Quality" addresses the grade and level of the evidence (Oxford Scale: see table 3 or appendix E2 for more detail). The columns which present relative risks (RRs) and risk differences (RDs) define the magnitude of the observed associations, in the context of the particular technology and outcome (column 5) being studied (n.b., the result-specific study number is the number of primary studies which derived the RRs and RDs presented in the table; the bracketed number of secondary studies have complimentary but heterogeneous results—e.g., based on a very different outcome—presented only the technology-specific discussions). For more detail regarding vote counts and grade levels, please see the methods section (2.3.5: Data synthesis).

Columns 2 (study direction) and 4 (evidence quality) support the value of the above exercise of carefully investigating sources of inter-study heterogeneity. The remainder of the table addresses the magnitude of the associations, as well as a few issues of data consistency.

2.5.2 Comment

This systematic review provides a comprehensive overview of the effectiveness of drug-dispensing technologies and systems. It is very broad. It is the first to assess several drug-distribution elements, including order communication technologies like e-medication profiles; physician education about prescription writing; and bed-proximal drug dispensing. Previous reviews have focused on computerization,[46-48;54;197] although the AHRQ also adopted a broad approach with its review of technologies to improve patient safety.[3] Compared to the AHRQ report, the advantages of this literature review are as follows: 1) The literature review is systematic, deriving from a common electronic search strategy (developed by an experienced librarian), and performed by a common set of reviewers who communicated frequently. 2) The analysis should have gained internal consistency across technology assessments by using a single reviewer. 3) Compared to more focused reviews, this report provides a meta-synthesis of evidence for several related technologies, which is beneficial from the perspective of priorization, and helpful in identifying important co-interventions.

This systematic review disagrees with previous reviews more in terms of study interpretation than in terms of its summary of studies. An important disagreement relates to CPOE. Previous reviews have quoted favourable data about CPOE+CDSS and applied it to suggest that hospitals should increase their use of CPOE.[3;46;47] This review found that CPOE alone has minimal evidence in its favour: that only the studies of CPOE+CDSS suggest potential benefits. There were many studies of CPOE+CDSS that associated the technology with error reductions; however, a core question about CPOE+CDSS is whether hospitals generally can implement systems which prevent ADEs as well as self-described errors. Given the apparent importance of the CDSS software to the impact of CPOE+CDSS, it would be desirable to incorporate a mechanism of sharing successfully derived decision rules, to avoid system-level omissions[198] and other errors. Such a CPOE system should be linked to the pharmacy MAR, to prevent transcription errors.

Compared with the addition of CPOE+CDSS, the systematic review found that the addition of clinical pharmacists was associated with larger and statistically more certain ADE reductions. Using an addition clinical pharmacist also was associated with greater error reductions. However, the systematic review did not include a recent, above-mentioned study on the prevention of venous thromboembolism (published too late to enter into the formal literature review).[196] Had we included it, the apparent difference between adding CPOE+CDSS, versus adding a clinical pharmacist, might have become indeterminate. In contrast to the AHRQ report, which dismissed the effect size of pharmacokinetic dosing and placed appropriate use of venous thromboembolism on top of its "clear opportunities for safety improvement,"[3] this review found quantitatively similar effects of pharmacokinetic dosing, pharmacist anticoagulant management, and nomograms (albeit derived from

heterogeneous studies with several associated uncertainties). A recent systematic review showed that drug doses tend to be higher with computer support, which could explain an improved achievement of therapeutic drug levels.[197]

The evidence for CDSS alerts was generally less impressive than for CDSS+CPOE, although it prevented many errors related to corollary orders (e.g., for antibiotic prophylaxis). This fits with the finding of a broader review of CDSS technologies, which observed that "studies in which users were automatically prompted to use the system described better performance compared with studies in which users had to actively engage the system [73% vs. 47%, p=.02]."[55]: essentially, that direct integration into normal work processes is important.

This review agrees with the AHRQ that the evidence for automated dispensing systems and unit-dose systems is unimpressive.[3] Because of the ubiquitousness of drug dispensing, it is possible that such systems could exert meaningful effects; however, those effects have not been demonstrated.

Another disagreement with the AHRQ report relates to bar-coding. The AHRQ accepted uncontrolled data and concluded that with bar-coding it is easy to demonstrate benefits, whereas this review excluded uncontrolled data and found minimal evidence about bar-coding. If the benefits of bar-coding are important and easy to demonstrate, they should be demonstrated in a good controlled trial.

A few systems that were associated with fairly large but uncertain error reductions were CDSS for dose-calculations, bed-side drug storage, physician training with regard to prescription-writing, and the dedicated night-officer teams. The uncertain observations of reduced mortality with a couple of system changes were intriguing; such outcomes would be useful to note generally in technology assessments.

2.5.2 Limitations

There are several threats to the validity of this systematic review: they relate to limitations of the underlying data, and limitations of the review process. Most of the studies were observational studies: as such they did not impose control over group comparability. As well, most of the studies lacked concurrent controls, and their single "pre" and "post" measurements did not rule out fortuitous temporal associations. Many of the studies were clearly biased: for example, comparing dispensing errors assuming no transcription errors in one of two arms (by comparing doses dispensed to the pharmacy MAR in one arm, and doses dispensed to the original prescription in the other arm). Such biases were noted in the results section. It is unclear in many studies how to identify the confounders and effective co-interventions: sometimes this is a reporting issue, but in many cases there is minimal knowledge about what needs to be controlled.

The operationalization of the outcomes reflects many investigators' attempts to predict patient events which are relatively low in frequency compared to the background event-rate. Using outcomes of errors, preventable ADEs, ADEs, and potential ADEs filters out the background event rate, which increases the power of studies to detect differences in event rates. The error outcome definitions tend to focus on the errors targeted by the technology rather than offer a comprehensive evaluation of all errors; therefore, the relative risk reduction observed in each study probably overstate the relative risk reduction of all errors, and may ignore unintended errors created by the new technology. There were a few examples of diverging study estimates based on different methods of error ascertainment(e.g., [132;133;187]).

The clinical significance of errors and ADEs is not always obvious. Errors are heterogeneous, with different risks of not being caught, and most have no direct effect on a patient's well-being. ADEs are a heterogeneous and diffuse outcome, yet they do not serve as global health-status measures; they may be insensitive to high-frequency errors than have a low risk of harm. In general, studies focused on harms due to errors of commission, which may not be representative of global harms due to the combination of errors of commission and omission.

Other potential limits to internal validity are that personnel often were aware they were being evaluated, and funding sources were declared only rarely. Generalizability is limited also in that much of the evidence about technology involves highly customized, advanced applications of unique systems by committed groups of experts.

To some degree, these studies (perhaps with the exception of some anti-coagulation protocols) are all self-evaluations, in which the designer or champion of the system change evaluated his/her work. This has implications in terms of study conduct and outcome measurement. Error is in the eye of the beholder, and preventability in the eye of the reviewer. Therefore, self-evaluations of technologies or systems designed to address errors specific to the evaluators' concern are likely to overstate the benefits of the technologies or systems. This criticism may apply particularly to studies of prescription errors (CPOE, CDSS, prescription-writing) where error can be more a matter of judgment than of compliance with a validated standard. Indeed, referring back to the broad CDSS review, "successes" were far more common in evaluations performed by CDSS creators than in independent evaluations (74% vs. 28%, p=.001).[55]

Most of the studies assessed the technologies in terms of their intended effects. In many cases, these technologies are likely to have unintended effects, as they disrupt normal processes and sometimes take people's time away from other activities. For example, one unit-dose system for controlled substances was twice as time-consuming for pharmacists and nurses. The error rate with controlled doses declined (95% CI=-0.19, -0.06), while the non-controlled substance errors increased

(95% CI=0.0120 0.056) such that the overall error rate increased (95% CI=0.0023, 0.04). This evidence is not definitive but it should be a caution. Likewise, qualitative studies have identified potential problems with systems that seem not to have been studied quantitatively and explicitly: e.g., with CDSS, problems related to data fragmentation, inadequate coordination, and limiting user interfaces.[199]

Another limitation is that almost every technology was evaluated when it was new. Machines break down. Computers crash. Embedded knowledge in pharmacokinetic-dosing models, nomograms, and CDSS does not update itself. Training effects decay. Very few evaluations confirmed the maintenance of an early association: those that did tended not to show convincing associations early after technology or system implementation.

The threat of publication bias may be greater in this set of studies due to a reluctance to admit having caused patients potentially preventable harm. A potential example of this barrier among the CPOE plus CDSS studies is an investigator's publication of positive results from Feb 1993 - 94 in a high-impact journal[69] prior to his dissemination of negative results of an earlier implementation in Oct 92- Dec 93 in a less prominent publication.[67] The flipside is that some of the literature has a self-congratulatory note, which supports a concern about publication bias in the light of self-evaluation.

Limitations specific to the review process include the literature identification strategy; the moderate inter-rater agreement for article selection; the unvalidated process of data extraction and analysis; the unvalidated process of study quality assessment; and the inability to assess the threat of publication bias.

The literature review also excluded studies published before 1985, which excludes some evidence for older technologies like unit-dosing.[160] The rationale behind the exclusion was that pharmacy and nursing practice studies from more than 20 years ago would have limited application to current hospital care. The electronic literature search has not been updated since 2002, so it excludes some recent evidence. The electronic search was also limited by the use of the study outcome as a necessary condition of study consideration. This may be particularly problematic with regard to studies that report on ADEs and potential ADEs but not errors, since the search strategy relies on proper indexing of medications' adverse effects—a fairly subjective concept. A possible consequence is this review's heavy reliance on the non-electronic search, which is harder to replicate than the electronic search. An approach to this problem could have been to iteratively design the electronic search in a manner which would include more of the articles identified non-electronically, and presumably other related articles.

Following the selection of potentially relevant studies, the inter-rater agreement regarding these articles' inclusion in the review was only moderate: the kappa score was 0.54 (95% CI=0.47,

0.61). The disagreement reflected key differences in approach, which were resolved only *post hoc*: i.e., when faced with the trials in the review. As one might expect, the nurse, pharmacist, and bachelor of science/ epidemiology student differed in their perceptions of what constituted an outcome of interest: e.g., what constituted a medication error, or a preventable adverse drug event. For example, the pharmacist was most willing to call adverse events related to drug dosing "preventable." The inter-rater heterogeneity calls attention to a strength of the literature-selection process: that it was preferable to resolve interdisciplinary differences on a study-by-study basis instead of in broad, global statements and small, focused reviews which leave implicit, discipline-specific assumptions unexplored. Because the review was open to any technology, it was difficult to anticipate differences that could arise, and much of the application of the inclusion criteria was left to individual interpretation and addressed only through discussion which followed the initial step of screening articles. For example, only one of three reviewers initially included studies which observed changes in the rates of incident reports following encouragements to submit incident reports: studies which did not include an intervention to change the process of drug distribution and an outcome to measure the impact of that process. Nevertheless, the inconsistency among reviewers is an important limitation.

The process of data extraction and analysis was largely unvalidated. Furthermore, when I began the review I had never studied drug distribution, and my medical background is minimal, which limited my ability to assess the severity of errors and ADEs. My questions were informed by experts, however. I had access to a nurse with an epidemiology background; a pharmacist with a background in systematic reviews; an internist with a background in epidemiology and patient-safety expertise; a statistician with expertise in systematic-review methodology; and a supervisor with qualitative-research expertise. Although the reliability of my work was not assessed, the direction of my work was guided by experts throughout.

This study is limited, too, by its unvalidated method of study-quality assessment. A recent review of study quality-assessment tools found that, of 194 tools identified, only six were potentially suitable for use in systematic reviews.[200] Each tool requires revision to address what were considered important quality domains. Furthermore, none of the potentially suitable tools is specific to the pre/post study, which is the dominant type of study in this review: such specificity would be particularly valuable since the analyses subgrouped studies by design. To address the quality of individual studies, this review collected and assessed information about the important quality domains: i.e., the creation of groups, blinding, soundness of information, follow-up, analysis of comparability, and analysis of outcome. Information about these quality domains was evaluated in a manner specific to the topic of medication error and adverse drug events related to hospital care, and

summarized according to the Oxford Centre's guidelines (which albeit seemed geared toward patient-level exposures as opposed to system-level interventions).[62]

Normally, funnel plots aid in the exploration of the relationship between studies' estimates of effect, and the error in studies' estimates of effect. In cases where more than two RCTs were meta-analyzed, I went through the approach of looking through funnel plots, which in itself did not suggest publication bias; however, with so few studies and such small numbers, publication bias was difficult to assess.

Because all observational studies are prone to bias (even those studies with the most precise results),[58] funnel plots of observational data are not particularly informative: the most precise study results do not provide an unbiased reference estimate with which to compare the other study results. As suggested by Egger,[58] observational study analyses focused on likely sources of heterogeneity.

Finally, with more than 20 heterogeneously assessed technologies, there is no practical way to limit the alpha-error to 0.05. I assessed technologies in broad strokes with an awareness of the limitations of doing so.

2.5.2 Conclusion

To summarize, the limitations of the evidence add uncertainty to recommendations about technology use. Based on the evidence gathered in the review, it seems that the most promising technology for current application is the clinical pharmacist, followed by CDSS for CPOE in advanced applications. The evidence for pharmacokinetic dosing and nomograms is also quite suggestive about avoiding ADEs. The next most promising group of technologies included electronic medication record linkage, bed-side drug dispensing, physician education about prescription-writing, and unit-dose systems—with automated dispensing, CDSS for dispensing calculations, and dedicated night officer teams perhaps a notch below. The technologies with the least promising evidence were as follows: CPOE, computerized pumps, standard drug protocols, verbal orders, self-administration, double-check, decentralized pharmacy, e-medication profile creation, bar-coding, altered drug administration models, and multifaceted interventions guided primarily by the FMA, RCA, and CQI frameworks.

High-quality evaluations would shed light on likely benefits of any of the above technologies; however, CDSS for CPOE, bar-coding for drug administration, and sleep-oriented scheduling seem particularly promising as areas of future research and quality improvement.

Thus concludes chapter 2, the systematic review. Chapter 3 describes the survey of pharmacy directors, and chapter 4 integrates the findings of chapters 2 and 3.

3. Survey

3.1 Survey Introduction

In Canada, a large population-based chart review suggests that, every year, 185 000 adult, non-obstetric, non-psychiatric hospital admissions are associated with adverse events, of which 70 000 are potentially preventable, and 16 000 are potentially preventable deaths.[49] Drugs and fluids accounted for 24% of adverse events, making them the second most common class of adverse event (after surgical). About half of drug-related adverse events are preventable.[12]

Concern about the risk of medical error has led to calls for systemic change to health-care delivery systems.[46;50;201] In Canada, the federal government has expressed a newfound willingness to invest in health-care, particularly in the area of patient safety. The 2003 budget allocated $10-million annually to create a new Canadian Patient Safety Institute, and $600 million to accelerate the development of secure electronic patient records, "which are vital to quality care and patient safety."[51] Meanwhile, about to be completed is a large systematic review of technologies intended to prevent medication errors in hospitals: for example, Computerized Physician Order Entry (CPOE) systems; Computerized Medication Administration Records (c-MARs); Clinical Decision Support Systems (CDSS) for physician or pharmacist order entry; Automated medication dispensing devices; Pharmacy-based IV admixture services; Unit-dose drug distribution systems; bar-coding; Clinical pharmacy services; and Continuous Quality Improvement (CQI) programs.

In the light of current interest in patient safety, and a recently updated systematic review of the literature on the effectiveness of technologies in the prevention of medication errors, it is timely to examine the use of these technologies in Canadian hospitals. No peer-reviewed surveys have characterized the prevalence of error-preventing technologies in Canada, or potential determinants of technology use (see Appendix 1: literature search for surveys). Eli Lilly's privately contracted survey[202] describes the use of the technologies in CCOHTA's review, with the exception of satellite pharmacy and CDSS for CPOE. However, the Eli Lilly survey suffers from several limitations. These include: a relatively low response rate (57%); an incomplete sampling frame; vagueness in its statistical methods (e.g., unit of analysis), and a frequent absence of reporting on the intensity of use of the technologies.

3.1.2 Survey Objectives

3.1.2.1 Primary

The primary survey objective was to describe the prevalence of the use of the major technologies for preventing medication errors (in order to later compare use of the major technologies against the evidence of effectiveness).

3.1.2.2 Secondary

A secondary objective was to determine potential barriers and supports to technology use in the present and in the future. These include

1. hospital pharmacy directors' attitudes toward the level of use of the technologies
2. hospital pharmacy directors' perceptions of medication errors in their hospitals (i.e., their perceived need for error-preventing technology)
3. hospitals' plans for changes in the intensity of the use of the technologies.

The final objective was to identify potential independent predictors of technology use, from among the first two variables listed above, as well as hospital size, and budget per bed.

3.2 Methods

Dillman's recommendations203 guided the development and implementation of the survey methodology.

3.2.1 Sample Frame

The sample frame consisted of Canada's 100 largest acute-care hospitals. The ranking of hospitals' size according to bed numbers relied on the Canadian Healthcare Association's (CHA) database[204] supplemented with lists supplied by the Quebec and Ontario health ministries. Hospitals were counted as acute-care hospitals if they had a minimum of either 50% acute-care beds, or 200 acute-care beds (see Appendix 2 for bed classifications). Eli Lilly's list[205] was used in gathering additional pharmacy director contact information. Pharmacy directors were asked to respond on behalf of their acute-care hospitals.

A simple random sample was considered, and ruled out for the following reasons. The technologies under review were predominantly studied in large hospitals, and are more suitable for use in large hospitals (given infrastructure requirements and economies of scale). We anticipated that, for the most part, small hospitals would be unlikely to use the technologies, based on previous surveys[202;206]: consequently, it was expected that there would be little information to gain by surveying them. There was a concern that a simple random sample would do a poor job of representing the new technologies such as computerized physician order entry whose use is rare even in large hospitals. Finally, the largest hospitals account a large proportion of hospital beds, inpatients treated, and money allocated toward hospital care.

3.2.2 Questionnaire Development and Review

Questionnaire development involved a first draft, external review, and revision. Two hospital pharmacists, two patient-safety experts, a survey methodologist, a nurse, and CCOHTA's communications department reviewed the preliminary questionnaire. A revised questionnaire was piloted on four English and two French pharmacy directors, and revised again in response to the pilot.

Revisions consisted of changes to the wording of questions about medication error, and formatting changes. The survey questions were composed in English, and translated into French: a bilingual pharmacist reviewed each translation.

3.2.3 Questionnaire Content

Both English and French surveys were 2¼ pages long. They asked eleven questions, four of which included fifteen parts - one for each of the technologies of interest (see Appendix 3b for a copy of the survey).

For each of the technologies, the questionnaire asked about the hospital's use of the technology (yes, no; if yes, % of beds serviced by it); about the hospital's plans for changes in the level of technology use; and about the pharmacy director's opinion of the level of technology use. The survey also asked whether the respondent could provide quantitative or qualitative estimates of the risk of patient harm due to medication error.

Respondents were asked to characterize technology use, attitudes to technology, and error perceptions a little further. For example, they were asked (if applicable) about the number of full-time-equivalent (FTE) pharmacists that provide clinical pharmacy services, and the total number of FTE pharmacists. To characterize the relative strength of attitudes to the level of technology use, the questionnaire asked which technology the respondent wanted his/her hospital to invest in next. To characterize the basis of reported perceptions of medication error, the questionnaire asked if the respondent or the hospital used any method to identify patients harmed by medication errors. Finally, the questionnaire provided space for comments.

The full series of cover letters and the attached questionnaire and glossary of technology definitions are presented in Appendices 3 (English) and 4 (French).

3.2.4 Survey Implementation Strategy

Each pharmacy director was pre-notified with an email or fax several days in advance of the questionnaire and cover letter. The cover letter asked pharmacy directors who chose not to respond to identify a subordinate pharmacist who could respond on their behalf. Non-responders received a telephone reminder ten days after receiving the questionnaire; a second reminder letter and replacement questionnaire after an additional ten days; and a final telephone call accompanied by a replacement questionnaire at least 14 days later. All 100 largest acute-care hospitals were surveyed.

3.2.5 Ethics

The survey was approved by the Ottawa Hospital Research Ethics Board.

3.3 Analysis

3.3.1 General

Data quality control involved re-checking the initial data entry against the original questionnaires as wells as range and logic checks which identified inconsistent data.

Means, medians, ranges, inter-quartile ranges, and standard deviations were calculated for all continuous variables. Frequency distributions were generated for non-continuous variables. More specific analyses were as follows.

3.3.1. Respondent Characteristics

To help compare the characteristics of survey respondents to non-respondents, Fisher tests and t-tests were conducted and p-values were reported.

3.3.2 Response Validity

Two related gauges of response validity were as follows: the Spearman correlation of survey-reported total beds with the total number of beds reported in the CHA guide, as well as the overall means (the former to check for variation; the latter to check for bias).

3.3.3 Prevalence of Technology Use

The prevalence of unit-dose systems (use or no use) was modeled in opposition to the use of controlled/carded, traditional, or ward-stock pharmacy (because one of the above technologies must be used to provide drugs to patients). To quantify the intensity of application of pharmacists to hospital beds, the quantity of FTE pharmacists per hospital bed serviced was calculated.

Potential predictors of technology use were investigated using several logistic regression models. A limitation of using several logistic regression models is the potential for non-independence of the use of the different technologies. Prior to the logistic modeling, we examined correlations between pairs of predictor variables, and correlations between pairs of outcome variables, to investigate the potential non-independence of the predictor variables and of the logistic models themselves. A correlation greater than 0.3 was considered noteworthy.

Logistic regressions modeled two sets of odds ratios for each technology: the odds of using a technology, and of using a technology in at least 90% of hospital beds (cut-offs used in the Eli Lilly survey). The modeling was to employ the following potential predictors: the number of beds, the hospital budget per hospital bed; the respondent's opinion of the hospital's level of technology use; and the respondent's perception of the risk of patient harm due to error (low versus moderate or high). As the technologies are targeted towards acute care, the primary "bed number" predictor of technology was the number of acute-care beds; however, sensitivity analyses employed the total number of hospital beds, expressed as a continuous variable, and dichotomized at <=500 or >500 as in the Eli Lilly survey.

A limitation of using several logistic regression models is the potential for non-independence of the use of the different technologies. Prior to the logistic modeling, we examined correlations between pairs of predictor variables, and correlations between pairs of outcome variables, to investigate the potential non-independence of the predictor variables and of the logistic models themselves. A correlation greater than 0.3 was considered noteworthy.

Finally, responder comments were grouped together in related categories.

SAS version 8 generated univariate distributions (means, SDs, ranges) and performed chi-square tests, Fisher tests, Pearson correlations, Spearman correlations, and binomial logistic regression. For more detail on the statistical analyses, see Appendix 5: Determination of the prevalence of technology use.

3.4 Results

3.4.1. Respondent Characteristics

Seventy-eight percent of the surveyed hospitals responded (78/100); another 5% of potential responders declined. Of the responders, 90% (70/78) were pharmacy directors, 6% were other managers (e.g., assistant directors, operations coordinators), and 4% were staff pharmacists.

Table 26 contrasts the characteristics of responders and non-responders: their numbers of beds, admissions, province, budget per bed, and teaching status. As shown in the table, responding and non-responding hospitals had similar numbers of beds (both total and acute), rates of admission, and budgets per bed. Response rates varied by province ($p=2x10^{-6}$); however, the survey represents almost all provinces well, as only the response rate in Newfoundland fell below 60%.

Table 26: Comparison of responding hospitals to non-responding hospitals[a]

Variable	Responders (n=78)		Non-responders (n=22)		p-value
	N	Mean (median, min-max)	N	Mean (median, min-max)	
Total Beds	78	499 (412, 180-2104)	22	552 (400, 238-1481)	0.48**
Total Acute Beds	69	364 (311, 101-1149)	21	400 (291, 121-812)	0.50**
Admissions	63	19627 (17684, 5077-54693)	19	21297 (21092, 4500-41696)	0.52**
Province	78		22		.000002*
NF		0 (0%)		2	
NB		3 (100%)		0	
NS		3 (100%)		0	
PEI		1 (100%)		0	
QC		21 (66%)		11	
ON		28 (85%)		5	
MB		3 (60%)		2	
SK		2 (100%)		0	
AB		8 (100%)		0	
BC		9 (82%)		2	
Total budget per bed (1000s)	53	358 (330, 144-1004)	18	333 (304, 165-997)	.59**
Teaching status	78	29%	22	45%	0.20*

[a]based on Canadian Healthcare Association and Ontario and Quebec ministry data
*Fisher's exact test
** t-test
n: survey response
N: item response

3.4.2. Response Validity

A gauge of the validity of self-reported answers is a comparison of the total number of beds reported by respondents and by the CHA and ministry-supplemented list. On average, respondents reported having 17 more total hospital beds than the predetermined list; the Spearman correlation was 0.91 (n=69).

3.4.3 Primary Objective: Prevalence of Technology Use

The proportion of hospitals that use each technology, and the percentage of beds in each hospital serviced by each technology, are presented in Table 27.

Table 27: Technology Use

n.b. N represents the number of responders

Technologies were ordered by proportion of hospitals which are technology users

	Users of Technology		Percentage of Beds Serviced	
Technology	N	%	N	Mean, median, inter-quartile range
Clinical Pharmacy Services for inpatients*	78	97	66	69, 71, 58-100
-pharmacokinetic monitoring		92		
-patient counseling		88		
-interdisciplinary rounds attendance		81		
-medical rounds attendance		62		
-other**		21		
Pharmacy-based IV admixture service	77	81	71	60, 74, 10-100
Computerized Decision Support System for Pharmacy Staff Order Entry	77	77	69	72, 100, 10-100
Unit-dose system (even if limited wardstock is available)	76	75	70	55, 57, 0-100
Computerized Medication Administration Record	78	67	77	55, 80, 0-100
Traditional Pharmacy	77	59	70	35, 38, 0-68
Automated Dispensing	78	56	76	35, 10, 0-90
Satellite Pharmacy	78	50	66	9, 0, 0-18
-Oncology		27		
-Intensive Care Unit		11		
-Operating Room		8		
-Emergency Department, Neonatology (each)		4		
-Cardiology, psychiatry, and bone-marrow transplant (each)		3		
-Critical care, hematology, pediatric, veteran's, other		1		
Continuous Quality Improvement Program (with personnel time formally allocated to "system-based quality improvement" or "patient-safety" activities)	77	49	69	***
Ward-stock Pharmacy	73	16	73	3, 0, 0-0
Controlled/ Carded Dosing	77	30	77	8, 0, 0-5
Bar-coding for Drug Dispensing	78	9	77	6, 0, 0-0
Computerized Physician Order Entry	78	9	77	6, 0, 0-0
Bar-coding for Drug Administration	78	1	77	0.6, 0, 0-0
Computerized Decision Support System for Computerized Physician Order Entry	78	1	78	1, 0, 0-0
Other technology	78	9	75	6, 0, 0-0

*Clinical pharmacy services employ a mean of 10.8 full-time equivalents (inter-quarticle range=2-15, n=66), or 3.3 full-time-equivalent pharmacists per 100 hospital beds serviced (inter-quartile range=1.4-4.1, n=64.

** e.g., pharmaceutical care; specific assessment and monitoring of antibiotics and anticoagulants; and a post-partum self-medication program

***The measure of implementation was the allocation of FTE: mean 0.2, median 0, inter-quartile range 0-0.2

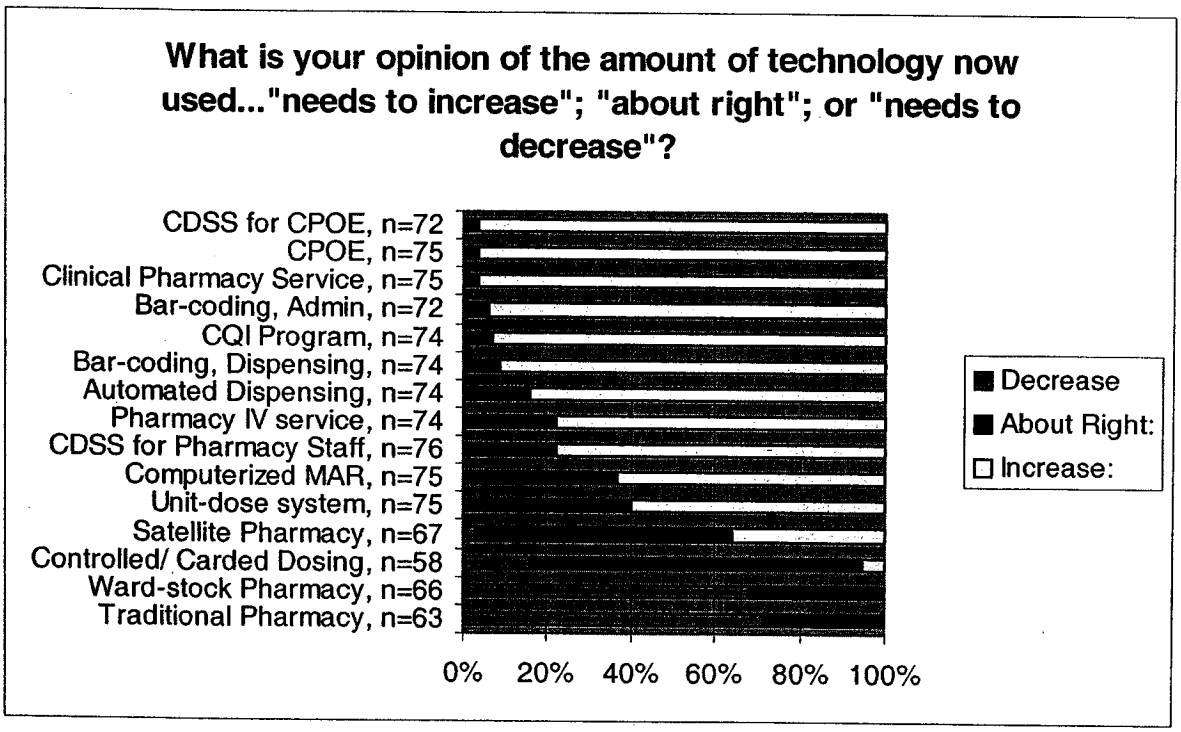
Clinical pharmacy services were most common in hospitals: in 97% of hospitals, in a mean of 69% of beds. Clinical pharmacy services employed a mean of 10.8 full-time FTEs, or 3.3 FTE pharmacists per 100 hospital beds serviced. Pharmacy-based IV admixture services, computerized decision support systems for pharmacy staff order entry, unit-dose systems, and computerized medication administration records were used in 67 to 81% of hospitals, in 55-72% of beds.

Traditional pharmacy, automated dispensing, satellite pharmacy, and CQI programs were used in middling amounts: at 49-59% of hospitals, in 35%, 35% and 9% of beds, respectively. Ward stock and controlled/carded dosing were used in 16% and 30% of hospitals, in less than 10% of the beds. CPOE, CDSS for CPOE, and bar-coding for drug dispensing and administration were used in less than 10% of hospitals, in no more than 6% of beds. Hospitals also used automated TPN compounding equipment, IV admixture preparation machines, technology for the support of narcotics, (paperless) electronic fax of orders, and pharmacy-printed nurse care plans ("other" category).

3.4.4. Secondary Objective: Attitudes to Technology Use

Figure 1 presents pharmacy directors' attitudes to the level of use of each technology.

Figure 1: Opinion of the local level of technology use



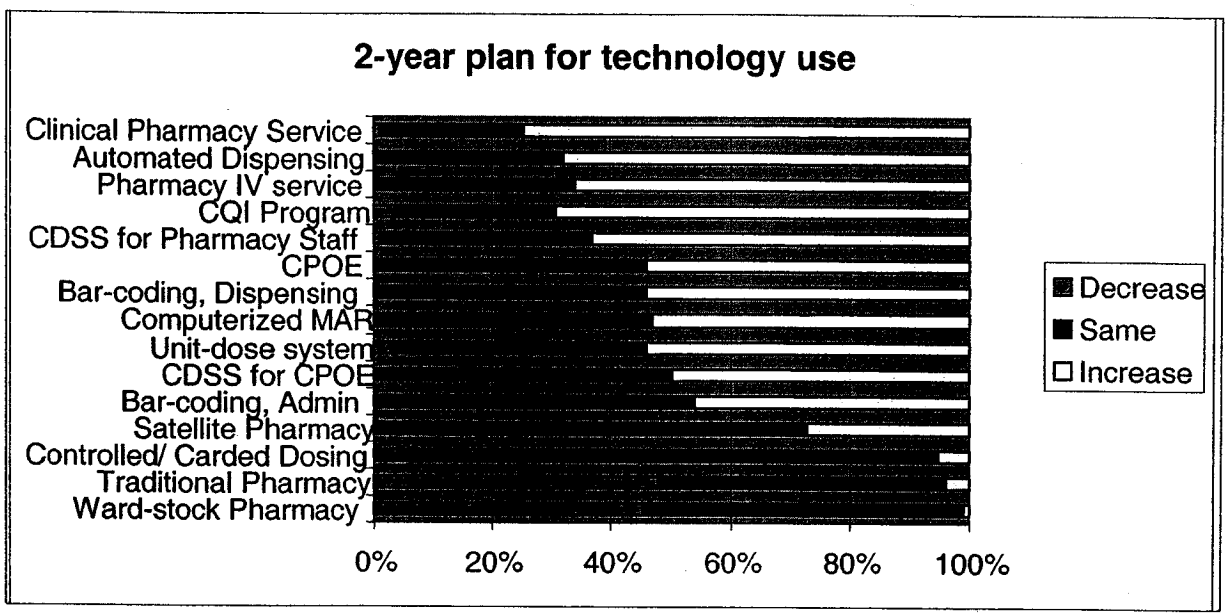
Ninety percent or more of respondents felt that the use of bar-coding, CQI, CPOE, clinical pharmacy services, and CDSS for CPOE should increase. In fact, most respondents felt that the amount of the technologies used for the care of inpatients at their hospitals should increase, with the exception of satellite pharmacy (36% should "increase"), controlled carded dosing (5% "should increase," 16% should decrease), ward-stock (68% should decrease), and traditional pharmacy (71% should decrease). A third of respondents would have their hospital's next investment in technology be automated dispensing, followed by bar-coding for dispensing and/or administration (25%),

computerized physician order entry (12%), clinical pharmacy services (7%), and computerized medication records (7%).

3.4.5. Secondary Objective: Plans for Change in Technology Use

Respondents indicated that many of their hospitals have plans to increase the amount of technologies that they use within the next two years (figure 2).

Figure 2: Plans for changes in technology use

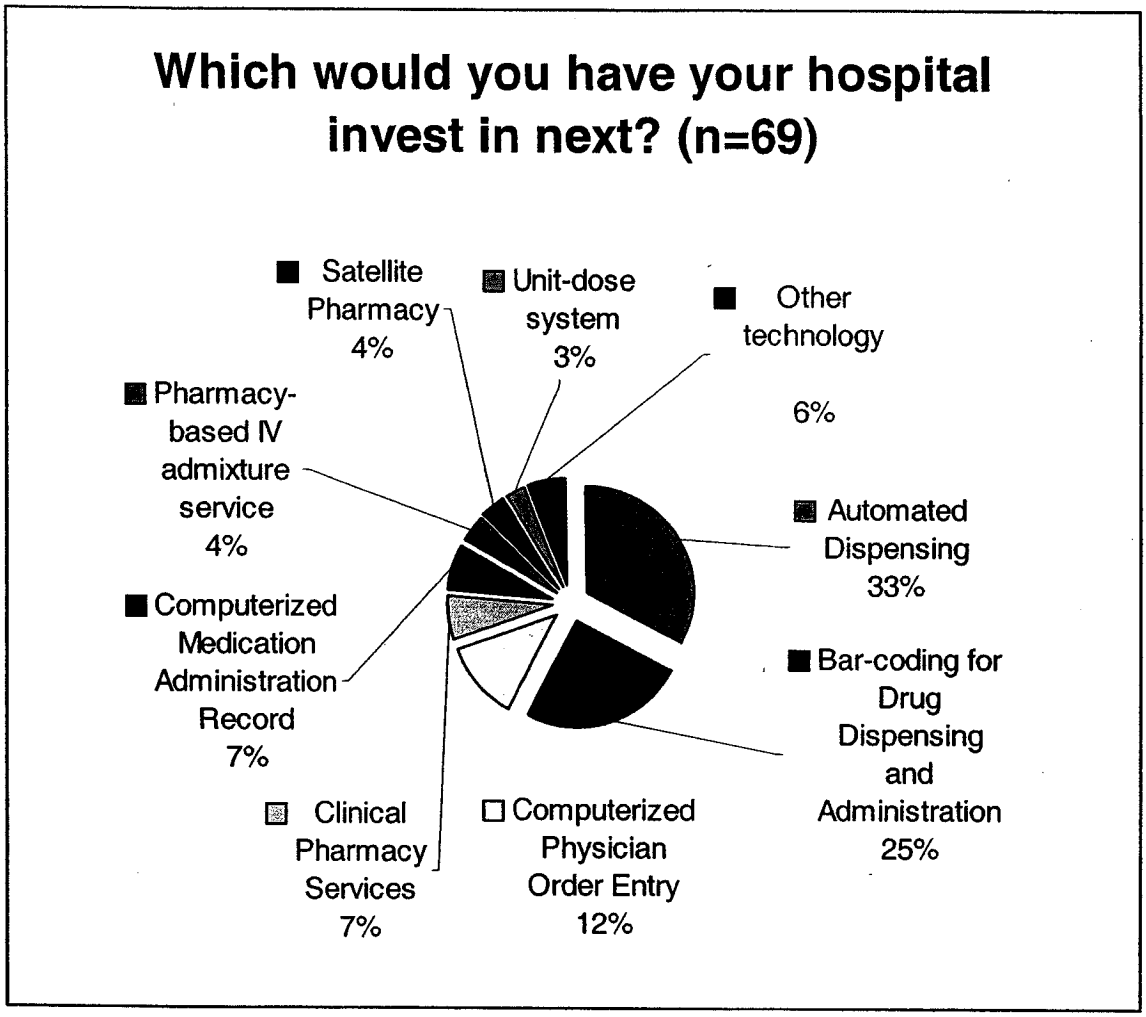


Note: no more than 3 missing observations to any of the questions about plans

Respondents reported plans to change the local level of technology use less frequently than they reported favourable attitudes towards change.

Two-year plans to expand CDSS for pharmacy staff, CQI, Pharmacy IV services, and automated dispensing, and clinical pharmacy services ranged from 63% to 74%. Plans for increases in bar-coding for administration, CDSS for CPOE, unit-dose systems, computerized MARs, bar-coding for dispensing, and CPOE ranged from 46% to 54%. Twenty-seven percent planned more satellite pharmacies. The technologies with planned decreases in use (with % who planned decreases) were controlled/carded dosing (17%), traditional (48%) and ward-stock (45%) pharmacy.

Figure 3: Preferred Technology



Other technologies included
-a standardized city-wide computer system
-a web-based system for nursing unit/ central pharmacy order-communication
-an on-line medication administration record
-computerized decision support for computerized physician order entry
-a new pharmacy computer
-continuous quality improvement

3.4.6. Secondary Objective: Perception of Medication Error

Although 84% (64/76) answered that they or their hospital employ a method of identifying patients who are harmed by medication errors, only 26% (of 69) estimated the incidence of harm due to medication error. One commented that the error rate is "impossible to estimate due to under-reporting."

Estimates of the number of patients harmed by medication error varied widely, from 0 to 26000 in the last year (or .003 to 1 per admission). The median estimated number harmed was 36 (n=19); the median estimated rate per 100 admissions was .26 (IQR=.57 to 1.2). Thirty-nine percent of respondents considered the risk of experiencing harm as a result of medication error to be low; 53% considered it moderate, and 8% considered it high (n=62).

3.4.7. Spontaneous Comments about Implementing New Technologies

A few respondents commented on the difficulty of obtaining funding for new technology. "The level of technology adoption in the hospital also depends on the vision, skill and support of the Information system department." "Most of it isn't ready for prime-time...we're sometimes implementing immature technology [and] need to shake down the technology . . . [One] problem is the interfaces": for example, "Our POE system is not linked with our pharmacy system. This increases complexity of order processes and may contribute to increased errors." Three others commented on a desire for an improved CDSS.

3.4.8. Secondary Objective: Potential Independent Predictors of Use

An examination of the Pearson bivariate correlations of potentially predictive variables (acute-care beds; total beds; budget per bed; opinion of the level of use; and perception of the risk of patient harm) found no correlations greater than 0.3, other than the total number of acute-care beds with the total number of beds (R=0.81). Likewise, no pairs of technologies, other than automated dispensing and unit-dosing (R=0.54), and bar-coded dispensing and satellite pharmacy (0.34), had correlations greater than 0.3. This suggested that it was appropriate to employ multiple logistic models to examine potential predictors of technology use. Thus, we proceeded with separate, technology-specific models, with the exception of automated dispensing and unit-dosing dispensing, which were considered redundant (automated dispensing devices dispense unit doses).

In single-predictor models, respondents at hospitals that used the technologies more were less likely to say that their hospitals should increase their level of technology use. For example, the median odds of responding that the use of a technology needed to increase were 80% lower among users of the technology than among non-users (median OR=.20, n=7, range .061, for unit-dosing, to 1.27, for satellite pharmacy; the 95% C.I of the calculated median OR was .024 to 1.65: the 95% CIs for unit-dosing was .008 to.49, and for satellite pharmacy,.46-3.5). The median odds of responding that the use of a technology needed to increase were 85% lower at hospitals in which at least 90% of beds were serviced by the technology (versus those that did not have 90%): median OR= .15, n=7, range, range <.001 for clinical pharmacy services to .83; 95% C.I. of the median OR was .05 to.46, of the lowest OR was not calculable, and of the highest OR was.29-2.4). Thus, respondents' attitudes to their hospitals' levels of technology use seem likely to be reflections of hospital levels of

use. To avoid a likely confounding of cause and effect, respondents' attitudes to their hospitals' levels of technology use were not entered into the multi-predictor logistic models as potential predictors.

Likewise, error perception was not entered into multi-predictor models of technology use, due to the low percentage of respondents who estimated the local error rate (26%). A notable result which came from investigating the association of technology use with error perception (low vs. medium or high) was that respondents' odds of perceiving a low risk of patient harm due to medication error—as opposed to a medium-to-high risk—were 6.0 times higher (95% CI = 1.9-19.2) among respondents whose hospitals had deployed unit-dose systems in at least 90% of beds.

What remained as potential model predictors, then, were three measures of bed numbers (number acute, continuous; number total, continuous; above or below 500 total, binary). Table 28 displays statistically significant associations between hospital characteristics and any technology use of the 14 technologies of interest, minus a few of the technologies. As there was only one user of computerized decision support for physician order entry, and one user of bar-coding for drug administration, it was not possible to make statistical inferences about possible predictors of those technologies' use. Also, given the association between unit-dosing and automated dispensing, it was thought redundant to present two associations in Table 28.

Table 28: Statistically Significant Potentially Independent Predictors of the Use of Technologies (/11 technologies*)

Use of	**Per 100-Acute-bed Increase** OR (95% confidence interval)	**Per Budget Increase of $50000/bed** OR (95% confidence interval)
Automated dispensing	2.00 (1.25-3.2)	-
Bar-coding for dispensing	1.35 (1.003-1.82)	-
Pharmacy intravenous admixture service	2.6 (1.13-6.1)	-
Satellite pharmacy	1.81 (1.2-2.7)	-
Computerized physician order entry	-	1.61 (1.09-2.37)

*two had one user; the use of unit-dose was correlated with automated dispensing (R=0.54). we present the relationship with the number of acute-care beds as opposed to the total number of beds since the trial-based evidence in the systematic review comes mostly from the acute-care setting, and the technologies seem indicated primarily in the acute-care setting

The following associations were observed when allowing multiple predictor variables into the logistic regression models (one hospital size measure at a time). In terms of hospital size, the total number of beds was associated only with the use of automated dispensing. Hospital size of more than 500 total beds was associated with automated dispensing, plus unit-dosing, pharmacy IV admixture services, and satellite pharmacies. The number of acute-care beds was associated with the above four technologies—automated dispensing, plus unit-dosing, pharmacy IV admixture services,

and satellite pharmacies—and bar-coding (there was a similar association between bed numbers greater than 500 and bar-coding which did not reach statistical significance). The hospital's budget per bed was associated only with any use of computerized physician order entry. Please see Appendix 6 for more details about the logistic modeling.

3.5 Discussion

This survey is unique in addressing hospital plans for change in technology use, and pharmacy directors' attitudes to technology use and perceptions of medication error. Furthermore, the survey's response rate of 78% makes its results highly representative of Canada's 100 largest acute-care hospitals. Clinical pharmacy services, pharmacy IV admixture services, CDSS for pharmacy order entry, unit-dose systems, and computerized MARs are the most widely used of the technologies investigated: used at least nearly 70% of hospitals. They service most of the beds in most of the hospitals: an average of between 55% and 69% of beds. Twenty-one percent of respondents would choose one of the five technologies as their hospital's next investment. Among this group of established technologies, clinical pharmacy services appear to be a particular priority for expansion. Clinical pharmacy is the technology most commonly planned for expansion, although automated dispensing, pharmacy IV services, and CQI were close behind: in terms of pharmacy director priorities, clinical pharmacy services lag behind automated dispensing, bar-coding, and CPOE, and only tied with the computerized MAR.

Automated dispensing units are also used in a majority of hospitals, although their bed coverage lags significantly behind that of unit-dose systems. The most popular "next investment," and high up on plans for expansion, automated dispensing could free human resources to provide more clinical pharmacy services. In contrast to automated dispensing devices, half of hospitals have CQI programs and satellite pharmacies, but they were low priorities for expansion--although the directors commonly expected CQI programs to expand and were generally positively inclined towards them.

In spite of pharmacy directors' very unfavourable opinion of traditional and ward-stock pharmacy, the use of traditional pharmacy persists, although total ward-stock has been almost eliminated. Controlled/carded dosing is common in small areas of these acute-care hospitals. Respondents' high opinion of the superiority of the unit-dose system to traditional, ward-stock, and controlled/card systems was reflected in their six-times higher likelihood of perceiving a low risk of patient harm due to medication error when their hospitals had deployed unit-dose systems in at least 90% of beds (as suggested by the Lilly report).

The least commonly used technologies, the ones with the greatest potential for expansion, were bar-coding, CPOE, and CDSS for CPOE. Bar-coding is the second-most-popular technology to invest in next (25%), and CPOE is third (12%).

Illustrating the difficulty of integrating new technologies into existing systems, the Eli Lilly survey noted that only 3 of 9 CPOE users had linked their CPOE systems to their Pharmacy

Information Systems.[202] This suggests that integration of new information technologies into existing systems may be a long process.

As in the Eli Lilly survey[202] and an American survey,[206] the number of beds was often associated with technology use. On the whole, results did not differ greatly from the Lilly survey. Compared to the Lilly survey, this survey had a higher response rate (57% versus 78%), a smaller sample of hospitals with a larger average number of beds (312 versus 499), and a much shorter questionnaire. Compared to the Lilly survey, this survey's respondents reported more unit-dosing (bed-weighted, 45% vs. 53%), less CDSS for pharmacy (77% versus 93%), and a greater percentage of pharmacists providing clinical pharmacy services (39% vs. 53%, although Lilly saw 45% in teaching hospitals which tend to be larger). Within the thesis survey sample, there were positive associations between the number of beds and the use of clinical pharmacy and unit-dosing, and a negative association between size and use of CDSS for the pharmacy system. Thus, these differences between studies are consistent with the variation inside the thesis survey. Proportionally, the two surveys were within a couple percentage points with regard to the use of IV admixture services, controlled/carded dosing, CPOE, and CDSS for CPOE.

The associations with the number of hospital acute beds and the hospital budget per bed suggest that hospital resources may limit hospitals' ability to adopt many of the technologies intended to prevent medication error. Pharmacy directors' comments about the immaturity of some technologies support this hypothesis, in that they suggest a requirement for the resources to develop a technology locally.

Respondents' median estimates of medication-error rates were consistent with the Harvard Medical Practice Study (HMPS) in New York,[12;15] although lower than estimated through more sensitive methods[19], or suggested by the recent Canadian study. Respondents' median estimate worked out to 0.26/100 admissions harmed by medication errors, versus the HMPS-estimated 0.33/100 admissions, and the Bates-estimated 1.8/100 admissions (and 1.8 drug-or fluid-related AEs/100 admissions in Canadian hospitals, of which an unknown number are preventable).[14] However, extensive variation among estimates of patient harm due to medication error and extensive non-response suggest that pharmacy directors are uncertain about the impact of medication error, which most feel is a moderate risk. This uncertainty inhibits the deployment of appropriate error-preventing measures. Uncertainty about the magnitude of the impact of medication error is a barrier to a proportional response to the problem. Also, uncertainty about the magnitude of the impact suggests uncertainty about the nature of the harm caused by medication error, which detracts from the priorization of efforts to prevent the medication errors which cause the most readily prevented ADEs.

Potential limitations of survey data collection include coverage error, non-response bias, and measurement error. Mixing modes of survey communication reduced coverage error, in that the unavailability of one contact address (e.g., email) did not prevent a hospital's inclusion in the sample frame. Survey non-response bias is a potential survey limitation; however, given the low rate of non-response and the similar recorded characteristics of responders and non-responders, the bias likely is limited in magnitude. Self-report is a limitation but respondents accurately reported bed size. Measurement error may have resulted from respondents' lack of knowledge, social acquiescence, or variation in respondents' definitions of "current" use. Mixing survey distribution media is unlikely to have introduced variation, as the same MS Word file was emailed and faxed. The inability to determine temporal relationships limits the exploration of potential determinants of technology use.

With this study of the use of error-preventing technologies in a representative sample of Canada's 100 largest acute-care hospitals, it is now possible to examine the correspondence between technology use, and the evidence of the technology's effectiveness. The identification of potential determinants of the use of specific technologies may also facilitate a dissemination strategy which reflects both the evidence of effectiveness, and our Canadian context.

What follows in chapter 4 is an overall discussion which integrates the results of the systematic review (chapter 2) and survey (chapter 3: i.e., this chapter).

4. Overall discussion

Adverse drug events caused by medication errors are regular occurrences in Western hospitals: probably in at least about 1% of patients, and likely in several times that number (see section 1.3.1). Cost analyses suggest that these ADEs increase hospitalization costs on the order of US$2000 per admission when they occur in the United States.[27;33]

This thesis comprises a systematic review to assess the evidence of the effectiveness of hospital-based interventions in the prevention of such events, and a Canadian survey to determine the use of such technologies (and potential barriers and supports to technology use).

Systematic review

The systematic review synthesized the evidence published from 1985 to 2002 about all inpatient drug-distribution technologies related to medication error and adverse drug events. The review included 135 articles, which provided 154 sets of relevant comparisons. The evidence was consistently favourable; however, it is not possible to draw firm conclusions about technologies' effectiveness due to the limitations of the included studies: e.g., due to the observational nature of 89% of the technology comparisons. The limitations of the data in this review are related to threats to individual studies' internal validity, the threat of publication bias, study heterogeneity, moderate inter-rater agreement with regard to study inclusion, and the unvalidated process of data extraction and analysis. Also, the study questions often were limited to the intended effects of the newly minted technologies, and they rarely addressed clinical outcomes.

Of the 23 technology groupings, it seems that the most promising intervention for clinical application is the clinical pharmacist, but that future research may elucidate important roles for CDSS for CPOE, bar-coding for drug administration, or sleep-oriented scheduling.

Only the studies of clinical pharmacists, kinetic dosing, nomograms, and CDSS (mainly with CPOE) offered compelling evidence about avoiding preventable ADEs or all-cause ADEs: only CDSS and clinical pharmacists are indicated for broad patient allocations. The estimated benefit with clinical pharmacists was similar to CDSS+CPOE, which was much greater than with CDSS unlinked to ordering. These prescription-related technologies scored Bs and a C according to the Oxford Grading Scheme, which is better than the other technologies but not conclusive.

Almost all the remaining technologies altered drug dispensing and administration. Their evaluations relied on assessments of the error rate or potential ADEs, with essentially no patient follow-up on preventable or all-cause ADEs. Of these interventions, some of the more promising (scoring Oxford Cs) were electronic medication record linkage, bed-side drug dispensing, physician education about prescription-writing, and unit-dose systems. Automated dispensing also scored a C,

but was associated with quantitatively small benefits. CDSS for dispensing calculations and dedicated night officer teams scored Ds but suggested potentially sizeable benefits.

The evidence for the following technologies was consistent with regard to error reductions but D-level and generally not dramatic: CPOE, computerized pumps, standard drug protocols, verbal orders, self-administration, double-check, decentralized pharmacy, e-medication profile creation, bar-coding, altered drug-administration models, FMA, RCA, CQI, and multi-faceted interventions.

Promising technologies for future research included CDSS for CPOE, as well as bar-coding for drug administration and sleep-oriented scheduling.

Survey

About 78% of Canada's largest acute-care hospitals responded to the survey about technology use. The characteristics on responding hospitals and non-responding hospitals were similar. The main limitation of the survey is that it relies on self-report.

Of the technologies investigated, clinical pharmacy services were most common: in 97% of hospitals and a mean of 69% of beds. Next were pharmacy-based IV admixture services, CDSS for pharmacist order entry, unit-dose systems, and computerized MARs, in 67 to 81% of hospitals, and in 55-72% of beds. Traditional pharmacy, automated dispensing, satellite pharmacy, and CQI programs were used in middling amounts: at 49-59% of hospitals, in 35%, 35% and 9% of beds, respectively. Ward stock and controlled/carded dosing were used in 16% and 30% of hospitals, in less than 10% of the beds. CPOE, CDSS for CPOE, and bar-coding for drug dispensing and administration were used in less than 10% of hospitals, in no more than 6% of beds.

Most pharmacy directors reported hospital plans to increase the use of most of the technologies: 60-80% planned to increase clinical pharmacy services, automated dispensing, pharmacy IV services, CQI, and CDSS for pharmacy staff; 40-60% planned to increase CPOE, bar-coding, computerized MARs, unit-dosing, CDSS for CPOE; 27% planned to increase satellite pharmacy use; and 5% or less planned to increase controlled/carded dosing, traditional pharmacy, and ward-stock pharmacy.

Pharmacy directors felt that the use of most technologies should increase: especially (>90%) CDSS for CPOE, CPOE, clinical pharmacy services, bar-coding both for administration and dispensing, and CQI. 78 to 84% felt that automated dispensing, pharmacy IV services, and CDSS for pharmacy staff should increase. The percentage which felt that unit-dosing and computerized MARs should increase was in the low 60s. 36% felt that satellite pharmacy use should increase. No more than 3% of pharmacy directors felt that the use of the above technologies should decrease; however, 16%, 68% and 71% felt that controlled/carded dosing, ward-stock, and traditional pharmacy should decrease, compared with 5%, 0%, and 0% who felt it should increase.

Although 84% of hospitals employ a method of identifying patients harmed by medication errors, only 26% estimated the incidence of harm due to medication error. This item non-response may reflect a concern about privacy or a genuine lack of pharmacy director knowledge about the harm caused by medication errors in their hospitals.

Pharmacy directors' favourite technologies were automated dispensing (33%), bar-coding (25%), CPOE (12%), clinical pharmacy services (7%), and computerized MARs (7%).

How does the use correspond to the evidence of effectiveness? (see Table 29)

The following discussion is not complete, in that it does not consider implementation costs, nor does it consider benefits outside of those that accrue directly to the patient. The evidence has many gaps which have been noted. In focusing on medication safety, this review did not consider other potential benefits of the technologies. This review has attempted not to confuse the absence of evidence with evidence of absence; nevertheless, the absence of evidence is a source of uncertainty.

The survey itself raised a red flag about the generalizability of the studies in the systematic review. Pharmacy directors' comments about technologies' immaturity and the need to customize it locally emphasize the potential variability of technological applications, and consequent uncertainty about their results.

That said, clinical pharmacy was the technology with relatively generalizable evidence of the greatest benefit to patients, and was used most commonly in hospitals: on average, in 69% of beds (inter-quartile range, IQR, of 58-100). On average, hospitals employed one clinical pharmacist for every 30 beds, which is half of what was employed at the two studies with intensive follow-up which suggested that clinical pharmacy could provide the greatest benefits to patients.[105;106] Given that the clinical pharmacy study which merely changed pharmacist responsibilities was negative,[69] patients may benefit from increased clinical pharmacy staffing, in spite of widespread bed coverage by clinical pharmacists. Thus, hospitals' frequent plans to expand clinical pharmacy services seem appropriate as a way to invest from among the technologies in this review.

The evidence for the use of the other technologies investigated by the survey was limited to comparisons of error rates (the survey did not quantify the use of nomograms and pharmacokinetic dosing, whose scope is limited to sub-populations within hospitals). The survey found relatively high use of a couple of older technologies whose evidence received a C-grade: unit-dosing, and CDSS for pharmacists (which depends on the Computerized Medication Administration Record). Automated dispensing also received a C-grade: it was used in a mean of only 35% of beds, but was frequently slated for increased use, and was first among pharmacy directors' priorities for expansion.

Hospitals generally used less of the technologies which had less evidence of effectiveness, such as satellite pharmacies, bar-coding, and CPOE. The exceptions to the rule among the surveyed

technologies were e-medication profiles and CQI programs. E-medication profiles were commonly used, in 67% of hospitals; however, they are necessary for CDSS, which had better evidence, and may be useful for functions such as inventory management. CQI programs were difficult to assess on their own, although they were in half of hospitals and slated for expansion in 69%.

Table 29: Comparison of the effectiveness and use of single interventions

Evidence for Effectiveness	Technology	Prevalence (%)	Bed Coverage (mean %)	% Technology use should increase *minus* % technology use should decrease
Decent (grade A-C: not D/D) evidence about preventable or all-cause ADEs	Clinical pharmacy	97	69	96
	CPOE+CDSS	1	1	96
	Kinetic dosing	92		
	Nomograms	not determined		
Medication errors prevented (Grade C)	CPOE linked to MAR	not determined		
	Bed-side dispensing	not determined		
	Physician education	not determined		
	Unit-dose systems	75	55	59
	Automated dispensing	56	35	84
	highly automated systems	not determined		
Medication errors prevented dramatically (Grade D)	CDSS for dispensing calculations	not determined		
Medication errors prevented (Grade D)	CPOE	9	6	96
	Computerized pumps	not determined		
	Drug protocols	not determined		
	Verbal orders	not determined		
	Self-administration	not determined		
	Double-check	not determined		
	Decentralized pharmacy	50	9	33
	e-medication profile	67	55	63
	Bar-coding for dispensing	9	6	91
	Bar-coding for administration	1	0.6	94
	Drug-administration models	not determined		

Based on the evidence from the systematic review, it would be worth considering expanding clinical pharmacy services instead of automated dispensing, since the evidence suggests greater benefits from clinical pharmacy services than from automated dispensing (regardless of whether the automated dispensing replaces an existing unit-dose system or an existing ward-stock system). Another concern is that pharmacy directors' enthusiasm for technologies like CPOE and bar-coding

precedes decent evidence of the technologies' effectiveness, a situation not unique to this area of health care. A pessimist might say that there is no good evidence for the effectiveness of any of the technologies; however, currently, the evidence for bar-coding and CPOE is particularly unconvincing, and the managers of hospitals' drug distribution appear particularly enthusiastic about these technologies. Hospitals that do implement CPOE should be encouraged to link CPOE to the pharmacy records, and to develop their systems of CDSS (which likely requires other database links).

Research implications

The systematic review found that the evidence consistently favoured the technologies, but was uncertain due to study limitations. Future research should be guided by either an objective to confirm high-magnitude benefits, or the objective of evaluating technologies with minimal evidence whose use appears likely to change significantly in the next several years. Studies should attempt to replicate the clinical pharmacy studies in manner which minimizes pharmacists' awareness of their publishable evaluation, to minimize the reactivity of the study measurement: ideally, with pharmacists randomized at a group level, to evaluate system-level effects; with clinically meaningful and reliable outcomes, to decrease uncertainty about benefits; and with varying pharmacist-to-patient ratios, to determine optimal pharmacist staffing levels (recall that the trials used higher staffing ratios than Canadian hospitals). Future studies may also evaluate bar-coding and CPOE: their use is currently low (<10% of hospitals), but about 95% of pharmacy directors want them in their hospitals, so their use seems likely to increase significantly in spite of the poor state of existing evidence. Finally, potentially large effects have been noted with sleep-oriented scheduling; future research may elucidate ways of using it to improve safety.

In terms of the design of future studies, an ideal study would be comprehensive, compare comparable groups, measure meaningful and reliable outcomes, and be generalizable.

Studies should assess the whole system that is perturbed. The study population should include the entire population that is affected by the system change, and study outcomes should assess both the potential benefits and risks of new technology. In a process that involves multiple steps, studies should measure errors at the end of the process. Given that error measures are frequently insensitive and of questionable validity, it would help to augment them with a measure that reflects follow-up of patient outcomes (or simply follow up on patients without bothering much with errors) and of the system in time (i.e., not just when new).

If randomization is impossible to ensure comparability, technologies should be compared in systems that seem similar in terms of both patient and provider characteristics, which includes the stable use of other technologies (time-series analysis can address time-related biases). The outcome measure should be the same in both groups. The general rules apply, in terms of prospective

measures being desirable; it is important not to rely on incident reporting systems, which are of poor quality.

Generalizability issues that are perhaps more applicable to these technologies are the promotion of evaluations of externally developed technologies (as opposed to local self-evaluations), and technology applications that reflect "normal" hospital conditions (as opposed to promotional technology support from equipment vendors).

Finally, given the scarcity of health-care resources (and hospitals' fixed budgets), it is important to generate data about cost-effectiveness, and ideally about cost-utility if possible. Many of the technologies are expensive to implement: there are costs in the purchase and maintenance of added equipment, costs in personnel time for the implementation of new systems, and often routine costs in additional personnel time needed to carry out the elements of drug distribution that are meant to be made safer (the alternative, demanding more of unpaid time, may have negative externalities: increasing the workload related to one set of tasks may detract from the performance of other tasks).

There may be cost savings if a system saves employee time: however, it seems that systems that offer direct savings in employee time are automated systems that are expensive to purchase. There may be savings if the system prevents errors that cost the health-care system money: for example, by extending lengths of stay. It is also conceivable that a medication error that hastens the onset of palliative care or death may reduce health-care system costs by preventing sick patients' subsequent costly acute-care use; however, we have not seen this modeled. Finally, the cost of litigation might be altered.

Managerial implications

At higher managerial levels, a variety of unevaluated systems have been implemented: e.g., the Canadian Medication Incident Reporting and Prevention System, task forces, etc. The purely informational and analytic systems may be viewed as partial means to an end: they do not intrinsically lead to change[207] Governments should not invest too much money or place excessive faith in analyses of incident reporting systems or others that are fundamentally limited by data quality (section 1.8). To address likely publication biases and thereby avoid investing in harmful or ineffective technologies, it would be helpful to establish a prospective registry of patient-safety evaluations. Another potentially useful system-wide undertaking would be a flexible, open-source CDSS. As schools of medicine and pharmacy teach much of this information already and increasingly make it Internet-accessible, formalizing decision rules need not involve a re-invention of the wheel, and the work of coordination offers an opportunity to coordinate clinical teaching with clinical practice.

Hospital managers should recognize the serious limitations of the epidemiological evidence supporting the ability of the technologies to avoid adverse drug events through medication-error prevention. Given the scarcity of health-care resources and fixed hospital budgets, it is important to weight likely benefits against costs. Managers should be wary of investing large sums of money in untested technologies for the sole purpose of improving medication safety, especially if they are making cutbacks elsewhere. The evidence suggests that if hospitals choose to invest more in the area of medication safety, they are likely to benefit patients more with increased clinical pharmacy staffing than by implementing CPOE and bar-coding.

Reference List

1. Romanow RJ. Improving access, ensuring quality. *Building on values: the future of health care in Canada*, pp 137-58. Saskatoon: Commission on the Future of Health Care in Canada, 2002.

2. Committee on Identifying Priority Areas for Quality Improvement. Priority areas for national action: transforming health care quality. Adams, K. and Corrigan, J. M. 2003. National Academies Press.

3. Agency for Health Care Research and Quality. Making health care safer: a critical analysis of patient safety practices. Rockville, MD: Agency for Health Care Research and Quality, 2001.

4. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. *Journal of the American Medical Association* 1997;**277**:312-7.

5. Malcom, W, Carlson, R. A, Tucker, C. L., and Wilfinger, R. Veterans affairs: eliminating medication errors through point-of-care devices. 2000. 2000.

6. Institute for Safe Medication Practices. Frequently Asked Questions. http://www.ismp.org/Pages/ismp_faq.html . 2005.

7. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F *et al.* Medication errors and adverse drug events in pediatric inpatients. *Journal of the American Medical Association* 2001;**285**:2114-20.

8. Nebeker, J. R., Barach, P., and Samore, M. H. Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting. Annals of Internal Medicine , 795-801. 2004.

9. Barach P,.Small SD. Reporting and preventing medical mishaps: lessons from non-medical near miss reporting systems. *BMJ* 2000;**320**:759-63.

10. World Health Organization (WHO). WHO technical report (498). 1972.

11. Forster AJ, Asmis TR, Clark HD, Al Saied G, Code CC, Caughey SC *et al.* Hospital Patient Safety Study: incidence and timing of adverse events in patients admitted to a Canadian teaching hospital. *CMAJ* 2004;**170**:1235-40.

12. Leape LL, Lawthers AG, Brennan TA, Johnson WG. Preventing medical injury. *QRB.Qual.Rev.Bull.* 1993;**19**:144-9.

13. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. *J.Gen.Intern.Med.* 1993;**8**:289-94.

14. Baker, G. R., Norton, P., Flintoft, V., Blais, R., Brown, A., Cox, J., Etchells, E., Ghali, W. A., Hebert, P., Majumdar, S. R., O'Beirne, M., Palacios-Derflingher, L., Reid, R. J., Sheps, S., and Tamblyn, R. M. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. Canadian Medical Association Journal 170(11), 1678-1686. 2004.

15. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA *et al.* The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N.Engl.J.Med.* 1991;**324**:377-84.

16. Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ *et al.* Incidence and types of adverse events and negligent care in Utah and Colorado. *Med.Care* 2000;**38**:261-71.

17. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. *Med.J.Aust.* 1995;**163**:458-71.

18. Davis P, Lay-Yee R, Schug S, Briant R, Scott A, Johnson S *et al.* Adverse events regional feasibility study: indicative findings. *N.Z.Med.J.* 2001;**114**:203-5.

19. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D *et al.* Incidence of adverse drug events and potential adverse drug events. Implications for prevention. *Journal of the American Medical Association* 1995;**274**:29-34.

20. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG *et al.* Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N.Engl.J.Med.* 1991;**324**:370-6.

21. Ebbesen J, Buajordet I, Erikssen J, Brørs O, Hilberg T, Svaar H *et al.* Drug-related deaths in a department of internal medicine. *Arch.Intern.Med.* 2001;**161**:2317-23.

22. Wilson DG, McArtney RG, Newcombe RG, McArtney RJ, Gracie J, Kirk CR *et al.* Medication errors in paediatric practice: insights from a continuous quality improvement approach. *Eur.J.Pediatr.* 1998;**157**:769-74.

23. Brennan TA, Hebert LE, Laird NM, Lawthers A, Thorpe KE, Leape LL *et al.* Hospital characteristics associated with adverse events and substandard care. *Journal of the American Medical Association* 1991;**265**:3265-9.

24. Vincer MJ, Murray JM, Yuill A, Allen AC, Evans JR, Stinson DA. Drug errors and incidents in a neonatal intensive care unit. A quality assurance activity. *Am.J.Dis.Child.* 1989;**143**:737-40.

25. Cullen DJ, Sweitzer BJ, Bates DW, Burdick E, Edmondson A, Leape LL. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Crit.Care Med.* 1997;**25**:1289-97.

26. Murray MD. Information technology: the infrastructure for improvements to the medication-use process. *Am.J.Health Syst.Pharm.* 2000;**57**:565-71.

27. Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA *et al.* The costs of adverse drug events in hospitalized patients. *Journal of the American Medical Association* 1997;**277**:307-11.

28. Roseman C,.Booker JM. Workload and environmental factors in hospital medication errors. *Nurs.Res.* 1995;**44**:226-30.

29. Booker JM,.Roseman C. A seasonal pattern of hospital medication errors in Alaska. *Psych.Res.* 1995;**57**:251-7.

30. Bell CM,.Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N.Engl.J.Med.* 2001;**345**:663-8.

31. Lambert BL. Predicting look-alike and sound-alike medication errors. *Am.J.Health Syst.Pharm.* 1997;**54**:1161-71.

32. Buchanan TL, Barker KN, Gibson JT, Jiang BC, Pearson RE. Illumination and errors in dispensing. *Am.J.Hosp.Pharm.* 1991;**48**:2137-45.

33. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *Journal of the American Medical Association* 1997;**277**:301-6.

34. Pestotnik SL, Classen DC, Evans RS, Burke JP. Implementing antibiotic practice guidelines through computer-assisted decision support: clinical and financial outcomes. *Ann.Intern.Med.* 1996;**124**:884-90.

35. Ottawa Civic Hospital Drug Management Re-design Team. Prescription for Change. 1996. Ottawa Civic Hospital.

36. Reason JT. Human error. Cambridge (UK): Cambridge University Press, 1990.

37. al Shakhaa WM,.Zairi M. Delivering effective health care through teamwork: the role of pharmaceutical care management. *Health Manpow.Manage.* 1998;**24**:212-21.

38. Cohen MR, Senders J, Davis NM. Failure mode and effects analysis: a novel approach to avoiding dangerous medication errors and accidents. *Hosp.Pharm.* 1994;**29**:319-30.

39. Rex JH, Turnbull JE, Allen SJ, Vande Voorde K., Luther K. Systematic root cause analysis of adverse drug events in a tertiary referral hospital. *Jt.Comm.J.Qual.Improv.* 2000;**26**:563-75.

40. Flynn EA, Barker KN, Pepper GA, Bates DW, Mikeal RL. Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities. *Am.J.Health Syst.Pharm.* 2002;**59**:436-46.

41. Rothman KJ, Greenland S. Modern Epidemiology. Philadelphia: Lippincott Williams & Wilkins, 1998.

42. Hayward RA,.Hofer TP. Estimating hospital deaths due to medical errors: preventability is in the eye of the reviewer. *Journal of the American Medical Association* 2001;**286**:415-20.

43. Forster AJ, Halil RB, Tierney MG. Pharmacist surveillance of adverse drug events. *Am.J.Health Syst.Pharm.* 2004;**61**:1466-72.

44. Marino BL, Reinhardt K, Eichelberger WJ, Steingard R. Prevalence of errors in a pediatric hospital medication system: implications for error proofing. *Outcomes Manag.Nurs.Pract.* 2000;**4**:129-35.

45. Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. *J.Gen.Intern.Med.* 1995;**10**:199-205.

46. Bates, D. W. and Gawande, A. A. Improving Safety with Information Technology. New England Journal of Medicine 348, 2526-2534.

47. Leape LL, Berwick DM, Bates DW. What practices will most improve safety? Evidence-based medicine meets patient safety. *Journal of the American Medical Association* 2002;**288**:501-7.

48. Bates DW. Using information technology to reduce rates of medication errors in hospitals. *BMJ* 2000;**320**:788-91.

49. Classen, D. C. Clinical Decision Support Systems to Improve Clinical Practice and Quality of Care. JAMA 280(15), 1360-1361. 1998.

50. Richardson WC. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington: National Academy Press, 2001.

51. Building the Society Canadians Value. Department of Finance . 18-2-2003.

52. US Food & Drug Administration. FDA Rule Requires Bar Codes on Drugs and Blood to Help Reduce Errors. FDA . 5-11-2004. 6-8-0004.

53. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. *Journal of the American Medical Association* 1998;**280**:1339-46.

54. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch.Intern.Med.* 2003;**163**:1409-16.

55. Garg, A. X., Adhikari, N. K., McDonald, H., Rosas-Arellano, M. P., Devereaux, P. J., Beyene, J., Sam, J., and Haynes, R. B. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 293(10), 1223-1238. 2005.

56. McAuley, L., Pham, B., Tugwell, P., and Moher, D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses. Lancet 356(9237), 1228-1231. 2000.

57. Fleiss JL. The measurement of interrater agreement. *Statistical methods for rates and proportions*, pp 212-36. New York: John Wiley, 1981.

58. Egger M. Systematic reviews in health care: meta-analysis in context. London: BMJ Publishing Group, 2004.

59. Information Management System Group and Revman Advisory Group. Review Manager. (4.2). 2004. The Nordic Cochrane Centre, The Cochrane Collaboration.

60. Petitti DB. Approaches to heterogeneity in meta-analysis. *Stat.Med.* 2001;**20**:3625-2633.

61. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

62. Centre for Evidence-based Medicine. Levels of Evidence and Grades of Recommendation. Oxford . 2001.

63. West DW, Levine S, Magram G, MacCorkle AH, Thomas P, Upp K. Pediatric medication order error rates related to the mode of order transmission. *Arch.Pediatr.Adolesc.Med.* 1994;**148**:1322-6.

64. Bizovi KE, Beckley BE, McDade MC, Adams AL, Lowe RA, Zechnich AD *et al.* The effect of computer-assisted prescription writing on emergency department prescription errors. *Acad.Emerg.Med.* 2002;**9**:1168-75.

65. Bizovi KE, Beckley B, McDade M, Adams A, Zechnich A, Hedges J. The effect of computer-assisted prescription writing on emergency department prescription errors. *Acad.Emerg.Med.* 2001;**8**:499.

66. Chessare, J. B., Dibelka, N., Hughes, P., Mehegan, D., Merrill, C., O'Rourke, Y. C., Wong, K., and Woodson, J. Using improvement science to reduce medication errors at an academic medical center [abstract]. 8th International Scientific Symposium on Improving Quality and Value in Health Care . 2002. 28-7-2003.

67. Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, Ma'Luf N *et al.* The impact of computerized physician order entry on medication error prevention. *J.Am.Med.Inform.Assoc.* 1999;**6**:313-21.

68. Bates, D. The Impact of computerized physician order entry on medication errors. 2001. Toronto. Breaking the Silence: Error in Healthcare.

69. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM *et al.* Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *Journal of the American Medical Association* 1998;**280**:1311-6.

70. Teich JM, Merchia PR, Schmiz JL, Kuperman GJ, Spurr CD, Bates DW. Effects of computerized physician order entry on prescribing practices. *Arch.Intern.Med.* 2000;**160**:2741-7.

71. Taylor R, Manzo J, Sinnett M. Quantifying value for physician order-entry systems: a balance of cost and quality. *Healthc.Financ.Manage.* 2002;**56**:44-8.

72. Myers TF, Venable HH, Hansen JA, NICU Clinical Effectiveness Task Force. Computer-enhanced neonatology practice evolution in an academic medical center. *J.Perinatol.* 1998;**18**:S38-S44.

73. Chertow GM, Lee J, Kuperman GJ, Burdick E, Horsky J, Seger DL *et al.* Guided medication dosing for inpatients with renal insufficiency. *Journal of the American Medical Association* 2001;**286**:2839-44.

74. Rind DM, Safran C, Phillips RS, Wang Q, Calkins DR, Delbanco TL *et al.* Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch.Intern.Med.* 1994;**154**:1511-7.

75. Durieux P, Nizard R, Ravaud P, Mounier N, Lepage E. A clinical decision support system for prevention of venous thromboembolism: effect on physician behavior. *Journal of the American Medical Association* 2000;**283**:2816-21.

76. Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF, Jr. *et al.* A computer-assisted management program for antibiotics and other antiinfective agents. *N.Engl.J.Med.* 1998;**338**:232-8.

77. Burke JP,.Pestotnik SL. Antibiotic use and microbial resistance in intensive care units: impact of computer-assisted decision support. *J.Chemother.* 1999;**11**:530-5.

78. Evans RS, Classen DC, Pestotnik SL, Lundsgaarde HP, Burke JP. Improving empiric antibiotic selection using computer decision support. *Arch.Intern.Med.* 1994;**154**:878-84.

79. Burke JP. Maximizing appropriate antibiotic prophylaxis for surgical patients: an update from LDS Hospital, Salt Lake City. *Clin.Infect.Dis.* 2001;**33 Suppl 2**:S78-S83.

80. Evans RS, Pestotnik SL, Burke JP, Gardner RM, Larsen RA, Classen DC. Reducing the duration of prophylactic antibiotic use through computer monitoring of surgical patients. *DICP* 1990;**24**:351-4.

81. Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. *Ann.Pharmacother.* 1994;**28**:523-7.

82. Evans RS, Pestotnik SL, Classen DC, Burke JP. Evaluation of a computer-assisted antibiotic-dose monitor. *Ann.Pharmacother.* 1999;**33**:1026-31.

83. McMullin ST, Reichley RM, Watson LA, Steib SA, Frisse ME, Bailey TC. Impact of a Web-based clinical information system on cisapride drug interactions and patient safety. *Arch.Intern.Med.* 1999;**159**:2077-82.

84. Grain F, Brudieu E, Guimier C, Calop J. Analyse des erreurs de prescription et de l'activité de pharmacie clinique dans une unité de soins informatisée. *J.Pharm.Clin.* 1999;**18**:56-7.

85. Levenson D. Software helps reduce adverse events and determine financial costs. *Rep.Med.Guidel.Outcomes Res.* 2001;**12**:5-7.

86. Silverman JB, Stapinski CD, Churchill WW, Neppl C, Bates DW, Gandhi TK. Multifaceted approach to reducing preventable adverse drug events. *Am.J.Health Syst.Pharm.* 2003;**60**:582-6.

87. Raehtz KG,.Walker PC. Computer-assisted TPN calculations: time savings and improved accuracy associated with use of a minicomputer. *Hosp.Pharm.* 1988;**23**:800-4.

88. Horn W, Popow C, Miksch S, Kirchner L, Seyfang A. Development and evaluation of VIE-PNN, a knowledge-based system for calculating the parenteral nutrition of newborn infants. *Artif.Intell.Med.* 2002;**24**:217-28.

89. Gard JW, Starnes HM, Morrow EL, Sanchez PJ, Perlman JM. Reducing antimicrobial dosing errors in a neonatal intensive care unit. *Am.J.Health Syst.Pharm.* 1995;**52**:1508, 1512-3.

90. Burton ME, Ash CL, Hill DP, Handy T, Shepherd MD, Vasko MR. A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. *Clin.Pharmacol.Ther.* 1991;**49**:685-94.

91. Begg EJ, Atkinson HC, Jeffery GM, Taylor NW. Individualised aminoglycoside dosage based on pharmacokinetic analysis is superior to dosage based on physician intuition at achieving target plasma drug concentrations. *Br.J.Clin.Pharmacol.* 1989;**28**:137-41.

92. Hickling K, Begg E, Moore ML. A prospective randomised trial comparing individualised pharmacokinetic dosage prediction for aminoglycosides with prediction based on estimated creatinine clearance in critically ill patients. *Intensive Care Med.* 1989;**15**:233-7.

93. Lynch TJ, Possidente CJ, Cioffi WG, Hebert JC. Multidisciplinary protocol for determining aminoglycoside dosage. *Am.J.Hosp.Pharm.* 1992;**49**:109-15.

94. Destache CJ, Meyer SK, Rowley KM. Does accepting pharmacokinetic recommendations impact hospitalization? A cost-benefit analysis. *Ther.Drug Monit.* 1990;**12**:427-33.

95. Mungall DR, Anbe D, Forrester PL, Luoma T, Genovese R, Mahan J *et al.* A prospective randomized comparison of the accuracy of computer-assisted versus GUSTO nomogram--directed heparin therapy. *Clin.Pharmacol.Ther.* 1994;**55**:591-6.

96. Casner PR, Reilly R, Ho H. A randomized controlled trial of computerized pharmacokinetic theophylline dosing versus empiric physician dosing. *Clin.Pharmacol.Ther.* 1993;**53**:684-90.

97. Verner D, Seligmann H, Platt S, Dany S, Almog S, Zulty L *et al.* Computer assisted design of a theophylline dosing regimen in acute bronchospasm: serum concentrations and clinical outcome. *Eur.J.Clin.Pharmacol.* 1992;**43**:29-33.

98. Dager WE, Albertson TE, De Almentero DR, Fiset C. Impact of therapeutic drug monitoring of intravenous theophylline regimens on serum theophylline concentrations in the medical intensive care unit. *Ann.Pharmacother.* 1992;**26**:1287-91.

99. Hurley SF, Dziukas LJ, McNeil JJ, Brignell MJ. A randomized controlled clinical trial of pharmacokinetic theophylline dosing. *Am.Rev.Respir.Dis.* 1986;**134**:1219-24.

100. Gonzalez ER, Vanderheyden BA, Ornato JP, Comstock TG. Computer-assisted optimization of aminophylline therapy in the emergency department. *Am.J.Emerg.Med.* 1989;**7**:395-401.

101. Welty TE,.Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. *Ann.Pharmacother.* 1994;**28**:1335-9.

102. White RH, Hong R, Venook AP, Daschbach MM, Murray W, Mungall DR *et al.* Initiation of warfarin therapy: comparison of physician dosing with computer-assisted dosing. *J.Gen.Intern.Med.* 1987;**2**:141-8.

103. Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. *Clin.Pharm.* 1987;**6**:37-45.

104. Vadher B, Patterson DL, Leaning M. Evaluation of a decision support system for initiation and control of oral anticoagulation in a randomised trial. *BMJ* 1997;**314**:1252-6.

105. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI *et al.* Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *Journal of the American Medical Association* 1999;**282**:267-70.

106. Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on Rounding Teams Reduce Preventable Adverse Drug Events in Hospital General Medicine Units. *Arch.Intern.Med.* 2004;**163**:2014-8.

107. Falconnier AD, Haefeli WE, Schoenenberger RA, Surber C, Martin-Facklam M. Drug dosage in patients with renal failure optimized by immediate concurrent feedback. *J.Gen.Intern.Med.* 2001;**16**:369-75.

108. Scarsi KK, Fotis MA, Noskin GA. Pharmacist participation in medical rounds reduces medication errors. *Am.J.Health Syst.Pharm.* 2002;**59**:2089-92.

109. Cut medication errors in half with ED pharmacist. *ED Manag.* 2002;**14**:88-90.

110. Pickrell L, Duggan C, Dhillon S. From hospital admission to discharge: an exploratory study to evaluate seamless care. *Pharm.J.* 2001;**267**:650-3.

111. Smythe MA, Shah PP, Spiteri TL, Lucarotti RL, Begle RL. Pharmaceutical care in medical progressive care patients. *Ann.Pharmacother.* 1998;**32**:294-9.

112. Hick HL, Deady PE, Wright DJ, Silcock J. The impact of the pharmacist on an elective general surgery pre-admission clinic. *Pharm.World Sci.* 2001;**23**:65-9.

113. Mamdani MM, Racine E, McCreadie S, Zimmerman C, O'Sullivan TL, Jensen G *et al.* Clinical and economic effectiveness of an inpatient anticoagulation service. *Pharmacotherapy* 1999;**19**:1064-74.

114. Dager WE, Branch JM, King JH, White RH, Quan RS, Musallam NA *et al.* Optimization of inpatient warfarin therapy: impact of daily consultation by a pharmacist-managed anticoagulation service. *Ann.Pharmacother.* 2000;**34**:567-72.

115. Ellis RF, Stephens MA, Sharp GB. Evaluation of a pharmacy-managed warfarin-monitoring service to coordinate inpatient and outpatient therapy. *Am.J.Hosp.Pharm.* 1992;**49**:387-94.

116. To EK,.Pearson GJ. Implementation and evaluation of a Pharmacist-Assisted Warfarin Dosing Program. *Can.J.Hosp.Pharm.* 1997;**50**:169-75.

117. Dranitsaris G, Spizzirri D, Pitre M, McGeer A. A randomized trial to measure the optimal role of the pharmacist in promoting evidence-based antibiotic use in acute care hospitals. *Int.J.Technol.Assess.Health Care* 2001;**17**:171-80.

118. Meisel S, Sershon L, White D. Reducing adverse drug events and medication errors using rapid cycle improvement. *Qual.Manag.Health Care* 1998;**6**:15-28.

119. Phillips WS, Smith J, Greaves M, Preston FE, Channer KS. An evaluation and improvement program for inpatient anticoagulant control. *Thromb.Haemost.* 1997;**77**:283-8.

120. Brown G,.Dodek P. An evaluation of empiric vs. nomogram-based dosing of heparin in an intensive care unit. *Crit.Care Med.* 1997;**25**:1534-8.

121. Hollingsworth JA, Rowe BH, Brisebois FJ, Thompson PR, Fabris LM. The successful application of a heparin nomogram in a community hospital. *Arch.Intern.Med.* 1995;**155**:2095-100.

122. Cruickshank MK, Levine MN, Hirsh J, Roberts R, Siguenza M. A standard heparin nomogram for the management of heparin therapy. *Arch.Intern.Med.* 1991;**151**:333-7.

123. Nemeth JS, Marxen TL, Piltz GW. Weight-based protocol for improving heparin therapy. *Am.J.Health Syst.Pharm.* 1996;**53**:1164-6.

124. Rivey MP,.Peterson JP. Pharmacy-managed, weight-based heparin protocol. *Am.J.Hosp.Pharm.* 1993;**50**:279-84.

125. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann.Intern.Med.* 1993;**119**:874-81.

126. Alvis JM, Reves JG, Govier AV, Menkhaus PG, Henling CE, Spain JA *et al.* Computer-assisted continuous infusions of fentanyl during cardiac anesthesia: comparison with a manual method. *Anesthesiology* 1985;**63**:41-9.

127. Theil DR, Stanley TE, III, White WD, Goodman DK, Glass PS, Bai SA *et al.* Midazolam and fentanyl continuous infusion anesthesia for cardiac surgery: a comparison of computer-assisted versus manual infusion systems. *J.Cardiothorac.Vasc.Anesth.* 1993;**7**:300-6.

128. Ruiz R, Borches D, González A, Corral J. A new sodium-nitroprusside-infusion controller for the regulation of arterial blood pressure. *Biomed.Instrum.Technol.* 1993;**27**:244-51.

129. van den Nieuwenhuyzen MC, Engbers FH, Burm AG, Vletter AA, van Kleef JW, Bovill JG. Computer-controlled infusion of alfentanil versus patient-controlled administration of morphine for postoperative analgesia: a double-blind randomized trial. *Anesth.Analg.* 1995;**81**:671-9.

130. Leape LL, Kabcenell AI, Gandhi TK, Carver P, Nolan TW, Berwick DM. Reducing adverse drug events: lessons from a breakthrough series collaborative. *Jt.Comm.J.Qual.Improv.* 2000;**26**:321-31.

131. Hume M. Changing hospital culture, systems reduces drug errors. *Exec.Solut.Healthc.Manag.* 1999;**2**:1, 4-9.

132. Wisconsin hospital finds creative ways to reduce ADEs; avoids the "quick fix" approach. *Health Care Cost Reengineering Rep.* 1999;**4**:85-9.

133. Resar, R. K. and Midelfort, L. One oganization's approach to medication safety. 2001. Toronto. Breaking the Silence: Error in Healthcare.

134. Farbstein K,.Clough J. Improving medication safety across a multihospital system. *Jt.Comm.J.Qual.Improv.* 2001;**27**:123-37.

135. Mitchell KA, Jones EA, Meguid MM, Curtas S. Standardized TPN order form reduces staff time and potential for error. *Nutrition* 1990;**6**:457-60.

136. Meyer TA. Improving the quality of the order-writing process for inpatient orders and outpatient prescriptions. *Am.J.Health Syst.Pharm.* 2000;**57 Suppl 4**:S18-S22.

137. Muñoz Labián M, Pallás Alonso CR, de La Cruz Bertolo J, López Maestro M, Moral Pumarega MT, Belaustegui Cueto A. Errores en las prescripciones médicas en una unidad neonatal. *An.Esp.Pediatr.* 2001;**55**:535-40.

138. Showing and telling lessons on safety. *Jt.Comm.Benchmark* 2001;**3**:6-7.

139. Thorn DB, Sexton MG, Lemay AP, Sarigianis JS, Melita DD, Gustafson NJ. Effect of a cancer chemotherapy prescription form on prescription completeness. *Am.J.Hosp.Pharm.* 1989;**46**:1802-6.

140. Gardulf A,.Nordström G. Correctly written drug prescriptions important for the nurses' drug handling -- but reviews of in-patients drug prescriptions demonstrated errors. *Vard Nord.Utveckl Forsk* 1998;**18**:4-8.

141. Bourke JL, Bjeldbak-Olesen I, Nielsen PM, Munck LK. Enstrenget medicinhåndtering. På vej mod øget sikkerhed. *Ugeskr.Laeger* 2001;**163**:5356-60.

142. Elkharrat D, Chastang C, Lecorre A, Caulin C. Prospective assessment of an intervention to rationalize prescribing of nonsteroidal anti-inflammatory drugs. *Am.J.Ther.* 1998;**5**:225-32.

143. Ross LM, Wallace J, Paton JY. Medication errors in a paediatric teaching hospital in the UK: five years operational experience. *Arch.Dis.Child.* 2000;**83**:492-7.

144. Almond M, Gordon K, Kent JR, Jones BW, Nice SW, Dhillon S. The effect of the controlled entry of electronic prescribing and medicines administration on the quality of prescribing, safety and success of administration on an acute medical ward. *Br.J.Healthc.Computing Inf.Manage.* 2002;**19**:41-2, 44-6.

145. Jarman H, Jacobs E, Zielinski V. Medication study supports registered nurses' competence for single checking. *Int.J.Nurs.Pract.* 2002;**8**:330-5.

146. Whitmore CK,.Wardian SM. Chemotherapy administration precheck verification. *Hosp.Pharm.* 1985;**20**:751-4.

147. Ness JE, Sullivan SD, Stergachis A. Accuracy of technicians and pharmacists in identifying dispensing errors. *Am.J.Hosp.Pharm.* 1994;**51**:354-7.

148. Milliken DL,.Gervais AA. The impact of computerization on medication discrepancies in a centralized unit dose drug distribution system. *Hosp.Pharm.* 1990;**25**:650-2.

149. Lacasa C, Roure C, Martinez J, Tuneu L, Alguersuari N, Ayra J. Control de calidad de la dispensación de medicamentos en dosis unitarias en sistemas manual e informatizado [Control of quality of the dispensation of drugs in unit dose in manual and computerized systems]. *Farmaci.Clin.* 1994;**11**:600-4.

150. Minnick A, Leahey M, Pischke-Winn K. The impact of patient point-of-view pharmacy delivery on labor and quality. *Nurs.Econ.* 1994;**12**:45-50.

151. Camac KJ, Fisher MJ, Norris DE. Medication errors -- a comparative study of drug storage sites. *Aust.J.Hosp.Pharm.* 1996;**26**:234-7.

152. Enderlin GM,.Summerfield MR. Implementation and analysis of a non-floor stock controlled substance unit dose system in a pediatric hospital. *Hosp.Pharm.* 1992;**27**:9-13.

153. O'Brodovich M,.Rappaport P. A study pre and post unit dose conversion in a pediatric hospital. *Can.J.Hosp.Pharm.* 1991;**44**:5-15, 50.

154. Brunel P,.Robelin N. Étude comparative de deux méthodes de dispensation des médicaments : nominale journalière et globale hebdomadaire. *J.Pharm.Clin.* 1995;**14**:262-8.

155. Taxis K, Dean B, Barber N. Hospital drug distribution systems in the UK and Germany--a study of medication errors. *Pharm.World Sci.* 1999;**21**:25-31.

156. Dean BS, Allan EL, Barber ND, Barker KN. Comparison of medication errors in an American and a British hospital. *Am.J.Health Syst.Pharm.* 1995;**52**:2543-9.

157. Stroup JW,.Dinel BA. Implementation and evaluation of a decentralized pharmacy service. *Can.J.Hosp.Pharm.* 1985;**38**:94-7.

158. Shah NR, Emont AJ, Johnson VP. Total quality management in action: pharmacy system changes to decrease medication incidents and increase clinical services. *Hosp.Pharm.* 1994;**29**:676, 679-80.

159. Thomas JA, Martin V, Frank S. Improving pharmacy supply-chain management in the operating room. *Healthc.Financ.Manage.* 2000;**54**:58-61.

160. McNally KM, Page MA, Sunderland VB. Ward stock and unit-supply drug distribution: influence on nursing time, pharmacy time and medication errors. *Aust.J.Hosp.Pharm.* 1997;**27**:22-7.

161. Klein EG, Santora JA, Pascale PM, Kitrenos JG. Medication cart-filling time, accuracy, and cost with an automated dispensing system. *Am.J.Hosp.Pharm.* 1994;**51**:1193-6.

162. Ray MD, Aldrich LT, Lew PJ. Experience with an automated point-of-use unit-dose drug distribution system. *Hosp.Pharm.* 1995;**30**:18, 20-3, 27-30.

163. Kratz K,.Thygesen C. A comparison of the accuracy of unit dose cart fill with the Baxter ATC-212 computerized system and manual filling. *Hosp.Pharm.* 1992;**27**:19-20,22.

164. Schwarz HO,.Brodowy BA. Implementation and evaluation of an automated dispensing system. *Am.J.Health Syst.Pharm.* 1995;**52**:823-8.

165. Borel JM,.Rascati KL. Effect of an automated, nursing unit-based drug-dispensing device on medication errors. *Am.J.Health Syst.Pharm.* 1995;**52**:1875-9.

166. Wilson AL, Hill JJ, Wilson RG, Nipper K, Kwon IW. Computerized medication administration records decrease medication occurrences. *Pharm.Pract.Manag.Q.* 1997;**17**:17-29.

167. Mekhjian HS, Kumar RR, Kuehn L, Bentley TD, Teater P, Thomas A *et al.* Immediate benefits realized following implementation of physician order entry at an academic medical center. *J.Am.Med.Inform.Assoc.* 2002;**9**:529-39.

168. Low DK,.Belcher J, V. Reporting medication errors through computerized medication administration. *Comput.Inform.Nurs.* 2002;**20**:178-83.

169. Meyer GE, Brandell R, Smith JE, Milewski FJ, Brucker P, Coniglio M. Use of bar codes in inpatient drug distribution. *Am.J.Hosp.Pharm.* 1991;**48**:953-66.

170. Puckett F. Medication-management component of a point-of-care information system. *Am.J.Health Syst.Pharm.* 1995;**52**:1305-9.

171. Brown SJ, Cioffi MA, Schinella P, Shaw A. Evaluation of the impact of a bedside terminal system in a rapidly changing community hospital. *Comput.Nurs.* 1995;**13**:280-4.

172. Gebhart F. VA facility slashes drug errors via bar-coding. *Drug Top.* 1999;**143**:44.

173. Patterson ES, Cook RI, Render ML. Improving patient safety by identifying side effects from introducing bar coding in medication administration. *J Am Med Inform Assoc* 2002;**9**:540-53.

174. Beger D, Messenger F, Roth S. Self-administered medication packet for patients experiencing a vaginal birth. *J.Nurs.Care Qual.* 1999;**13**:47-59.

175. Phelan G, Kramer EJ, Grieco AJ, Glassman KS. Self-administration of medication by patients and family members during hospitalization. *Patient Educ.Couns.* 1996;**27**:103-12.

176. Poster EC,.Pelletier L. Primary versus functional medication administration: monitoring and evaluating medication error rates. *J.Nurs.Qual.Assur.* 1988;**2**:68-76.

177. Kruse H, Johnson A, O'Connell D, Clarke T. Administering non-restricted medications in hospital: the implications and cost of using two nurses. *Aust.Clin.Rev.* 1992;**12**:77-83.

178. Burruss RA, Ashworth DN, Arikian VL. Medication administration by non-RN personnel: a safe and cost-effective response to the RN shortage. *Health Care Superv.* 1993;**11**:64-74.

179. Carey RG,.Teeters JL. CQI case study: reducing medication errors. *Jt.Comm.J.Qual.Improv.* 1995;**21**:232-7.

180. Gilliand BF, Stanislav GH, Constantin JJ, Schwinghammer TL. Program for reviewing returned medications. *Am.J.Hosp.Pharm.* 1992;**49**:860-3.

181. Gottlieb DJ, Parenti CM, Peterson CA, Lofgren RP. Effect of a change in house staff work schedule on resource utilization and patient care. *Arch.Intern.Med.* 1991;**151**:2065-70.

182. Hayman JN. Microcomputer-assisted monitoring of medication-dispensing errors. *Am.J.Hosp.Pharm.* 1989;**46**:1806-9.

183. What makes patients safer? Simplicity, standardization succeed in heparin program. *Clin.Resour.Manage.* 2000;**1**:166-8.

184. Burruss RA, Carroll NV, Schraa C, Burton B. Outsourcing inpatient IV compounding: expense and medication error implications. *Pharm.Pract.Manag.Q.* 1996;**16**:52-9.

185. Scott MG, McElnay JC, Burnett KM. Using bar-code technology to capture clinical intervention data in a hospital with a stand-alone pharmacy computer system. *Am.J.Health Syst.Pharm.* 1996;**53**:651-4.

186. Weeks WB, Mills PD, Dittus RS, Aron DC, Batalden PB. Using an improvement model to reduce adverse drug events in VA facilities. *Jt.Comm.J.Qual.Improv.* 2001;**27**:243-54.

187. Rozich JD,.Resar RK. Medication safety: one organization's approach to the challenge. *J.Clin.Outcomes Manage.* 2001;**8**:27-34.

188. Silver MP,.Antonow JA. Reducing medication errors in hospitals: a peer review organization collaboration. *Jt.Comm.J.Qual.Improv.* 2000;**26**:332-40.

189. Joiner GA. Developing a proactive approach to medication error prevention. *J.Healthc.Qual.* 1994;**16**:35-9.

190. Wermers MA, Dagnillo R, Glenn R, Macfarlane R, St.Clair V, Scott D. Planning and assessing a cross-training initiative with multi-skilled employees. *Jt.Comm.J.Qual.Improv.* 1996;**22**:412-26.

191. Schaubhut RM,.Jones C. A systems approach to medication error reduction. *J.Nurs.Care Qual.* 2000;**14**:13-27.

192. Tholl DA, Wager MS, Sajous CH, Myers TF. Morphine use and adverse effects in a neonatal intensive care unit. *Am.J.Hosp.Pharm.* 1994;**51**:2801-3.

193. Koren G. Trends of medication errors in hospitalized children. *J.Clin.Pharmacol.* 2002;**42**:707-10.

194. Goldspiel BR, DeChristoforo R, Daniels CE. A continuous-improvement approach for reducing the number of chemotherapy-related medication errors. *Am.J.Health Syst.Pharm.* 2000;**57 (Suppl 4)**:S4-S9.

195. McNally KM, Page MA, Sunderland VB. Failure-mode and effects analysis in improving a drug distribution system. *Am.J.Health Syst.Pharm.* 1997;**54**:171-7.

196. Kucher, N., Koo, S., Quiroz, R., Cooper, J. M., Paterno, M. D., Soukonnikov, B., and Goldhaber, S. Z. Electronic alerts to prevent venous thromboembolism among hospitalized patients. New England Journal of Medicine 352(10), 969-977. 2005.

197. Walton R, Dovey S, Harvey E, Freemantle N. Computer support for determining drug dose: systematic review and meta-analysis. *BMJ* 1999;**318**:984-90.

198. Juurlink DN, Mamdani MM, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *Journal of the American Medical Association* 2003;**289**:1652-8.

199. Koppel, R., Metlay, J. P., Cohen, A., Abaluck, B., Localio, A. R., Kimmel, S. E., and Strom, B. L. Role of computerized physician order entry systems in facilitating medication errors. JAMA 293(10), 1197-1203. 2005.

200. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F *et al.* Evaluating non-randomised intervention studies. *Health Technol.Assess.* 2003;**7**.

201. Quality of care: patient safety. Report by the Secretariat. *Fifty-fifth World Health Assemby. Provisional agenda item 13.9 A55/13*, 2002.

202. McKerrow, R., Johnson, N., Long, S., Hall, K. W., Rappaport, P., Harding, J., Roberts, N., and Bussieres, JF. Hospital pharmacy in Canada survey: medication incidents. Eli Lilly Canada . 2002.

203. Dillman DA. Mail and Internet Surveys: The Tailored Design Method. New York: John Wiley & Sons, 2000.

204. Canadian Healthcare Association. Canadian Health Facilities Directory. Ottawa: Southan Information Products, 2002.

205. Hospital Pharmacy in Canada Survey. Hospital Pharmacist Look-up. Eli Lilly . 2002.

206. Ringold DJ, Santell JP, Schneider PJ. ASHP national survey of pharmacy practice in acute care settings: dispensing and administration--1999. *Am.J.Health Syst.Pharm.* 2000;**57**:1759-75.

207. Tuffs A. Germany sets up a system for reporting medical mistakes. BMJ 330(7497), 922. 2005.

208. McNally KM,.Sunderland VB. No-blame medication administration error reporting by nursing staff at a teaching hospital in Australia. *Int.J.Pharm.Pract.* 1998;6:67-71.

Appendices: Introduction and Systematic Review

APPENDIX A: electronic literature search

In MEDLINE®, CANCERLIT® , and TOXFILE® (full search details are available upon request).

CCOHTA's search was designed to identify reports that described all of the following components:

1) an outcome of medication errors or adverse drug events
   (e.g., items 1 and 2 for MEDLINE, CANCERLIT, and TOXFILE, below)
2) a hospital setting
   (items 4 and 5 for MEDLINE, CANCERLIT, and TOXFILE);
3) a medication-error prevention technology, defined broadly
   (items 7, 8, and 9 for MEDLINE, CANCERLIT, and TOXFILE);

and

4) essentially any study design
   (items 11 to 16 for MEDLINE, CANCERLIT, and TOXFILE),

published no earlier than 1985 (due to concerns about the feasibility of the project, and a sense that studies published prior to 1985 would have little applicability today).

THE ELECTRONIC LITERATURE SEARCH (SAMPLE)

February 4, 2002, updated Nov 6, 2002

In Dialog® de = descriptor, ie. Medical Subject Heading (a controlled, thesaurus term)
ti = title (i.e. word has to occur in title field of the bibliographic record)
ab = abstract (ie word has to occur in abstract field of bibliographic record)
! = explode; picks up narrower terms as well, i.e. terms which are conceptually subsets of a broader term. For instance, medication errors! also picks up medication errors, hospital
()= words must be adjacent
(n)=words must be near each other, i.e. occur in the same field of the bibliographic record, but not necessarily adjacent
? = truncation symbol

DATABASES	LIMITS	KEYWORDS
Dialog®OneSearch®		
MEDLINE® 155 CANCERLIT® 159 TOXFILE® 156	1985+	1. medication errors! 2. [medication(n)error? OR medication(n)adverse(n)effect? OR medication(n)incident? OR medication(n)mistake? OR dispens?(n)error? OR dispens?(n)incident? OR dispens?(n)mistake? OR prescrib?(n)error? OR prescription(n)error? OR prescrib?(m)mistake? OR prescription(n)mistake? OR drug(n)administ?(n)error? OR drug(n)administ?(n)incident? OR drug(n)administ?(n)mistake? OR drug(n)order?(n)error? OR drug(n)order?()incident? OR drug(n)order?(n)mistake? OR drug(n)monitor?(n)error? OR drug(n)monitor?(n)mistake? OR adverse(n)drug(n)reaction? OR adverse(n) drug?(n)event? OR

adverse(n)drug(n)effect? OR adverse(n)drug()incident?]/ti,ab
3. **Set 1 OR Set 2**
4. [hospital departments! OR hospital units! OR hospitals! OR (pain clinics OR maternal-child health centers OR rehabilitation centers OR residential facilities OR hospices)/de
5. health()system?/ti,ab OR hospital? OR rehabilitation()cent? OR hospice? OR pain()clinic? OR residential()facilit? /ti,ab)]
6. Set 4 OR Set 5

7. (medication systems! OR hospital information systems OR medical informatics computing! OR drug information services!) OR (drug therapy, computer-assisted OR medical informatics applications OR decision support systems, clinical OR clinical laboratory information systems OR decision making, computer-assisted OR decision support systems, management OR information systems OR medical records systems, computerized OR integrated advanced information management systems)/de
8. [alert?(n)system? OR clinical(n)alert? OR drug(n)distribution(n)system? OR unit()dose? OR unit()dosage? OR peripheral()order()entr? OR robot? OR bar()cod? OR automat?(n)drug? OR administration()schedul? OR automat?(n)alert? OR charting OR kardex OR comput?(n3)medicat?(n3)administr?(n3)record? OR computer?(n)order?(n)entr? OR pyxis OR pyxisveri5 OR docudose OR docuscan OR script()pro OR scriptpro OR baker()cell OR autros OR bppoc OR OR cpoe OR visualmed OR leapfrog OR pocketscript OR invision OR sunrise()clinical()manager OR clinicomp OR lastword]/ti,ab
9. pharmacists/de OR nurses! OR nursing staff! OR medical staff, hospital! OR nursing staff, hospital OR physicians! OR nurses' aides! OR pharmacists' aides OR physician assistants! OR (pharmacist? OR nurse? OR physician? OR doctor? OR medical(w)staff OR psychiatrist? OR opthalmologist? OR pediatrician? OR gastroenterologist? OR medical(w)student? OR risk()manager? OR nursing()student?)/ti,ab
10. **Set 7:Set 9**

11. dt = (clinical trial OR clinical trial, phase i OR clinical trial, phase ii OR clinical trial, phase iii OR clinical trial, phase iv OR meta-analysis OR controlled clinical trial OR randomized controlled trial OR multicenter study OR review OR review literature OR review, multicase OR review of reported cases)
12. clinical trials! OR review literature! OR cohort studies! OR case-control studies! OR data collection! OR **risk management** OR (double-blind method OR random allocation OR meta-analysis OR evaluation studies OR case report OR case-control studies! OR organizational OR case studies OR feasibility studies OR clinical protocols OR peer review, research OR observation OR pilot projects OR **theoretical**

study OR program evaluation OR **quality assurance, health care OR total quality management** OR **medical audit OR questionnaires/** de
13. [(random? OR controlled()trial? OR controlled() clinical() trial? OR clinical() trial? OR double() blind? OR historical()control? OR pre()measurement OR post()measurement)]/ti,ab
14. (multicent? trial? OR multi cent? trial? OR meta analy? OR metaanaly? OR meta-analysis)/ti,ab
15. [research() integration OR research() overview? OR quantitative()review? OR quantitative() overview? OR methodologic() review? OR methodologic() overview?]/ti,ab
16. [systematic()overview? OR systematic()review? OR integrative()research OR quantitative()synthesis OR comparative()stud? OR prospective()stud? OR retrospective()stud? OR single()blind? OR triple() blind? OR treble() blind? OR dummy OR sham OR rct OR quality(3n)improvement? OR cqi OR tqi OR total()quality()improvement OR total()quality()management? OR case()stud? OR case()series OR case()report? OR **organizational()stud?** OR review? OR **self()report?]**/ti,ab
17. **Set 11:Set 16**

18. **Set 3 AND Set 6 AND Set 10 AND Set 17**
19. Set 18/1985:2002
20. Set 19 from 155 (MEDLINE)
21. Set 19 from 159 (CANCERLIT)
22. Set 19 from 156 (TOXFILE)

23. economics! OR quality of life!
24. (economic? OR quality of life? OR cost? OR price? OR pricing OR expenditure? OR budget? OR qol OR qaly OR quality adjusted life year? OR discount? OR willingess to pay OR affordability or discount)/ti,ab
25. Set 23 OR Set 24
26. Set 3 AND Set 6 AND Set 10 AND Set 25
27. Set 26/1985:2002
28. Set 27 from 155 (MEDLINE) (Economic results)
29. Set 27 from 159 (CANCERLIT) (Economic results)
30. Set 27 from 156 (TOXFILE) (Economic results)

APPENDIX B: CCOHTA's Protocol (Fisher *et al*)

Canadian Coordinating Office for Health Technology Assessment

Protocol for Medication Errors in Hospitals Project #162

Project Team:

Andrea Fisher, RN, MSN, MSc,
CCOHTA, Project Lead Researcher
Michel Boucher, B Pharm, MSc,
CCOHTA, Research Officer – Pharmaceutical
Bruce Brady, MSc,MA,
CCOHTA, Health Economist
Janet Joyce, B.A., M.L.S.
CCOHTA, Information Specialist
David K.U, BSc Pharm, MSc Pharm
President & CEO, Institute for Safe Medication Practices Canada

Project Reviewers:

George Wells, PhD, Scientific Advisory Panel, CCOHTA
Dr. Charles Wright, Scientific Advisory Panel, CCOHTA
Ross Baker, PhD, University of Toronto (to be confirmed)
Dr. Pat Croskerry, Dalhouise University (to be confirmed)

1.0 Background

Medication errors in hospitals are common, costly, and often preventable. Although most errors are minor, a small proportion result in an injury or preventable adverse drug event (ADE).[1] Although there is no reliable Canadian data on errors, ADE have been rigorously studied in United States, United Kingdom, and Australia. ADE ranged from 10-19% of all reported cases of medical errors.[2-4] Bates et al. (1993) found the rate of ADE to be about 10 per 1,000 patient days; over half (56%) of the events were judged to be preventable.[4] Canadian experts estimate that ADE in Canadian hospitals are likely to occur at similar high rates.[5]

Since the release of the (U.S) Institute of Medicine's report, To Err is Human (1999)[6] there has been considerable attention paid to the problem of medical errors in health care. This report was successful in capturing the attention of the public, by highlighting the extent of medical errors in the US. Authors of the report emphasize that most errors are not due to individual incompetence, but are the result of system failures. In two tertiary hospitals, Leape et al. (1995)[7] evaluated systems failures that underlie errors causing ADE and found that seven system failures accounted for 78% of the errors. The authors reported that system changes to improve information systems could help to decrease errors.

Health technologies, such as physician/provider-order entry, may help to provide part of the solution in the development of more effective systems to address system failures. Bates and colleagues studied the use of physician-order entry and reported a 55% reduction in serious medical errors.[1] Physician evaluators in a review of preventable and potential ADE found that unit-based clinical pharmacists could have potentially prevented the majority of errors.[8]

The overall objective of the CCOHTA project is to perform a systematic review of the existing literature to assess the clinical effectiveness of health technologies in the prevention of medication errors in hospital settings. The primary outcome of the systematic review will be medication errors and ADEs, preventable and potential in hospitals settings. Secondary outcomes of the study will include non-clinical outcomes (human and financial resources). Various health technologies identified in the comprehensive literature search will be considered for analysis. A review of economic studies of such technologies will also be undertaken, and the analytical approach that would be used to assess the cost effectiveness and budget impact of these technologies will be outlined.

2.0 Research Objectives

1. To perform a systematic review of the literature to assess the clinical effectiveness of health technologies in the prevention of medication errors in hospital settings:
Examples of Technologies include:

Treatment Decision-making:	*Computerized Physician/Provider Order Entry, Pharmacist Participation on the Ward*
Dispensing/Administering:	*Robots, Bar Coding, Automated Dispensing Devices, Computerized Medication Administration Records, Unit Dosing*
Monitoring:	*Computerized Warning of Potential Medication Errors and/or Adverse Drug Events, Pharmacist Participation on the Unit*

2. To: (a) perform a systematic review of the literature assessing the cost effectiveness and budget impact of using health technologies in the prevention of medication errors in hospital settings, and (b)

outline the analytical approach that would be used if the reader was to perform a cost effectiveness analysis and a budget impact analysis of these technologies for a particular jurisdiction.

3.0 Methods

For details of the search terms, syntax, and logic see attached Appendix A.
A OneSearch® of the bibliographic electronic databases MEDLINE®, TOXFILE®, CANCERLIT®, EMBASE®, BIOSIS Previews®, and Pharmaceutical News Index (PNI®) will be performed on the Dialog® system using strategies specific to each database, and duplicate references will be eliminated. Depending on the number of references, the search retrieval will be limited to searching from 1970, 1975 or 1980.

Other databases, such as Cinahl, via CINAHL*direct*® Online Services, and The Cochrane Library on CD-ROM, via The Cochrane Collaboration & Update Software, will be searched for relevant references. References on the economic aspects of the topic will be supplemented by searching HEED (Health Economic Evaluations Database) on CD-ROM via OHE-IFPMA Database Ltd.

A variety of approaches to identifying and retrieving grey literature (for example abstracts from meetings and conferences, policy papers, etc.) will be employed, such as Internet searching using a variety of search engines. The websites of known organizations participating in initiatives in the field of medical errors and patient safety, such as the Canadian Medical Society, Health Canada, and others, will be scanned.

In addition, CCOHTA's HTA Checklist of websites, which includes member agencies of the International Network of Agencies for Health Technology Assessment (INAHTA), for example, Agency for Healthcare Research and Quality (AHRQ), and specialized databases (for example, the University of York NHS Centre for Reviews and Effectiveness) will be scanned.

The investigators will hand-search the bibliographies of relevant papers for additional references, and experts identified by the investigators through reading and participation in meetings related to the topic, will be consulted.

b. Study Selection Inclusion and Exclusion Criteria and Procedures

The selection inclusion criteria for this review are that the study must: 1. contain information about medication errors; 2. contain information about health technologies; 3. be relevant to hospital settings (i.e. acute, critical, rehabilitation, and long term care populations); nursing home settings and retirement homes with assisted living programs will be excluded; 4. contain all study designs, case studies and comparative studies; and 5. be published in 1985 or later. No language restrictions will be placed on the selection of abstracts and for the inclusion of papers in the report. JJ will conduct a pilot project to evaluate the proposed search methods. The search may be adapted based on the findings of the pilot.

Two reviewers will independently be involved in the selection of relevant studies as well as in the data abstraction. Each reviewer will independently use a standardized data abstraction form to abstract data from each identified study. Additional variables that will be abstracted for studies of the economic review will include the type of economic study, comparator, study perspective, types of costs and consequences, data sources, assumptions, and handling of uncertainty.

c. Study Quality Assessment

d. Constraints and Risk Management

Access to unpublished information from technology vendors may be a challenge consideration. David U, a well-recognized clinical expert in health technologies, will provide valuable assistance in obtaining unpublished and published studies.

References

1. Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, MA'Luf N, et al. The impact of computerized physician order entry on medication error prevention. J Am Med Inform Assoc 1999;6(4):313-21.

2. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. Med J Aust 1995;163(9):458-71.

3. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et. al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med 1991;324(6):377-84.

4. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med 1993;8(6):289-94.

5. Baker RG, Norton P. Making patients safer! Reducing error in Canadian healthcare. HealthcarePapers 2001;2(1):10-31.

6. Kohn LT, Corrigan JM, Donaldson MS, editors, for the Committee on Quality of Health Care in America, Institute of Medicine. To err is human: building a safer health system. Washington: National Academy Press, 1999. Available: http://books.nap.edu/books/0309068371/html/index.html.

7. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. JAMA 1995;274(1):35-43.

8. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA 2001;285(16):2114-20.

APPENDIX C: Kappa Calculation

Kappa statistic for multiple raters

Let n represent the number of articles,
m_i represent the number of raters who assessed whether or not to include the i-th article,
x_i represent the number of raters who chose to include the i-th article,
m_{ave} represent the average number of rater opinions per article, and
$p_{overall}$ represent the overall proportion of articles chosen for inclusion.

Then

$$\hat{k} = 1 - \frac{\sum_{i=1}^{n} \frac{x_i(m_i - x_i)}{m_i}}{n(m_{ave} - 1)(p_{overall})(1 - p_{overall})}$$

where

$$m_{ave} = \sum_{i-1}^{n} m_i / n$$

and

$$p_{overall} = \sum_{i=1}^{n} \frac{m_i}{(n)(m_{ave})}$$

Reference

Fleiss JA. Statistical Methods for Rates and Proportions 2nd ed. New York: John Wiley & Sons, 1981. ch. 13, p. 225-228.

APPENDIX D: Data Abstraction Tool

Date of abstraction:_____
Reviewer's initials:_____ Reference manager number:_____

Study Information

Author(s):_____
Country where study carried out:_____
Year of publication:_____
Funding source:_____ Conflict(s) of interest:_____
notes:

Study Design

Study type: (rct, cohort, pre-post, case-study):_____
Study design (prospective, retrospective):_____
Number of centres:_____
Study setting (teaching/non-teaching, pediatric/adult; whole hosp./specific units; specialized center)

Outcome measures (definitions)
Medication errors

Preventable adverse drug events

Potential adverse drug events/ near-misses

Type of interventions/health technologies

1.

2.

3.

Description of study population

general

1.

2.
3.

Observation periods 1.

2.

3.

was study analysis conducted on an ITT basis? _____yes _____no

Study Findings:

n.b.,
please report standard deviations, standard errors, statistical tests, p-values, etc
please define observation periods, if they differ from what's defined above, in the left-most column:
e.g., for pre/post studies, state time frame of measurement

Outcome	**Group 1:**	**Group 2:**	**Group 3:**

Error-ascertainment method

(please *check all that apply*)		If Y, who ascertained errors?Incident reporting
(retrospective)	0	n/a
Study-elicited voluntary report	0	_____
Chart review-single, retrospective	0	_____
Chart review-repeated daily	0	_____
Direct observation	0	_____
Other (specify):	0	_____
Undefined	0	_____

Limitations / other comments:

APPENDIX E1: Systematic Review Analyses (original plan, from thesis proposal)

Subgroups 1) technologies and 2) study designs (pre/post, cohort, RCT)

Sensitivity Analyses:

MAJOR ONES

Variable	States
POPULATION	
Hospital type	-pediatric -adult
OUTCOME	
Error-ascertainment method	-direct observation -retrospective chart review -incident reporting -combination
Definition of error	-an error that reaches the patient -errors including potential errors
Stage of error (*n.b.* should overlap with ascertainment method)	-all -prescription -transcription/ verbal communication errors -dispensing (by pharmacy) -administration
INTERVENTION	
length of follow-up	T.B.D.

MINOR ONES

POPULATION	
Type of ward	-ICU -Non-ICU
Hospital type	-teaching -non-teaching
Hospital size	-bed number
Number of centers	1 >1
OUTCOME	
# of independent error observers	1 >1

APPENDIX E2: Oxford Evidence Grading System

"Levels of Evidence and Grades of Recommendation

Introduction

. . . these levels and grades speak only to the validity of evidence about prevention, diagnosis, prognosis, therapy, and harm. Other strategies, described elsewhere in the Centre's pages, must be applied to the evidence in order to generate clinically useful measures of its potential clinical implications and to incorporate vital patient-values into the ultimate decisions.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:

□ EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)

□ OR a Systematic Review with troublesome (and statistically significant) heterogeneity.

□ Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1 - 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	Level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation."

APPENDIX F: Computerized Physician Order Entry (CPOE), Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment (- limitation. + strength)
[63]	Physician entered Rx directly into the computer (comp)	Physician wrote onto a drug order sheet; unit clerk OE to computer (written) (also, verbal: dr. told nurse: policy-restricted situations)	Cohort: all orders over 3 months	Pediatric, teaching hospital, USA	errors in orders at the point of entry into computer system ("dosage error, transcription error, wrong patient," etc); adverse pt outcomes due to order-transmission error	routine review by pharmacist & incident report	-confounded +investigator intentions: study objective was to assess verbal orders
[64;65]	1) computer-assisted Rx-writing: prescribers either a. choose from a pick-list, which contains Rx info (e.g., dose, freq), and links Rx info to pt-identifiers and weight for pts <50kg b. type in Rx not on pick-list (pediatrics, etc) 2) reminders to complete fill-in Rx	hand-written prescriptions, stamped with patient-information	Pre/post Pre: 1/5/99-30/6/99 implemented 3/2000 Post 1/5/00-30/6/00 (OE) 1/5/00 - 15/5/00 (written)	ED Pre: 7036 pt. visits; 2326 hand-written Rx for 1459 pts Post: 7845 pt. visits; 1594 CPOE Rx for 1056 pts. 380 written Rx, USA	identified pharmacist clarifications	Pharmacist-documented routinely	-extrapolated hand-written orders post-CPOE

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment (- limitation. + strength)
[66]	CPOE, (following sequentially: education forced allergy listing)	Pre-CPOE	Interrupted time-series: nov-99 to sep-02	Teaching hospital, adult, USA	Medication errors (misc)	Not declared	More error (mean RR=1.1) during implementation

APPENDIX G: Computerized Decision Support Sytem (CDSS)+/-Computerized Physician Order Entry (CPOE), Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[67; 68]	1. CPOE pick-lists; lab- result display; less transcription (some pre-approved order sets); some drug-allergy, drug-drug interaction check; drug-lab alerts; orders hand-carried to pharmacy 2 allergy alert included cross-sensitivity check (page alerts); orders hand-carried to pharmacy 3 more drug-interaction checks: with notification when ordering; restricted KCl; orders electronically linked to pharmacy	paper-based orders; no automated decision support	Pre/post x 3 Pre Oct - Nov '92 (51 days) 1 Oct - Dec '93 (68 days) 2. Nov- Dec '95 (49 days) 3. Mar-Apr '97 (52 days) -implementation in the interim	2 gen med, 1 ICU, adult teaching hospital, USA	Medication errors: errors in process of ordering, dispensing, or admin. Missed-dose errors: doses unavailable to nurses when needed (wrong-time or omission errors)	Pharmacists & nurses study-elicited voluntary report & review of medication sheets by trained reviewers	4 observation periods. 2 studies at same site. Pre/post funder is Am. Soc. Health-system pharmacists
[69]	CPOE: drug menu (default, range of pot. doses); paper MAR; computerized lab results; suggested consequent orders; limited drug-allergy, drug-drug, and drug-lab checks + ½ wards: new pharmacist workflow	Hand-written orders.	Pre: Feb-Jul 1993 (6 months) Post: Oct 94- Jul95 (9 months) (implementation intervening)	726-bed tertiary care adult hospital, USA	medication errors, prev. ADE, pot ADEs	study-elicited voluntary reporting by nurses, pharmacists, clerical personnel; physician chart review on weekdays	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[70]	CDSS for CPOE recommends dose and frequency & performs rule-based checks for erroneous orders, omissions	Paper-based orders (essentially blank forms)	Pre/Post 6 months pre 1st month post 1 year post 2 years post	720-bed adult teaching hospital, USA	excessive doses: exceeded highest recommended dose -- (divided by the total # doses). high-risk drug excluded (anti-neoplastic anticoagulants, sympatho-mimetic drugs)	Pre: investigators' review of paper-based pharmacy records Post: captured by automated system (misses workarounds)	-no review of appropriatenes s of dose for individual cases. –high-risk drugs excluded
[71]	CPOE with alerts & guidance to warn clinicians of potential medication errors	Non-computerized physician orders	Pre/Post. 2-year observation. implemented beginning Mar 99; for >90% of pts in May 2002	Specific unit of an adult hospital, USA	Rx error	Undefined method (pharmacy & medical staff)	-undefined setting, timing, event rate
[72]	CPOE + CDSS implemented first on 1/3 of the unit, then fully	Pharmacist OE	pre: 1993 post: 1994 -implemented over 2 years	Pediatric teaching hospital: 10% increase in discharges, same pt-days, USA	Error in written orders, OE, dosage, pharmacy formulation	Staff incident report	-incident report, timing unclear

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[73]	Renally adjusted computer-assisted dosing (CDSS for CPOE applies expert panel recommendation to lab database)	CDSS for CPOE did not consider renal function	4 alternating 8-week blocks of intervention & control periods	Orders for nephrotoxic and/or renally cleared drug (14% of drug orders) , USA	inappropriate drug dose or freq: *a priori*, nephrologist, internist, pharmacist determined optimal dose	logic provided by what expert panel recommended	
[74]	CDSS alert: if serum creatinine rose >=44uM, emails notified drs (mean 9) of the change & of patient's potentially nephrotoxic & renally excreted medications	No-alert	Alternating time-series Months 1-3, 10-12, 16-18 Months 4-9, 13-15 Jan 22, 1990-July 4, 1991	>=18 years old, on nephrotoxic drug, whose serum creatinine increased >=44umol , USA	severe renal impairment: 2-fold serum creatinine increase to at least 177uM (0.5mg/dL): Bonney's criteria	automated, from lab database	+non-intrusive test, interrupted time-series matching secular trend -interruptions may decrease alert fatigue. pot. differences in testing

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[75]	CDSS notifies dr. of discrepancies with hospital guidelines, explains its suggestion, and prints instructions and Rx for chart *after* dr. enters clinical data	CPOE, no CDSS	3 x 10-week intervention periods; 4x 10-week control periods; 4-week "washout" between each period	orthopedic surg dept, 1000-bed hospital, FRA	Rx error: Omission: of recommended anticoagulant Wrong: Rx when CDSS proposes no anticoagulant PE, DVT	Errors: computerized classification defined by local experts PE, DVT as routinely diagnosed	-non-adherence to local guideline not always wrong -only Rx orders through system +effect while in use, not when removed. Similar pt. char neutral: $ from Direction des Hopitaux, Ministere de l'Emploie
[76]	anti-infective CDSS + CPOE (@bedside, nursing stations, OR, ER, and remotely). suggests appropriate antibiotic regimen*. order of non-CDSS drug required physician explanation * based on 5-yr LDS record if available, and pt-data	Pre	Pre/post (prospective) Pre: June 92-June 94 Post: July 94 – June 95	12-bed shock-trauma ICU, LDS Similar: pt-char, a-b. Tx duration pre & post USA	ADEs caused by anti-infectives drug-allergy alerts xs dose alerts susceptibility mismatches	Electronic chart review (possibly automated)	(4@LDS targeted known allergies & admin errors, & saw them decrease) -automated electronic chart review is standard for intervention, too. No accounting for system bypasses

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[77]	Computerized physician anti-infective OE	Pre	Pre: 1994 Post: 1998 (intervention in 1996)	receiving anti-infectives at LDS, USA	ADEs	Computerized ADE monitor (+negligible voluntary reporting)	- same year, retrospective chart review found antibiotic associated d ADE rate of 18.8% vs. this study, 1.2%
[78]	CDSS: antibiotic consultant for common infection sites (blood, wound, lower resp tract, abscess, urinary tract) determines likely pathogens based on prior 5 years of lab data, updated monthly; suggests 5 most effective antibiotic regimens (noting allergies & renal problems)	Pre	Pre/post PRE: 20-weeks pre-any CDSS & subsequent 20 weeks for random half of drs. With CDSS: 20 weeks for each group	random sample of each day's +ve cultures from inpts--first culture from each infected site (>1 possible / pt), USA	Inappropriate order (drug choice, basically)	lab record review by investigators	
[34; 79]	CDSS for prophylactic*, empiric**, and therapeutic antibiotic use** *re: case-selection, delivery time, intra-operative dosing, and Tx duration **alerts & advice re. resistance, untreated infection; dose, route, interval; absent current renal function data.	Pre	Pre: 1988 Implemented in 1989 Post: 1989, 1994	Antibiotic-treated pts at LDS (% pts with prophylaxis same in 85 & in 94) LDS, USA	Antibiotic-associated ADEs	Retrospective chart review (by epidemiology dept)	+ repeatedly associated with intervention, from add/remove/ add back in

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[79]	86: pharmacist put prophylaxis reminder sticker in chart re. computer alert. 87: hospital leadership shown local study & made multidisciplinary team of department leaders 88: nurses responsible for first prophylactic dose (checklist in chart). 91, 93-98: CDSS made standing order for prophylaxis in indicated pts, on computerized OR schedule	85-87: multiple persons responsible for admin of anti-microbial prophylaxis	Interrupted time-series (retrospective) 3-6 months per year: 85, 86, 88, 89, 92, 93, 94, 94-84, 98	surgical pts indicated for antibiotic prophylaxis (re. local guidelines) at LDS, USA	Prophylactic Ab doses: % early/ late / omitted (out of n)	Retrospective chart review (by epidemiology dept)	CDSS: good evidence that errors reduced (from add/remove/ add back in) -making nurse responsible may have contributed
[80]	Computer identified pts with antibiotic prophylaxis >48hrs; clinical pharmacist placed stop order stamp in chart	Pre	Pre: 85 (yr 1) Post: 86 (yr 2)	LDS: 520-bed adult, private, teaching, USA	pts receiving antibiotics 48hrs post-surgery without evidence of infection in computerized record	Automated computer record review (medical & lab)	- automated stop order may be not appropriate sometimes. program stopped after 1 yr
[81]	CDSS alerted pharmacists of previously identified drug allergies. inservice education about drug admin rates for antibiotics	inservice education about recognizing ADEs clinically & how to use the computer	pre: year 1 (May-89 to Apr-90) post: year 2 (May-90 to Apr-91) year 3 (May-91 to Apr-92)	LDS: 520-bed adult, private, teaching, USA	Allergic or idiosyncratic ADEs (not ADRs)	Retrospective chart review (by epidemiology dept)	targeted known allergies & admin errors, targeted them, and saw a decrease - sustained decreased 2 years post-intervention

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[82]	clinical pharmacists receive a daily list of suggested dose adjustments, based on CDSS xs antibiotic dose alert, based on patient's renal function -mandatory in 12-bed ICU; voluntary elsewhere in 520-bed hospital	Pre	pre: 2 years (Apr-93 to Mar-95) post: 1 year (Apr-95 to Mar-96)	Receiving vancomycin gentamicin, imipenem, cefazolin, cefuroxime LDS: 520-bed adult, private, teaching, USA	ADEs due to study antibiotics # pts who received xs dose	Retrospective chart review (by epidemiology dept)	
[77]	Computerized physician anti-infective order entry	Pre	Pre: 1994 Post: 1998 (intervention in 1996)	Receiving anti-infectives at LDS, USA	ADEs	computerized ADE monitor (+negligible voluntary reporting)	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[76]	CDSS for anti-infectives + CPOE (available at bedside, nursing stations, OR, ER, and remotely; alerts physicians to latest pt-info from records & suggests appropriate antibiotic regimen; based on 5-yr LDS record if available, and data on infection, pt., allergies, drug-drug-interaction, toxicity, and LDS) (non-CDSS-drug Rx req'd dr. explanation)	Pre (unclear)	Pre/post (prospective) Pre: June 1992-June 1994 Post: July 1994 – June 1995	12-bed shock-trauma ICU, private 520-bed hospital Similar: pt-char, a-b. Tx duration pre & post USA	ADEs caused by anti-infectives #alerts: -drug-allergy -xs dose, considering renal function susceptibility mismatches mean # days anti-infective dose	Electronic chart review (possibly automated)	
[83]	pharmADE added to commercial CDSS: alert report faxed to pharmacy; expected ADEs & Tx options shown for the interaction	Commercial CDSS warned drug interactions (updated in the last month of its evaluation)	Pre: Jan '94 to Sept '95 Post: Jan '96 - Dec '97	Teaching general hospital (92-94% of records available), USA	cisapride used with an azole antifungal; # ADEs related to targeted interactions	Pharmacists' retrospective review of computer records	Cisapride was 71% new alerts: the main effect
[84]	2) pharmacy OE & CDSS, and clinical pharmacist 1 day / wk for drug monitoring and pharmaceutical interventions (also "reglobalized" drug distribution)	No computerized pharmacy order-entry system; no clinical pharmacist	Pre & Post (12 wks for the 3 phases, altogether)	2 units, 53 resp beds, teaching, FRA	prescription errors, particularly wrong drug , wrong dose, wrong duration	Pharmacist comparison of guidelines with patient record	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[85]	CDSS, called Excalibur Patient Safety Net	Pre	Pre: not defined Post: one year	private, adult teaching hospital, USA	drug-related mistakes, toxic Rxns to digoxin	Not declared	Funds: Centre for Clinical Computing, AHRQ, John H. Hartford Foundation
[86]	-CDSS for CPOE indicated the correct heparin infusion rate in mL/hr -to simplify drip-rate calculations, standard heparin concentration changed from 50u/mL to 100u/mL (response to observed increase in heparin-infusion errors (reviewed quarterly))	Pre	Time-series: Oct/99 to Sept/01 intervention implemented in Apr, 2001	Pts. receiving heparin infusions in 726-bed acute adult teaching hospital, USA	Errors involving heparin-infusion rates	Incident report	
[87]	Computer calculation of ped. TPN doses	One pharmacist/ technician calculates; other checks	Pre/post (12-week periods)	80% (pre) & 85% (post) of orders Pediatric, teaching hospital, USA	% divergent values	Pre (manual): investigator's calculation +/- 5% ne calculation team's calculation Post: check on data entry into computer	–data collection methods (e.g., sample size, outcome ascertainment). -poor comparability of outcomes

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[88]	Vienna Expert System for Parenteral Nutrition of Neonates HTML - based, supports calculations	Hand calculation of parenteral nutrition solution	Cohort (timing not declared)	neonatology ICU patients receiving parenteral nutrition, Austria	Prescribing error, severity rated as -potentially life-threatening (eg, dangerous [K+]) -major (eg, [Ca++] low for bone mineralization) -minor/ clinically irrelevant	Not declared	-Non-comparability of outcome assessment ($: Austrian Ministry)
[89]	Local dosing guidelines for antimicrobials printed on the back of each page -using spreadsheet program, pharmacist calculates pt-specific dose, attached to the pharmacy-prepared syringe -nurse verifies protocol-entry criteria & signs -ordering physician verifies & signs at night, shift-charge nurses calculate doses, which pharmacists verify in the morning	manual system (unclear what checks existed)	Pre-intervention the 2 years following implementation	Neoantes receiving anti-microbials in 72-bed neonatal ICU, USA	Dose-calculation errors	Not declared note overlap with adjacent Study	

APPENDIX H: Kinetic-dosing, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[90]	Computer program set initial dose which it adjusted based on peak and trough serum aminoglycoside concentrations	physicians dosed aminoglycosides (received peak & trough serum aminoglycoside levels after initial infusion)	RCT (at physician level)	VA hospital. Pt with suspected infection & decision to treat it with aminoglycoside. Exclusions: Tx <48hours; initial serum creatinine >2mg/dL; aminoglycoside Tx in prior 14 days; Hx of aminoglycoside toxicity; serum [aminoglycoside], renal-function tests unavailable, USA	nephrotoxicity: rise in serum creatinine level of: 0.5 mg/dL if initial value was <=1.5mg/L 30% if initial value was >1.5mg/L	serum levels drawn within 48hrs of Tx initiation (investigators)	-confounding with different doctors, patients excluded if non-compliant. Doctor-level allocation (n=17), patient-level analysis
[91]	3 blood samples for Sawchuk one-compartment model: due prior to 2nd dose at ~8hrs. sample times depended on creatinine clearance	Attending medical team aimed for a peak plasma concentration of 6-10mg/L, trough of 1-2mg/L	RCT	Pt received 3mg/kg loading dose of gentamicin or tobramycin in first 3 days (excluding ICU). NZ	At 2, 5 days: [peak] or [trough], [peak], [trough] outside target Decreased creatinine clearance (reversible) Mortality	Prospective, by pharmacists	-potential to generalize + no dropouts, apparently. Pt comparability
[92]	3 blood samples for modified Sawchuk one-compartment model: due prior to 2nd dose at ~8hrs. sample times depended on creatinine clearance	nomogram: 1.7mg aminoglycoside/kg/ 8hrs for inpts with normal creatinine clearance; dose interval varied inversely with aminoglycoside clearance	RCT	ICU pt, after receiving 3mg/kg loading dose of aminoglycoside. NZ	Aminoglycoside peak plasma concentration outside optimum range of 6-10mg/L at 48-72hr	Prospective, pharmacists	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[93]	>Surgical resident picks loading & maintenance dose using nomogram printed on back of antimicrobial order forms (mod. Cockcroft & Gault equation) >Staff pharmacist checks order; pharmacokinetic analysis to recommend changes + training for drs, nurses, pharmacists	No standardized method for physicians or pharmacists to 1) choose an aminoglycoside 2) determine loading & maintenance doses 3) monitor a pt's response 4) obtain blood samples 5) adjust a patient's dosage if aminoglycoside levels are outside the therapeutic range	Pre: Apr-Jul 85 (4 months) < period for implementing the intervention seemed lengthy> Post: Feb - May 87 (4 months) Post: Feb-June 88 (5 months)	>=18yrs, received aminoglycosides >=3 days; no prev. aminoglycosides nor prior dialysis surgical unit, 550-bed Army Research hospital, USA	Number reaching therapeutic dosage (peaks of 5-10mg/L, troughs of <2mg/L) Possible nephrotoxicity (serum [creatinine] increased 1) >0.5mg/dL if baseline <3.0mg/dL ; 2) >1.0mg/dL if baseline >=3.0mg/dL	Retrospective chart review by pharmacist or physician	- several failed pilots (regression to mean). -AE follow-up only if kidney toxicity. +pt comparability
[94]	physician accepted all clinical pharmacy service recommendations for the patient	physician did not accept all clinical pharmacy service recommendations for the patient	Cohort (retrospective) : 11/1/88 to 15/1/88	>=18 years old, receiving aminoglycoside antibiotics (IV or IM) for gram-negative or systemic enterococcal infections [excluded dialysis], adult teaching hospital, USA	Nephrotoxicity (>=0.5mg/dL rise in serum creatinine); low first-peak concentration; low second-peak; concentration; unknown second peak (presumably after low first peak); high first trough concentration; high second trough concentration	retrospective review	-excluded patient if kinetic-recommend-ed dose not implemented in 48 hours

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[95]	bolus of 5000 units; females 1100u/hr, males 1400u/hr bayesian forecasting program is a function of: age, weight, smoking Hx, heparin-dosing Hx, APTT Hx, baseline APTT	nomogram: GUSTO trial guidelines for dosage, APTT determinations, dose modification	RCT (patient's hospital similar-length stays)	MI patients eligible for recombinant TPA (FDA guideline), 2 adult teaching hospitals, USA	APTTR >=1.5 within 24 hours APTT ratios [<1.5, 1.5-2.5, or >2.5] in [1st 24 hrs & during hospital stay] Bleeding	Prospective: investigators' recording	-potential to generalize +pt comp
[96]	"kinetic": theophylline adjustments made based on hand-held computer program which considers two early measures of serum theophylline (linear, one-compartment model)	"empiric": primary-care physicians told to aim for a 15mg/L theophylline level, based on two early measures of serum theophylline concentrations	RCT (patient's hospital stays)	>=18 yrs old, diagnosed with asthma or COPD, teaching, medicine service in hospital, USA	Pot: Subtherapeutic theophylline level (<10mg/L) just before discontinuation of IV theophylline infusion; toxic theophylline level (>20mg/L) Prev: theophylline toxicity	Prospective: investigators' recording	-not "normal practice": patients in whom lab tests weren't performed weren't evaluated. -pt comp (in kinetic, more weight CHF, smoking, male, 1st concentration)

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[97]	Pharmacokinetic computer-program-determined theophylline dosing	Physician-determined theophylline dosing	RCT (patient's period of being hospitalized)	ER visitors because of acute bronchospasm if IV theophylline had not been administered, and initial nebuliser therapy with salbutamol did not relieve the bronchospasm, 1400-bed adult teaching hospital, Israel	% time below recommended therapeutic range (<=10ug/mL) % time outside recommended therapeutic range (<=10ug/mL or >20ug/mL)	Prospective: investigators' recording	-tiny sample -pt comp
[98]	Pharmacist theophylline Therapeutic Drug Monitoring regimen (Koup et al.'s method; programmable calculator)	Staff doctors determined IV theophylline dosing regimen	Pre: 2 months Post: 2 months	medical ICU pts receiving IV theophylline: post: mean 26kg heavier (88 vs 62), 6/14 vs 1/11 smokers, USA	Cardiac arrythmias plasma concentrations (Cps) outside of desired range (supra/sub therapeutic Cps-10-20mg/L target)	n/a	+system-level intervention

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[99]	Nomogram determined initial IV aminophylline loading & infusion doses (based on weight & height) Non-linear least-squares regression determined IV theophylline loading, IV infusion, and oral doses - target is 15mg/L, based on 4 venous samples on day 1, 2 samples later on	Attending medical officers determined IV loading, IV infusion, and oral doses blood samples taken once per day	RCT (stratified)	Adult patients, ER, Australia	Serum theophylline concentration >20mg/L , >25mg/L, <10mg/L. On days 2 & 3, severe: breathlessness; palpitations; eight other symptoms (wheeziness, night wheeze, cough) and side-effects (nausea, tremulousness, agitation, blurred vision, diarrhea)	Prospective: investigators' recording	-potential to generalize

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[100]	Bayesian dosing post 4-hour reading	Nomogram targeted 10-20mg/L serum theophylline. ED residents adjusted doses based on 4-hr blood level	RCT (hospital stay)	Pts >=18yrs with IV aminophylline for acute asthma exacerbations ED, teaching, adult, USA Excluded: pregnancy, hypersensitivity to theophylline or aminophylline, outpt dyphylline, core pulmonary biventricular failure; [theophylline]> 20mg/L	Adverse Rxn to Tx	Prospective by pharm D	-excluded 15/82 protocol violations
[101]	Pharmacist responsible for daily drug monitoring: adjusting vancomycin dosages (mix of one- and two-compartment models), documenting changes in the pt's chart (TDM for other drugs, too)	Care by an intern closely supervised by her resident & attending dr; investigators suggested a 5mg loading dose each day for 3 days	Cohort: two-years after initiation of the service: during vancomycin therapy, June 1990-Mar 1991)	>=4 days IV vancomycin, >=18yrs old, initial creatinine clearance >0.33mL/sec (est) [Excluded if white-cell count<=1000/pL, critical-care unit, concurrent amphotericin], 1100-bed teaching hospital, USA	nephrotoxicity: rise in serum creatinine level of >0.5 mg/dL during vancomycin therapy (>44umol/L)	Lab data (investigator-collected)	-Selection by dr.: TDM less diabetics (2% vs. 16%) or on amino-glycoside (15% vs. 24%): -only TDM care providers aware of study

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[102]	Pharmacist or dr. familiar with the software, but not expert in managing warfarin therapy. The software describes the pharmacodynamic response to warfarin, using information about patient age, height, weight, smoking habits, and alcohol intake	intern supervised by her resident & attending physician; investigators suggested a 5mg loading dose each day for 3 days	RCT (6 months in the latter half of the academic year (Dec 1, 1984 to June 30, 1985))	mean 59 yrs, 90% male, groups balanced except 59% smokers in pharmacodynamic vs. 36% smokers in intern, Two adult teaching hospitals (veterans), USA	Bleeding (major/ minor). >6 days to reach target PR. pts with a high PR. while on warfarin, % days: high/low total high or low (1.8+/- 0.4) 10-14 days after maintenance dose, wrong PR. bleed.	Prospective: investigators' recording	Control interns supervised by residents may not dose as well as pharmacists/ doctor with computer support +ITT
[103]	2. after day 3, dosage adjusted by clinical pharmacist using analogue-computer program 3. after day 3, linear regression defined a single dose, encouraged if considered accurate	after day 3, physicians adjusted doses without assistance	RCT	adults who've received warfarin 10mg daily for 3 days, USA	Prothrombin ratio <=1.3; 1.31-2.5, >=2.5	Prospective, by pharmacists	+pt. Comparability

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[104]	ctrl + CDSS: 1st 3 days, based on daily INR & dose; outpts, based on target INR, actual INR, previous INR, previous dose. Model is simple proportional derivative	gave doctors anti-coagulation guidelines (Drugs & Therapeutics Bullentin), pts Dept of Health's anticoagulation booklet	rct (pt-level)	inpts who required warfarin initiation (excluded: >2 warfarin doses, known maintenance doses, taking oral anticoagulant other than warfarin) PRE: median 88 (5-389) POST: median 93 (3-392), UK	Time to INR >=2, to stable dose. INR <2 on hospital D/C. pts didn't get dose stability pre endpoint. pseudoevents (INR<=2.5 or >=5). INR>=5 av time to >pseudoevent (known compliance) % time in therapeutic range- inpt % time in therapeutic range- outpt Haemorrhage -due to INR >3 Thromboembolism -due to INR <2	prospective monitoring, highly structured (by investigators)	-possibly contaminated: same doctors for 2 groups. non-compliance.

APPENDIX I: Clinical Pharmacist, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[19; 69]	TEAM= new pharmacist work flow: more available on the unit, eg with daily ICU rounds; distributed dilution charts, drip-rate calculation program; standard labels for IV; pharmacy-nurse communication log + POE co-intervention	POE co-intervention	randomized units (8): pre: Feb-Jul 1993 (6 months) post: Oct 94-Jul95 (9 months) (implemented in the intervening period)	no Team: 1 ICU, 3 general Team: 1 ICU, 3 general USA	events/1000pt-day: prev. ADEs non- intercepted pot. ADEs non-intercepted serious drug errors (total)	study-elicited voluntary reporting by nurses, pharmacists, clerical personnel; physician chart review on weekdays	Funding: Am. Soc. Health-system Pharmacists

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[105]	experienced senior pharmacist rounded with ICU pt-care team each morning, (1/2 FTE for 17-bed ICU) -present for for rest of morning -on call later	Traditional hospital pharmacy services (pharmacist present in ICU but did not do rounds)	Cohort (prospective) : 01/02/93 to 31/07/93 Implemented: beginning May 94 Post: 01/10/94 to 07/07/95	Random pts selected from med. ICUs, Large 3^0 -care hospital USA	Prev. ADE: injury caused by an error in the use of a medication (e.g. hypotension, bleeding) ADE: injury related to drug use	Retrospective chart review by nurse/ pharmacist, reviewed by 2 physicians	-Tech generalizability (99% acceptance rate). Funding: Am. Soc. Health-system Pharmacists, Risk-Management Foundation +concurrent control. -Funding: Am. Soc. Health-system Pharmacists, Risk-Management Foundation
[106]	2 pharmacists for rounding with pts (6 different ones. Ratio of 1pharmacist: 15 pts)	Pharmacist order review (no pharmacist on rounding team. 1 pharmacist: 30 patients)	Cohort. Assessor-blinded	2 gen med wards similar age, sex, race, co-morbidities USA	Prev. ADE: undesired drug RxN, pot. prevented through drug selection or management	Blinded Senior pharmacists reviewed ED notes, progress notes, nursing flow sheets, order, MARs, lab results	+patient comparability. assessor-blinding. -Accepted 147/150 interventions (high!).

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[107]	full-time pharmacist taught interns rules of dosing: rounded with drs (alternately) on one ward (saw pts 1/4 days). Chart review daily on other 2 wards. optimized dosages for drugs >=70% renally eliminated, whenever serum creatinine determined	Interns supervised by board-certified residents	pre/post at dose level	3 adjacent 13-bed units in an 87-bed teaching adult, hospital: pre: averaged 7years older, but less severe renal failure (17% vs 25%) & fewer renally excreted drugs (1.0 vs 1.4/pt), Switzerland	Xs doses: not adjusted for low renal function	Pre: chart review Post: prospective obs (by pharmacist)	pre/post Targeted
[108]	Clinical pharmacist's daily rounds (including investigating allergies, monitoring lab results, reviewing appropriate-ness of drug orders. pt education	pharmacist rounded with admitting team and saw pts on 1st inpt day (although Rx reviewed routinely, only pts on high-risk drugs monitored after day 1)	cohort, matched (prospective): May 1-May 31, 2000	pts matched for age, sex, LOS, # drug orders, and nursing unit: 1/19 general medical services in a 600-bed teaching hosp, USA	discrepancy between notes, deviation from "optimizing medication use" manual re: indication, dose, monitoring. Prescribing error. Admin error (includes wrong time). Pharmacy error (includes wrong or missing docu., inappropriate dosing recommendation) Discharge error: discharge instruction differs from inpt instructions without docu. explaining	Blinded retrospective comparison of [admission, transfer, and discharge notes] and [medication orders & MAR] by senior pharmacist	+ systematic, blinded reviewers. - confounding with record quality: calls discrepancies in recording errors. small sample

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[109]	ED pharmacist	no ED pharamacist	pre/post (timing unclear)	All ED pts., USA	medication errors	Not declared	-vague method
[110]	old pharmaceutical care + GP's drug Hx record compared vs admission drug Hx. Pt education	pharmaceutical care with pt. education upon request	Cohort (pro) Hospital admission to 2 weeks post-discharge	sample from gen. med. ward: >-18 years old, English speaking, no mental illness, telephone access, D/C on 4 meds; mean age of ctrl patients 8 yrs higher (68 vs. 60; but fewer drugs 6.1 on D/C vs. 7.1), UK	discrepancies at admission -intentional -unintentional discrepancies at discharge -intentional -unintentional	comparison of GP record & admission drug Hx by pharmacists	-restricted pop (English-speakers..). staff seem aware of study. 1 more drug /pt in int.
[111]	Pharmaceutical care: experienced clinical pharmacist. used pt evaluation & pt drug profile. Routine communication of desired outcomes with other disciplines; Completed 6-page worksheet giving drs recommendations	Pharmacokinetic dosing upon consultation Pre-Post & case-study (prospective)	Pre: 8 weeks (Mar 27-May 19, 95); 1-month pause; Post: 8 weeks (Jun 19-Aug 11, 95)	Step down unit of medical ICU; acute, teaching hospital: Patients had to be admitted & discharged over an 8-week period (131/179 admitted); reported pt char similar pre & post, USA	ADRs/pts (minor/ moderate/ severe) perceived effect of changes to therapy	Chart review of pts who received drugs associated with Tx for ADRs: clinical pharmacist blinded to pt's Tx status	-required admission & D/C in 8 weeks (death possibly excluded) Borderline stat sig. Funding: Am. Soc. Hosp. Pharmacists. Pharmacia-Upjohn

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[112]	Pre-admission care: pharmacist takes written medication Hx; writes usual meds & items routinely req'd in in-pt chart; makes recommendations. surgeon #2	standard post-admission ward visit: checked drug chart for errors & omissions; intervened when necessary. surgeon #1	Cohort	consecutive pts from one surgeon assigned to pharmaceutical care & matched to another surgeon's pts: short-stay elective general surgery ward, adult, teaching, UK	Wrong drug, omission, recommended other dosage Modified Hatoum grade of intervention's signficance	Retrospective chart review, by pharmacists	
[84]	3) pharmacy OE & CDSS, and clinical pharmacist available 5 days per week for drug monitoring and pharmaceutical interventions	1) no clinical pharmacist, no pharmacy OE. 2) clinical pharmacist 1 day / wk for drug monitoring & pharma-ceutical intervention.pharmacy OE & CDSS	Interrupted time series 12 weeks (3 tech sequentially)	2 units, 53 respirology beds, teaching, FRA	prescription errors, particularly wrong drug, dose, duration	(seemingly) comparison of guidelines with patient record by pharmacists	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[113]	24hrs, 7-day/ wk pharmacist-managed anti-coagulation service. Used Raschke[125] weight-based UFH dosing nomogram & modified Fennerty flexible induction warfarin nomogram	Usual care	Prospective cohort (June 96 to Apr 97), while hospitalized	Pts admitted for Tx of DVT or PE & received IV UF Heparin. Exclusions (42/92 in usual care; 33/83 in pharm): thrombolytic therapy, LMWH, sub-cut. Adjusted-dose UFH, <24hrs IV heparin, >48hrs from hospital admission to heparin initiation, LOS prolonged by co-morbidity, USA	Major bleeding (associated with elevated INR): HgB down >2g/dL; >=2u blood transfused; or retroperitoneal, cranial, or prosthetic joint bleed. Minor = not major. Heparin-induced thrombocytopenia (drops under $100x10^3/mm^3$ or if already less, decreases >50%) Time from start of Tx to >therapeutic threshold (aPTT >48sec or 1.3-2.5), time to aPTT in ther. range	Prospective, investigators	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[114]	Pharmacy-consult for drs' warfarin dosing; also eliminated polybrene (heparin neutralizer) from heparin preparation	Physician-managed warfarin dosing	Pre/post (historical cohort matched to prospective cohort, re. Tx indication) Pt follow-up day 1 on warfarin to 3 months post D/C no pharmacy consult: pts on warfarin in Feb-June 92 implemented: began June 93, mandated 95; mandated pharmacy consult: pts on warfarin in Jan-June 95	pts >=18 years receiving warfarin for the first time for the prophylaxis or treatment of venous thromboembolism (DVT &/or PE), arterial disease (stroke, coronary stenting, atrial fib), mechanical valve, 400-bed teaching hosp, USA	# patients with INR >6.0, pt-days with INR >6.0 bleeding (1st admission) pts receiving drugs with major interactions pts with INR <1.8 at D/C. readmissions at 1 & 3 months, given -bleeding -thrombosis	92-retrospective chart review; 95 prospective data collection pharmacists and/or physicians	-historical cohort vs. matched prospective cohort

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[115]	Pharmacy inpt warfarin-monitoring service. included lab review, dosage-change recommended, screening for drug interactions, dr & pt education, and recommendations for outpt-clinic follow-up -inpt service screened pts on heparin re: warfarin Tx -same pharmacists worked inpt & outpt clinics	No pharmacist consultation, monitoring, or education by pharmacist	pre-post (retrospective) Pre: admissions between 1/3/86 to 31/5/88 (822 days) implemented 1/6/88 Post: admissions between 1/6/88 to 31/12/89 (578 days) 90-day follow-up post-discharge	pts on warfarin (exclusions: no warfarin Rx at D/C, or warfarin Tx for <6weeks post-hospital-D/C; warfarin Tx pre-admission put PT within therapeutic range; ineligible for follow-up at hospital's outpt clinics) adult teaching hosp, USA	pts readmitted to hospital or visited the ED because of warfarin toxicity (bleeding--major or minor); pts whose thrombosis recurred (admission or ED)	Pre: retro. chart review. Post: monitoring by pharmacist service	- records differed pre vs post. excluded if Treatment stopped early. post: 0.7 fewer co-morbidities, RD (substance abuse)= -26%

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[116]	Pharmacist-assisted warfarin-dosing according to local protocol; pharamacists' changes req'd dr. approval	physicians determined dosing	Pre/ Post pre: 4 weeks prior to implementation (not clear exactly when in relation to intervention) PAWD: all 6 weeks of pilot program (Marh 21-May 1, 1994)	Pre: cardiology unit post: vascular surgery & cardiology units (adult, teaching hosp, CAN)	Thrombo-embolic events; Bleeding (minor, or major: assoc'd with loss of >=20g/L of hemoglobin, req'd blood transfusion, or intracranial, intraocular, intra-articular, retroperitoneal) INR>4 per pt; pts without target INR by day 5	Prospective, treating physicians and pharmacists	Pre/post minor bleeds seen -Internal Validity vascular surgical patients only post: more males, prosthetic valves, valve repairs, fewer DVTs treated
[117]	Pharmacist recommend alternatives to cefotaxime when indicated, or ensured an appropriate dose, through a) verbal reminder b) face-to-face outreach for drs. who hadn't modified Tx	No-intervention	RCT, 6 months (concurrent)	Pt char similar (eg, hospital site, gender, 1^0 infection site, prescriber), 2 adult teaching hospitals, Toronto, CAN	cefotaxime Rx that did not meet hospital Rx guidelines: indication or dose	Prospective data collection, by clinical pharmacists	RCT -bias to null: 8% of control group excluded because of risk of no intervention. contamination of education +blinding
[118]	Pharmacist checks hypnotics Rx to package-recommended dose, changes excessive dose & notifies dr. later	Pre	pre/post (timing unclear)	Older pts, USA	starting dose of hypnotics which is excessive relative to the package-recommended age-specific dose	Pharmacy check (basically, self-report)	Pre/post. Part of large CQI program. little detail of study

Appendix J: Nomogram, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[125]	Weight-based nomogram determined heparin dosing in 1st 48 hours	Standard nomogram determined heparin dosing in 1st 48 hours	RCT: Pts admitted May 91 to Jan 92. in-hosp follow-up for all; 3-month fu for pts with D/C diagnoses of venous thrombo-embolism	IV heparin for PE, proximal DVT, unstable angina, or acute non-coronary arterial ischemia Exclusions: recent anticoagulant or thrombolytic therapy; active bleed; acute major cerebral vascular event; Hx of heparin-induced thrombocytor allergy 700- & 250-bed adult teaching hosp, USA	Reaching therapeutic APTT range within 24 hrs, 48 hrs nomogram error rate-e.g., failure to adjust heparin infusion rate when indicated bleeding (major/minor); recurrent venous thrombo-embolism; hearin-induced thrombocytopenia	prospective recording by dr. & pharm D, blinded	-unbalanced groups

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[123]	weight-based heparin nomogram -physician-initiated, -nurse-adjusted: sliding scale (modified Raschke[125]); added charts with relevant calculations; pharmacy and nursing education	fixed-dose heparin regimen - unclear who managed it	pre-post (retrospective) pre: 6-weeks (Feb, Mar 93) post: 7 months (Mar Sep 94) unclear time of intervention	protocol-based heparin dosing in cardiac care unit (421-bed community hospital), USA	Complications related to heparin use Therapeutic APTT not reached at 6hrs, 12 hrs, 24 hrs	retrospective chart review by pharmacists	Major change in patient population (post: more DVT & PE, les unstable angina or MI) Multi-faceted intervention
[124]	Pharmacy-managed weight-based heparin protocol (PTTs every 8 hrs)	Old nurse-managed fixed-dose protocol	Pre/post (Retro) Pre: Jan 87 – Nov 89 Post: Dec 89 – June 91	Pts. receiving heparin according to protocol Excluded: protocol violations, pts with thromboembolic disease ruled out, cardiac, thrombolytic tx , recent heparin Tx USA	Mean time to first PTT >= 1.5 hrs # PTTR >=1.5 in 24, 48 hrs mean % PTTs per pt: <1.5, 1.5-2.0, >2.0, >3.0 # pts with PTTR>3.0 bleeding	chart review, retro	-Efficacy analysis. -Pop highly selected (42/ 143 identified, which excluded deviations from protocol errors) → groups comparable but perhaps not generalizable

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[120]	nurses use weight-based heparin nomogram with target PTT of 60-85 sec; once the nursing staff independently adjusted the heparin- infusion rate based on PTT results (nomogram directs follow-up PTT measurements)	Non-standardized empirical heparin dosing; adjustments made only after a physician's order	pre-post (retrospective) Pre: 1/1/94 - 1/12/94 Post: 12/1/94 - 1/1/96	11-bed ICU (med/surg): pts' heparin initiated in the ICU for ischemic heart disease (including AMI); DVT or PE; atrial fib; mech heart valve; mesenteric vein or jugular vein thrombosis]. CAN	Thrombosis Gastrointestinal hemorrhage Nose/throat hemorrhage IV site hemorrhage	retrospective chart review, pharmD & MD	- More in std. group had clotting tendency (46% vs. 33%) or bleeding tendency (21% vs. 8%)—no allocation concealment. +similar # APTT tests, response time from phlebotomy for APTT and dose adjustment, time from diagnosis to treatment initiation

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[121]	Heparin nomogram (voluntary use): target APTT 60-85 sec	normal pre-trial practice (both: 1°-care drs treat with internist consults)	Pre/post: Pts admitted between (pre) Jan 1, 1991 – Mar 31, 1993 (post) June 1, 1993-Dec 31, 1993 nomogram instituted Apr 1993	DVT or PE as a primary reason for admission (excluding later –ve confirmatory test, early transfer; no heparin Tx; missing info (7cases). 2 non-teaching adult community hosp, CAN	APTT times (sec) <50, 50-59, 60-85, 86-95, 96-120, >120	daily chart review by research assistant (random sample validated with main investigators)	-Unclear when APTT determinations took place +similar baseline pt-char
[122]	Hematologists used their 3rd-iteration nomogram	Hematologists treated patients without a nomogram	Pre/post Heparin Tx: Pre: Jan 1 87 to Jun 30 88 Post: Jan 1, 89 to Nov 1, 89	documented venous thromboembolism referred to the hematology service. excluding previous thrombo-lytics, adult teaching hosp, CAN	pt with never a therapeutic APTT; % therapeutic APTTs at 24 & 48hrs; non-therapeutic APTT after therapeutic APTT	1. Pre: retrospective chart review 2. Post-prospective data collection by MD/nurse	-Different methods of data collection pre/post +similar pt-char +Heart & Stroke foundation funded

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[119]	Combined prescription and monitoring charts which include nomogram for initiating heparin & warfarin protocol	standard medical charts	pre: 28 days in April/May post: 28 days in Nov/Dec Implementation sometime in between	receiving heparin or warfarin, excluding: day-attenders, prophylatic heparin; missing records, 700-bed hosp, UK	On heparin, % time with APTTR <1.5, 2.6-4.5, >4.5 On warfarin, % time spent with INR <2.0, >4.5 Bleed	% time from all lab results; retrospective chart review for bleeding (investigators)	- detection bias possible: 49% increase in overall # of APTTs
[113]	24hrs, 7-day/ wk pharmacist-managed anti-coagulation service. Used Raschke[125] weight-based UFH dosing nomogram & modified Fennerty flexible induction warfarin nomogram	Usual care	Prospective cohort (June 96 to Apr 97), during hospitalization	Pts admitted for Tx of DVT or PE & received IV UF Heparin. Exclusions (42/92 in usual care; 33/83 in pharm): thrombolytic therapy, LMWH, sub-cut. Adjusted-dose UFH, <24hrs IV heparin, >48hrs from hospital admission to heparin initiation, LOS prolonged by co-morbidity, USA	Major bleeding (associated with elevated INR): HgB down >2g/dL; >=2u blood transfused; or retroperitoneal, cranial, or prosthetic joint bleed. Minor = not major. Heparin-induced thrombocytopenia (drops under $100x10^3/mm^3$ or if already less, decreases >50%) Time from start of Tx to >therapeutic threshold (aPTT >48sec or 1.3-2.5), time to aPTT in ther. range	Prospective, investigators	pt comparability is the main threat with cohort

*authors assumed linear progression between lab values

APPENDIX K: Computerized Pumps, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[126]	Computer-programmed fentanyl dosing: 1. Stable: continuous infusion, set-point of 7.5ng/mL (3-compartment open model) 2. Variable: continuous infusion initially set at 7.5 ng/mL but later adjusted by dr.	Fentanyl received as an initial bolus dose (150-250ug) prior to laryngoscopy, with additional (150-250ug) bolus doses given later	Cohort (prospective)	CABG pts, with baseline sys BP >100 mmHg; ejection fraction .40; age<75yrs. adult teaching hosp, USA	Hypotensive and hypertensive episodes: >30sec with sys BP <90mm Hg and >170 mm Hg	Prospective (Hewlett Packard Model 7402A)	-generalizability sample size tightly controlled trial conditions- -limited follow-up (to describe importance of hypertensive & hypotensive episodes)
[128]	Bedside blood-pressure monitor controls an infusion pump using fuzzy logic	"manual" control	RCT	post-op cardiovascular pts, 55-70 yrs old (mean 59), receiving Na nitroprusside for high bp, teaching hosp, Spain	time not in target blood-pressure gap (70-80mg Hg), in each of first 4 hours (values stored / 20sec)	Prospective (monitoring), apparently by the machine	close monitoring locally developed; no clinically significant outcomes values stored /20sec

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[127]	Computer-assisted continuous infusion (CACI) set to achieve midazolam concentration of 75-150 ug/mL, fentanyl concentration of 2-7ug/mL, with clinician permitted to vary doses for midazolam induction, and fentanyl maintenance	manually controlled infusion of fentanyl	Double-blinded RCT (baseline pre-induction until chest closure and conclusion)	Elective CABG. Exclusions: recent Hx of unstable angina, myocardial infarction, chronic narcotic, anti-depressant use, or alcohol abuse; or valve repair; or need for rapid-sequence induction, Teaching, USA	Hemodynamic control (average mean arterial pressure and heart rates)	Prospective monitoring, investigators	investigators commented that no difference was observed
[129]	Computer-controlled morphine admin	pt-controlled morphine admin	RCT 0-32 hrs post-op	18-65 yrs, post-orthopedic surgery with >=1hr general anesthesia, ASA physical status I or II; excluded: Hx cardiovascular, pulmonary, hepatic, or renal disease, Netherlands	Nausea, vomiting, urinary retension, sedation score >3, itching	prospectively, noted at least every 10min, by investigators	similar ADEs with computer & patient control (less pain-VAS>3-with computer system)—less internally valid, generalizable

APPENDIX L: Hospital drug-specific protocols, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[130]	narcotics dosing protocol (guided by IHI)	Pre	15 months (Feb to Sept): time series intervention's timing unclear	oncology & orthopedic units, USA	Mean # ADEs/month	Not declared	-IHI study, little definition of study methods
[130]	heparin protocols (IHI)	pre	pre/post (timing unclear)	1/ 13 hospitals implementors of 18 hosp attempting, USA	- hrs to therapeutic PTT -pharmacist interventions/ order	not declared	-highly selected example (1/13 who implemented) -IHI study (reporting to superiors)
[131]	Non-punitive policy; Standardized chemotherapy protocols; Changed order-entry system; Rule that chemo must begin during the day, while physician & pharmacist are on site (other changes too)	disciplinary system based on an oncology nurse's number of errors	two years between pre & post measures	Oncology unit, pediatric hosp, USA	"actual and potential" error (ie, errors whether or not they reached pts)	Not declared	-reporting variability: follows 10-15 fold increased reporting after new non-punitive policy
[130]	Standard Chemo: orders, admin times, high-dose ceilings (IHI)	pre	pre/post (timing unclear)	1 hosp, USA	Chemotherapy ADEs/month	not declared	-IHI study

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[130]	Insulin ordering protocol (IHI)	Pre	pre/post (timing unclear)	3 hosp, USA	Hypoglycemic episodes	not declared	3/7 who implemented IHI study
[118]	pre-printed sliding scale insulin protocol	Pre	Pre/post (timing unclear)	Hosp, USA	potential errors due to handwriting, unapproved abbrev, overlapping blood sugar ranges, untimely treatment of high blood sugar	not declared	-List of "successes"
[131]	after clinical pharmacist studied charts of pts on insulin: comprehensive diabetic flow chart for diabetic care info; standardized glucose - monitoring times; educated nurses (inservice); priorized food delivery for diabetic patients & used electric heating trays to warm food at the right time	baseline	pre/post (retrospective-timing unclear)	Pt. taking insulin on medical/ surgical unit, USA	errors related to insulin distribution	Not declared	- errors undefined (how, what)
[132;133]	Standard hospital insulin protocol	Drs. chose insulin protocols	Pre: Feb-Mar 98; post Apr-Aug 98	adult teaching hosp, USA	Insulin errors & hypoglycemic events	incident report	

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[134]	Revised pain-management flow sheet skill checklist for standardized type of pt-controlled analgesia pump New equianalgesic charts and drug-calculation reference	Pre	Pre Jun 7, 1997- Mar 15, 1999 post Mar 16, 1999 - Nov 2000	Pts receiving pt-controlled analgesia, teaching hosp, USA	Patient-controlled analgesia incidents	incident report	very small numbers; sketchy description
[135]	new total nutritional admixture (TPN form for drs checked by pharmacists: -defined a standard concentration of nutrients, electrolytes, vitamins, with space for individualized solutions -added corollary orders	old TPN form for pharmacy which listed parenteral nutrition ingredients	4 months pre & post, with no break for implementation: (June -Sept pre, Oct-Jan post)	Patients receiving parenteral nutrition, teaching hosp, USA	# patients total # errors -infusion rate -%lipid/%glucose -% amino acid -electrolytes -trace elements & vitamins -heparin	PN Rx errors tabulated daily by study investigators	fewer patients pre than post--either TPN use increased, or data collection was less complete "pre" multiple errors possible per order

APPENDIX M: Physician education, Study Characteristics

	Intervention (vs. "Pre")	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[136]	1) presentation of results & plan to 4 hospital committees, several medical staff meetings, resident orientation and conferences 2) anonymous problem orders published in regular clinic staff newsletters	Pre: Apr, 1997: 7 days Between Apr-Jul 1997—intervention began (& continued) Post: July 1997 (3 months later) 24 hours Feb & Aug 2000	486-bed non-teaching hospital (adult environment) USA	Non-adherence to ISMP criteria (mostly clarity): illegible. no signature wrong pt. ambiguous.	Order review by investigator	-"soft" outcomes funds: Pfizer
[137]	post "clinical session" with >presentation of first X-sectional analysis (pre) >discussion of recommendations for drug-error prevention (by Am Acad Ped)	Pre: 2 days in '99 Int in '99 Post: '00, 1 yr post (not Mon or Fri)	Newborns in intensive or intermediate-care (random samples of Rx), teaching hospital. SPA	All Rx errors: illegible or doubtful / wrong dose / unspecified route of admin	Order review by pediatrician from another service	-Timing unclear

	Intervention (vs. "Pre")	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[130]	Hospitals informed drs. re: standards: eg, to write legibly, eliminate certain abbrev. Mailed drs. their illegible & non-standard orders, with explanation on a pink slip	pre/post (timing unclear)	Hospital from Institute for Healthcare Improvement collaboration, USA	nonstandard* or illegible orders (*e.g., use of certain abbrev)	Not declared	-Selection: 1/3 success stories from 21 system changes (IHI) -methods vague
[138]	Posted Rx-writing guidelines. Published problematic orders Displayed felt-tip pen labeled "lethal weapon"	Pre/ Post Pre: 7 x 24-hr periods Intervention period: 10 months Post: unclear	Whole hospital, USA	Problematic orders (12/15 potential error elements, listed below*)	Not declared	-vague outcome
[139]	2) education, index cards, and a newsletter series for staff who order neoplastic drugs 3) special preprinted form required for all orders of IV & oral neoplastics; pharamacist order review	1) Jan-Feb '85 (4 wks) >form in March 1986 > 2 months education, Mar to May 2) Jun '85 (4wks) 3) June (1wk) & Sept (3wk) 1986	Receiving neoplastic drugs at teaching hospital, USA	completeness: route, dose, dosage, freq diagnosis, height weight, surface area, regimen errors prevented by use of form	Record review by pharmacists (retro)	

*illegible, incomplete, writing for vial/ ampoule, improper abbrev, apothecary system, improper modification, felt-tip pen, "u" units, use of trailing zeros, no leading zeros, no signature, no beeper, verbal, illegible signature))

APPENDIX N: Physician education and New Prescription Forms, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[140]	New Rx sheet with "more self-instructive layout and better space to write." drs and nurses trained in new government regulations about drug handling and Rx writing	Old Rx sheet	Pre: 6 months, Post: 12 months, 6 months after "Pre" (with intervention in between)	#1 Discharged patients; adult environment (4 medical / surgical units) #2: unclear SWE	Rx incorrectly written (vs. Swedish regulation): drug name (e.g., not approved name), dosage form, strength, route, dosage	Retrospective review of prescriptions by nurses	Rx guidelines with unclear relationship to error in drug delivery
[141]	Joint chart for Rx & admin; communication of results of a prescription audit via newsletter	Separate Rx records in pts' case records & nurses' drug admin charts	Pre: 1999 Post: 1 yr post-implementation	Pre, half of pt records were selected as longest LOS; other half arbitrary; Post, consecutive series of records. Netherlands	Detailed prescription regarding dose, freq, and admin	Retrospective chart review by pharmacists	Disadvantages: printing & storage expenses, need for increased size of medication record; cost of compliance monitoring; complication of ordering for prescribers

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[139]	2) education, index cards, and a newsletter series for staff who order antineoplastics 3) preprinted form required for all orders of neoplastics; pharmacist order review, compliance monitoring	Pre	1) Jan-Feb '85 (4 wks) >form in March 1986 > 2 months education, Mar to May 2) Jun '85 (4wks) 3) June (1wk) & Sept (3wk) 1986	Receiving neoplastic drugs at teaching hospital, USA	% completeness: route, dose, dosage, freq diagnosis, height weight, surface area, regimen errors prevented by use of form	Retrospective record review by pharmacists	-comparability of pts, errors pre & post (chart disagreement vs. loss of info re. dosage, freq, and route) -separate records more inclusive of all Rx than is joint record (lost records error-prone)

APPENDIX O: Specialized Physician Education or Forms, Study Characteristics

	Intervention (vs. "pre")	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
118	-chemotherapy order form prompts detail on drug, dose, route, frequency, and special instructions. -Pt. and drug info more available -clarified accountabilities of nurses and pharmacists	pre/post (timing unclear)	Chemotherapy pts (from whole hospital), USA	potential errors per order (including elements missing)	Not declared	-List of "successes"
142	Education about ministry guidelines, mainly to prevent unwarranted prescriptions -group sessions. daily small-group briefings. posters throughout ED. Pocket 10-page manuals	5 days pre, then 45 days of intervention, then 5 days post (without intervening delay)	ED pts interviewed by investigators & seen by dr who attended both pre & post sessions and reached diagnosis and Tx decision.; pt char similar pre & post. teaching hosp. FRA	NSAID-related prescription errors: Violations-NSAIDs prescribed for non-indications; against absolute contraindications (e.g., uncontrolled gastroduodenal ulcer); or lacking indicated adjunct treatment (e.g., rehydration) Inadequacies-NSAID Tx deemed unsuitable to the condition	prospective (pt interviews, and questionnaires for doctors) by investigators from ED	-selective blinding Pre: doctors unaware of study objectives Post: unclear whether doctors aware of study objectives

	Intervention (vs. "pre")	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
143	began training doctors about IV drugs, esp. chemo	junior doctor induction began in Sept-94; IV in Sept 97 Pre. "at the beginning" Post "at the end"	Pediatric teaching hospital, UK	errors involving doctors (wrong drug/ dose/ route/ risk of known allergic reaction)	incident report	-reported error rate overall higher than in beginning or end -new incident reporting form -Observation periods poorly defined

APPENDIX P: Verbal Orders, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
63	physician verbally communicated order to nurse (verbal) -- hospital policy to restrict verbal orders to certain situations	Physician wrote onto a medication order sheet & unit clerk entered data into the computer (written) physician entered order directly into the computer system (comp)	Cohort 3 months (all orders): Oct1-Dec 31, 1992	Pediatric teaching hospital, USA	errors in orders at the point of entry into computer system ("dosage error, transcription error, wrong patient," etc) adverse patient outcomes caused by order-transmission error	routine review by pharmacist & incident report	-verbal orders limited to certain situations. possible confounding with order complexity, practitioner. excluded Rx entered by nurse-practitioners and clinical-nurse specialists
118	Prohibited telephone orders to clerical personnel: only registered nurses could take calls	Pre	Pre/post	USA	error rate	Not declared	-Little detail of study

APPENDIX Q: Double-check, Single-intervention Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[143]	Double-check in pharmacy on all drugs dispensing & error-report form changed to look less punitive	Pre	Pre: Aug 94 –Jan 96 (22 months); Post: Feb 96 to Aug '99 (43months) -implementation in between	303-bed pediatric teaching hosp, UK	wrong med/dose/ preparation/ time/ route/ label unauthorized drug / omission/	incident report (misc)	-new incident report form, under-reporting (mean of 1.02 dispensing errors/10,000 bed-days). unusual choice of observation periods
[145]	Single-check of drug for admin by qualified registered nurses, except drugs: needing calculations, of addiction, cytotoxic, "new & unfamiliar", epidural & other nerve block; insulin, blood & blood products, >2g KCl	Double-checking by nurses of all medication to be administered	Pre/post: double-check: all drugs admin Mar - Sept, 2000 single-check: drug admin using single-check protocol	Teaching hosp, Australia	# incident reports	incident report by error-maker (nurse)	- biased: post period excluded double-checked meds

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[146]	>prior to change in chemotherapy, nurse completes verification form reviewed by 2nd nurse, approved by satellite pharmacist: form completion requires consultation with parenteral administration cards takes ~9.3 minutes >classes: (10 hrs tot)	Pre	Pre: 8 months Implementation (education): 10 weeks Post: 28 months	hematology-oncology unit, adult teaching hosp, USA	Chemotherapy admin errors (includes wrong dose, infusion, freq, omission)	incident report: nurses, mostly	-extensive verification may leave less time for incident reporting and other useful activities. only 3 events observed pre, 1 post
[147]	Dispensing error verification by full-time, level A, certified techs with 1+ yrs of inpt hospital experience, who passed a training program [comprehensive sessions + ASHP* training manual, skills exam, and an accuracy >99.8% on 1500 doses]	pharmacists routinely verifying dispensing errors	Pre/ post (prospective) 1/8/91 to 31/10/91 (3 months) 1/11/91 to 31/1/92 (3 months)	3 non-teaching adult hospitals: 229-bed & 160-bed HMO-owned staff-model hospitals; 237-bed community non-profit hosp, USA	Dispensing errors Identified by checker Dispensing errors Allowed (unit-dose fill-lists vs medication-drawer filling): subgroup-serious potentially: wrong drug/strength; less serious, omission/ extra dose/ right med but wrong dosage form	prospective; errors allowed were a random sample identified by study coordinator	-Tech selection: experienced, passed training course with a test at the end. routine for pharmacists, but special role for technicians.

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[132;133]	2) + Formal reconciliation of patient medications by physicians & nurse sat discharge 3) + RN & RpH sign for Formal reconciliation	1) new formal reconciliation of all pt meds upon admission	time series (prospective) 1/5/1998 - 7/6/1998 (weekly measures); admission rec implemented 1/?/98; discharge rec 4/20/98; RN RpH rec 5/11/98	pts whose meds were reconciled on admission: medical telemetry unit at a 160-bed adult-teaching hosp, USA	Pot ADEs & ADEs	Weekly chart review (unblinded) by investigators (MD)	-1 of 2 pilots reported, of 10 tried. vague temporal relationship of intervention and outcome. Outcome: vague definition ("error & pADE+ADE used interchangeably) >1ADE possible / patient

*American Society of Hospital Pharmacists

APPENDIX R: Double-check, Multi-intervention Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[148]	Tech checks pharmacist order-entry vs physician order. Computerized pharmacy dept. max 4hrs/person/ day of pharmacy OE. special delivery bins on nursing units for interim doses	max 7.5 hrs/person/ day for pharmacy OE	Pre: 1987 Pharmacy computerization: Apr 1988 Post: Nov 1988 (12 consecutive days)	37 cardiology and coronary-care unit beds, 460-bed adult teaching hospital, CAN (Kingston)	contents of a pt's drug bin disagrees with nursing profile; missing-dose phone calls	comparison of unit-dose bin contents to nursing profile by nurse & pharmacist	-reactive first measure (audit)
[149]	Pharmacy edited computerized lists for preparation & review of drug carts	Copy of Rx to prepare the pt's drug drawer (*in both arms*, 1 pharmacist & 1 tech check Rx vs. drugs dispensed)	Pre/post (1 month each) implementation in 1992	358-bed private non-teaching adult hospital (86% occupancy, 5.3-day median LOS), Spain	Drug in pt's drawer ≠ Rx shown on... (pre) photocopy of Rx, (post) pt's electronic medication profile	Pharmacist comparison of record of Rx with meds dispensed	-standard of comparison changes pre vs post Tech Gen. Computer MAR system & extra check vs. manual system

APPENDIX S: Drug Distribution: Bed-proximal Drug Storage, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. +strength)
[151]	Drugs locked at the bedside (except injectables and "dangerous" drugs)	Drugs locked in a drawer immediately outside pt's room	Cohort (prospective): 5 x 8hr shifts (3 morning, 2 evening)	30-bed surgical ward, adult, teaching, Australia	"actual" medication errors, excluding injections (reached pt)	direct observation (observed admin; then compared with orders), by nurse educators	+Nice comparability of within-ward comparison (similar staff, patients, time, work environment; same pharmacy)
[150]	PPOV1 -Cartridge exchange at "doorside" servers, which store 2 patients' medications separately; -drug kardexes at doorside servers -narcotics, stat, and newly ordered drugs stored at central carts PPOV2 Same as PPOV2, except stat and newly ordered drugs delivered to the doorside server	Traditional: delivery of unit-dose cartridges to medication carts (3/ ~37-bed unit); drug kardexes at the central station, and carried to the 3 carts as needed	Cohort (1992) PPOV: random doses from 30 days Traditional: convenience sample	PPOV: 37-bed orthopedic surgery unit Traditional: Other units within the surgery dept. USA	Dose given differs from order Dose given, no order Med. ordered, not on records Doses omitted, not circled Doses omitted, circled, reason undocumented	Nurses' chart review	-Hardly any errors observed; unclear what happened re. "pre" measure of traditional method & error rates (either not measured, or not reported)
			pre/post & cohort 1st half of 1992	PPOV: 37-bed orthopedic surgery unit Traditional: Other units within the surgery dept., USA	# nurse pages to pharmacy (almost always due to missing doses)	Routine pharmacy records (by pharmacist)	
			Pre/ post day & evening shifts	37-bed orthopedic surgery unit, USA	medication missing	direct observation by nurse	
[118]	Relocated medication cart away from the central nursing station, closer to the patient's room	Pre	pre/post (timing unclear)	USA	medication error	Not declared	Nurses liked the change; not enough data to prove equivalence

APPENDIX T: Drug Distribution: Unit-dose systems vs. Ward-stock

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Ascertainment	Comment: (- limitation. + strength)
[152]	Unit-dose system modified for controlled drugs (other drugs had unit-dose already).	Ward-stocked controlled substances	Pre-post (retrospective) 6 months each	186-bed ped. hosp, all inpt wards, USA	administration errors most likely (omission, unauthorized drug, etc)	Incident report by RN and pharmacist	-incident report. Tech generalizability (time-intense) unit-dose for controlled drugs 2X -time-consuming for pharmacists and nurses => negative externality eg admin of controlled substances declined [(14000 vs 12000 doses; 8.6% vs 5.7% of doses].

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Ascertainment	Comment: (-limitation. +strength)
153	Unit dose and centralized IV additive system (stat doses ready to administer in pharmacy)	"Traditional" (ward stock): nurses prepared med in 2 separate medication rooms	Pre & Post: 3 weeks, each (just prior, then 8 wks post intro; both: 100 hrs on all nursing shifts) Inventory errors checked daily)	Sick Kids, CAN	Admin errors (omission, wrong time (>30' off), etc) Inventory Management: (expired meds/ no expiry date/ caps off bottles/ etc)	Disguised observer technique, pharmacists	+Relatively good quality vs. others - severity
			12 months pre & post	Sick Kids, CAN	Medication incidents	Incident report	Row methodologically noteworthy (same study as above except measure). attributed to pharmacy follow-up of doses left in bins
154	Unit-dose: pharmacist OE & check. tech checks OE, then fills pt's medication boxes (for med trolley) with the help of sound & light cues	Ward stock: pharmacy-replenished weekly; nurses retranscribe Rx to each pt's 24-hr Tx containers	Cohort (matched) Ward: Apr 1 - May 31 1993 Unit-dose: May 1 - June 30 1993	6 psych wards matched on 15 factors (pt-activity, staff levels, pt acuity...); each group had 2 gen, 1 infant/ juvenile ward. FRA	Rx & med dispensed differ (omission, wrong time, etc); Severity (important/ moderate, minor)	Direct obs. of filled mediction cassettes, by pharmacist	-Technology and control generalizability (France). everyone knew about the study (Hawthorne)

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Ascertainment	Comment: (-limitation. +strength)
[156]	US unit dose: 24-hour med cycle. 1 delivery/ half-hour. Pharmacist OE. Pyxis. E-MARs sent to ward.	UK ward stock: pharmacy deliveries twice daily; Combined dr. & nurse Rx sheet and MAR	US: Aug '93, 8 periods UK: May/June '93, 96 periods (schedule systematic)	US: 2 med/ surg units UK: 2 gen med, 2 gen surg, 2 geriatric units	omission/ wrong drug, route, etc per opportunity for error	Direct observation by pharmacist	-different error ascertainment methods: a) of comparing with original order b) non-reactive measure in US, reactive measure in UK -US vs. UK: different organisational cultures, work schedules, demands on nurses, patient populations, etc
[155]	GER unit dose: pharmacists visited twice /day, verified OE & printed medication profiles. Baxter ATC212; tech filled & pharmacist verified individual pt drawers	UK: Rx in bedside pt chart; 80% ward-stock (drug trolley) 20% pharmacy-dispensed	Cohort (prospective) UK: all drug rounds observed GER 36/40 drug rounds, 3-yrs post intro	UK: 2 gen med wards, (mean LOS 5, 2.5; bed occupancy 90%, 94%) GER: 1 resp, 1 urology, GER (mean LOS 11, 9; bed occupancy 86%, 96%)	dose admin differs from Rx (excluding wrong-time)	direct obs. by pharmacists	-unit char very different (countries, specialties, LOS, occupancy, D/Cs) [Funding: UK NHS; German Academic Exchange Service]

APPENDIX U: Drug Distribution: Decentralized Pharmacy

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[157]	1) FTE pharmacist allocated to 5th floor decentralized pharmacy service	2) central, computer-ized unit-dose system	Cohort (retrospective) 1) 1979, 1980, Mar-Dec 1981 2) Mar-Dec 1982	1) 59 acute-care beds 2) 365 other beds of 3^0-care hosp, CAN (London)	medication error (misc)	Incident report, pharmacy	-Temporal variation overwhelms
[158]	3. roving pharmacist rounds every half hour to designated (mapped) units, confers with head nurse/designee, checks medication-order accuracy, and does daytime order entry (OE) (evening: central OE)	1. central pharmacy 2. inter-disciplinary review	1: '87-90 2: 91 3: 92, 93 (interventions in fall '90, Dec 91-Jan 92)	303-bed community acute non-teaching hosp, USA	Medication incidents (misc.): eg, omission, timing, dup	incident report by staff	- new sensitivity of incident reporting with new system of transcription and checks
[159]	Pharmacist reviews orders on the ward and can dispense the first doses from a mobile cart direct to doctor	Ward stock	Pre (?), then 3 months Post int.	OR, non-teaching, adult, USA	did not administer preoperative drugs in the hour pre- incision	Not declared	-number of events not defined

APPENDIX V: Drug Distribution: Decentralized Pharmacy + Bed-proximal Dispensing

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[160]	satellite pharmacy to individual patients' bedside drawers (5-day unit-supply); hourly, new pts' drug info collected	Ward stock + traditional pharmacy	Crossover: 2 weeks pre & post, 1 week for implementation	Ctrl: 30-bed gen med ward Int: 24-bed gen surg, 6- bed renal med (non-ped. env), Australia	drug administered differs from medication chart excluded injectable & controlled drugs	Disguised observer, pharmacist	

APPENDIX W: Automated dispensing: Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Outcome Ascertainment	Comment: (- limitation. + strength)
[161]	ATC-212 (except <2.5% controlled & low-use substances)	computerized fill list for tech cassette fill	Pre/Post: 3 weeks, each (10/92-2/93)	650-bed hospital: 12-36 patient-care areas. USA	Cart-filling errors (vs. computer's fill-list)	2 observers	
[162]	Medstation Rx adapted as a point-of-use (Beta-test)	Traditional centralized unit-dose cassette fill	Pre/Post: 6 weeks, each	26-bed medicine unit. USA	Filling Errors (vs original Rx)	Pharmacist (systematic)	- comparability of unit-dose cassette-fill vs. Medstation cabinet fill
[163]	ATC-212 fills unit-dose carts	Manual fill of remainder of unit-dose carts	Cohort: same 2 medication carts	64 /173 beds in VA hospital. USA	Cart-filling errors caught	Pharmacist, routinely	-manually filled drugs less-often used and less familiar. Errors caught routinely
[164]	Medstation Rx. pt medication profile display & automated dispensing	Traditional unit-dose exchange system (Pyxis Medstation stored narcotics for 3 months prior to Rx)	Pre/Post: 2 months each (2 months to Implement)	36-bed surg & 8-bed cardiac ICU. USA	Dispensing omissions (log of nurses' requests)	Reviewed log of nurse requests	-New incident-reporting form. # reported errors increased 1.76 times: >30% on 6/7 nursing units: 5/5 ctrl units

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Outcome Ascertainment	Comment: (- limitation. + strength)
[165]	Medstation Rx -all drugs -2 per unit	Manual unit-dose carts; narcotics and some floor stock in Medstation	Pre/ Post periods matched for day and shift	Beds…86 gen. med/ surg + specialty: 24 pre, 34 post. 600-bed USA teaching hosp	Disp or admin error (omission, etc):	Direct observation (dose vs. MAR & dr's original Rx)	-Reactive measure Nurses told: medication system being studied for improvement. (binomial approx to Poisson)
[66]	Pyxis	Unclear	Pre / Post: 2 months, each (6 month interim)	whole non-ped hospital, USA	Medication errors	Incident report	incident report is limited by process change: e.g., fewer human checks on process (averaged two months pre & post)
[162]	Medstation Rx adapted as a point-of-use (Beta-test)- same study as above	centralized 24-hr unit-dosing	Pre & Post	Non-pediatric, USA	Wrong-time indicators (1st dose) -wait for it -calls for it	not declared	observation periods, sample size unclear; machine may run out of stock and increase waits later on

APPENDIX X: E-medication profile Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Outcome Ascertainment	Comment: (- limitation. + strength)
166	Separate manual nursing MAR & computerized pharmacy records	Computerized MAR shared between nurses & pharmacists	Pre/post with time-series data Pre: Jul 93 - Jun 94 Post Jul 94 - Jun 95 (implemented Feb-May)	362 bed teaching hospital, USA	error in transcription, dispensing, administration (includes wrong time, omission) that could or did injure pt	Staff's* incident reports (*pharmacists, pharmacy technicians, nurses, physicians)	Interrupted time-series analyzed as pre/post + time-series data (year over year lines don't cross pre/post) -Outcome: Vague definition, Incident report. Implementation during "pre" period. Tech Generalizability
167	Linked e-MAR + CPOE	manual MAR + CPOE	Pre/post -Random samples of charts over 3 days in (12/00, 1/01)	2 surgical units, adult teaching hosp environment, USA	error in order transcription: transcribed incorrectly/ without corresponding Rx/ not at all	Audit of e-MARs & of manual MARs (assuming by investigators)	-Observation of e-MAR. Company-funding. Tech Generalizability

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome Definition	Outcome Ascertainment	Comment: (- limitation. + strength)
[144]	CPOE+CDSS (wireless notebook) Nurse eMAR (palm pilot) PC Auto Disp. Bar-code, admin	Paper-based system used while training for upcoming computerization (1-3 days for all)	Pre: 3 months (concurrent with implementation period) Post: 3 months	33-bed medical ward, with specialty interest in renal care. teaching, UK	-Prescriptions illegible or instructions unclear at the time of administration (% omissions)	Direct observation by pharmacist	-Tech Generalizability ($$$, manufacturer support). "software for EMPSA, drug dictionaries, and CDSS remain problematical" -soft outcome
[149]	Pharmacy edited computerized lists for preparation & review of drug carts	Copy of Rx to prepare the pt's drug drawer (*in both arms*, 1 pharmacist & 1 tech check Rx vs. drugs dispensed)	Pre/post (1 month each) implementation in 1992	358-bed private non-teaching adult hospital (86% occupancy, 5.3-day median LOS), Spain	Drug in pt's drawer ≠ Rx shown on... (pre) photocopy of Rx, (post) pt's electronic medication profile	Pharmacist comparison of record of Rx with meds dispensed	-standard of comparison changes pre vs post Tech Gen.

APPENDIX Y: Bar-coding, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Study Validity (-/+)	Comment: (- limitation. + strength)
[169]	Bar-coded unit doses & medication cassettes for dose check (locally adapted) -for dispensing	Pharmacist check in satellite pharmacy	Cohorts (March & April 1990)	Satellite pharmacy for a 78-bed gen med area, teaching hospital, USA	dose in cassette differs from computer medication profile	Both direct observation: Ctrl: pharmacist verification (#2) Int : single tech observation	+concrete outcome
[168]	-bar code of patients & medication -apparently verifies correct patient, drug, dose, time, route -linked to CPOE & pharmacy computer	No bar-coded administration	Pre: 12 months pre-implementation then 1 month Post: 12 months post-implementation	2 med / surg units, teaching hospital, USA	Discrepancy in drug admin, (e.g., dose late missing, omitted, wrong)	-Pre: nurses' incident report Post: nurses' incident reports + bar-code system's automatic log. Funds: One Touch Technologies	-more sensitive error ascertainment post

APPENDIX Z: Highly Automated, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Pop. & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[170]	Clinicare by Clinicom: Clinicians* enter data electronically through portable, wireless terminals (bar-coding scanners, keypads, or touch screens (*unclear what data by whom) Clinical info available on computer monitors at patients' bedsides, at pharmacies, patient-care units, physician and resident lounges Nurses provided with printout of pharmacy medication profile & alerted to potential omissions (1hr after drug was due & 1hr before end of shift) Nurse selects patient's name on a computer screen outside double room, or scans patient's bar-coded wrist band; then scans the medication bar-code to verify the medication's appropriateness (education-two nurses hired to teach other nurses)	Pharmacist order-entry with CDSS; nursing dept. kept manual medication profile and MAR *Comparison: CPOE, eMAR, bar-coding for admin*	Pre-'91 Implement-ed '91-'92 1993 1994	326-bed adult teaching hosp, USA	Deviations from original physician's order Deviations from hospital standards set by nursing & pharmacy dept (includes wrong drug, wrong dose, wrong time, incorrect transcription to MAR vs. computer profile, wrong patient, omission)	incident report, nurse, pharmacist, physician	-includes transcription errors that may not lead to "actual" error. "The Clinicare learning curve for many nurses was steep" "The first year of using the Clinicare system was trying"

	Intervention	Comparator	Design & Follow-up	Pop. & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[171]	Clinicare by Clinicom bedside terminal system (one at each bed, two at central nursing station, hand-held portable terminals, computer entry & review of data; reader of medication bar-codes on hand-held devices) *unclear if drug appropriateness checks & alerts, as in the other Clincare study[170] Interim hospital downsizing	Pre *Comparison: CPOE, eMAR, bar-coding for admin*	The month pre-imple-mentation 8-month implementation 5 months pre- imple-mentation	35-bed surg unit, non-teaching, USA	a variation from standard practice	incident report, staff	-co-intervention: hospital downsizing. - Vague re: duration of observation, # doses observed, error definition, what bar-coding did neutral comment: differs from other Clinicare study in poorer description of intervention & results, smaller sample size, and higher reported error rate

	Intervention	Comparator	Design & Follow-up	Pop. & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[144]	Physician enters medication orders using a wireless notebook computer, at the patient bedside CDSS checks for drug interactions, wrong doses, and duplicate therapies Nurse accesses electronic medication profile & MAR on a palm pilot Nurse indicates when the system should open the medication drawer and indicate the right medication in the drawer Bar-coding of patient & medication for administration	Paper-based system used while training for upcoming computerization (1 day for physicians, nurses, and dieticians; 3 days for pharmacists; also for clerical staff) *Comparison:* CPOE, CDSS, eMAR, point-of-use auto disp, bar-code admin	Pre: 3 months (concurrent with implementation period: no time in between) Post: 3 months	33-bed medical ward, with a specialty interest in renal care, adult teaching, UK	*Prescriptions illegible or instructions unclear at the time of administration (outcome counted with eMAR)* % omissions (due to medicines being unavailable/ due to patient refusal / other reason)	Direct observation, pharmacists	-Constant computer support by manufacturer not realistic. more time-consuming for doctors and nurses. software for EMPSA, drug dictionaries, and CDSS remain problematical

	Intervention	Comparator	Design & Follow-up	Pop. & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
5;172	handheld wireless computers with integrated bar-code scanners -check on drug, dose, time (bar-coded drug packages, patient wristbands (&provider ID)); alerts to nurse if not met -pharmacy/nurse alerts re. pot. allergies & adverse RxNs + joint e-MAR for pharmacy & nursing shows which meds are due for administration (wireless laptops)	No bar code + separate manual nursing MAR	Pre: 1993 (seems to be <=12 months) Implemented in 1994; hospital-wide in 1995 Post: 1998, 1999 (1994) some time-series available	VA medical centre: all inpt, USA	Errors by the pharmacy or nursing (misc: med, dose, patient, time, omission)	incident report	-numerical discrepancy: stated overall medication rate decrease -70%, but I calculated -81%. system's automated "remov[al] of medications from a patient's prescription list". qualitative study commented on loss of coordination between physicians and doctors, difficulty providing MD access to MAR, occasional workarounds, loss of flexibility-eg re tapering doses, med delivery at expense of other nursing duties

APPENDIX AA: Self Administered Medication (SAM), Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[174]	SAM: on admission to post-partum unit, nurse gives pts standard pharmacy-prepared SAM package; educates patient to take meds and document administration (few meds, standardized)	Pt. calls nurse; if drug given doesn't meet pt needs, dr. contacted; nurse preps & administers medication (many meds customized)	Pre: 50 deliveries per month Post: slated to double to 100 deliveries per month through 1/3 of post period	post-partum unit, non-teaching hosp, USA	Oral medication errors -includes, but not limited to, wrong drug, patient allergy, and omission errors	Retrospective chart review	-"post" time period undefined neutral: less narcotic use (not intrinsically bad: in follow-up. survey, all patients were satisfied)
[175]	SAM: Nurse-educator assesses how well pt understands drugs and explains SAM . pharmacist gives session if necessary (e.g., if >=3 drugs) Patient & live-in care partner become responsible for med administration & recording	rest of hospital	Cohort (retrospectiv e)	1 unit vs. rest of teaching hosp, USA	Wrong med, dose, pt, time, route, or rate; duplication; omission; other.	Incident report	-Self-admin group has 1/4 the Rx /discharge; selected for ability to self-medicate. no control for patient acuity. since staff less involved in med admin , SAM group may have lower incident-report sensitivity

APPENDIX AB: Drug-administration models, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[176]	each nurse administers meds for her own pts (primary model)	designated medication nurse on each shift (functional)	Cohort 12 months	Functional: 2 child & 2 adolescent units primary: 2 adult psych, 1 geropsych, 2 neuro units, USA	Admin errors: wrong pt, dosage, drug, route, time, omission, extra dose, unordered drug, past expiry date, other (e.g, no consent)	Incident report by nurses	-very different populations (age, #doses given per unit)
[176]	each nurse administers meds for her own pts (primary). drug cards not used; new staff hired	designated medication nurse on each shift (functional)	pre/post (retrospectiv e) -the year pre -the year post -2nd year post	child & adolescent neuropsychiatric units (2 of 1 type and 1 of the other), USA	Admin error: wrong pt/ drug/ time. omission. drug chart not signed. drug given twice/ though discontinued	Incident report + night nurse's audits of the MAR by nurse	-encouraged reporting in post period
[177]	two nurses, including a registered nurse, administered medication	One registered nurse administered medication	two-group, randomized (post- cross-over ignored) 23 weeks	Geriatic assessment & rehab unit, wards A, B, C, Australia	admin error: wrong pt/ drug/ time. omission/ drug chart not signed. drug given twice/though DCd	MAR review once per week (98%) & incident report (2% of reported errors) by nurse	-insensitive, especially re. non-omission errors

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[178]	Unlicensed technician administers drugs (unit dose)	Registered nurse administers drugs (unit-dose)	Cohort (1 yr) RNs: night shifts Unlicensed personnel: day & night shifts	psychiatric unit, USA	omission errors, wrong-time errors (1-hr range if normal; 10-minute range if urgent)	incident report + clinical pharmacist's investigation of requests for extra of different doses, and utilization checks	-RNs at night. Unlicensed personnel day & night. possible reporting difference
[179]	IV training module, including a booklet, taught drip rate calculation	Pre	pre: months 1-6 training: months 7-12 post-training: months 14 (13ish)-21	Adult, teaching hosp, USA	IV drug errors that reached pt: total, wrong dose, omission, other (wrong patient, route, time) Rx of suspect validity	incident report	-decrease gradual over time. No clear blip with intervention
[118]	special procedures for transcription onto the MAR	Pre	Pre/post (timing unclear)	One hosp, USA	Potential misinterpretation of the MAR	Not declared	1/9 reported of 15 projects undertaken through IHI (IHI biases like reporting to supervisors, etc)

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[180]	Returned-dose log (excluded doses often withheld: eg, laxatives). completion: 10' for nurses, 15'-20' for pharmacists Pharmacy and nurse managers routinely discussed daily review of type of drugs returned & reasons.	Early	2-stage post intervention 4-month pilot; measured at: Month 1 & Month 8 of program	400-bed adult teaching hosp, USA	Dispensed doses that were returned	routinely, documented, nurses & pharmacists	early/late in program

Appendix AC: Unique, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[181]	32 internal medicine house officers organized in 14 teams of one intern (PGY1) & one resident (PGY 2or3) with a 7 day rotation. 2 short-call days (admit 8am-6pm), 1 off-call day, 1 short-call, 1 off-call, one long-call (8am-10pm - 16hr day) – exception: Friday 8am- Sat 8am 2 night teams alternated 10-14hr shifts (admitted pts after 10pm) from Sun-Thurs	32 internal medicine house officers organized in 16 teams of one intern (PGY1) & one resident (PGY 2or3) with a 4 day rotation. Day 1. short-call day (admits 8am-2pm) Day 3. long-call day (admits 8am -10am - at least 32 hours) Days 2 & 4. non-admitting days	Jan 20, 1988 to Feb 20, 1988 (1 month) Implemented March 5, 1988 Mar 20, 1988 to Apr 20, 1988 (1 month)	193 acute internal medicine beds, teaching, adult, USA	Potentially serious medication error committed by internal medicine house officers (wrong medication, wrong dose/wrong schedule/wrong patient/omission) Potentially serious physician medication errors, physician discharge medication orders	Pharmacy quality-assurance data	-20% shorter mean L.O.S. Increased intern/resident experience Hawthorne effect (motivating participants through change & evaluation of change) Seem like errors caught +Pt char, described in detail, appeared very similar

Unique in a less significant way							
	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
182	Emphasis on personal responsibility: pharmacy supervisors submit information re. drug-dispensing errors to the pharmacy director, who assigns a numerical value to the error's severity. The point values determine the need for educational intervention, discipline, or reward	no policy to deal with employees who erred repeatedly; drug dispensing errors not monitored, only the most serious errors investigated	pre: unclear post 3 yrs later; implemented Feb 1986	inpt & outpt orders at adult, 900-bed teaching hosp, USA	Pharmacy dispensing errors (some identified before drug administered, some not detected after administered)	Self-reported when errors identified Inpatient medication errors were reported by nursing personnel (and by patients for ambulatory care orders)	-Low sensitivity of measure (20 errors in one month for 964 beds). Possible reluctance to report errors with punitive system Mix of in-pt & out-pt errors from hospital pharmacy dispensing

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
183	-simplified heparin ordering & documentation -new heparin order form with guidance about heparin Tx -extra lab/ pharmacy communication: eg, lab computer system flagged tests that were ordered but not performed; lab printed PTT test results in pharmacy -separate systems of heparin management integrated under pharmacy management -LMW heparin use encouraged	"Byzantine" ordering & documentation process: e.g., pharmacist's order for dose adjustment is flagged by a unit coordinator, transcribed by a pharmacy tech & double checked by a nurse & pharmacist Two systems of heparin management: pts on thrombolytics by cardiologists; pts not on thrombolytics, pharmacists	pre/ post (timing unclear)	Coronary-care unit (adult, non-teaching), USA	reported heparin order errors per month	probably incident report (not declared)	-Data collection unclear (sample size, timing of observation and implementation, error definition)

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[184]	Outsourced IV admixture compounding (integrated with hospital clinical computer system)-contract implemented through CQI program & contingent on study results Technician reminded nurses of missed doses (and recycled unused doses)	in-house IV admixture compounding : 12-yr-old facilities didn't meet AHSP guidelines; space & IV supply shortages	Pre: One week, two weeks prior to implementation Post: One week beginning 30 days after implementation	3 units (medical oncology, 2 med surg (1 pediatric, 1 with several hospice beds)), acute non-teaching hosp, USA	administration omission errors (dose scheduled but not admin'd, given the absence of a clinically justifiable reason)	reviews of medication cart fill list, medical record, MAR; interviews of nurses	-Contractual quality obligation and evaluation is unsustainable. -technician reminders probably converted omissions to wrong-time errors (unmeasured) +nurses blinded to study, improving the reliability of error determinations

APPENDIX AD: Continuous Quality Improvement (CQI) /multifaceted

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[186]	over a 7 (6-9) month period, Breakthrough Series faculty coached interdisciplinary* teams in QI techniques at 3 2-day face-to-face seminars, and at a distance through conference calls and surveys (*suggested 0.2 FTE physician, 0.3 FTE pharmacist, 0.3 FTE nurse) ; 18/22 teams continued their QI work until the end of follow-up	Baseline	Pre/post baseline vs. end of course (7 or 6-9 months post-baseline) baseline vs. 6 months after end of course -QI implementation : from baseline to 6-9 months later	27 participants of 172 hospitals; 22 teams made initiatives, USA	medication errors averted (during 7 month collaborative period, during following 6 months)	unvalidated self-report by participating QI teams	-IHI: data reported is close to a self-evaluation -acquiescence bias re. central Breakthrough Collaboration -did not define baseline measures or how they were collected -interventions hardly described - no data from 4 projects: 1 heparin, 1 insulin, 2 warfarin + two measures suggests sustained changes without central organization did not count increased numbers of drug errors as increases Funds: VA health system

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
132;133; 187	Attended IHI Breakthrough Collaborative Series, then a) standardized equipment and processes within the hospital; b) developed a "culture of safety"; and c) automated as a "last resort," based on preparation: having 1) developed a safety leadership structure: care-unit safety coaches (physician-nurse teams) and safety-management committee (with a subcommittee chaired by CEO) 2) identified safety problems using "trigger tools" (incident reports, patient & staff complaints, staff interviews, chart review) 3) identified key areas for changes (heparin, warfarin, insulin, chemotherapy, renal-adjusted dosing, concentrated electrolytes, narcotics & sedatives, pt-controlled analgesia, infusion pumps, drug-allergy)	pre-initiative	Pre: Jan-Feb 1997 Post: July 2000 - May 2001	310-bed adult teaching hosp, USA	"errors" or "pot. ADEs and ADEs"	retrospective chart review (MD unblinded)	(multiple time points) -IHI. vague definition of outcome, population, intervention. measure sensitivity issues. no steady baseline measure

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[188]	13 hospital teams participated in a series of 4 seminars to encourage medication safety 5 hospitals redesigned MARs; 8 attempted to improve access to allergy information; 8 standardized and simplified medication procedures; 7 restricted access to potentially lethal drugs; 5 instituted nursing-education programs; several other initiatives	no intervention	the week prior to the individual's response to the survey (about 6 months pre & post intervention)	8 hosp, USA	Respondent observed a medication error in the past week (types--ordering; transcription & verification; dispensing & delivery; administration) -the medication error observed by the respondent did not reach the patient	survey (response rate indeterminate) nurses, pharmacists, physicians, others	-selection 13 / 39 invitees participated - losses to follow-up: 27% (3/11 hospitals) didn't provide follow-up data -survey response -funding: Health Care Financing Administration, which initiated QI program

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[22]	CQI program in year 2 (Medication error committee for the 19 beds met at 3-month intervals; reported back to unit staff in the form of written updates, and recommended changes in policy and practice to reduce the frequency of errors)	CQI program in year 1 (Medication error committee for the 19 beds met at 3-month intervals; reported back to unit staff in the form of written updates, and recommended changes in practice)	"pre/post"	15-bed pediatric cardiac ward and 4-bed pediatric cardiac ICU, teaching hosp, UK	actual error: error reached the patient total errors: mistake made in any stage of the provision of medication to a patient level-0 error: error prevented from reaching a patient serious error: error capable of producing permanent organ damage or death [Errors were classified in 3 categories (prescribing, administration, supply). They were also categorized as serious or non-serious]	anonymous incident report by nurses, pharmacists, doctors	Unclear what was actually done
[79]	Hospital's "continuing efforts"	Pre	Pre 1996 Post 1999	Open-heart surgery patients. 520-bed private, adult, teaching acute-care hospital (LDS, USA)	Errors associated with deep sternal or mediasternal infections	Retrospective chart review (epi dept)	errors prevented, but similar # infections

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[185]	4 clinical pharmacists attempted to meet their targeted standards for % acceptance, then analyzed & reviewed their interventions after each of 3 cycles	pharmacists documenting their interventions	4 weeks interim review 4 weeks interim review 4 weeks	333 adult beds, Ireland	Pharmacist intervention types (unacceptable orders clarified; accepted recommendations re. non-policy or nonformulary drug, route or method of admin, dose, dosage freq, Tx duration, pharmacokinetic or thepeutic drug monitoring; acted upon suspected ADR; followed up on clinically important interactions); Interventions' significance (detrimental; of no importance; important but not improving pt. care; important & improves pt-care; very important & prevents major organ failure or a serious ADR; potentially life-saving)	Prospective: pharmacists' self-evaluation (through locally developed method of bar-coding)	-self-assessment non-specific: study includes interventions initiated by pharmacists (90%), doctors (8%), nurses, (1.5%). Funds: Northern Ireland Steering Committee

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[190]	Units combined & changes led by multidisciplinary team 1. Created multiskilled workers (nursing aide + patient transport + environment services tasks) -tasks performed by registered nurses, licensed practical nurses, and unlicensed care practitioners -secretaries cross-trained to handle admission, discharge, and financial verification -extensive 4-5 week training program for new employees (US$100,000 budgeted) 2. New employees hired 3. New architecture -remodeled central nursing station, added 2 nursing stations, medication cupboards built outside each room -new floor plan, paint, wall-paper, curtains, etc	Pre-intervention	pre/post pre: 1993; post: 1995	pre: One neurological unit + One orthopedics unit post: One 30-bed combined unit non-teaching, USA	medication errors per month	Not declared	nurse-led study, so medication errors likely to be mostly admin

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[192]	3 new policies 1) physicians asked to select indications from a list in the CPOE system 2) an analgesia- or sedation-assessment scale was added to nursing flow sheets, for hourly assessments 3) endotracheal intubation became a requirement before ophthalmic cryosurgery	Pre-intervention	May 1-Oct 31, 1992 (6 months) Jan 1-June 1, 1994 (6 months) implementation in the interim period	Morphine-treated in NICU, USA	adverse reactions to morphine, including changes to respiratory status, blood pressure, and urinary output	Chart review (unclear by whom) Check re; overlap with adj. study	-small # events

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[189]	Led by a committee of pharmacists and nurse responsible for reporting on quality; medical quality assurance joined later. study and dissemination of organizational error frequency prompted: Standardization of medication administration times; push to improve delivery times (more frequent pharmacy rounds, evaluation of ordering process); better labels on generic drugs; educational interventions (one-on-one teaching & study materials developed by nursing staff development dept. - reviews of medication administration standards, common errors, and case studies)	pre-interventions	pre/post	within a 507-bed teaching hospital, adult environment, USA	a deviation from a physician's charted order	incident report, nursing, pharmacy, perhaps others	-unclear: relation of intervention timing to error decrease. vague outcome. Potential association of error-detection sensitivity with motivational techniques

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[91]	medication administration review & safety committee (nurses, pharmacists, information systems analysts, risk manager) had performed a prospective chart review, and -implemented Pyxis automated dispensing -moved medication dispensing areas to quieter places -simplified administration times -reorganized charting documents -implemented computer-reminders of scheduled medications not given, or not charted, and computer-generated reports on uncharted & double-charted medications -structured medication-related communication (physician "call-back" message boards for nurses; pharmacy fax contact #; nursing staff observed pharmacy dept; nurses notified of pharmacy-identified errors)	Medication administration review & safety committee (nurses, pharmacists, information systems analysts, risk manager) had begun its work	Early in implementation: Dec '97 to Dec '98 late in implementation: 1 to 2 years later	525-bed non-profit non-teaching adult hosp, USA	Documentation errors: transcription, preparation, dispensing, or distribution phases; includes uncharted or double-charted medications; wrong patient, dose, route, or time; charge errors	not declared	-vague definitions of: outcome, and timing of intervention with respect to outcome measurement

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[193]	1993-CPOE without decision-support several initiative from 1993 onwards: multidisciplinary committee (pharmacist, clinical pharmacologist, pediatrician, administrator) & subcommittee (above + nursing representative) conducted interviews and reviewed procedures, creating -a list of hazardous drugs that could kill a child in the event of an incremental error, implementation of a double-check system of hazardous-drug-dose calculation -ongoing removal of hazardous drug from wards, where drugs not required on a stat basis -division of clinical pharmacology & toxicology tests all medical trainees' dosing calculations -Medication Incident Review Committee investigates potential solutions to major medication errors -pediatric ICU created & implemented a computer program that calculates an appropriate volume of a stock solution of drugs given child's weight & age	"pre"	Time-series April 1, 1990-Mar 31, 1991, ...(annually) ... April 1, 1998-Mar 31, 1999 CPOE in 1993; CQI began Jan 1993	Pediatric teaching, CAN (Sick Kids)	Medication errors, actual + potential: allergy, extra dose, omission, unordered drug, wrong dose, wrong route or site, wrong time, wrong IV rate, wrong IV solution, incompatibility, medication expired, unauthorized administration, narcotic discrepancy Medication errors, actual: medication errors that reached patients -minor-not affecting pt's health -moderate-affecting pt's health but not life-threatening -severe-potential or actual risk to patient's life	incident report, all staff	-vaguely specified interventions confounded with secular changes. incident report +consistency of several indicators

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[194]	Comprehensive, interdisciplinary continuous-improvement approach to current system which led to 23 modifications between 1995 and 1999 (computer support by Eclypsis consultants); including: i) std chemo nomenclature, ii) computer system enhancements (automated dose calculation, route restriction, protocol-specific laboratory parameters automatically added to computer-generated orders, iii) checklist for preparation and administration of chemotherapy and automated nursing care plan, iv) on-line access to drug information & investigational drug sheets, v) educational program & certification program for medical & paramedical staff involved in chemotherapy. Improvements to the reporting system for chemotherapy prescribing errors (near misses) & medication errors that affect patients were also made.	CPOE (Eclipsys system) with chemotherapy protocol-specific ordering screens managed by pharmacy	Changes implemented from June 95 to Dec 1999; measured % change from beginning of program vs end (~4.5 yrs)	pts (inpt & outpt) receiving chemo at 325-bed teaching hospital with outpt & extended care, USA	prescribing errors: serious [adverse events likely to occur] or temporary [medically reversible or no AE likely to occur (includes orders which cannot be dispensed as written]	Pharmacists incident-report + routine pharmacist log (medical information system)	-Unclear timing of observation, implementation; discipline for class I errors may affect reporting; no absolute #s (funds: Pfizer)

APPENDIX AE: Failure Mode Analysis & Root Cause Analysis, Study Characteristics

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
195; 208	Failure Mode & Effects analysis identified changes to ward-stock - provision of a current drug reference text; standardization of medication administration round times, and of a number of commonly used medication protocols (e.g., dexamethasone dose reduction, phenytoin); clinical pharmacist removes unrequired medications from the drug trolley daily	nursing staff educated about study aims & procedure; "non-punitive" error-reporting emphasized	pre: 23 days ; roughly 0-day implementation period; post: 31 days (Aug-Sept 96)	30-bed surgical & medical ward, teaching, adult environment, Australia	Drug errors -omission -wrong dose -extra dose -unordered drug -wrong formulation -wrong route -inadequate documentation -wrong time (minor) -wrong time (major) errors/day extrapolated errors/dose	Nurses' incident report - `with stimulated, no-blame reporting	-incident report -reporting stimulations (sensitivity, reactivity) -historical control with disguised observers showed under-reporting (no surprise). Funding: Soc. Hosp. Pharmacists of Australia

	Intervention	Comparator	Design & Follow-up	Population & Setting	Outcome (what's measured)	Outcome Ascertainment	Comment: (- limitation. + strength)
[39]	root-cause analysis guided implementation of 22 changes to medication use (floor-stock limits, visual cues for look-alike materials, availability of a clinical pharmacist, policy for written medication orders, weight-based pediatric dosing requirement, height & weight data mandatory in a computer which has computerized weight-based dose checks, standardized stock solution concentrations, beeper #s required on orders, limited privileges to order "high-risk" drugs, dual dose calculations by nurses, concentrated KCl removed from floor stock, tracking of chemo orders, double-checks for allegy, emphasis on system-related improvement through leadership	Pre	Pre: August '96 to July '97 (12 months); Post: August '97 to Dec '98 (17months) - implementation of non-punitive approach began around Oct. '96	624-bed teaching hosp, USA adult (80%) and pediatric (20%) DRG-adjusted disease severity was stable	pot. ADEs "actual" ADEs fatal ADEs not-fatal pot. & actual ADEs	incident report, esp. from clinical pharmacists and case managers who review almost all charts daily	-incident report -possible regression to mean. process prompted by first month of "pre" period -few ADEs observed

APPENDIX AF: TABLES OF STUDY RESULTS

Table 6a: Computerized Physician Order Entry, Risk of Medication Error and Adverse Drug Events

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD * 100.	(95% CI)
West[63]	Cohort (1)	Computer Physician Order Entry (6985 orders) vs Hand-written (7056 orders)	order errors *by attending dr. *by residents AEs due to order transmission error	0.74 0.94 1.15 1	(0.50, 1.09) (0.37,2.3) (0.57,2.3) (no event)	-0.22/order -0.07 0.08 0	(-0.50,0.06) (-0.9,0.8) (-0.3,0.4)
Bizovi[64;65]	Pre/post (1)	Computer Physician Order Entry, pick-list (1594 computer orders + 380 written from first 15/ 60 days) vs Hand-written (2326 orders)	Errors/ order	OR= 0.48 (modeled)	(0.31,0.73	-1.2/order (adjusted)	
Chessare[66]	Time-series (1)	Computer Physician Order Entry (n: na) vs Pre (n: na)	Medication errors	0.78	(na)	-0.1/pt-day	(na)

*subgroup CI Confidence Interval. RR: relative risk. RD: risk difference. OR: odds ratio. na: not available. Pt: Patient

Table 6b: Computerized Physician Order Entry, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	6. Relative Risk (95% CI) or (Range)	7. 100 x Risk Difference	Unit of Risk Difference
CPOE alone	3:0:0	Fill-in, picklist, na	D (4)	3	0.74 (0.5, 1.09) or 1 (na); OR=0.48 (0.3, 0.7); 0.8 (na)	-0.22 -1.2 -0.1	Order error / order Order error / order Misc. error / pt-day

1^0: primary. 2^0 secondary. Pt patient. OR odds ratio

Table 7a: Anti-infective management at the LDS Hospital: Risk of Medication Error and Adverse Drug Events

Study Characteristics						Results			
Study	Design (# centres)	Comparison (sample size)			Outcome	RR (95% CI)		RD (95% CI)	
Evans[80]	Pre/post (1)	CDSS recommends to clinical pharmacist antibiotic prophylaxis <=48hrs (3991 pts)	Vs	No CDSS (3655 pts)	Antibiotics too long /pt # antibiotic (Ab) doses / pt with extra Ab	0.89 0.68	(0.83, 0.96) (p<0.001 [C])	-0.031/pt -6doses/pt	(-0.05 -0.012)
Pestonik, Burke[34;79]	Pre/post /post (1)	CDSS for antimicrobials' prophylactic, empiric, and therapeutic use (n: na)	vs	No CDSS (n: na)	Antibiotic-ADEs/ Ab-treated pt 89 vs 88 94 vs 88 Antibiotic-associated mortality/ Ab-treated-pt (94 vs 88)	0.52 0.36 0.73	(na) (na) (na)	-0.25/ pt -0.33/ pt -0.010/pt	(na) (na) (na)
Burke[79]	Interrupt-ed time-series (1)	Chart reminder 86 (1830 pts)	vs	None (1621 pts)	Wrong-time or omitted / dose	0.7	(0.65, 0.74)	-0.18 / dose	(-0.21,-0.15)
		no charted reminder, nurse responsible for 1st prophylactic antibiotic 88 (746pts)	vs	Charted Reminder (1830pts)		0.90	(0.81 1.01)	-0.04 /dose	(-0.08,-0.0015)
		plus CDSS standing prophylaxis order 91 (310pts)		No CDSS					
		93 (230pts)	vs	88 (746pts)		0.11	(0.06 0.18)	-0.34	(-0.38,-0.30)
		94-98 (430 to 626pts)	vs	92 (386pts)		0.15	(0.07 0.32)	-0.17	(-0.22,-0.12)
		minus CDSS standing prophylactic. order 92 (386 pts)	vs	92 (386pts)		0.05	(0.03 0.08)	-0.19 /dose	(-0.23,-0.15)
				CDSS					
			vs	91 (310pts)		5.0	(2.8, 8.9)	0.16 /dose	(0.11, 0.20)
Evans[78]	Pre/post (1)	CDSS: antibiotic consultant re: blood, wound, lower respiratory tract, abscess, urinary tract (266 orders)	vs	No CDSS (273 orders)	Inappropriate physician order	0.88	(0.67, 1.17)	-0.034/order	(-0.11,0.04)

Study Characteristics						Results			
Study	Design (# centres)	Comparison (sample size)			Outcome	RR (95% CI)		RD (95% CI)	
Evans[81]	Pre/post (1)	CDSS: drug allergy for pharmacists & in-service education re: drug admin (~23000 pts)	vs	Pre (n~23000 pts)	ADEs	0.15	(0.058,0.30)[A]	-0.00039/pt	(na)
					-known allergies	0		-0.00011	(na)
					-inappropriate admin	0.05		-0.00016	(na)
					-other (e.g., first-time use)	0.32		-0.00013	(na)
Evans[76]	Pre/post (1)	computerized physician anti-infective order entry (545 pts)	vs	Pre (1136 pts)	ADEs caused by anti-infectives/ patient	0.30	(0.10, 0.84)	-0.017	(-0.03,-0.006))
					Susceptibility mismatches/ patient	0.12	(na)	-0.16[B]	(na)
						0.50	(na)	-0.064[B]	
					Drug-allergy alerts/ patient	0.45	(na)	-0.20[B]	
					Excess dose alerts / patient [f(renal function)]	0.46	(p<0.002)[D]	-3.2	
					mean days anti-infective dose/ anti-infective-treated- patient				
Evans[82]	Pre/post (1)	CDSS for pharmacy: computerized dose-adjustment (4483 pts)	vs	No CDSS (~8901 pts)	ADEs due to study antibiotics/ patient	0.33	(0.19, 0.60)	-0.0061	(-0.01,-0.0035)
					Patients who received excess dose	0.87	(0.83, 0.91)	-0.065	(-0.08,-0.047)
Burke[77]	Pre/post (1)	Computerized physician anti-infective order entry (n: na)	vs	None (n: na)	Preventable ADEs/ pt	0.03	(na)	-0.012/pt	(na)

[A]exact, Poisson rates [B]chi-square test (by study authors) [C]t-test [D]Mann-Whitney U-test (by study authors)

CI Confidence Interval. CDSS Computerized Decision Support System. Ab antibiotic. ADE Adverse Drug Event. pts patients.

Table 7b: Computerized Decision Support System (CDSS) plus Computerized Physician Order Entry: Risk of Prescription Error

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)			Outcome	RR (95% CI)	RD (95% CI)
Myers[72] [71]	Pre/post (1)	CPOE+CDSS (broad) (7431 pt-days)	vs	None (7331 pt-days)	Any Rx Error	0.17 (0.04, 0.50)[A]	-0.0026/pt-day
Taylor[71]	Pre/post (1)	CPOE+CDSS (broad) (n: na)	vs	None (n: na)	Any Rx Error	0.5 (na)	na
Bates[67] (see below as well)	Interrupted time-series (1)	-CPOE+CDSS (broad) (492 orders) -more allergy CDSS (471 orders) -more drug-drug CDSS, KCl limited, e-linkage (475 orders)	vs	Pre (379 orders)	Non-missed-dose	0.37 (0.30, 0.46)[A] 0.41 (0.34, 0.52)[A] 0.14 (0.10, 0.20)[A]	-0.020/order -0.19/order -0.025/order (-0.91, -.68, -1.15, per pt-day)
Teich[70]	Pre/post (1)	CPOE+CDSS (broad) (263549 orders)	vs	None (64594 orders)	Xs dose	0.27 (0.24, 0.30)	-0.12 / dose (-0.15, -0.09)
Evans[76]	Pre/post (1)	CPOE+CDSS (antibiotic) (545 pts)	vs	None (1136 pts)	Xs dose	0.45 (p< 0.01)[B]	-0.20 / order
Chertow[73]	Repeated pre/post (1)	Renally adjusted (5490 orders)	vs	Fixed CPOE + CDSS (8950 orders)	Wrong dose or freq	0.70 (na)	-0.21 / order
Bates[67] (see above as well)	Interrupted time-series (1)	-CPOE+CDSS (broad) (492 pts) -↑ allergy CDSS (471 pts) -↑ drug-drug CDSS, KCl limited, e-linkage (475 pts)	vs	None (379 pts)	Missed dose	1.18 (1.02, 1.36)[A] 1.09 (0.93, 1.27)[A] 1.51 (1.31, 1.74)[A]	0.005/ order (na) 0.002/ order (na) 0.014 / order (na)
Durieux [75]	Repeated pre/post (1)	CPOE+CDSS (heparin) (859 orders)	vs	None (1112 orders)	Heparin-order error	0.30 (0.22, 0.41)	-0.016errors/pt (-0.03, -0.005)

[A]exact, Poisson rates [B]Mann-Whitney U (by authors)

Xs: Excess. CI Confidence Interval. CPOE Computerized Physician Order Entry. CDSS Computerized Decision Support System. Rx Prescription

Table 7c: Computerized Decision Support System, Alerts for a Broad Indication: Risk of Pharmacy-accepted Order error

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)			Outcome	RR, or Relative Mean* (95% CI)	RD, or Mean Difference* (95% CI)
McMullin[83]	Pre/post (1)	CDSS: Customized previous commercial system (3048 orders)	vs	Old CDSS (3048 orders)	# pharmacy-accepted Rx errors	0.34 (0.27, 0.43)	-0.059 / cisapride order (-0.071, -0.047)
Levenson[85]	Pre/post (1)	CDSS: New commercial system (n: na)	vs	Old CDSS (n : na)	# pharmacy-accepted Rx errors	0.87 (na)	----
McMullin[83]	Pre/post (1)	CDSS : Xs-dose alerts (3048 orders)	vs	No such alerts (3048 orders)	Xs dose duration	0.39 (p< 0.001')	-2.5 days (p< 0.001')
Evans[82]	Pre/post (1)	CDSS : Xs-dose alerts (3655 pts)	vs	No such alerts (3991 pts)	Xs dose duration	0.62 (na')	-1.8 days (na')

Xs: Excess. CI Confidence Interval CPOE Computerized Physician Order Entry. CDSS Computerized Decision Support System. Rx Prescription

Table 7d: Computerized Decision Support System (CDSS) for Dispensing Calculations: Risk of Drug Error

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)			Outcome	RR (95% CI)	RD/order (95% CI)
Raehtz[87]	Pre/post	CDSS (252 orders)	vs	None (257 orders)	Pharmacy TPN calculation error: >5% error	0 (0, 0.10)[A]	-0.12 /TPN
Horn[88]	Cohort (1)	CDSS (50 orders)	vs	None (50 orders)	Pharmacy TPN calculation error:		
					any error	0.18 (0.08, 0.39)	-0.54 /TPN (-0.70, -0.39)
					major error	0.56 (0.2, 1.5)	-0.08/TPN (-0.22, 0.055)
Gard[89]	Pre/post	CDSS+Double-check (n: na)	vs	None (n: na)	Antimicrobial dose-calculation errors / month	0 (na)	-5 / month (na)
Silverman[86]	Time-series presented as pre/post	CDSS+1 day/ wk clinical pharmacist (6 months)	vs	None (18 months)	Month with an error involving heparin-infusion rates	0 (p= 0.059)[A]	-0.44 /mont (-0.67, 0.06)[A]

[A]exact calculation, binomial proportions

CI Confidence Interval CDSS Computerized Decision Support System. TPN Total Parenteral Nutrition. Rx Prescription

Table 7e: Computerized Decision Support System (CDSS) with or without Computerized Physician Order Entry (CPOE): Risk of Adverse Drug Events

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)			Outcome (ADE type)	RR (95% Confidence Interval)	RD (95% Confidence Interval)
Bates[67] Bates [67] Bates [67]	Interrupted time-series	CPOE + CDSS (broad) (1): (492 pts) (2): (471 pts) (3): (475 pts)	vs	None (379 pts)	Preventable ADE	 2.0 (0.67, 6.9) [B] 0.38 (0.036, 2.3) [B] 0.36 (0.035, 2.2) [B]	 0.0028/pt-day (na) -0.0018/pt-day (na) -0.0019/pt-day (na)
Bates[69]	Pre/post (1)	CPOE + CDSS (broad) (n=12218 pt-days)	vs	None (?)	Preventable ADE	0.83 (0.58, 1.20) [B]	-0.00081/pt-day (na)
Bates[67] Bates [67] Bates [67]	Interrupted time-series (1)	CPOE + CDSS (broad) (1): (492 pts) (2): (471 pts) (3): (475 pts)	vs	None	All-cause ADE	 1.01 (0.60, 1.8) [B] 0.73 (0.38, 1.4) [B] 0.58 (0.29, 1.13) [B]	 0.0002/pt-day (na) -0.0040/pt-day (na) -0.0062/pt-day (na)
Bates[69]	Pre/post (1)	CPOE + CDSS (broad) (12218 pt-days)	vs	None (n: ?)	All-cause ADE	0.95 (0.79, 1.15) [B]	-0.0008/pt-day (na)
Bates[67] Bates[67] Bates[67]	Interrupted time-series (1)	CPOE + CDSS (broad) (1): (492 pts) (2): (471 pts) (3): (475 pts)	vs	None	Potential ADE	 0.33 (0.07, 1.2) [B] 0.12 (0.003, 0.89) [B] 0 (0, 0.41) [B]	 -0.0031/pt-day (na) -0.0041/pt-day (na) -0.0047/pt-day (na)
Bates[69]	Pre/post (1)	CPOE + CDSS (broad) (12218 pt-days)	vs	None (n : ?)	Potential ADE	0.16 (0.09, 0.28) [B]	-0.0051/pt-day (na)
Durieux[75]	Repeated pre/post (1)	CPOE + CDSS (heparin) (859 orders)	vs	None (1112 orders)	Pulmonary Embolism or Deep Vein Thrombosis	0.86 (0.14, 5.2)	-0.00037/pt (-0.0048 , 0.0041)
Evans[76]	Pre/post (1)	CPOE + CDSS (antibiotic) (545 pts)	vs	None (1136 pts)	Antibiotic ADE	0.30 (0.10, 0.84)	-0.017/ pt (-0.029, -0.0058)
Burke[77]	Pre/post (1)	CPOE + CDSS (antibiotic) (n: na)	vs	None (n: na)	Antibiotic ADE	0.03 (na)	-0.012/pt (na)
Evans[81]	Pre/post (1)	CDSS (antibiotic), No Δ CPOE (~23000 pts)	vs	None (~23000 pts)	Antibiotic ADE	0.15 (0.058, 0.30) [B]	-0.00039/pt (na)

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)			Outcome (ADE type)	RR (95% Confidence Interval)	RD (95% Confidence Interval)
Evans[82]	Pre/post (1)	CDSS (antibiotic), No Δ CPOE (3655 pts)	vs	None (3991pts)	Antibiotic ADE	0.33 (0.19, 0.60)	-0.0061/pt (-0.0087, -0.0035)
Rind[74]	Interrupted time-series (1)	CDSS (renally excreted), No Δ CPOE (267 pts)	vs	None (295 pts)	Serious renal impairment	0.45 (0.21, 0.96)	-0.041/pt (-0.078, -0.0039)
McMullin[83]	Pre/post (1)	CDSS (Cisapride) (3048 pts)	vs	Old CDSS (3048 pt)	ADE due to targeted interaction with Cisapride	0 (0, 2.5) [A]	-0.017 /pt (-0.051, 0.026) [A]
Levenson [85]	Pre/post (1)	CDSS (Digoxin) (n : na)	vs	Old CDSS (n: na)	Toxic Digoxin Reaction	0.10 (na)	na

[A]exact, binomial proportions [B]exact, Poisson rates [C]t-test (pt-days were not reported post)
CPOE Computerized Physician Order Entry. ΔCPOE: change in existing CPOE. CDSS Computerized Decision Support System. Pt Patient
Bates: (1)CPOE+CDSS: first application (2)more allergy CDSS (3) more drug-drug CDSS, KCl limited, e-linkage (n=475)

TABLE 7f: Computerized Decision Support System (CDSS), Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
CDSS +/- CPOE	23:0:0	CDSS +CPOE	B (2c)	6	Median 0.27 (R: 0.14,0.5; Stat Sig=4)	-0.3 to 115	ADE /pt-day
			C (2c)	1	1.5 (1.3, 1.7)	1.4	Missed-dose error /pt-day
		CDSS alerts	C (2c)	2	0.34 (0.3, 0.4); 0.87 (na)	-6 na	Cisapride order error /order --
		CDSS (calculation)	D (4)	2 (2)	0 (0, 0.1); 0.18 (0.08, 0.4)	-12, -54	Order error /order
		CDSS+CPOE	C (2c)	2	0.83 (p=0.4); 0.36 (0.04, 2)	-0.08 -0.19	ADE /pt-day
		CDSS+CPOE , antibiotic		2	0.03 (na)-broad 0.3 (0.1,0.8)-ICU	-1.2 -1.7	Antibiotic ADE /pt Antibiotic ADE /pt
		CDSS+CPOE, heparin		1	0.86 (0.1, 5)	-0.04	Heparin ADE /pt
		CDSS alert	C (2c)	2	0 (na) 0.2 (0.1, 0.3)	-1.7, -0.04	Cisapride ADE /pt Digoxin ADE /pt

ADE Adverse Drug Event. CDSS Computerized Decision Support System. CPOE Computerized Physician Order Entry. ICU Intensive Car Unit. Pt Patient R Range. 1^0,2^0 primary, secondary

Table 8a: Kinetic-dosing, Risk of Potential Adverse Drug Events and Adverse Drug Events

n.b., see abbreviations defined below the table

Study Characteristics							Results						
Study	Design (centres)	Comparison (sample size)				Outcome		RR	(95% CI)		RD	(95% CI)	
		Drug Indication				Definition	Time						/
Lynch[93]	Pre/Post/ Post (1)	Aminoglycoside	Kinetic dosing + Nomogram: (time 1 68, t2 100 pts)	vs	Status quo (49 pts)	*# reaching therapeutic [Drug] in*	<24 hr 25-48hr 49-72hr after 72hr never no data	3.4, 3.0 1.7, 1.3 1/0, 1/0 0.7, 0.6 0.05,0.18 0, 0.2			.49, .41* .04, .02 .04, .13 -.06, -.07 -.27, -.24 -.24, -.20 **1 vs. (2 & 3), p<.005*			Pt
Lynch[93]	Pre/Post/ Post (1)	Aminoglycoside	Kinetic dosing + Nomogram (time 1 68, t2 100 pts)	vs	Status quo (time 1 68, t2 100 pts)	*Possible nephrotoxicity*	in hospital	0.60, 0.24	(0.19, 1.9) (0.06, 0.94)		-0.05 -0.09	(-0.16, 0.06) (-0.19, 0.01)		Pt
Begg[91] (as-treated,	RCT (1)	Aminoglycoside	Kinetic dosing (22 pts)	vs	Guided medical team,with target (23 pts)	*[peak] or [trough] outside target.* *[peak] outside target.*	2 days	0.63 0.50	(0.43, 0.91) (0.28, 0.89)		-0.38 -0.44	(-0.61 -0.14) (-0.73, -0.16)		Pt
Begg [91]	RCT (1)	Aminoglycoside	Kinetic dosing (22 pts)	vs	Guided medical team,with target (23 pts)	*[peak] outside target.* *[trough] outside target.*	5 days	0.67 0.69	(0.3, 1.3) (0.4, 1.2)		-0.25 -0.28	(-0.63, 0.13) (-0.62, 0.07)		Pt

Study Characteristics							Results				
Study	Design (centres)	Comparison (sample size)				**Outcome**		**RR**	**(95% CI)**	**RD**	**(95% CI)**
		Drug Indication				Definition	Time				
Hickling [92]	RCT (1)	Aminoglycoside	Kinetic dosing (15 pts)	vs	Nomogram (17 pts)	*Targeted peak outside 6-10mg/L plasma*	48-72hr:	0.08	(0.006, 0.40) *	-0.77	(-0.93, -0.41) *
Burton [90]	RCT (1)	Aminoglycoside	Kinetic dosing (72 pts)	vs	Status quo (75 pts)	*Nephrotoxicity*	in hospital	0.60	(0.18, 1.95)	-0.04	(-0.12, 0.05)
Destache [94]	Cohort (1)	Aminoglycoside	Kinetic dosing: all recommendations accepted (75 pts)	vs	Aminoglycoside Kinetic dosing: NOT always accepted (35 pts)	Nephrotoxicity	in hospital	0.56	(0.18, 1.71)	-0.063	(-0.19, 0.068)
Destache [94]	Cohort (1)	Aminoglycoside	Kinetic dosing: all recommendations accepted (75 pts)	vs	Aminoglycoside Kinetic dosing: NOT always accepted (35 pts)	Low 2nd peak	in hospital	0.17	(0.06, 0.50)	-0.26/pt	(-0.42, -0.10)
Destache [94]	Cohort (1)	Aminoglycoside	Kinetic dosing: all recommendations accepted (75 pts)	vs	Aminoglycoside Kinetic dosing: NOT always accepted (35 pts)	High 1st trough	in hospital	1.21	(0.34, 4.3)	0.018	(-0.10, 0.14)
Destache [94]	Cohort (1)	Aminoglycoside	Kinetic dosing: all recommendations accepted (75 pts)	vs	Aminoglycoside Kinetic dosing: NOT always accepted (35 pts)	High 2nd trough	in hospital	0.27	(0.07, 1.07)	-0.11	(-0.23, 0.02)

Study Characteristics							Results				
Study	Design (centres)	Comparison (sample size)			**Outcome**		**RR**	**(95% CI)**	**RD**	**(95% CI)**	
		Drug Indication			Definition	Time					
Mungall [95]	RCT (2)	Heparin	Kinetic dosing (66 pts)	vs Nomogram (83 pts)	APTTRs <1.5, 1.5-2.5, >2.5	24hrs	1.09	(0.77, 1.54)	0.04	(-0.12, 0.20)	LT
Mungall [95]	RCT (2)	Heparin	Kinetic dosing (66 pts)	vs Nomogram (83 pts)	*APTTRs <1.5, 1.5-2.5, >2.5*	Hosp stay	0.81	(0.58, 1.1)	-0.05	(-0.13, 0.03)	LT
Mungall [95]	RCT (2)	Heparin	Kinetic dosing (66 pts)	vs Nomogram (83 pts)	adverse clinical event		0	(0, 0.63) *	-0.23	(-0.43, -0.07) *	Pt
Mungall [95]	RCT (2)	Heparin	Kinetic dosing (66 pts)	vs Nomogram (83 pts)	Bleed		1.04	(0.16, 6.8)	0.00	(-0.14, 0.16)	Pt
Casner [96]	RCT (1)	Theophylline	Kinetic dosing (17 pts)	vs Guided medical team (with target) (18 pts)	*theophylline level <10mg/L or >20mg/L*	Just before D/c of infusion (mean: 3 or 4 days)	0.76	(0.24, 2.4)	-0.07	(-0.36, 0.22)	Pt
Casner [96]	RCT (1)	Theophylline	Kinetic dosing (17 pts)	vs Guided medical team (with target) (18 pts)	*Theophyllin e toxicity*	IH	0	(0, 6.8)*	-0.06	(-0.29, 0.13) *	Pt
Verner [97]	CCT (1)	Theophylline	Kinetic dosing (10 pts)	vs Status quo (15 pts)	*theophylline not 10-20ug/mL*	ED	<0.20	(na)	<-0.40	(na)	Time
Dager [98]	Pre/Post (1)	Theophylline	Kinetic dosing (14 pts)	vs Status quo (11 pts)	*Cardiac arrhythmias (no other AE noted)*	in hospital	0.39	(0.09, 1.8)	-0.22	(-0.56, 0.12)	Pt

Study Characteristics								Results				
Study	Design (centres)	Comparison (sample size)				**Outcome**		**RR**	**(95% CI)**	**RD**	**(95% CI)**	
		Drug Indication				Definition	Time					
Dager [98]	Pre/Post (1)	Theophylline	Kinetic dosing (147 lab tests)	vs	Status quo (151 lab tests)	*inappropriate serum theophyllines*	in hospital	0.21	(0.11, 0.38)	-0.28	(-0.37, -0.20)	LT
Hurley[99]	RCT (1)	Theophylline	Kinetic dosing (47 pts)	vs	Status quo (41 pts)	*Serum theophylline >20mg/L or <10mg/L*	Day 1, end Day 2, end	0.63	(0.28, 1.4)	-0.10	(-0.27, 0.07)	Pt
Hurley[99]	RCT (1)	Theophylline	Kinetic dosing (37 pts)	vs	Status quo (37 pts)	*severe breathlessness,* *severe palpitations,* *severe toxicity,* *other 6 side effects*	Day 2 Day 3 *day 2* *day 3*	0.52 0.34 0.46 0.30 no significant differences	na	-0.27 -0.33 -0.36 -0.39	na	Pt
Gonzalez [100]	RCT (1)	Theophylline	Kinetic dosing (37 pts)	vs	Nomogram (30 pts)	Nausea or vomiting		1.62	(0.32, 8.3)	0.04	(-0.09, 0.18)	Pt
Welty[101]	Cohort (1)	Vancomycin	Kinetic dosing (61 pts)	vs	Status quo (55 pts)	*vancomycin-related renal insufficiency*	in hospital	0.28	(0.10, 0.80)	-0.17	(-0.30, -0.04)	Pt
White[102]	RCT (2)	Warfarin	Kinetic dosing (39 pts)	vs	Guided medical team,with target (36 pts)	*Bleeding* *[major (GI)]* *[-minor]*	in hospital, 10-14 days after maintenance dose	0	(0, 1.3)*	-0.08 [-0.03] [-0.06]	(-0.20, 0.02)*	Pt

Study Characteristics							Results				
Study	Design (centres)	Comparison (sample size)			**Outcome**		**RR**	**(95% CI)**	**RD**	**(95% CI)**	
		Drug Indication			Definition	Time					
White [102]	RCT (2)	Warfarin	Kinetic dosing (39 pts)	vs Status quo (36 pts)	*>6 days to target PR*	in hospital	0.15	(0.02, 1.2)	-0.14	(-0.27, -0.01)	Pt
White [102]	RCT (2)	Warfarin	Kinetic dosing (39 pts)	vs Status quo (36 pts)	*any supratherapeutic PR*	in hospital	0.31	(0.07, 1.43)	-0.12	(-0.26, 0.02)	Pt
White [102]	RCT (2)	Warfarin	Kinetic dosing (39 pts)	vs Status quo (36 pts)	*non-therapeutic PR* *sub-therapeutic* *supra-therapeutic*	in hospital	Relative Mean= 0.72 0.76 0.51		Mean Difference =-0.16 -0.12 -0.029	(-0.28, -0.038)	Tim
White [102]	RCT (2)	Warfarin	Kinetic dosing (39 pts)	vs Status quo (36 pts)	*non-therapeutic PR*	10-14 days after maintenance dose	0.31	(0.07, 1.4)	-0.12	(-0.26, 0.02)	Pt
White [102]	RCT (2)	Warfarin	Kinetic dosing (39 pts)	vs Status quo (36 pts)	*bleeding complication* *(or thrombus: no patient in either group had thrombo)*	10-14 days after maintenance dose	0.26	(0.11, 0.63)	-0.43	(-0.65, -20)	Pt

Study Characteristics							Results				
Study	Design (centres)	Comparison (sample size)			Outcome		RR	(95% CI)	RD	(95% CI)	
		Drug Indication			Definition	Time					
Carter[103]	RCT (1)	Warfarin	Kinetic:linear model (22 pts)	vs Status quo (34 pts)	*prothrombin ratio <=1.3 or >=2.5*	in hospital	0.78	(0.39, 1.5)	-0.03	(-0.12, 0.06)	LT
					>=2.5		0.64		-0.43		
					<=1.3		1/0		0.02		
Carter [103]	RCT (1)	Warfarin	Kinetic: analogue (31 pts)	vs Status quo (34 pts)	*prothrombin ratio <=1.3 or >=2.5*		0.33	(0.14, 0.80)	-0.10	(-0.17, -0.03)	LT
					>=2.5		0.22		-0.12		
					<=1.3		1/0		0.01		
Carter [103]	RCT (1)	Warfarin	Kinetic:linear model (22 pts)	vs Status quo (34 pts)	PTR not Stabilized pre-discharge	in hospital	0.72	(0.35, 1.5)	-0.12	(-0.38, 0.13)	Pt
Carter [103]	RCT (1)	Warfarin	Kinetic: analogue (31 pts)	vs Status quo (34 pts)	PTR not Stabilized pre-discharge	in hospital	0.80	(0.44, 1.5)	-0.09	(-0.32, 0.15)	Pt
Carter [103]	RCT (1)	Warfarin	Kinetic:linear model (22 pts)	vs Status quo (34 pts)	*time to stabilization*	in hospital	0.87		-1.1		Day
Carter [103]	RCT (1)	Warfarin	Kinetic: analogue (31 pts)	vs Status quo (34 pts)	*time to stabilization*	in hospital	0.81		-1.6		Day
Vadher[104]	RCT (1)	Warfarin	Kinetic dosing (72 pts)	vs Guided medical team,with target (76 pts)	*Days to INR >=2*	in hospital	1		0	(p= 0.24)	-

Study Characteristics							Results				
Study	Design (centres)	Comparison (sample size)				**Outcome**		**RR**	**(95% CI)**	**RD**	**(95% CI)**
		Drug Indication				Definition	Time				
Vadher [104]	RCT (1)	Warfarin	Kinetic dosing (72 pts)	vs	Guided medical team,with target (76 pts)	Days to stable warfarin dose	in hospital	0.78		-2	(p= 0.01)
Vadher [104]	RCT (1)	Warfarin	Kinetic dosing (72 pts)	vs	Guided medical team,with target (76 pts)	INR <2 on hospital D/C	in hospital	0.53	(0.17, 1.7)	-0.05	(-0.14, 0.04)
Vadher [104] ITT	RCT (1)	Warfarin	Kinetic dosing (72 pts)	vs	Guided medical team,with target (76 pts)	pts didn't get dose stability pre endpoint	in hospital	0.83	(0.40, 1.7)	-0.03	(-0.15, 0.09)
Vadher [104] ITT	RCT (1)	Warfarin	Kinetic dosing (72 pts)	vs	Guided medical team,with target (76 pts)	pseudoevents (INR<=2.5 or >=5) INR>=5	in hospital	0.61	(na)	-16	(na)
Vadher [104] ITT	RCT (1)	Warfarin	Kinetic dosing (72 pts)	vs	Guided medical team,with target (76 pts)	*% time in therapeutic range-inpatient*	in hospital	0.85	(na)	-0.07	(na)

*exact, CI on proportions	Hrs Hours	RCT Randomized Controlled Trial.
APTTR: activated partial thromboplastin time ratio (vs. baseline)	IH in-hospital	RD Risk Difference.
CI Confidence Interval	INR International Normalized Ratio	RR Relative Risk.
D/c Discharge	LT Lab Test	Vs Versus.
ED Emergency Department	[Peak], [Trough] concentrations: peak, trough.	
GI Gastrointestinal	PR, PTR Prothrombin Ratio	

Table 8b: Meta-analyses of Warfarin Studies' Adverse Drug Events

Outcome	Studies	RD (95% CI);	Chi² (P=)	I²	RR (95% CI);	Chi² = (P =)	I²
Dose not stabilized/ patient	White, Carter, Vadher [102], [103] [104]	-0.06 (-0.13, 0.02);	0.62 (p=0.89)	0%	0.74 (0.48, 1.14);	0.77 (p=0.86)	0%
Bleed	White, Vadher [104], [102]	-0.04 (-0.09, 0.01);	0.95 (p=0.33)	0%	0.44 (0.15, 1.28)	0.77, (p=0.38)	0%
Thrombus	White, Vadher [104], [102]*	+0.02 (-0.03, 0.06);	1.41 (p=0.24)	29%	4.2 (0.48, 37) *	Not estimable*	na*
Bleed or Thrombus	White, Vadher [104], [102]	-0.03 (-0.13, 0.07)	2.32 (p=0.13)	57%	0.61 (0.07, 5.1);	2.10 (p= 0.15)	52%

*10372 unweighted in RR since no events observed

Table 8c: Meta-analyses of Adverse Event Data in Pharmacokinetic Dosing Studies

Study description (n)	Study	RD (95% CI)	Chi² (p=)	I² (%)	RR (95% CI)	Chi² = (P =)	I² (%)
Excluding excluders of protocol violations (4)	Casner[96] Mungall[95] White[102] Vadher[104]	-0.05 [-0.14, 0.04],	6.0 (p=0.11)	50	0.56 [0.20, 1.60]	4.1 (p=0.25)	27
RCT all-inclusive (6)	Burton[90] Casner[96] Gonzalez [100] Mungall[95] White[102] Vadher[104]	-0.03 [-0.09, 0.02]	7.1 (p=0.21)	30	0.70 [0.37, 1.34]	5.3 (p=0.38)	5

Table 8d: Pharmacokinetic Dosing, data summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% CI) or (Range)	8. 100 x RD	Unit of RD
Kinetic dosing	15:0:0		C (2b)	11 (1)	Median mean=0.63 (Range: 0.1, 0.81)	Median mean: -9 (Range:-77,-4)	Potential ADE /pt
			A (1a)^	4 (?)	0.56 (0.2, 1.6)	-5 (-14, 4)	ADE /pt

^almost given a "minus" which would lead to a grade of D.

ADE Adverse Drug Event. CI Confidence Interval. Pt Patient. RD Risk Difference. 1^0,2^0 primary, secondary

Table 9a: Pharmacist with a broad clinical role (clinical pharmacy or pharmaceutical care): Risk of Drug Errors

Study Characteristics					Results		
Study	Des7ign (# centres)	Comparison (sample size)	Outcome	error type, then fuller definition	RR (95% CI)	RD (95% CI)	
Scarsi[108]	Cohort, matched (1)	Admission (35 pts) vs Daily rounds (35 pts)	All	Proportion of patients with error Errors/patients #Rx errors/patient	0.78 (0.56, 1.08) 0.5 (na) 0.62 (na)	-0.17/pt (-0.38, 0.04) -1.3/pt (na) -0.51/pt (na)	
na[109]	Pre/post (1)	ED pharmacist (n: na) vs Pre (n: na)	All	All	0.50 (na)	na	
Grain[84]	Pre/post (1)	FTE (n: na) vs Part-time (1 day/ wk) clinical pharmacist (n: na)	Rx	Rx errors /Rx	0.89 (na)	-0.018/Rx (na)	
Falconnier[107]	Pre/post (1)	FTE pharmacist (renal adjustment) (70 doses in 481 pts) vs Pre (192 doses in 806 pts)	Xs dose	excess doses/ renally eliminated doses	0.29 (0.21, 0.40)	-0.48/dose (-0.60, -0.35)	
Pickrell[110]	Cohort (1)	GP's drug history record compared vs admission drug history. Patient education (15 pts) vs Not compared (17 pts)	Dis-crepancy not intended on D/C	/drug	0.20 (0.12, 0.33)	-0.48/drug (-0.60, -0.37)	

D/C Discharge ED Emergency Department FTE Full Time Equivalent GP General Practitioner Pt Patient RD Risk Difference. RR Relative Risk. Rx Prescription Vs Versus Xs Excess

Table 9b: Specific Pharmacist Interventions, Risk of Drug Error

Study Characteristics				Results					
Study	Design	Comparison (intervention vs. none)	Outcome	RR (95% Confidence Interval)			RD*100	(95% Confidence Interval)	
Dranitsaris[117]	RCT (2)	Pharmacist recommends changes to cefotaxime Rx (162 Rx vs None (147 Rx)	Wrong prescription/ prescription	0.81	(0.56,	1.16)	-6	(-16,	4)
			-indication	0.91	(0.6,	1.4)	-2	(-11,	7)
			-dose	0.43	(0.2,	0.89)	-8	(-15,	-1.3)
Meisel[118]	Pre/post (1)	Pharmacist review of hypnotic order (n: na) vs None (n: na)	Excess dose/ prescription	0	(na)		-75	(na)	

RD Risk Difference. RR Relative Risk

Table 9c: Risk of Adverse Drug Events with a Broad Application of Clinical Pharmacists

Study Characteristics					Results			
Study	Design (# centres)	Comparison (sample size)		Outcome: i.e., ADE type	RR	(95% CI)	RD	(95% CI)
Smythe [111]	Pre/post (1)	Pharmaceutical Care (131 pts)	vs None (135 pts)	All-cause ADE	0.13	(0.016, 1.016)	-0.052/ pt	(-0.094, -0.0091)
Leape[105]	Cohort (1)	Clinical pharmacy rounds (as pre/post for consistency) (861 pt-days, 75 pts)	vs None (787 pt-days, 75 pts)	All-cause ADE: Any ADE in a pt Total # ADEs	0.35 0.26	(p<.001) (0.12, 0.54)*	-2.1/100pt-day -3.2/100pt-day	
		control arm, time 2 vs. time 1 (461 pt-days, 50pts)	*ctrl (644 pt-days,75 pts)*		*1.3*	*(0.71, 2.6)**	*.2/100pt-day*	
Leape[105]	Cohort (1)	Clinical pharmacy (ICU rounds) (as pre/post gives consistency) (861 pt-days, 75 pts)	vs None (787 pt-days, 75 pts)	Preventable ADE: Any prev.ADE in pt Total # pADEs	0.34 0.25	(p<.001) (0.04, 0.94)	-0.67/100pt-day -1.0/100pt-day	
		control arm, time 2 vs. (461 pt-days, 50pts)	*time 1 ctrl (644 pt-days, 75 pts)*		1.1	(0.33, 4.4)*	0.1/100 pt-day	
Bates[69]	Cluster RCT (1)	Clinical pharmacy (rounds) + multi-faceted QI (13304 pt-days)	vs None (11235 pt-days)	Preventable ADE	1.26	(0.83, 1.9)*	0.9/100 pt-day	
Kucukarslan[106]	Cohort (1)	Clinical pharmacy (ward rounds) (86 pts, 350 pt-days)	vs None (79pts, 339 pt-days)	Preventable ADE	0.22	(0.02, 1.04) *	-2.1/100pt-day	
Bates[69]	Cluster RCT (1)	Clinical pharmacy (rounds) + multi-faceted (13304 pt-days)	vs None (11235 pt-days)	Potential ADE	1.23	(0.61, 2.5)*	0.27/100 pt-day	

*exact, Poisson rates

CI Confidence Interval. ICU Intensive Care Unit. Pt Patient QI quality improvement. RD Risk Difference. RR Relative Risk. Rx Prescription Vs Versus

Table 9d: Pharmacist-managed Warfarin Programs and the Risk of Adverse Drug Events: a) in hospital. b) post-discharge

i) In Hospital

Study Characteristics				Results				
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)		RD	(95% CI)
Dager[114]	historical cohort vs. matched prospective cohort (1)	Pharmacist-managed warfarin (60 pts) vs non-pharmacist-managed warfarin (60 pts)	Bleed	0.17	(0.01,	1.04)*	-0.08/pt	(-0.18, 0.0025)*
Ellis [115]	Pre/post (1)	Pharmacist-managed warfarin (52 pts) vs non-pharmacist-managed warfarin (97 pts)	Bleed	0.37	(0.03,	2.4)*	-0.032/pt	(-0.10, 0.054)*
To [116]	Pre/post (1)	Pharmacist-managed warfarin (34 pts) vs non-pharmacist-managed warfarin (24 pts)	Bleed	1.36	(0.2,	10)*	0.02 /pt	(-0.14, 0.20)*
To [116]	Pre/post (1)	Pharmacist-managed warfarin (34 pts) vs non-pharmacist-managed warfarin (24 pts)	Thrombus	0	(0,	7.3)*	-0.03 /pt	(-0.16, 0.08)*
Ellis [115]	Pre/post (1)	Pharmacist-managed warfarin (52 pts) vs non-pharmacist-managed warfarin (97 pts)	Thrombus	1.24	(0.2,	7.2)	0.0075/pt	(-0.055, 0.07)

*exact, binomial proportions

CI Confidence Interval. Pt Patient RD Risk Difference. RR Relative Risk. Vs Versus

ii) Post-discharge [leads to readmission 1, 3 months post-discharge (cumulative)]

Study Characteristics				Results				
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)		RD	(95% CI)
Dager[114]	Pre/post* (1)	Pharmacist-managed warfarin (60 pts) vs non-pharmacist-managed warfarin (60 pts)	Bleed, 1 month	1	(0.1,	10)*	0 /pt	(-0.07, 0.07)*
			Bleed, 3 months	0.39	(0.09,	1.7)	-0.05/pt	(-0.13, 0.033)
			Thrombus, 1 month	0.25	(0.03,	2.2)	-0.05/pt	(-0.12, 0.02)
			Thrombus, 3 months	0.6	(0.15,	2.4)	-0.03/pt	(-0.12, 0.06)

*historical cohort matched to prospective cohort

RD Risk Difference. RR Relative Risk. Vs Versus

Table 9e: Anticoagulation programs and the Risk of Adverse Drug Events

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	Odds Ratio	RR (95% CI)	RD (95% CI)	
Phillips[119]	Pre/post (1)	Anticoagulation program (55 pts) vs None (52 pts)	Bleed	1.4 (0.2, 12)		0.01/pt	
Mamdani[113]	Cohort (1)	Anticoagulation program (50 pts) vs None (50 pts)	Bleed		0 (0, 1.9)*	-0.04/pt (-0.14,	0.034)*
Mamdani [113]	Cohort (1)	Anticoagulation program (50 pts) vs None (50 pts)	Thrombus		1/0 (0.14, 1/0)	0.02/pt (-0.06,	0.11)*
Mamdani [113]	Cohort (1)	Anticoagulation program (50 pts) vs None (50 pts)	Non-therapeutic INR at discharge		0.69 (0.38, 1.2)	-0.13/pt (-0.34,	0.07)

INR international normalized ratio. Pt patient. RD Risk Difference. RR Relative Risk. Vs Versus

Table 10a: Nomograms (all Heparin-related). Risk of Adverse Drug Events and Potential Adverse Drug Events

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)	Outcome			RR (95% CI)	RD (95% CI)
			Test	Outcome Group Time point	"Therapeutic" Range		
Hollingsworth [121]	Pre/post (2)	Nomogram (1278 tests) vs Status quo (1037 tests)	APTT	% in range	(50-85sec)	0.84 (0.77, 0.92)	-0.09 /LT (-0.13, -0.04)
Phillips[119]	Pre/Post (1)	Nomogram (83 pts) vs Status quo (88 pts)	APTTR	% time in range	(<1.5, >4) *[[<2.6,>4: sensitivity analysis]]*	0.63 *[0.95]*	-0.139 / hour *[[-0.030)]]*
Mungall[95]	RCT (2)	Kinetic dosing (66 tests in 25 pts) vs Nomogram (83 tests in 26 pts)	INR	% in range	(1.5-2.5)	1.09 (0.77, 1.54)	0.04 /LT) (-0.12, 0.20
Mamdani[113]	Cohort (1)	Nomogram: weight-based (50 pts) vs Status quo (50 pts)	APTT	% in range	(48-71sec)	0.89	-0.62 /LT (na)
Mamdani [113]	Cohort (1)	Nomogram: weight (50 pts) vs Status quo (50 pts)	APTT	therapeutic at time 12 hr	(48-71sec)	0.67 (0.26, 1.7)	-0.06 /Pt (-0.20, 0.08)
Mamdani [113]	Cohort (1)	Nomogram: weight (50 pts) vs Status quo (50 pts)	APTT	therapeutic at time 24 hr	(48-71sec)	0.67 (0.2, 2.2)	-0.04 /Pt (-0.09, 0.01)
Nemeth [123]	Pre/post (1)	Nomogram: weight (71 pts) vs Status quo (25 pts)	APTT	therapeutic at time 24 hr	(46-70 sec) ((1.5-2.3))	0.16 (0.07, 0.38)	-0.44 /Pt (-0.64, -0.23)
Cruickshank[122]	Pre/post (1)	Nomogram (50 pts) vs Status quo (53 pts)	APTT	therapeutic at time 24 hr	(60-85sec)	0.55 (0.35, 0.85)	-0.28 /Pt (-0.47, -0.10)
Raschke [125]	RCT (2)	Nomogram: weight-based (62 pts) vs Nomogram (53 pts)	APTT (INR)	therapeutic at time 24 hr	(46-70) ((1.5-2.3))	0.67 (0.47, 0.97)	-0.20 /Pt (-0.38, -0.02)
Mamdani [113]	Cohort (1)	Nomogram: weight-based (50 pts) vs Status quo (50 pts)	APTT	therapeutic at time 48 hr	(48-71sec)	0.25 (0.03, 2.2)	-0.06 /Pt (-0.14, 0.02)

Study Characteristics						Results	
Study	Design (# centres)	Comparison (sample size)	Outcome			RR (95% CI)	RD (95% CI)
			Test	Outcome Group Time point	"Therapeutic" Range		
Cruickshank [122]	Pre/Post (1)	Nomogram (50 pts) vs Status quo (53 pts)	APTT	therapeutic at time 48 hr	(60-85sec)	0.48 (0.25, 0.91)	-0.22 /Pt (-0.39, -0.04)
Raschke [125]	RCT (2)	Nomogram: weight-based (62 pts) vs Nomogram (53 pts)	APTT (INR)	therapeutic at time 48 hr	(46-70) ((1.5-2.3))	0.63 (0.42, 0.94)	-0.21 /Pt (-0.39, -0.03)
Mamdani [113]	Cohort (1)	Nomogram: weight-based (50 pts) vs Status quo (50 pts)	APTT	Never therapeutic in	(48-71sec)	0 (0, 1.9)*	-0.04 /Pt (-0.14, 0.034)*
							Mean Difference
Hollingsworth [121]	Pre/Post (2)	Nomogram (82 pts) vs Status quo (81 pts)	APTT	Time-to-therapeutic -	(60-85)		-32.6hrs /Pt (p< 0.0001) [b]
Cruickshank [122]	Pre/Post (1)	Nomogram (50 pts) vs Status quo (53 pts)	APTT	Time-to-therapeutic -	(60-85)		-30.90 hrs /Pt (p<.001) [b]
Raschke [125]	RCT (2)	Nomogram: weight-based (62 pts) vs Nomogram (53 pts)	APTT (INR)	Time-to-therapeutic -	(46-70) ((1.5-2.3))		-12.0 hrs /Pt (P<0.001) [b]
Brown [120]	Pre/Post (1)	Nomogram: weight-based (30 pts) vs Status quo (30 pts)	APTT (INR)	Time-to-therapeutic -	(1.5-2.5)		-23 hrs /Pt (-42, -19)
Mamdani [113]	Cohort (1)	Nomogram: weight-based (50 pts) vs Status quo (50 pts)	APTT	Time-to-therapeutic	(48-71 sec)		-1.7hrs /Pt (P=0.14) [b]

Study Characteristics							Results	
Study	Design (# centres)	Comparison (sample size)	Outcome				RR (95% CI)	RD (95% CI)
			Test	Outcome Group	Time point	"Therapeutic" Range		
Nemeth [123]	Pre/Post (1)	Nomogram: weight-based (71 pts) vs Status quo (25 pts)	ADE	Bleed	-		na (no events)	na /pt (-0.14, 0.05)*
Raschke [125]	RCT (2)	Nomogram: weight-based (62 pts) vs Nomogram (53 pts)	ADE	Bleed	-		0.55 (0.10, 3.2)	-0.03 /pt (-0.10, 0.05)
Brown [120]	Pre/Post (1)	Nomogram: weight-based (30 pts) vs Status quo (30 pts)	ADE	Bleed	-		0.80 (na)	-0.03 /pt (na)
Mamdani [113]	Cohort (1)	Nomogram: weight-based (50 pts) vs Status quo (50 pts)	ADE	Bleed			0 (0, 1.9)*	-0.04 /pt (-0.14, 0.034)*
Raschke [125]	RCT (2)	Nomogram: weight-based (62 pts) vs Nomogram (53 pts)	ADE	Thromb	-		0.20 (0.04, 0.86)	-0.20 /pt (-0.37, -0.04)
Brown [120]	Pre/Post (1)	Nomogram: weight-based (30 pts) vs Status quo (30 pts)	ADE	Thromb	-		0 (0, 2.0)*	-0.07 /pt (-0.22, 0.06)*
Mamdani [113]	Cohort (1)	Nomogram: weight-based (50 pts) vs Status quo (50 pts)	ADE	Thromb			1/0 (0.14, 1/0)	0.02 /pt (-0.06, 0.11)*

*exact, CI on binomial proportion
[B]subgroup with Venous Thrombus
[b] Kaplan Meier

ADE Adverse Drug Event. APTT(R) Activated Partial Thromboplastin Time (Ratio). INR international normalized ratio. KM Kaplan Meier. LT Lab test. Pt patient. RD Risk Difference. RR Relative Risk. SD Standard Deviation. Thromb Thrombus or Embolism. Sec Second. Vs Versus

Table 10b: Nomograms, Data Summary

1. Technology or system (comparison vs. none)	2. Study direction	3 Technology or System Class	4. Quality (design)	5. Result-specific study #	7. RR	8. RD x 100	
	Pro: con: neutral		Grade (Level)	# 1^0 study (# 2^0 study supporting)	(95% CI) R(ange) (Sg=# Stat sig)		Unit
Nomogram	8:0:0	Heparin	B (2b)	5		Median Mean Difference: -23 (Range: -1.7, -33)	Potential ADE
			B (2b)	3	0.5 (0.1, 3) 0.8 (na) 0 (0, 1.9)	-3 -3 -4	ADE: Bleed / pt / pt / pt
				2	0 (0, 2), 1/0 (0.14, 1/0)	-7 +2	ADE: Thrombus /pt /pt

ADE Adverse Drug Event. CI Confidence Interval. Pt Patient. R Range. 1^0,2^0 primary, secondary

Table 11a: Computerized Pumps. Risk of Potential Adverse Drug Events and Adverse Drug Events

Study Characteristics					Results					
Study	Design (# centres)	Comparison (sample size)			Outcome	Mean difference	(95% CI)	RR	(95% CI)	RD / pt (95% CI)
Alvis [126]	Cohort (1)	Computer-assisted 1. stable fentanyl doses (10 pts)	vs	No computer assist (10 pts)	Episodes of: Hypotension: #pt/pt			0.8	(0.3, 2.1)	-0.10 (-0.5, 0.3)
					tot # /pt [D]			0.5		-0.50
					Hypertension #pt/pt			0.8	(0.4, 1.9)	-0.10 (-0.5, 0.3)
					tot # /pt [D]			0.7		-0.30
		2. variable (doctor-targeted) doses (10 pts)	vs	No assist (10 pts)	Hypotension: #pt/pt			0.4	(0.1, 1.6)	-0.30 (-0.7, 0.10)
					tot # /pt [D]			0.3		-0.70
					Hypertension #pt/pt			0.5	(0.2, 1.5)	-0.30 (-0.7, 0.12)
					tot # /pt [D]			0.3		-0.70
van den Nieuwenhuyzen [129]	RCT (1)	Computer-controlled alfentanil (9 pts)	vs	pt-controlled morphine admin (10 pts)	Minutes with Visual Analogue Scale (/10, higher with more pain) > 3.0	-175	(-310, -39) [B]	1.0	(0.72 1.3)	-0.011 (-0.28 0.26)
					Nausea/ Vomiting			1.0	(0.61 , 1.6)	-0.022 (-0.39 0.35)
					Urinary retention			0.51	(0.14 , 1.9)	-0.27 (-0.74, 0.20)
Ruiz [128]	RCT (1)	Computer-assisted continuous infusion of midazolam & fentanyl (40 pts)	vs	Manual control of fentanyl , post-op (20 pts)	Mean distance [C] from target blood-pressure gap (70-80mg Hg), in					
					Hour 1	-9.5	(-11.3, -7.8)			
					Hour 2	-8.4-	(-10.6, -6.2)			
					Hour 3	8.1	(-9.7, -6.5)			
					Hour 4	-2.8	(-4.8, -0.8)			

Study Characteristics				Results		
Study	Design (# centres)	Comparison (sample size)	Outcome	Mean difference (95% CI)	RR (95% CI)	RD / pt (95% CI)
Theil [127]	RCT (1)	Compare vs computer-assisted (12 pts) Manual midazolam & fentanyl continuous-infusion anesthesia (for cardiac surgery) (12 pts)	*Mean Arterial Pressure*			
			Baseline	-11 (-19.2 2)		
			Induction	-3.6 (-14, 7)		
			Intubation	1.0 (-4.3, 6.3)		
			Skin incision	-5.6 (-12, 1.0)		
			Sternotomy	-7.2 (-12, -2.8)		
			Upon cardiopulmonary bypass	-0.2 (-5.3, 4.9)		
			End cardiopulmonary bypass	0.1 (-3.6, 3.8)		
			Chest closure	-0.2 (-4.5, 4.1)		
			Heart Rate			
			Baseline	-3.6 (-13, 6)		
			Induction	-4.1 (-14, 5.9)		
			Intubation	-2.3 (-11, 6.0)		
			Skin incision	-3.0 (-16, 10)		
			Sternotomy	-2.6 (-11, 6.0)		
			Upon cardiopulmonary bypass	na		
			End cardiopulmonary bypass	-8.4 (-17, 0.7)		
			Chest closure	2.8 (-4.8, 10)		
			Std. Dev. (MAP)	0.65 (p=0.22[A])		
			Std. Dev. (HR)	-3.2 (p=0.0055[A])		

[A]Wilcoxon Rank Sum Test

[B] t-test

[C]authors defined distance as the difference between actual blood pressure and the nearest end of the target blood pressure interval

[D]#pt/pt: i.e., proportion of patients with an episode of hypertension or hypotension.

tot #/pt: i.e., total number of episodes of hypertension or hypotension divided by the number of patients

HR Heart Rate. MAP Mean Arterial Pressure. RD Risk Difference RR Relative Risk

Table 11b: Computerized Pumps, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI)	8. 100 x Risk Difference	Unit of Risk Difference
Computer pumps	4:0:0	Peri-operative use	D (1b-)	3	0.8, (0.3, 2), 0.4 (0.1, 1.6)	 -9.5	hypertensive episode /pt hypotensive episode /pt torr from target@1hr /pt

CI Confidence Interval. Pt Patient. RR Relative Risk. 1^0,2^0 primary, secondary

Table 12a: Drug-specific Protocols, Risk of Medication Error and Adverse Drug Events

Study Characteristics					Results	
Study	Design (# centres)	Comparison (sample size)		Outcome	RR – or Relative Mean* (95% Confidence Interval)	RD – or mean difference*. (95% Confidence Interval)
Leape [130]	Pre/post (1/13 who implemented)	Heparin protocols (n: na)	vs Pre (n: na)	mean hrs to therapeutic PTT pharmacist interventions (% of orders)	0.30* (na) 0.48	-16 hrs* (na) -32% (na)
Leape [130]	Pre/post (1/3 successes /21 system changes)	narcotics dosing protocol (n: na)	vs Pre (n: na)	ADEs/month	0.125 (na)	-10.5/month (na)
Hume [131]	Pre/post (1)	Std. protocol for chemo which begins while physician & pharmacist on-site (n: na)	vs Pre (n: na)	Actual & potential errors	0.15 (na)	--- ---

Study Characteristics				Results	
Study	Design (# centres)	Comparison (sample size)	Outcome	RR – or Relative Mean* (95% Confidence Interval)	RD – or mean difference*. (95% Confidence Interval)
Leape [130]	Pre/post (1 success story of 9 hospitals)	Chemo protocols (n: na) vs Pre (n: na)	Chemo ADE / month	0.50 (na)	--- ---
Leape [130]	Pre/post (3/7 who implemented it)	Insulin protocol (n: na) vs Pre (n: na)	Hypoglycemic episodes per month	0.38 (na)	-10/month (na)
Hume [131]	Pre/post (1)	diabetic flow chart for diabetic care. standard glucose-monitoring times; educated nurses; priorized food delivery for diabetics (n: na) vs Pre (n: na)	insulin errors	---- ---	Probably about -1 / pt-day (na)
Meisel [118]	Pre/post (1)	pre-printed sliding scale insulin protocol (n: na) vs Pre (n: na)	potential errors per patient	0 (na)	-4.4/pt (na)
Resar [132;133]	Pre/post (1)	Hospital-standardized insulin protocol (n: na) vs Pre (n: na)	insulin errors & hypoglycemic events	0.59 (na)	-0.027 units (na)
Farbstein [134]	Pre/post (1)	Standardization and info more available re: patient-controlled analgesia (612 days) vs Pre (646 days)	patient-controlled analgesia incidents/ day	0.56 (na)	-0.032 /day (na)
Mitchell [135]	Pre/post (1)	New TPN form: std (alterable) [CHO] [glucose] [lipid] & recommended dose of electrolytes, trace elements & vitamins, added heparin (1017 pts) vs Pre (682 pts)	total errors/ total patients	0.12 (na)	-0.82/pt (na)

ADE Adverse Drug Event. CI Confidence Interval. Hrs Hours. IHI Institute for Healthcare Improvement. PTT Partial Prothrombin Time. RD Risk Difference. RR Relative Risk. Vs. Versus

Table 12b: Drug-specific Protocols, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR	(95% CI) or (Range)	8. 100 x Risk Difference	Unit of RD	
Drug protocols	10:0:0	varied	D (4)	6	Median: 0.26	(0,0.59)=range: CI na	Median -82	Error	/pt
		varied	D (4)	3	0.12	(na)	-10	ADE	/month
					0.38	(na)	-10		/month
					0.50	(na)			-

ADE Adverse drug event CI Confidence Interval. Pt Patient. RR Relative Risk. RD Risk Difference. 1^0,2^0 primary, secondary

Table 13a: Physician education, Risk of Drug Error

Study Characteristics					Results					
Study	Design (# centres)	Comparison (sample size)		Outcome	RR	(95% CI)		RD/ Rx	(95% CI)	
na [138]	Pre/post (1)	Rx-writing Education & Feedback (n: unclear)	Vs Pre (orders from 24-hr periodsX7)	Error elements -improved -same -worse	 8 2 2	 (na) (na) (na)				
Meyer [136]	Pre/post (1)	Physician & resident education about prescription orders (654 orders)	Vs Pre (3740 orders)	Order (yr:1997) -illegible -ambiguous -incomplete -no signature: Order (yr:2000) -illegible -ambiguous -incomplete -no signature: wrong patient	 0 0 1.4 0.77 0 0 00 no events	 (0, (0, (0.4, (0.30, (0, (0, (0, (0, (0,	 0.04) [A] 1.5) [A] 5.7) 2.0) 0.06) [A] 2.3) [A] 3.1) [A] 0.74) [A] $2.2*10^{4}$) [A]	 -0.11 -0.003 0.0011 -0.002 -0.11 -0.003 -0.003 -0.01 no events	 (na) (na) (-0.004, (-0.010, (na) (na) (na) (na)	 0.006) 0.005)
Muñoz [137]	Pre/post (1)	Presentation to clinicians (100 orders)	Vs Pre (100 orders)	Wrong dose Illegible Unspecified route	1 0.36 0.18	(0.25, (0.17, (0.07,	3.9) 0.78) 0.44)	0 -0.14 -0.23	(-0.05, (-0.24, (-0.33,	0.05) -0.04) -0.13)
Leape [130]	Pre/post (/3 successes from 21 system changes)	Prescription-writing Education & Individual Feedback (n: na)	vs Pre (n: na)	Nonstandard* or illegible orders (*e.g., use of certain abbrev)	0.35	(na)		-0.13 (na)	(na)	
Thorn [139]	Pre/post (1)	Education required more complete & detailed info on Rx sheet (87 orders)	vs Pre (143 orders)	Rx missing: -route -dose -dosage -freq	 3.3 3.8 0.65 0.71	 (0.84, (1.01, (0.46, (0.39,	 13) 14) 0.91) 1.3)	 0.05 0.06 -0.18 -0.008	 (-0.01, (-0.002, (-0.31, (-0.04,	 0.11) 0.12) -0.05) 0.02)

[A]exact, Poisson rates Overall Grade (highest level): C (2c)

IHI Institute for Healthcare Improvement. Rx Prescription. RD Risk Difference. RR Relative Risk. Rx Prewscription.. Vs. Versus Yr. (calendar) year.

Table 13b: Physician education and new order form, Risk of Drug Error

Study Characteristics					Results	
Study	Design (centres)	Comparison (sample size)		Outcome	RR (95% CI)	RD (95% CI)
Gardulf [140]	Pre/post (1)	New vs. old Rx sheet and education about new legislation re: physician Rx-writing (226 orders)	vs pre (315 orders)	Info missing or illegible/ Rx: incorrectly written: 1. Oral & Parenteral 2. Oral Rx Parenteral Rx	 0.37 (0.28, 0.47) 1.08 (1.007, 1.17) 0.80 (0.77, 0.83)	 -0.36 /Rx (-0.43, -0.29) 0.04 /Rx (0.003, 0.008) -0.20 /Rx (-0.22, -0.16)
Thorn [139]	Pre/post (1)	*Education (included as background info)* (87 orders)	*vs pre*	*Missing/Rx* *-route* *-dose* *-dosage* *-freq*	 *3.3 (0.84, 13)* *3.8 (1.01, 14)* *0.65 (0.46, 0.91)* *0.71 (0.39, 1.3)*	 *0.05*/Rx *(-0.01, 0.11)* *0.06* /Rx *(-0.002, 0.12)* *-0.18* /Rx *(-0.31, -0.05)* *-0.008*/Rx *(-0.04, 0.02)*
		Then New Rx Form (pharmacist-verified) (77 orders	vs pre-educated	Missing/Rx -route -dose -dosage -freq	 0.62 (0.07, 5.8) 1.2 (0.2, 7.3) 0.10 (0.04, 0.3) 0.06 (0.01, 0.44)	 -0.008/Rx (-0.04, 0.03) 0.005 /Rx (-0.04, 0.05) -0.45/Rx (-0.55, -0.36) -0.20/Rx (-0.3, -0.13)
Bourke [141]	Pre/post (1)	-Joint chart for Rx & admin. -Newsletter: prescription audit results (n: na)	vs pre (n: na)	Detailed prescription regarding dose, freq, and admin/ Rx	0.58 (na)	-0.16 /Rx (na)

RD Risk Difference. RR Relative Risk. Rx Prescription.

Table 13c: Specialized Physician Education or Forms, Risk of Drug Error

Study Characteristics					Results			
Study	Design (# centres)	Comparison (sample size)		Outcome	RR	(95% CI)	RD	(95% CI)
Meisel [118]	Pre/post (1)	Special chemotherapy order form prompts details & patient & drug info more available (n: na)	vs pre (n: na)	Potential errors per chemo order	0	(na)	-1.7/Rx	(na)
Elkharrat [142]	Pre/post (1)	Education about ministry guidelines, mainly to prevent extra Rx (50 pts)	vs pre (50 pts)	errors/ NSAID-treated pts -violations -inadequacies	0.7 1.0 0.4	(0.3, 1.7) (0.3, 3) (0.1, 2)	-0.06/Rx 0 /Rx -0.06/Rx	(-0.21, 0.09) (-0.1, 0.1) (0.15, 0.04)
Ross [143]	Pre/post (1)	Doctors trained about IV drugs, esp. chemo (order of 10,000 pts)	vs pre (order of 10,000 pts)	Errors / year	0.5	(na)	3/year	(na)

NSAID Non-steroidal anti-inflammtory drug. RD Risk Difference. RR Relative Risk. Rx Prescription.

Table 13d: Physician Training and Order Forms, Data Summary

1. Technology or system (comparison vs. none)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (design) i.e., Grade (Level)	5. Result-specific study # # 10 study (# 20 study supporting)	7. Relative Risk (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
Doctor training or order forms	9:0:1	Training	C (2c)	3 (2)	0 (0, 0.04) 0.36 (0.2, 0.8) 0.35 (na)	-11 -11 -13	Rx error: illegible /order Rx error: illegible Rx error: non-standard
		Training + form	C (2c)	2 (1)	study1: 0.4,1.1,0.8 (0.3,0.5;1,1.2;0.8,0.8) study 2: 0.6, 1.2, (0.1,5,8; 0.2, 7; 0.1, 0.06 0.04,0.3; 0.01, 0.4)	-20 -10	Prescription error: /order missed or illegible elements

1^0,2^0 primary, secondary

Table 14a: Verbal orders, Risk of Medication Error

Study Characteristics				Results	
Study	Design (# centres)	Comparison (sample size)	Outcome	RR (95% CI)	RD*100 (95% CI)
West [63]	Cohort (1)	Verbal order (4221 orders) vs written (7056 orders) vs Computer Physician Order Entry (6985 orders)	Order errors/order	0.31 (0.16, 0.58) 0.41 (0.21, 0.80)	-0.6/order (-0.9, -0.3) -0.3/order (-0.6, -0.13)
Meisel [118]	Pre/post (1)	Prohibited telephone orders to clerical personnel (n: na) vs vs Pre (n: na)	Not declared	"no difference"	

CI: Confidence Interval. RD: Risk Difference. RR: Relative Risk.

Table 14b: Verbal Orders, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% CI) or (Range)	8. 100 x RD	Unit of Risk Difference
Verbal order	1:0:1		D (4)	2	0.3 (0.2,0.6) "no difference" (na)	-6	Order error /order

1^0 ,2^0 primary, secondary

Table 15a: Double-check, Risk of Medication Error

Study Characteristics					Results				
Study	Design (# centres)	Comparison (sample size)		Outcome	RR	(95% CI)	RD	(95% CI)	
Ross [143]	pre/post (1)	Double-check in pharmacy + new "friendly" error-report form vs. pre (22 months* (order of 10,000 admissions))	vs Pre (43 months*)	Drug-dispensing errors	0.60	(na)	-0.33 / month		
Milliken [148]	pre/post (1)	Technician checks. less pharmacist order - entry/day. special delivery bins (12 days)	vs Pre (12 days)	Discrepancies: meds in bin vs nursing profile Missing-dose phone calls	0.59 0.83	(na) (na)	(na) (na)		
Lacasa [149]	pre/post (1)	Computer MAR system & extra check vs. manual system (19297 doses)	vs Pre (18370 doses)	Dose in pt's drawer does not equal Rx	0.33	(0.29 ,0.37)	-4.5/dose	(-4.9,	-4.1)
Ness [147]	pre/post (3)	Special Technicians (experienced, passed training course) → Unique among these (151721 doses)	vs. routine pharmacist check (143952 doses)	Errors Allowed (ID'd by study) Dose-errors allowed Pot. serious errors in verification (background: # errors identified -pot. Serious)	 0.50 0.51 0.81 1.02	 (0.39 ,0.63) (0.23 ,1.04) * (0.75 ,0.86) (0.90 ,1.16)	 -0.0020/dose -0.00023/dose -0.00068/dose 0.0002/dose	 (-0.0026, (na) (-0.0088, (-0.0009,	 -0.0013) -0.0046) 0.0013)
Jarman [145]	Pre/post (1)	Single-check in limited situations vs. double-check always (n: na)	vs Pre (n: na)	# incident reports	0.8	(na)	-0.8/ month	(na)	
Whitmore [146]	pre/post (1)	Nurse and pharmacist verified chemo order change (n: na)	vs Pre (n: na)	Chemotherapy admin errors (includes wrong dose, infusion, freq, omission)	0.10	(na)	-0.33 / month	(na)	
Resar [132;133]	Time-series (1)	Formal Medication Order reconciliation (n: na)	vs Pre (n: na)	Errors, or potential ADEs + ADEs (terms used inter-changeably)	0.43	(na)	-125/ 100 admission	(na)	

*exact, Poisson rates.

ADE Adverse drug event. CI Confidence interval. ID'd Identified. RD: Risk Difference. RR: Relative Risk. Rx Prescription

Table 15b: Double Check, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference	
Double check	7:0:0		D (4)	3	0.6 (na)	-0.3	dispensing or administration error	/month
					0.1 (na)	-1		/month
					0.8 (na)	-0.1		/month
					0.43 (na)	-125		/pt

Pt Patient. RR Relative Risk. RD: Risk Difference. RR: Relative Risk. 1^0,2^0 primary, secondary

Table 16a: Bed-proximal Drug Storage, Risk of Drug Error

Study Characteristics				Results					
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)		RD	(95% CI)	
Camac [151]	Cohort (1)	Bed-side medication storage (pt- point of care) (98 doses) vs room-side storage (142 doses)	Actual error / dose-error -opportunity	0.41	(0.18,	0.90)	-10/dose	(-19,	-2)
			-commission	0.48	(0.21,	1.1)	-8/dose	(-15,	0.1)
			-omission	0	(0,	1.4) [A]	-3/dose	(-7,	1) [A]
			error led to medical intervention	no events			no events	(-3,	4) [A]
Minnick [150]	Cohort (1)	Two pt -point-of-view (PPOV) delivery systems (192 doses) vs none (1499 doses)	Dose given differs from order/ dose	0	(0,	15) [A]	-0.13/dose	(-0.57,	1.6) [A]
			Dose given, no order	0	(0,	2.7) [A]	-0.73/dose	(-1.4,	1.0) [A]
			Dose omitted (not circled or circled & reason undocumented)	1.0	(0.6,	1.7)	0.087/dose	(-4,	4)
			Med missing/dose	0.67			-1.8/dose	(na)	
			# pages/ pt-day (like missing dose)						
			PPOV1	0.86	(na)		-3/pt-day	(na)	
			PPOV2	0.47	(na)		-1.3/pt-day	(na)	
Meisel [118]	Pre/post (1)	drug cart moved closer to pt's room (n: na) vs Pre (n: na)	Medication error rate (not real data)	"no difference"					

[A] exact, CI on binomial proportions

CI Confidence Interval. RD: Risk Difference. RR: Relative Risk

Table 16b: Drug Distribution: Unit-dose vs. Ward-stock. Pre/Post studies of the Risk of Medication Error

Study Characteristics					Results					
Study	Design (# centres)	Comparison (sample size)			Outcome	RR	(95% CI)		RD	(95% CI)
Enderlin [152]	Pre/ post (1)	Unit-dose (12060 controlled substance 201178 non-controlled, 213328 total doses)	vs	Ward Stock (14238 controlled substance, 151355 non-controlled, 165593 total doses)	(CS) Controlled Substance errors/ CS doses *Already unit-dose*	0.57	(0.31, 1.06)		-0.09/dose	(-0.19, -0.06)
					Non-Controlled-Substance errors/ non-CS doses	1.4	(1.13, 1.7)		0.034/dose	(0.0120, 0.056)
					Total errors/ dose	1.24	(1.02, 1.5)		0.023/dose	(0.0023, 0.04)
O'Brodovich [153]	Pre/ post (1)	Unit-dose Satellite (241 doses)	vs	Ward stock (282 doses)	errors/ dose- opportunities	0.62	(0.45, 0.82)		-1.3/dose	(-21, -5)
					Errors except wrong-time/ opportunities	0.39	(0.17, 0.90)		-4.5 /dose	(-8, -0.82)
					Inventory Management Errors (audit):	0.29	(na)		*-63 (*100)/audit*	(na)
	Pre/ post (1)	Unit-dose Satellite (n: na)	vs	Ward stock (n: na)	# medication incidents / 12 months	1.58	(na)		+51/ a	(na)

CI Confidence Interval. CS Controlled substance. RD: Risk Difference. RR: Relative Risk.

Table 16c: Drug Distribution: Unit-dose vs. Ward-stock. Cohort studies of the Risk of Medication Error

Study Characteristics				Results				
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)		RD	95% CI
Brunel [154]	Cohort (1)	Unit-dose (4802 doses) vs Ward-stock (4057 doses)	Dispensing errors / dose	0.086	(0.037,	0.20)	-1.3/dose	(-1.7, -0.9)
Dean [156]	Cohort (2: 1 vs 1)	Unit dose, US (756 doses) vs Ward-stock, UK (919 doses)	admin errors/ dose opportunities	0.44	(0.32,	0.61)	-3.8/dose	(-5.6, -2.1)
			analysis restricted to med/surg wards	0.41	(0.29,	0.59)	-4.1 /dose	(-5.8 , -2.2)
Taxis [155]	Cohort (2: 1 vs 1)	Unit-dose GER (1318 doses) vs Ward-stock UK (842 doses)	Disp errors/ dose-error-opportunity	0.47	(0.31,	0.73)	-2.7 /dose	(-4, -1)

CI Confidence Interval. Disp Dispensing. GER Germany. NHS National Health Service. RD Risk Difference. RR Relative Risk. 1^0 ,2^0 primary, secondary. UK United Kingsdom. US United States.

Table 16d: Decentralized Services, Risk of Medication Error

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD	(95% CI)
Thomas [159]	pre/post (1)	Satellite pharmacy backed up by automated dispensing (n: na) vs ward stock (n: na)	failure to administer preoperative drugs during the hour prior to incision/ patient	0.51	(na)	-38/ pt	(na)
Stroup [157]	Cohort (1)	decentralized (1982) (n: na) vs centralized pharmacy service (1981) (n: na) (1980) (1979)	Medication Errors	0.88 1.3 1.5	(na) (na) (na)	-3/yr 5/yr -7/yr	(na) (na) (na)
		rest of hospital (1982) vs rest of hospital (1981)		1.15	(na)	19/yr	(na)
Shah [158]	(sparse) time-series (1)	Roving pharmacist transcription (92/93) (197096 pt-days) vs clerk order transcription (pre. 91, post review) (95489 pt-days)	Incidents	0.58	(0.48, 0.70	-0.00089/pt-day	(-0.0012, -0.0006)
		Roving pharmacist transcription + inter-disciplinary review (92/93) (197096 pt-days) vs clerk order transcription (181942 pt-days) (89/90) (178322 pt-days) (87/88)		0.40 0.65	(0.34, 0.47) (0.55, 0.76)	-0.0018/pt-day -.00066/pt-day	(-0.0021, -0.0015) (-0.0009, -0.0004)
		Concurrent Control (92/93) (92/93) vs *Concurrent Control* ('91) ('90)		1.14 1.04	(na) (na)		

CI Confidence interval. Pt Patient. RD: Risk Difference. RR: Relative Risk. Yr Year.

Table 16e: Automated dispensing, Risk of Medication Error

Study Characteristics					Results				
Study	Design (# centres)	Comparison (sample size)			Outcome	RR	(95% CI)	RD	(95% CI)
Klein [161]	Pre/post (1)	Baxter ATC-212 (3813 doses)	vs	tech fill (4029 doses)	Cart-filling errors / dose	0.78	(0.46, 1.30)	-0.19/ 100dose	(-0.57, .019)
Ray [162]	Pre/post (1)	Medstation Rx point-of-use unit fill (n: na)	vs	centralized unit-dose cassette fill (n: na)	filling errors/ dose	0.69	(na)	-0.28/ 100 dose	(-0.54, 0.036)
Kratz [163]	Cohort (2)	Baxter ATC-212 fill (12660 doses)	vs	Manual fill of unit-dose carts (2493 doses)	Cart-filling errors /dose	0.0021	(0.0010, 0.010)	-7.4/ 100 doses	(-8.4, -6.3)
Schwarz [164]	Pre/post (1)	Pyxis Medstation Rx (1464 pt-days)	vs	traditional unit-dose exchange system (1586 pt-days)	Dispensing omissions: per pt-day (mean) Med errors/month -surg -cardiac ICU	0.30 0.66 1.7	(na) (na) (na)	-0.38/pt.day/ unit -2.2/month 0.7/month	(na) (na) (na)
Borel [165]	Pre/post (1)	Pyxis Medstation Rx (929 doses)	vs	Manual unit-dose carts (873 doses)	medication errors/ dose-error opportunities	0.616	(0.48, 0.78)	-6.5 / 100 doses	(-9.7, -3.3)
Chessare [66]	Pre/post (1)	Pyxis (n: na)	vs	no Pyxis (n: na)	Medication errors per 100 pt-day	0.86	(na)	-0.05/100pt-day	(na)
Ray [162]	Pre/post (1)	Pyxis Medstation adapted as a point-of-use (n: na)	vs	centralized 24-hr unit-dose (n: na)	Mean wait for first medication dose (minutes) # nursing-unit calls for first dose	-- 0.1	 (na)	-44 minutes ---	(na)

CI Confidence Interval. ICU Intensive Care Unit. Pt Patient. RD Risk Difference. RR Relative Risk

Table 16f: Drug Distribution Studies—Bed proximal dispensing, Unit Dose, Decentralized Pharmacy, Automated Dispensing

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference	
Bed proximal dispensing	2:0:1		C (2c)	3	0.4 (0.2, 0.90) 0,0,1 "no difference"	-10 study's total: -1	Admin errors Admin errors	/dose /dose
Unit dose	5:0:0		C (2c)	3 (2)	Meta-analysis of 2 studies: 0.61 (0.47, 0.79)	-1.3	Admin errors	/dose
Decentraliz-ed pharmacy	3:0:1		D (4)	1	0.58 (0.48, 0.7)	-0.09	Admin error	/pt-day
				1	0.51 (na)	-38	Admin error (peri-operative med)	/pt
		+unit-dose	D (4)	1	0.22 (0.1, 0.4)	-8.5	Administration error	/dose
Automated dispensing	6:0:0		C (2c)	2 (2)	0.78 (0.46, 1.3) 0.69 (na)	-0.19 -0.28	Dispensing Error Dispensing Error	/dose /dose
			C/D (2c/4)	1 (1)	0.62 (0.5, 0.78)	-6.5	Administration Error	/dose

CI Confidence Interval. Pt Patient. RD: Risk Difference. RR: Relative Risk. 1^0,2^0 primary, secondary

Table 17a: E-medication profile, Risk of Medication Error

Study Characteristics				Results			
Study	Design (# centres)	Comparison	Outcome	RR (95% CI)		RD * 100	(95% CI)
Wilson [166]	Interrupted time-series analyzed as pre/post [see comment] (n: na)	Shared nurse- & pharmacy e-MAR (n: na) vs separate records (n: na)	All transcript or dispensing or administration occurrences / dose	0.6	(p< 0.0001)	-0.02/dose	(na)
Mekhjian [167]	Pre/post (1)	Linked eMAR to CPOE (396 orders) vs unlinked manual MAR & CPOE (888 orders)	Order transcription errors/ total # orders	0	(0, 0.05) [A]	-11.3/order	(na)
Almond [144]	Pre/post (1)	Wireless CPOE, eMAR, (+CDSS, point-of-use auto disp, bar-code admin which seem irrelevant) (18357 doses) vs paper-based system used while training for wireless (about 584 doses)	Prescriptions illegible or instructions unclear at the time of administration /dose	0	(na)	-1/100dose	(na)
Lacasa [149]	Pre/post (1)	Computer MAR system & extra check (19297 doses) vs manual system (18370 doses)	Dose in pt's drawer doesn't equal Rx /doses	0.33	(0.29, 0.37)	-4.5/dose	(-4.9, -4.1)

[A] exact, Poisson rates

CI Confidence Interval. CDSS Computerized Decision Support System. CPOE Computerized physician order entry. MAR Medication administration record. Pt Patient. RD Risk Difference. RR Relative Risk.

Table 17b: E-medication Profile, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
Electronic medication profile	4:0:0	Linked	C (2c)	1 (1)	0 (0, 0.05)	-11.3	Rx transcription error /order
				1	0 (na)	-1	At admin, Rx unclear /order
		Created	D (4)	1	0.33 (0.29, 0.37)	-4.5	Dispensing error /dose

CI Confidence Interval. RR Relative Risk. Rx Prescription. 1^0,2^0 primary, secondary.

Table 18a: Bar-coding, Risk of Medication Error

Study Characteristics				Results	
Study	Design (# centres)	Comparison	Outcome	RR (95% CI)	RD * 100 (95% CI)
Meyer [169]	Pre/post (1)	Bar-code for dispensing (by tech) (n: na) vs Pharmacist check (~ 20600 doses)	Dispensing error	0 (p=0.0000)*	-0.38 /dose (p= 0.0000) [A]
Low [168]	Pre/post (1)	Bar-code for admin (296552 doses) vs None (304000 doses)	Administration error	1.1 0.7, 1.7	$2*10^{-5}$ /dose - ($-3.9*10^{-5}$, $7.9*10^{-5}$)

[A]Fisher test (exact confidence interval did not compute) CI Confidence Interval. RD: Risk Difference. RR: Relative Risk.

Table 18b: Bar-code, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI)	8. 100 x Risk Difference	Unit of Risk Difference
Bar-code	1:1:0	For Dispensing	D (4)	1	0 p=0.0000	-0.38	Dispensing error /dose
		For Administration	D (4)	1	1.1 (0.7, 1.7)	0.002	Administration Error /dose

RR Relative Risk. 1^0,2^0 primary, secondary.

Table 19a: Highly Automated, Risk of Medication Error

Study Characteristics					Results			
Study	Design (# centres)	Comparison (sample size)		Outcome	RR	(95% CI)	RD	(95% CI)
Puckett [170]	Pre/post (1)	Clinicare by Clinicom (n: na)	vs pre (n: na)	Deviations from original physician's order ('93 vs 91)	0.41	(na)	-0.0010/dose	(na)
				Deviations from hospital standards set by nursing & pharmacy dept (includes wrong drug, wrong dose, wrong time, incorrect transcription to MAR vs. computer profile, wrong patient, omission) ('94 vs. '91)	0.29 (wrong drug .67, wrong time, .57, omission, .48, transcription to MAR -47%. Wrong pt, wrong dose: no change)	(na)	-0.0012 /dose	(na)
Brown [171]	Pre/post (1)	Clinicare by Clinicom bedside terminal system (n: na)	vs pre (n: na)	a variation from standard practice	1	(na)	0	(na)
Almond [144]	Pre/post (1)	Wireless notebook .. eMAR & bar-code (18357 doses)	vs pre (584 doses)	Omissions/ dose admin.	0.46	(0.36, 0.59)	-0.054/dose	(-.079, -.029)
				Rx illegible or instructions unclear at admin/ dose	0 (na)		-0.01/dose	(na)
Gebhart Malcom [5;172]	Pre/post (1)	Bar-coding for drug admin (bar-coded drugs and patient wristbands)	vs pre					
		1999* 1994 1998 *950081 doses	1993* *1885651 doses	Medication errors	0.36	(0.27, 0.47)	0.00014/dose	(-0.00017, -0.00011)
					0.58	(na)	0.000092/dose	(na)
				Pharmacy or nursing errors / month	0.19	(na)	-13.89/month	(na)

CI Confidence Interval. MAR Medication administration record. Pt Patient. RD: Risk Difference. RR: Relative Risk.

Table 19b: Highly Automated, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI)	8. 100 x Risk Difference	Unit of Risk Difference
Highly automated	3:0:1	CPOE, eMAR, bar-code, auto disp	C (2c)	1	0.46 (0.4, 0.6)	-5.4	Dispensing omission /dose
		e-MAR, bar-code, CDSS..	D (4)	3	0.36 (0.3, 0.5) 0.4 (na) 1 (na)	-0.014 -0.22 0	Misc. Error /dose

Auto Disp Automated dispensing. CI Confidence Interval. CDSS Computerized Decision Support System. CPOE Computerized physician order entry. MAR Medication administration record. RR Relative Risk. 1^0,2^0 primary, secondary.

Table 20a: Self Administered Medication, Risk of Medication Error

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD	(95% CI)
Beger [174]	Pre/post (1)	Self Admistered Medication (53 pts) vs nurse or physician called (33 pts)	Oral medication errors/ patient *(mostly dispensing & administration)*	0.25	(na)	-0.11 /pt	(na)
Phelan [175]	Cohort (1)	Self-administered medication program with nurse-educator (2611443 orders) vs Pharmacy (4094352 orders)	Wrong med/ wrong dose/ duplication/ wrong pt/ omission/ wrong time/ wrong route/ wrong rate/ other	0.76	(0.61, 0.95)	-0.000095/order (-0.01/discharge)	(-0.0017, -0.00002)

CI Confidence Interval. RD: Risk Difference. RR: Relative Risk.

Table 20b: Self-administered Medication, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI)	8. 100 x Risk Difference	Unit of Risk Difference
Meds self-administered	2:0:0		D (4)	2	0.25 (na) 0.76 (0.6, 0.95)	-11 -0.00095	Administration Error /pt

CI Confidence Interval. RR Relative Risk. 1^0,2^0 primary, secondary.

Table 21a: Drug administration-specific, Risk of Medication Error

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD	(95% CI)
Poster [176]	Cohort (1)	Nurse patients (215475 doses) vs Designated drug nurse (43074 doses)	Admin errors / 100 doses	0.48	(0.37, 0.63)	-0.091/100 dose	(-0.13, -0.05)
Poster [176]	Pre/post (1)	Nurse patients Yr1 (50441 doses) Yr2 (59508 doses) vs designated drug nurse + drug cards (54250 doses)	Admin errors / 100 dose	2.3	(1.4, 3.9)	0.055/100 dose	(0.02, 0.09)
				1.1	(0.6, 2.0)	0.005/100 dose	(-0.02, 0.03)
Kruse [177]	Two-group RCT (1)	2nd nurse for drug admin (23109 tablets) vs 1 nurse (19542 tablets)	Admin errors/ 100 dose	0.67	(0.48, 0.94)	-0.13 /100 dose	(-0.24, -0.02)
Burruss [178]	Cohort (1)	Unlicensed drug admin technician (4355 doses) vs RN (2785 doses)	omissions/ 100 doses given	0.094	(0.03, 0.31)	-1.0/100 dose	(-1.5, -0.6)
			wrong-time/ 100 doses given	0.20	(0.07, 0.6)	-0.57/100 dose	(-0.9, -0.23)
Carey [179]	Pre/post (1)	IV training module (n: na) vs Pre (n: na)	Pre vs. post#1 errors / month	0.92	(na)	-2/mon	(na)
			Pre vs. post#2 errors / month	0.63	(na)	-9.2/mon	(na)
Meisel[118]	Pre/post (1)	Procedure for MAR transcription (n: na) vs No procedure (n: na)	Potential MAR mis-interpretation	0.40	(na)	n/a	(na)
Gilliand [180]	Pre/post (early/late in program) (1)	Returned-dose log (~600 doses) vs No log (~600 doses)	Dispensed doses returned/ 100 doses	0.36	(0.32, 0.41) [A]	-0.7/100 dose	(-0.8, -0.6) [A]

[A] by extrapolating doses over 8 months to doses per month

MAR Medication administration record. RD: Risk Difference. RN: Registered nurse. RR: Relative Risk.

Table 21b: Drug-administration Specific, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. Relative Risk (95% CI)	8. 100 x Risk Difference	Unit of Risk Difference	
Drug admin models (eg, 10 vs functional)	6:1:0	2-nurse drug admin	D (4)	1	0.67 (0.5, 0.94)	-0.13	Administration Error	/dose
		Un-liscenced technician	D (4)	1	0.09 (0.03, 0.3)	-1.0	Omission Error	/ dose
					0.20 (0.1, 0.6)	-0.6	Wrong-time Error	/dose
		IV training	D (4)	1	post, post: 0.9, 0.6 (na)	-2, -9	Misc. Error	/100 months

CI Confidence Interval. IV Intravenous. 1^0,2^0 primary, secondary.

Table 22a: Unique Interventions: Risk of Medication Error and Adverse Drug Events

Study Characteristics				Results				
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)		RD	(95% CI)
Gottlieb [181]	Pre/post (1)	Dedicated "night" house officer teams (673 pts) vs Distributed rotation: longer shifts & more coverage hrs (579 pts)	Pot. serious dr. drug error / pt discharged	0.71	(na)		-0.049/pt	(na)
			Pot serious dr. drug error/ dr. discharge drug order	0.76	(0.29,	2.0)	-0.0037/order	(-0.02, 0.009)
			In-hospital Death	0.82	(0.39,	1.7)	-0.01/pt	(-0.06, 0.04)
Hayman [182]	Pre/post (1)	Emphasis on personal responsibility "Blame & educate" policy (n: na) vs Unsystematic policy (n: na)	Pharmacy dispensing errors / month	0.3	(na)		-14/ month	(na)
na[183]	Pre/post (1)	New, simplified heparin ordering & documentation process (1 month) vs Old process (1 month)	heparin order errors / month	0.27	(na)		-0.59/month	(na)
Burruss [184]	Pre/post (1)	Outsourced IV compounding & Technician reminded nurses of missed doses (3052 doses) vs Substandard in-house (e.g., inadequate space, supply shortages) IV compounding (2610 doses)	Administration omissions/dose	0.71	(0.53,	0.94)	-0.011/dose	(-0.02, -0.0019)
			-unit 1	0.6			-0.017/dose	
			-unit 2	0.7			-0.016/dose	
			-unit 3	1.2			0.004/dose	

IV Intravenous. Pt Patient. RD: Risk Difference. RR: Relative Risk.

Table 22b: Unique Interventions, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% Confidence Interval) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference	
Unique (eg, resident work schedule)	4:0:0		D (4)	1	0.71 (na) 0.76 (0.3,2) 0.82 (0.39, 1.7)	-4.9 / pt -0.4 / order -1 / pt	Rx error at discharge Rx error Mortality	/pt /order /pt

Pt Patient. RR Relative Risk. Rx Prescription. 1^0,2^0 primary, secondary.

Table 23a: Multi-faceted Interventions, Risk of Medication Error and Adverse Drug Events

Study Characteristics				Results	
Study	Design (# centres)	Comparison (sample size)	Outcome	RR (95% CI)	RD (95% CI)
Weeks [186]	Pre/post/post (18 x 1, out of 27)	IHI Breakthrough Series collaborative (interventions targeted toward outcomes) (n: na) vs Pre (n: na)	medication errors (during 7 month collaborative period, during following 6 months)		
			-Chemotherapy		-66,-66:-132/hosp (CIs na)
			-Electrolytes		-208,-68:-76/hosp
			-Heparin		-10,-10: -20/hosp
			-Heparin		-20, -24:-44/hosp
			-Heparin		-20,-70: -90/hosp
			-Heparin		-22,-34: -56/hosp
			-Heparin		-32,-48: -80/hosp
			-Heparin		-42,-42: -84/hosp
			-Heparin		-301,-258:-559/h
			-IV administration		-312-288: -600/h
			-IV solutions		-58, >0 /hosp
			-Medication and allergy verification		-259,-600: -859/h
			-Narcotics		-189,-126: -315/h
			-Polypharmacy		-12, >0 /hosp
			-Warfarin		?, -33: -33 /hosp
			-Warfarin		-56, >0: -56/hosp
			-Warfarin		-60, -90:-150 /h
			-Warfarin		-156, >0 /hosp
			benefit in ADE marker/ hospital		21/27

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD	(95% CI)
Resar, Rozich [132;133;187]	pre/post (1)	a) standardized equipment and process b) safety culture & employees c) automated focused on key areas- post-IHI (n: na) vs Pre (n: na)	Errors or (pot ADEs + ADEs) / dose	0.33	(na)	-0.0052/dose	(na)
Silver [188]	pre/post surveys (13)	Mix of post-QI collaborative interventions (833, 585 nurses, pharmacists, drs, other workers) vs Pre (1305,) 934 nurses, pharmacists, drs, others)	any medication error in the past week/ attendee	0.73	(0.61, 0.89)	-0.055 /wk	(-0.09, -0.022)
			observed error in medication process did not reach the patient/ attendee	1.12	(1.02, 1.2)	0.06 /worker	(0.013 0.12)
Wilson [22]	pre/post (1)	Evolution of CQI program (n: na) vs Pre (n: na)	All reported errors/a	0.81	(na)	-47/yr	(na)
			Administration errors	0.4		-42/yr	
			Prescription errors	1.0		-2/yr	
			Serious errors	0.5		-33/yr	
			Actual errors	1.0		-1/yr	
Burke [79]	pre/post (1)	Hospital's "continuing efforts" (16 infections) vs Pre (17 infections)	(associated errors) / (deep sternal or mediasternal infections)	0	(0, 0.60)[A]	-0.35/infection	(-0.59, -0.13)[A]

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD	(95% CI)
Scott [185]	pre/post/post (1)	Clinical pharmacists attempted to meet their targeted standards for % acceptance, then analyzed & reviewed their success X 3	Probability of (pharmacist intervention not being one that prevents a serious event)				
		-cycle 3 (29 orders clarifed vs cycle 1 (31 orders clarified)		0.90	(0.83, 0.97)	-0.09/intervention	(-0.15, -0.026)
		-cycle 2 (22 orders clarified) vs cycle 1(31 orders clarified)		0.90	(0.83, 0.89)	-0.09/intervention	(-0.15, -0.027)
Wermers [190]	pre/post (1)	1. multi-skilled workers vs Pre (n: na) 2. new employees 3. new architecture: e.g., bed-proximal dispensing (n: na)	Medication errors / month	0.44	(na)	-3.1/month	
Tholl [192]	Pre/post (1)	CPOE lists indications (CDSS); nursing gets sedation assessment form; endotracheal intubation pre-ophthalmic cryo-surgery vs Pre (n: na) (n: na)	adverse reactions to morphine, including changes to respiratory status, blood pressure, and urinary output	0.43	(na)	-0.67 / month	(na)
Joiner [189]	Pre/post (1)	Standardization of admin times; push to improve delivery times; better drug labels; education, local reviews vs pre (n: na) (n: na)	a deviation from a physician's charted order	0.8	(na)	na	

Study Characteristics				Results			
Study	Design (# centres)	Comparison (sample size)	Outcome	RR	(95% CI)	RD	(95% CI)
Schaubhut [191]	pre/post: early/late in implementing (1)	Pyxis + multi vs Pre (n : na) (6234 pt-days)	documentation errors	0.67	(na)	-0.07/ pt-day	
Koren [193]	time-series (1)	Multiple interventions vs pre (see above) (n: na) (n: na)	actual errors/year (92 vs. 98):	0.54	(na)	-458 /year	(na)
			actual+potential errors /dose				
			nurses,	0.54	(na)	-0.05/dose	(na)
			pharmacists,	0.25	(na)	-0.03/dose	(na)
			doctors	0.5	(na)	-0.02/dose	(na)
Goldspiel [194]	pre/post (1)	Chemo CPOE changed with consultants' help & checklist for prep & admin (n: na) vs pre (n: na)	Prescribing errors	0.77	(na)	---	
			Serious prescribing errors	0.47	(na)	---	

[A]exact, CI of binomial proportion

H Hospital. RD: Risk Difference. RR: Relative Risk. RD: Risk Difference. RR: Relative Risk. RD: Risk Difference. RR: Relative Risk. RD: Risk adf

Table 23b: Multi-faceted Interventions, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR (95% CI) or (Range)	8. 100 x Risk Difference	Unit of Risk Difference
CQI, multi-faceted	12:0:0		D (4)	7	Median (Range: 0.33, 0.81, 0.67 n=7. CIs na)	Median: -2800	Error, various /month (see technology-table re ADE) *

CI Confidence Interval. CQI Confinuous Quality Improvement. 1^0,2^0 primary, secondary.

Table 24a: Failure Mode Analysis and Root Cause Analysis, Risk of Medication Error and Adverse Drug Events

Study Characteristics				Results		
Study	Design (# centres)	Comparison (sample size)	Outcome	RR (95% CI)		RD (95% CI)
McNally [195]	Pre/post (1)	current drug reference text; standardization of drug admin times, and common drug protocols; clinical pharmacist removes unrequired medications from the drug trolley daily. (following RCA) (n: na) vs Pre (n: na)	Errors / dose	0.69 (na)		-0.01 /dose (na)
Rex[39]	Time-series (1)	FMA → 22 system changes (280,000 pt-days) vs Pre (180, 000 pt-days)	"Actual" ADEs/ pt-day	0.26 (0.02,	1.57) [A]	$-2*10^{-5}$ /pt-day (na)
			Pot. ADEs/ pt-day	0.40 (0.1,	1.4) [A]	$-2*10^{-5}$ /pt-day (na)
			Fatal ADEs/ pt-day	0 (0,	2.2) [A]	$-1*10^{-5}$ /pt-day (na)

[A]exact, Poisson rate Overall Grade (highest level): D (4)

CI Confidence Interval FMA Failure Mode Analysis. RCA Root cause analysis. RD: Risk Difference. RR: Relative Risk.

Table 24b: Failure Mode Analysis and Root Cause Analysis, Data Summary

1. Technology or system (*comparison vs. none*)	2. Study direction Pro: con: neutral	3 Technology or System Class	4. Quality (*design*): i.e., Grade (Level)	5. Result-specific study # # 1^0 study (# 2^0 study supporting)	7. RR	(95% CI)	8. 100 x Risk Difference Unit of Risk Difference	
Failure mode, Root cause analysis	2:0:0	Root cause analysis	D (4)	1	0.69	(na)	-0.01 Misc. Error	/ dose
		Failure-mode analysis	D (4)	1	0.26	(0.02, 1.6)	-0.002 ADE	/ pt-day

ADE Adverse Drug Event. Pt. Patient. 1^0,2^0 primary, secondary. 1^0,2^0 primary, secondary

APPENDIX AG: CCOHTA's Role and Michael Saginur's Role in the Systematic Review

CCOHTA first performed a pre-assessment of the potential feasibility and originality of a systematic review of the effectiveness of technologies intended to prevent medication errors, and adverse drug events. In 2001, CCOHTA's Devices and Systems Advisory Committee recommended that the systematic review be undertaken.

Study Stage	**CCOHTA's Role**	**My Role**
Study Question *-inclusion criteria*	Defined it	-Modified it to include not only preventable and potential ADEs, but all ADEs -Modified inclusion criteria to include not only preventable and potential ADEs as an outcome, but also all-cause ADEs. This clearly diverged from the intentions of the first CCOHTA project officer (AF), but later ended up being subsumed in the second (ultimate) CCOHTA project officer's interpretation of the definition of preventable ADEs.
Electronic Literature Search	Defined and executed it independently.	None
Data extraction form	Created	Modified: e.g., included information about Error-ascertainment method, and observation periods
Non-electronic literature search	Partial	Partial
Article Screening, data extraction	Every study	Every study
Table creation and data entry based on data extraction	Made 10-15% of initial table entries	Determined table format and entered 85-90% of table entries based on data extraction forms
Thesis Analysis? Conclusions? Discussion?	No	Yes

APPENDIX 1: Literature search for surveys (Janet Joyce: July 18,2002)

The search for surveys was conceptually very similar to the search for studies of effectiveness, in that it captured reports on studies (published no earlier than 1985) regarding

1) medication errors or adverse drug events
2) the hospital setting, and
3) a medication-error prevention technology, defined broadly.

Unlike the systematic-review search, the search for surveys did not search for designs like "clinical trials! OR cohort studies! OR case-control studies..."; instead it searched for two type of studies:

4) studies with a design like a "survey$ or questionnaire$ or interview" (items 1-5),

or

5) or studies whose subject was attitudes (of health personnel to technologies-items 6-7).

Database: CINAHL, ERIC, HealthSTAR, MEDLINE, PsycINFO
Search Strategy:

```
1      (data collection or questionnaires).kw,sh,kf. (231771)
2      interviews.kw,sh,kf. (46952)
3      exp interviews/ (61255)
4      1 or 2 or 3 (281051)
5      (survey$ or questionnaire$ or interview$).ab,ot,ti. (701098)
6      (attitude or attitude of health personnel or attitude to
computers).kw,sh,ti,kf. (73144)
7      ((((attitude adj2 technol$) or awareness) adj2 technol$) or
attitude$).ab,ot,ti. (190292)
8      4 or 5 or 7 (932052)
9      6 or 7 (237944)
10      medical errors.kw,sh,kf. (3752)
11      exp medical errors/ (35488)
12      (((((medical adj3 error$) or medication) adj3 error$) or
medication) adj2 adverse adj effect$).ab,ot,ti. (118)
13      (((medication adj3 incident$) or medication) adj3
mistake$).ab,ot,ti. (41)
14      (((((dispens$ adj3 error$) or dispens$) adj3 incident$) or
dispens$) adj3 mistake$).ab,ot,ti. (3)
15      (((((prescrib adj3 error$) or prescription) adj3 error$) or
prescrib$) adj3 mistake$).ot,ti. (1)
16      (((prescription adj3 error$) or prescription) adj3
mistake$).ab,ot,ti. (15)
17      (((drug adj3 administrat$ adj3 error$) or drug) adj3
administrat$ incident$).ab,ot,ti. (0)
18      (((drug adj3 order adj3 error$) or drug) adj3 order adj3
incident$).ab,ot,ti. (0)
19      (((drug adj3 order adj3 mistake$) or drug) adj3 monitor$ adj3
mistake$).ab,ot,ti. (0)
20      (((((drug adj3 monitor$ adj3 mistake$) or drug) adj3 monitor$
adj3 error$) or drug) adj3 monitor$ adj3 incident$).ab,ot,ti. (2)
21      (((adverse adj3 drug adj3 reaction$) or adverse) adj3 drug
adj3 event$).ab,ot,ti. (1796)
22      (((((adverse adj3 drug adj3 incident$) or adverse) adj3 drug$
adj3 effect$) or medical) adj3 error$).ab,ot,ti. (1388)
```

23 (((((surgical adj3 error#) or surgical) adj3 incident$) or surgical) adj3 adverse adj effect$).ab,ot,ti. (45)
24 10 or 11 or 12 or 13 or 14 or 15 or 16 or 20 or 21 or 22 or 23 (37876)
25 8 and 9 and 24 (292)
26 (medication systems or hospital information systems or medical informatics computing or drug information services or medical informatics applications or decision support systems, clinical or clinical laboratory information systems or decision making, computer-assisted or decision support systems, managment or information systems or medical records systems, computerized or integrated advanced information managemment systems or drug therapy, computer-assisted).kw,sh,kf. (44518)
27 (mail surveys or telephone surveys).kw,sh,kf. (973)
28 1 or 2 or 3 or 5 or 27 (814905)
29 (attitude measures or attitude change).kw,sh,kf. (23408)
30 6 or 7 or 29 (248494)
31 (((((alert$ adj3 system$) or clinical) adj3 alert$) or drug) adj3 distribution adj3 system$).ab,ot,ti. (131)
32 ((((((unit adj3 dose$) or unit) adj3 dosage$) or peripheral) adj3 order adj3 entr$) or robot$ or bar) adj3 cod$).ab,ot,ti. (520)
33 ((((charting$ or kardex or comput$) adj3 medicat$ adj3 administr$ adj3 record$) or computer$) adj3 order$ adj3 entr$).ab,ot,ti. (174)
34 (((((pyxis or pyxisveri5 or docudose or docuscan or script) adj3 pro) or scriptpro or baker) adj cell$) or autros or bppoc or cpoe).ot,ti. (7)
35 (((visualmed or leapfrog or pocketscript or invision or sunrise) adj clinical adj manager) or clinicomp or lastword).ab,ot,ti. (8)
36 31 or 32 or 33 or 34 or 35 (817)
37 26 or 36 (45106)
38 24 or 37 (82291)
39 28 and 30 and 38 (972)
40 remove duplicates from 39 (623)
41 ((((((automat$ adj3 drug$) or administration) adj3 schedule$) or peripheral) adj3 order$ adj3 entr$) or automat$) adj3 alert$).ab,ot,ti. (90)
42 36 or 41 (905)
43 4 or 5 or 27 (814905)
44 9 or 29 (248494)
45 24 or 26 or 36 or 41 (82345)
46 43 and 44 and 45 (972)
47 limit 46 to yr=1985-2002 (945)
48 remove duplicates from 47 (596)
49 exp medication systems/ (1491)
50 exp medical informatics computing/ (246451)
51 exp drug information services/ (5183)
52 exp medical informatics/ (300596)
53 49 or 50 or 51 or 52 (305364)
54 10 or 11 or 12 or 13 or 14 or 15 or 16 or 20 or 21 or 22 or 23 or 26 or 31 or 32 or 33 or 34 or 35 or 41 or 53 (346864)

```
55      1 or 2 or 3 or 5 or 27 (814905)
56      6 or 7 or 29 (248494)
57      54 and 55 and 56 (2340)
58      limit 57 to yr=1985-2002 (2312)
59      remove duplicates from 58 (1431)
60      from 59 keep 1006 (1)
61      from 59 keep 1-1431 (1431)
62      from 59 keep 1-10 (10)
63      from 59 keep 1-10 (10)
64      from 59 keep 1-1431 (1431)
65      from 59 keep 1-1431 (1431)
66      from 59 keep 1-1431 (1431)
67      from 59 keep 1-1431 (1431)
68      from 59 keep 1-1431 (1431)
```

APPENDIX 2: Acute-care bed definitions

Acute	Not Acute	Excluded	Distributed according to hospital's distribution of other beds
Acute care	Chronic Care	Bassinets	Veterans
Cardiac	Complex		
Critical Care	Detox		
Geriatric	Discharge planning unit		
Geriatric Assessment Unit	Extended Care		
ICCU/ stepdown	Long term		
Obs/ Gyn	Maternity		
Pediatric	Multi services		
Surgery	Orthopedics		
	Personal Care		
	Psych		
	Rehab		
	Short term Palliative		
	Transitional		

APPENDIX 3a: Cover letter #1 [English]

n.b., the exact format changed slightly in the transfer to this document

<title> <first name> <last name>

A few days from now you will receive an email requesting that you answer a brief questionnaire for a research project being conducted by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), in collaboration with the Institute for Safe Medication Practices (ISMP), Canada.

This project concerns CCOHTA's review of technologies and systems which are intended to prevent medication errors in hospitals. The study is an important one that will help us understand which technologies are being used in Canadian hospitals.

Thank you for your time and consideration.

Sincerely,

David U, MSc Pharm	Michel Boucher, B Pharm, MSc
CEO, ISMP – Canada	Research Pharmacist, CCOHTA

Q1. How many inpatient beds are found at your hospital? _____ beds		
TECHNOLOGY USE	Q2. Does your hospital use the technology ?	Q3. (If Yes) What percentage of your hospital's inpatient beds are serviced by the technology?
1. Automated dispensing devices (eg, Pyxis, Baxter ATC 212, Omnicell)	☐ No ☐ Yes →	_____ %beds
2. Computerized Medication Administration Record	☐ No ☐ Yes →	_____ %beds
3. Computerized Physician Order Entry	☐ No ☐ Yes →	_____ %beds
4. Clinical Decision Support System for physician computerized order entry (eg. "excessive dose" limits, (e.g., rule-based drug-drug interaction checks)	☐ No ☐ Yes →	_____ ____%beds
5. Clinical Decision Support System for pharmacy staff computerized order entry (eg. "excessive dose" limits, rule-based drug-drug interaction checks)	☐ No ☐ Yes →	_____ %beds
6. Bar-coding for drug dispensing	☐ No ☐ Yes →	_____ %beds
7. Bar-coding for drug administration	☐ No ☐ Yes →	_____ %beds
8. Unit-dose system (even if limited wardstock is available)	☐ No ☐ Yes →	_____ %beds
9. Controlled/Carded Dosing	☐ No ☐ Yes →	_____ %beds
10. Traditional pharmacy	☐ No ☐ Yes →	_____ %beds
11. Ward-stock pharmacy	☐ No	

	☐ Yes →	_____ %beds
12. Pharmacy-based IV admixture service	☐ No ☐ Yes →	_____ %beds
13. Satellite Pharmacy	☐ No ☐ Yes →	_____ %beds
(If Yes) Which units are serviced? ICU ☐ OR ☐ ED ☐ Other ☐ _____		
14. Clinical Pharmacy Services (for inpatients)	☐ No ☐ Yes →	_____ %beds
(If Clinical pharmacy services are offered to inpatients) a) Please indicate which clinical pharmacy services are provided. pharmacokinetic monitoring ☐ interdisciplinary rounds attendance ☐ medical rounds attendance ☐ patient counselling ☐ other _____ b) How many full-time equivalent pharmacists provide inpatient clinical pharmacy services? _____		
15. Continuous Quality Improvement program (with personnel time formally allocated to "system-based quality improvement" or "patient safety" activities)	☐ No ☐ Yes →	_____ # pharmacist FTE
16. Other Technology _____	☐ Yes →	_____ %beds

Q4. What is your opinion of the amount of technology now used for the care of inpatients at your hospital?				Q5. Please indicate whether your hospital is likely to increase or decrease the amount of technology that it uses, in the next 2 years.	
Needs to increase	About right	Needs to decrease		Increase	Decrease
☐	☐	☐	1 Automated medication dispensing devices (eg. Pyxis)	☐	☐
☐	☐	☐	2 Computerized Medication Administration Record	☐	☐
☐	☐	☐	3 Computerized Physician Order Entry	☐	☐
☐	☐	☐	4 Clinical Decision Support System for physician order entry	☐	☐
☐	☐	☐	5 Clinical Decision Support System for pharmacy staff order entry	☐	☐
☐	☐	☐	6 Bar-coding for drug dispensing	☐	☐
☐	☐	☐	7 Bar-coding for drug administration	☐	☐
☐	☐	☐	8 Unit-dose system	☐	☐
☐	☐	☐	9 Controlled/Carded Dosing	☐	☐
☐	☐	☐	10 Traditional pharmacy	☐	☐
☐	☐	☐	11 Ward-stock pharmacy	☐	☐
☐	☐	☐	12 Pharmacy-based IV admixture service	☐	☐
☐	☐	☐	13 Satellite Pharmacy	☐	☐
☐	☐	☐	14 Clinical pharmacy services for inpatients	☐	☐
☐	☐	☐	15 Continuous Quality Improvement Program	☐	☐
Q6. Of the technologies listed above (or others), which one would you have your hospital invest in next?					

Q7. How many inpatient full-time equivalent pharmacists are employed? _____ total
Q8. Are you the director or manager of pharmacy at your hospital? ☐ Yes ☐ No (If No), What is your job title?

		labelled with the patient's name, the drug name, the dispensed quantity, and directions for use. In acute-care hospitals, a three-day cycle is typical.
11	Ward-stock pharmacy	Within the hospital ward, nurses or other non-pharmacists perform the functions of a) storing drugs in bulk in a common floor stock b) manually selecting drugs from bulk storage, and c) distributing drugs to patients.
12	Pharmacy-based IV admixture service	All the drugs to be infused in a small volume parenteral (SVP) or a large volume parenteral (LVP) are prepared in a clean area operated by the pharmacy department
13	Satellite pharmacy	A subunit of the hospital pharmacy which is physically separated from the central pharmacy. It usually serves a specific ward.
14	Continuous Quality Improvement Program	Personnel time is formally allocated to "system-based quality improvement" or "patient safety" activities: either in the form of a) a dedicated position (or positions), or b) dedicated time of personnel specifically allocated to "quality improvement" or "patient safety" activities within their portfolios of responsibility.
15	Decentralized inpatient clinical pharmacists	The pharmacist works on the ward, interacting directly with patients and other healthcare professionals to enhance the design, implementation, and monitoring of patients' therapeutic plans.

APPENDIX 4a: Cover letter #1 [French]

Madame ____ / Monsieur ___,

L'Office canadien de coordination de l'évaluation des technologies de la santé (OCCETS), dans le cadre d'un projet de recherche entrepris en collaboration avec l'Institute for Safe Medication Practices (ISMP) du Canada, vous enverra dans quelques jours un télécopie vous demandant de répondre à un bref questionnaire.

En vertu de ce projet, l'OCCETS examine les technologies et systèmes qui permettent de prévenir les erreurs médicamenteuses en milieu hospitalier. L'importance de l'étude tient au fait qu'elle permettra de cerner les technologies et systèmes en usage à cette fin dans les hôpitaux canadiens.

Merci beaucoup de votre collaboration.

Veuillez agréer, Madame, Monsieur, l'expression de nos sentiments distingués.

David U, M.Sc. Pharm.
Directeur général, ISMP – Canada

Michel Boucher, B.Pharm., M.Sc.
Pharmacien-chercheur, OCCETS

Approbation du Conseil d'éthique en recherches de l'Hôpital d'Ottawa valide jusqu'au 18 février 2004

APPENDIX 4b: Cover letter & questionnaire [French]

Madame ____ / Monsieur ___,

L'Office canadien de coordination de l'évaluation des technologies de la santé (OCCETS) effectue une étude des technologies et systèmes qui permettent de prévenir les erreurs médicamenteuses en milieu hospitalier. Pour les besoins de cette étude, l'OCCETS collabore avec l'Institute for Safe Medication Practices (ISMP) du Canada. L'un des volets de cet important projet de recherche consiste en une enquête auprès des directeurs de pharmacie d'hôpital pour circonscrire l'usage actuel de ces technologies dans les hôpitaux canadiens. L'enquête a également pour objectif d'identifier les facteurs déterminants de l'utilisation de ces technologies. Les deux organisations espèrent que cette information se révèlera utile aux décideurs du réseau de la santé au Canada.

L'enquête est destinée aux directeurs de pharmacie de centres hospitaliers de soins aigus au Canada afin de cerner les technologies en usage à leur hôpital, connaître leur opinion quant au taux d'utilisation de ces technologies, et déterminer leurs perceptions des erreurs médicamenteuses dans leur hôpital. Michael Saginur, étudiant à la maîtrise à l'Université d'Ottawa, se charge de l'exécution de l'enquête dans le cadre de sa thèse de maîtrise. En raison du poste que vous occupez, vous êtes l'un des destinataires de l'enquête.

Veuillez prendre note que les réponses demeureront strictement confidentielles et que seules des synthèses de résultats seront diffusées sans qu'aucun répondant ne soit identifié. Nous vous prions de nous faire parvenir le questionnaire rempli, à l'exception des questions auxquelles vous ne désirez pas répondre le cas échéant. S'il vous est impossible de participer à l'enquête, nous vous saurions gré de désigner une personne de votre service qui pourra le faire. Si vous avez des questions au sujet de l'enquête, veuillez communiquer avec Michel Boucher par téléphone au 613 226-2553, poste 232.

L'OCCETS est une organisation sans but lucratif financée par les ministères de la Santé fédéral, provinciaux et territoriaux (prière de se rendre au site www.ccohta.ca pour obtenir de plus amples renseignements sur l'organisation). Le rôle de l'Office consiste à offrir de l'information fondée sur des données probantes au sujet des technologies de la santé existantes ou émergentes. Cette information est destinée principalement aux décideurs et gestionnaires en santé du Canada.

Nous vous remercions de votre collaboration à ce projet de recherche important.

Veuillez agréer, Madame, l'expression de nos sentiments distingués.

David U, M.Sc. Pharm.	Michel Boucher, B.Pharm., M.Sc.
Directeur général, ISMP – Canada	Pharmacien-chercheur, OCCETS

Notes : a) Si le centre hospitalier comprend plusieurs établissements, veuillez répondre au questionnaire en tenant compte de tous les établissements.
b) Un glossaire des diverses technologies accompagne le courriel afin d'en faciliter la compréhension.

Approbation du Conseil d'éthique en recherches de l'Hôpitale d'Ottawa valide jusqu'au 18 février 2004

Q1. Combien de lits compte votre hôpital ? _____ lits

TECHNOLOGIE	Q2. Cette technologie est-elle en usage à votre hôpital?	Q3. Dans l'affirmative, quelle proportion des lits de l'hôpital couvre l'application de cette technologie ?
1. Appareil de distribution automatisée (p. ex., Pyxis, Baxter ATC 212, Omnicell)	☐ Non ☐ Oui →	_____ _____ % des lits
2. Dossier informatisé d'administration des médicaments pour les soins infirmiers	☐ Non ☐ Oui →	_____ _____ % des lits
3. Système informatisé de prescription médicale	☐ Non ☐ Oui →	_____ _____ % des lits
4. Module d'aide à la décision clinique couplé à un système informatisé de prescription médicale (p.ex., indication de dose « excessive », vérification des interactions médicamenteuses)	☐ Non ☐ Oui →	_____ _____ % des lits
5. Module d'aide à la décision clinique couplé à un système informatisé de saisie d'ordonnance à la pharmacie (p. ex., indication de dose «excessive», vérification des interactions médicamenteuses)	☐ Non ☐ Oui →	_____ _____ % des lits
6. Système de lecture magnétique (code barre) pour la distribution des médicaments	☐ Non ☐ Oui →	_____ _____ % des lits
7. Système de lecture magnétique (code barre) pour l'administration des médicaments	☐ Non ☐ Oui →	_____ _____ % des lits
8. Système de conditionnement unitaire des médicaments (même si nombre limité de médicaments au commun)	☐ Non ☐ Oui →	_____ _____ % des lits
9. Système de distribution par plaquette alvéolaire	☐ Non	

	☐ Oui →	_____ _____ % des lits
10. Service de distribution traditionnel	☐ Non ☐ Oui →	_____ _____ % des lits
11. Médicaments au commun sur les unités de soins	☐ Non ☐ Oui →	_____ _____ % des lits
12. Centrale d'additifs aux solutions IV	☐ Non ☐ Oui →	_____ _____ % des lits
13. Pharmacie satellite	☐ Non ☐ Oui →	_____ _____ % des lits
Dans l'affirmative, veillez préciser les unités desservies? Soins intensifs ☐ Bloc opératoire ☐ Service des urgences ☐ Autre ☐ _____		
14. Services pharmaceutiques cliniques (pour patients hospitalisés)	☐ Non ☐ Oui →	_____ _____ % des lits
Dans l'affirmative, a) veuillez indiquer les services pharmaceutiques cliniques offerts. surveillance pharmacocinétique ☐ participation aux tournées interdisciplinaires ☐ participation aux tournées médicales ☐ service de conseils aux patients ☐ autre _____ b) combien de postes pour pharmacien (équivalents temps plein) sont dédiés aux services pharmaceutiques cliniques aux patients hospitalisés ? _____		
15. Programme d'amélioration continue de la qualité (soit, une période consacrée officiellement à des activités « d'amélioration de la qualité » ou « d'amélioration de la sécurité du patient »)	☐ Non ☐ Oui →	# de pharmaciens ETC _____
16. Autre technologie _____	☐ Oui →	_____ _____ % des lits

Q4. Quelle est votre opinion concernant le niveau d'utilisation actuel des technologies suivantes dans la prestation des soins aux patients hospitalisés de votre hôpital ?				Q5. Veuillez indiquer si votre hôpital prévoit accroître ou réduire, au cours des deux prochaines années, l'utilisation des technologies mentionnées. (*dans le cas où aucun changement n'est prévu, veuillez ne rien écrire*)	
Devrait augmenter	Approprié	Devrait diminuer		Accroître	Réduire
☐	☐	☐	1 Appareil de distribution automatisée (p. ex., Pyxis)	☐	☐
☐	☐	☐	2 Dossier informatisé d'administration des médicaments pour les soins infirmiers	☐	☐
☐	☐	☐	3 Système informatisé de prescription médicale	☐	☐
☐	☐	☐	4 Module d'aide à la décision clinique couplé à un système informatique de prescription médicale	☐	☐
☐	☐	☐	5 Module d'aide à la décision clinique couplé à un système informatique de saisie d'ordonnance à la pharmacie	☐	☐
☐	☐	☐	6 Système de lecture magnétique (code barre) pour la distribution des médicaments	☐	☐
☐	☐	☐	7 Système de lecture magnétique (code barre) pour l'administration des médicaments	☐	☐
☐	☐	☐	8 Système de conditionnement unitaire des médicaments	☐	☐
☐	☐	☐	9 Système de distribution par plaquette alvéolaire	☐	☐
☐	☐	☐	10 Service de distribution traditionnel	☐	☐
☐	☐	☐	11 Médicaments au commun sur les unités de soins	☐	☐
☐	☐	☐	12 Centrale d'additifs aux solutions IV	☐	☐
☐	☐	☐	13 Pharmacie satellite	☐	☐
☐	☐	☐	14 Services pharmaceutiques cliniques (pour patients hospitalisés)	☐	☐

☐	☐	☐	15. Programme d'amélioration continue de la qualité	☐	☐

Q6. Parmi les technologies mentionnées ci-dessus (ou d'autres), quelle est la prochaine technologie que vous souhaiteriez que votre hôpital acquiert?

Q7. Combien de postes pour pharmacien *(équivalents temps complets)* sont dédiés aux soins des patients hospitalisés? _____

Q8. Êtes-vous le directeur de la pharmacie de l'hôpital?

☐ Oui ☐ Non (Si 'Non') Quel poste occupez-vous ? _____

79

Glossaire

	Technologie	Définition
1	Appareil de distribution automatisée	Un appareil de distribution automatisée des médicaments consiste en appareil ou un cabinet, contenants des médicaments, et doté d'un mécanisme de distribution et de contrôle électronique des médicame de même que d'un mécanisme de suivi de l'utilisation des médicame... Ce système permet au personnel infirmier d'obtenir, au point d'utilisation, les médicaments destinés aux patients hospitalisés (AHRQ 2001). À titre d'exemples, mentionnons le système de distribution McLaughlin, le système Baxter ATC-212, et l'appareil Pyxis Medstation.
2	Dossier informatisé d'administration des médicaments pour les soins infirmiers	Une liste, générée par ordinateur, des médicaments prescrits à chacun des patients hospitalisés.
3	Système informatisé de prescription medicale	Le médecin prescrit l'ordonnance directement dans le système informatique.
4, 5	Module d'aide à la décision clinique couplé ou à un système informatisé de prescription medicale, ou à un système informatisé de saisie d'ordonnance à la pharmacie	Une base de données intelligente, qui vérifie automatiquement les ordonnances pour déceler, entre autres, des combinaisons de médicaments contre-indiquées, un risque de surdose ou de dose sous-optimale, des allergies médicamenteuses ou l'éventualité d'effets indésirables. Le module d'aide à la décision peut également offrir une source en ligne d'information clinique et des formules pour calculer des doses.
6	Système de lecture magnétique (code barre) pour la distribution des médicaments	Un code à barres est attribué à la préparation médicamenteuse pour vérifier la nature du médicament.
7	Système de lecture magnétique (code barre) pour l'administration des médicaments	Le codage du bracelet du patient et de la préparation médicamenteuse par code à barres permettrait de confirmer qu'il s'agit bien du médicament prescrit pour le patient en question.

	Technologie	Définition
8	Système de conditionnement unitaire des médicaments	Un système de distribution des médicaments en vertu duquel les médicaments s distribués en conditionnement de dose unitaire, prêts à être administrés par le pe infirmier qui les prélève dans le casier attribué au patient. Le casier du patient re ses médicaments conditionnés en dose unique, chaque conditionnement portant étiquette indiquant le nom et la dose du médicament. Les médicaments sont distribués par le service de pharmacie en quantité suffisante pour 24 heures en règle générale (dans les établissements de soins psychiatriques ou de soins de longue durée, la quantité de médicaments couvre trois jours, voire même une semaine). Grâce à ce système, le personnel infirmier n'a pas à prélever le médicament dans les médicaments gardés au commun ou dans le contenant du patient (comme c'est le cas pour une ordonnance individuelle).
9	Système de distribution par plaquette alvéolaire	Le service de pharmacie prépare les médicaments sous carte alvéolée (une carte recouverte d'une feuille d'aluminium d'un côté et comportant une alvéole en matière plastique de l'autre, enfermant les comprimés ou les capsules; les comprimés ou capsules sont extraits en perçant la feuille d'aluminium par la compression de l'alvéole). Une étiquette indiquant le nom du patient est apposée sur la carte. Le système est d'usage plu courant dans les établissements ou unités de soins de longue durée.
10	Service de distribution traditionnel	Le service de pharmacie prépare les médicaments prescrits au patient dans des contenants, comme des flacons ou des bouteilles. Les contenants portent une étiquette indiquant le nom du patient, le nom du médicament, la quantité de médicament et la posologie. Dans un hôpital de soins aigus, la quantité distribuée couvre en général trois jours.
11	Médicaments au commun sur les unités de soins	À l'unité de soins, un membre du personnel infirmier ou une personne autre qu'un pharmacien exécute les tâches suivantes : a) le stockage de médicaments en vrac, b) la préparation manuelle des médicaments en les prélevant dans les contenants et c) la distribution des médicaments aux patients.
12	Centrale d'additifs aux solutions IV	Tous les médicaments destinés à une administration parentérale, de petit volume ou de grand volume, sont préparés dans un local conçu à cet effet sous la direction du service de pharmacie.
13	Pharmacie satellite	Une sous-unité du service de pharmacie de l'hôpital est localisée à un endroit distinct de la pharmacie centrale. Habituellement, elle dessert une unité de soins particulière.
14	Services pharmaceutiques cliniques pour patients hospitalisés	Le pharmacien œuvre à l'unité de soins et interagit directement avec les patients et les autres professionnels de la santé pour améliorer la conception, la mise en application et la surveillance des plans de traitement.
15	Programme d'amélioration continue de la qualité	Programme consacré officiellement à des activités « d'amélioration de la qualité » ou « d'amélioration de la sécurité du patient », soit sous la forme de postes désignés comme tels ou de périodes attribuées précisément à « l'amélioration de la qualité » ou à la « sécurité du patient » dans la description des tâches.

APPENDIX 5: Determination of the prevalence of technology use

To determine the prevalence of technology use, the values of technology intensity among non-reporting technology users were imputed using the means of reporting technology users.

In the determination of the intensity of use of unit-dose, controlled/carded, and traditional systems, I assumed that ward-stock always co-exists as a secondary distribution system to meet specific ward needs: that the proportion of beds serviced by total ward-stock is the proportion not serviced by unit-dose, controlled/carded, and traditional systems. When the total reported percentage of beds serviced by unit-dose, controlled/carded, and traditional exceeded 100%, the total was proportionately standardized to 100%. Thus, in most cases,

total ward-stock = 100- (unit-dose +, controlled/carded + traditional)

and if reporting proportion of beds serviced by unit-dose, controlled/carded, and traditional systems exceeded 100%, then

unit-dose = (unit-dose) / (unit-dose + controlled/carded + traditional) * 100%

controlled/carded=(controlled/carded)/ (unit-dose+controlled/carded+trad.)*100%

traditional = (traditional) / (unit-dose + controlled/carded + traditional) * 100%

APPENDIX 6: Predictors of Technology Use: Satellite Pharmacy

Hospitals' number of acute-care beds was forced into a model of predictors of satellite pharmacy use (yes or no). On its own, a hospital's number of acute-care beds was quite a significant predictor of satellite pharmacy use:

OR(per 100 acute bed increase)= 1.81; 95% CI=(1.2-2.7); n=70.

Budget per bed was borderline significant as a single predictor of satellite pharmacy use:

OR (per $50,000 increase per bed) = 1.33; 95% CI=(1.02-1.73); n=53.

In a model that used the two putatively significant predictors of satellite pharmacy use, estimated odds ratios for the two potential predictors decreased, and lost their statistical significance:

OR(per 100 acute bed increase)= 1.50; 95% CI=(.976-2.3)

OR(per $50,000 increase per bed)= 1.15; 95% CI=(.90-1.47), n=47.

Thus, an automated stepwise model with a 5% cut-off for significance would not include either potential predictor. However, in a logistic model of satellite pharmacy use based on a hospital's acute-care bed number and restricted to responders whose number of acute-care beds and budget per bed was known, the magnitude and significance of increased numbers of acute bed decreased:

$OR(\text{per 100 acute bed increase})_{\text{restricted}} = 1.63$; 95% CI=(1.066-2.5), n=47.

The estimated association between the number of hospital acute-care beds and the use of satellite pharmacy was more similar in the two restricted models (n=47), than to the estimated association in the more inclusive model (n=70): both in terms of the point estimates and their confidence intervals. Also, given the negligible estimated effect of budget per bed in the model with the predictors acute beds and budget per bed, the budget per bed was not expected to exert much impact on the estimated association between acute beds and satellite pharmacy use. It appears likely that restricting the sample to those hospitals with a known budget per bed drove the loss of statistical significance of the association between the number of acute beds and satellite pharmacy use. Thus, the number of acute-care beds was forced into a model of satellite pharmacy use.