

IMPROVING ELECTRONIC HEALTH RECORDS
TO PROMOTE PATIENT SAFETY:
A SYSTEMATIC REVIEW

By

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES	iv
LIST OF ABBREVIATIONS	v
ACKNOWLEDGEMENTS	vi
ABSTRACT	viii
CHAPTER 1: INTRODUCTION	1
CHAPTER 2: MATERIALS AND METHODS	4
Process for screening the results of the literature search	5
Software used in screening the literature search results	7
Data extraction and synthesis	8
CHAPTER 3: RESULTS	10
CHAPTER 4: DISCUSSION	12
Systematic review findings	12
Interventions to improve patient safety with CPOE	17
Interventions to improve computerized medication decision support	19
Interventions to improve the ordering of appropriate laboratory monitoring of pharmacotherapy	23
Interventions to improve prophylaxis of venous thromboembolism	34
Interventions to reduce rates of medication errors in pediatric patients with electronic prescribing	45
Interventions to reduce rates of specific medication interactions	48
Interventions to improve the appropriateness of medication use in patients with renal insufficiency	51
Interventions to improve the appropriateness of medication choice and dosing for geriatric patients	57
Interventions to improve the appropriateness of medication dosing in special populations	66
Interventions to improve computerized decision support in specific clinical circumstances	68

Interventions to reduce inappropriate tablet splitting	71
Interventions to reduce the use of unapproved abbreviations	71
Interventions to enhance communication about prescribers' thought processes	73
Practical implications of the systematic review findings	74
CHAPTER 5: SUMMARY AND CONCLUSIONS	80
REFERENCES	81
APPENDICES	91
Appendix A: Detailed literature search strategies	92
Appendix B: Design of Microsoft Access database program for screening literature	107
Appendix C: Evidence tables for individual studies identified in the systematic review	116
Interventions to improve patient safety with CPOE	116
Interventions to improve computerized medication decision support	117
Interventions to improve the ordering of appropriate laboratory monitoring of pharmacotherapy	119
Interventions to improve prophylaxis of venous thromboembolism	125
Interventions to reduce rates of medication errors in pediatric patients with electronic prescribing	131
Interventions to reduce rates of specific medication interactions	133
Interventions to improve the appropriateness of medication use in patients with renal insufficiency	135
Interventions to improve the appropriateness of medication choice and dosing for geriatric patients	138
Interventions to improve the appropriateness of medication dosing in special populations	143
Interventions to improve computerized decision support in specific clinical circumstances	144
Interventions to reduce inappropriate tablet splitting	147
Interventions to reduce the use of unapproved abbreviations	148
Interventions to enhance communication about prescribers' thought processes	149

Appendix D: Summaries of the body of evidence for topics in the systematic review	150
Interventions to improve patient safety with CPOE	150
Interventions to improve computerized medication decision support	151
Interventions to improve the ordering of appropriate laboratory monitoring of pharmacotherapy	151
Interventions to improve prophylaxis of venous thromboembolism	152
Interventions to reduce rates of specific medication interactions	152
Interventions to improve the appropriateness of medication use in patients with renal insufficiency	153
Interventions to improve the appropriateness of medication choice and dosing for geriatric patients	154
Interventions to improve the appropriateness of medication dosing in special populations	155
Interventions to improve computerized decision support in specific clinical circumstances	155
Interventions to reduce inappropriate tablet splitting	156
Interventions to reduce the use of unapproved abbreviations	156
Interventions to enhance communication about prescribers' thought processes	157

LIST OF TABLES AND FIGURES

TABLES

Table 1. Inclusion and exclusion criteria for literature searches and screening.	6
Table 2. Summary of evidence on adding laboratory monitoring decision support to existing EHRs	31
Table 3. Summary of evidence on adding decision support to existing EHRs to improve VTE prophylaxis	42
Table 4. Summary of evidence on adding decision support related to renal impairment to existing EHRs	55
Table 5. Summary of evidence on adding decision support to existing EHRs to improve geriatric prescribing	63
Table 6. Summary of systematic review findings on modifications to EHRs to improve patient safety	77
Table 7. Event procedure code for Microsoft Access Database	113

FIGURES

Figure 1. Results of the systematic search of the literature on patient safety issues related to EHRs.	11
Figure 2. Comparison of annual publication rates of English language articles indexed in PubMed to rates of publication of HIT literature with direct or indirect relationships to patient safety.	15
Figure 3. Table properties for Microsoft Access database.	107
Figure 4. Design view of form to display and screen article titles.	108
Figure 5. Form used to display and screen article titles.	109
Figure 6. Form used to display abstract and citation information.	110
Figure 7. Example popup window that displays abstract and citation information.	111
Figure 8. Example popup window requests user initials upon quitting.	112

LIST OF ABBREVIATIONS

ADE adverse drug event

AHRQ Agency for Healthcare Research and Quality

CDSS clinical decision support system

CPOE computerized provider order entry

DVT deep vein thrombosis

EHR electronic health record

FDA Food and Drug Administration

FMECA failure mode, effects and criticality analysis

HIT health information technology

IT information technology

NSAID non-steroidal anti-inflammatory agent

PE pulmonary embolus

VTE venous thromboembolism

XML Extensible Markup Language

XSLT Extensible Stylesheet Language Transformation

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ABSTRACT

Recent national incentives have focused on the expansion of health information technology, including electronic health records (EHRs) as a way to address costs, improve quality, reduce medical errors and ameliorate other dysfunctional aspects of the United States health care delivery system. However, the design, implementation and use of EHRs are complex. Some EHRs may incorporate features that are intended to improve patient safety but may not actually do so. In other instances, EHRs may introduce new errors or types of errors that detract from patient safety. Thus, it would be beneficial for organizations and clinicians to become aware of evidence-based practices for improving existing EHRs and enhancing overall safety for patients

At the core of this project is a systematic review of the literature, which is intended to identify evidence on facets of existing EHRs that can influence patient safety. A comprehensive search was conducted for the years 1990 to 2010 of the following databases: MEDLINE (PubMed); CINAHL, Computer Source, Computers and Applied Sciences, Library, Information Science and Technology Abstracts (EBSCO Host); ISI Web of Knowledge; Cochrane (Wiley); Compendex - Engineering Village; IEEE Xplore and Scopus. Titles and abstracts for 39952 citations were screened for relevance to the topic of EHRs and patient safety by the project author. No specific types of study designs were excluded a priori. On this basis, 1704 articles were identified for further review of which full text was available for 1403 articles. Of these references, 49 examined the effects of a modification to an existing EHR that was intended to have

direct or indirect benefits for patient safety. Although a systematic search was not done for 2011 or 2012, 8 additional relevant studies from those years were identified during the completion of the project. No studies were able to be located that were aimed at minimizing new risks that may be associated with EHRs as compared to paper records. Data extraction and synthesis were done by the project author. The quality of individual studies was assessed using the recommendations of the Agency for Healthcare Research and Quality (AHRQ) for conducting systematic reviews. Due to the heterogeneity of study designs, no meta-analyses were done. Estimates of the strengths and limitations on the body of evidence relating to key topics were also done by the project author using AHRQ methodological recommendations.

The results of this systematic review provide strong support for incorporating alerts to improve prescribing for geriatric patients. A substantial number of well-designed studies also suggest that venous thromboembolism (VTE) related decision support is beneficial but data from weaker trials is less consistent. More limited support exists for alerts to improve prescribing in other subgroups of patients such as individuals with impaired renal function. Additional aspects of EHRs that are been widely assumed to contribute to patient safety have not been as well-studied and would benefit from further research. In addition, studies are needed to determine the best approaches for addressing the new types of errors that have arisen with EHR use.

CHAPTER 1

INTRODUCTION

The health care delivery system of the United States is widely viewed as costly, dysfunctional and prone to error (Aaron and Ginsburg, 2009; Wachter, 2009; Kohn et al. 1999). Proposals and national incentives to address these problems have focused on harnessing the potential benefits of technology and increasing the use of electronic record systems by health care institutions, clinicians and patients (Blumenthal, 2009; Blumenthal, 2010; Burke, 2010; D'Avolio, 2009; Greene, 2009). When used correctly, electronic health record (EHR) systems can enhance patient safety (Parente and McCullough, 2009; Institute of Medicine, 2011).

The complexities of EHR design and implementation require the coordinated efforts of many individuals and many interconnecting hardware and software elements, each of which can serve as an opportunity for error or unintended negative consequences. Consequently, safety can also be diminished by well-intentioned but poorly designed or implemented EHR systems that can introduce new types of errors (Magrabi et al., 2012; Hoffman and Podgurski, 2011; Institute of Medicine, 2011; Sittig and Singh, 2011; Magrabi et al. 2010; Palchuk et al., 2010; Strom et al., 2010a; Ash et al., 2007a; Ash et al., 2007b; Weiner et al., 2007; Campbell et al., 2006; Nebeker et al., 2005; Han et al., 2005; Koppel et al., 2005; McKibbon, et al. 2011). In enhancing patient safety, coordinated efforts will be needed at local and national levels in tracking safety concerns

and developing regulatory oversight and policy recommendations (Institute of Medicine, 2011; Bloomrosen et al. 2011; Sittig and Singh, 2009; Singh et al., 2011; Wright et al., 2011; Sittig and Classen, 2010; Borycki and Kushniruk, 2010).

To date, much of the national discussion related to EHRs and health information technology (HIT) has been aimed at making a case for HIT funding and promoting adoption (Blumenthal, 2009; Blumenthal, 2010). However, as adoption accelerates, users and organizations will need to make key decisions about specific elements of an EHR that will be most crucial in enhancing care and promoting safety. Basic EHR systems will typically include features such as clinician documentation, result viewing and management, electronic prescribing or order entry and clinical decision support. Nonetheless, within the context of a basic EHR system, users or organizations may only choose to purchase or activate specific features (Jha et al., 2010; DesRoches et al., 2008). In making such determinations, users and organizations should consider factors such as the strength of the evidence that a particular feature improves patient safety. In addition, when factors are identified that contribute to new types of errors, it would be important to determine the best approaches to minimize these risks.

As its primary purpose, this project intends to identify specific features that can be redesigned or added to existing EHRs in order to enhance patient safety. Goals of such modifications could include correcting aspects of EHRs that currently detract from safety or introduce new errors. In addition, such modifications could be aimed at reducing patient harms through features such as clinical decision support systems. To make a compelling case for costly additions or modifications to EHRs, it is important to identify the strength of existing evidence through systematic assessment of study quality and

findings, using information from rigorously designed studies whenever possible. Where relevant, this project will determine the specific types of organizations (e.g., large vs. small to moderate, multi-setting vs. single setting, multi-specialty vs. single-specialty, academic vs. non-academic) and settings of care (e.g., inpatient, outpatient, emergency) in which safety improvements have been observed.

CHAPTER 2

MATERIALS AND METHODS

Systematic literature review

At the core of this project is a systematic review of the literature, which is intended to identify evidence on facets of existing EHRs that can influence patient safety. A comprehensive search was conducted for the years 1990 to 2010 of the following databases: MEDLINE (PubMed); CINAHL, Computer Source, Computers and Applied Sciences, Library, Information Science and Technology Abstracts (EBSCO Host); ISI Web of Knowledge; Cochrane (Wiley); Compendex - Engineering Village; IEEE Xplore and Scopus. The specific search strategies that were used for each of these databases are provided in Appendix A.

The search of the MEDLINE database using the PubMed interface used a broad set of terms to capture literature relating to EHRs or EHR components, such as electronic prescribing or CDSS. Text word searches of article titles and abstracts were used to capture literature that may have been missed by MeSH subject heading categorization. Where indicated, multiple synonyms for key terms were incorporated including American and British spelling conventions. On pilot searches, using truncation of terms yielded a larger number of irrelevant results as compared with entering key terms individually. Thus, the latter approach was used for the final search although the resulting search strategy was complex. Limits were placed on the search results according

to exclusion criteria for the systematic review (see Table 1). However, results were not restricted on the basis of a narrowly defined research question, since one goal of the search was to identify a broad range of topics on which safety related EHR papers might be available.

For other databases, more general search terms were used. The goal of the search strategy was to be as comprehensive as possible within the defined date and language limits. A 20 year period for the search was selected to capture all relevant studies. Given the rapid advances in computers and technology, it seemed unlikely that older references would be relevant to modern EHR systems. The search strategies were limited to English, given the difficulties in accessing and translating non-English articles. No limits were placed on the types of studies that would be retrieved as part of the search process.

In addition to the searches of literature databases, other articles were identified during the course of the project by examining references in full text articles. Some additional, more recent references were also discovered in the process of reading the literature and finding full text documents. Publications of key authors, selected based on their expertise and quality of publications on the topics of EHRs and safety, were searched using the Web of Science Citation Index.

Process for screening the results of the literature search

The process for screening the results of the literature search relied on the previously determined inclusion and exclusion criteria for the systematic review (Table 1).

Table 1. Inclusion and exclusion criteria for literature searches and screening.

Inclusion criteria

Related to an EHR or EHR feature that could be used by clinicians in direct patient care AND could have a direct or indirect effect on patient safety

Study setting in an emergency department, outpatient or inpatient facility

Exclusion criteria

Other settings of care (e.g., home health, nursing homes, hospice)

Performance measurement or guideline adherence related to preventive care

Cost-effectiveness and cost-benefit analyses without clinical outcomes

Health information exchange as a sole purpose of the study

Stand-alone systems aimed at professional niches, if unconnected to CPOE/EHRs

Electronic reference materials (e.g., books, journals, databases)

Bioinformatics or other software used solely for research

Educational EHR systems used to train nursing or medical students

Chiropractic, podiatric, dental or veterinary EHRs

Patient generated personal health record systems

Secure electronic messaging systems

Billing, administrative or health information management systems

PACS and DICOM imaging systems

Laboratory processing systems

Pharmacy-specific systems

Bar code medication administration systems

Public health surveillance systems

Electronic registry systems

Natural language processing systems

Computer assisted diagnosis expert systems

As noted above, the search and screening processes intended to identify the widest range of interventions that could improve EHR safety. Thus, articles that were identified for further full text review included study designs other than randomized trials as well as topics that would not ordinarily be subjected to quantitative investigation. Such topics included articles on unintended consequences of EHRs, aspects of EHR usability or design that could influence data entry or cognitive errors, or ergonomics of EHR use.

Software used in screening the literature search results

After searching each of the literature databases, results were importing into Endnote (Version X4 for Windows, Thomson Reuters, New York, NY), which permitted batch elimination of duplicate citations. To facilitate the task of screening large numbers of study titles and abstracts in a rapid fashion, a database program was developed (see Appendix B) using Microsoft Access (Microsoft Corporation, Redmond, WA). Literature citations were exported from Endnote in Extensible Markup Language (XML) format and key fields (e.g., authors, title, source, abstract) were imported into Microsoft Access using an Extensible Stylesheet Language Transformation (XSLT) developed using XMLSpy (Version 2011, Altova, Inc., Beverly, MA). Some characters (e.g., &, <, >) could not be imported successfully into Microsoft Access and the Endnote records needed to be modified with text based substitutions (e.g., and, greater than, less than) before importing could proceed. For purposes of this project, all references were screened by the project author who is experienced in screening systematic review results for clinical practice guideline development.

Data extraction and synthesis

Each article that met the inclusion criteria was evaluated in detail and information from individual studies was extracted by the project author. This was facilitated by the use of software, Qiqqa (Quantisle, Ltd.; Cambridge, UK) that allows easy storage, searching and annotation of journal articles. The quality of individual studies was assessed using the recommendations of the Agency for Healthcare Research and Quality (AHRQ) for conducting systematic reviews (AHRQ, 2012). Estimates of the strengths and limitations on the body of evidence relating to key topics were also done by the project author using AHRQ methodological recommendations (AHRQ, 2012). Due to the heterogeneity of study designs, no meta-analyses were done.

Multiple different approaches are in use for rating the quality of research evidence and the strength of associated recommendations (AHRQ, 2002; AHRQ, 2012; Owens et al., 2009; Atikins et al., 2004), the AHRQ methodology was selected for several reasons. First, it incorporates many of the key features of the GRADE methodology, which is increasingly being used as an international standard for clinical practice guideline development and has been adopted by multiple professional organizations, the World Health Organization, the Cochrane Collaboration, the British Medical Journal, the United Kingdom's National Institute for Clinical Excellence and the United States' Agency for Healthcare Research and Quality. Additional advantages of this approach are that it can incorporate multiple types of evidence, can be used for systematic reviews and health technology assessments, provides explicit and comprehensive criteria for use and results in clear and pragmatic recommendations (Brozek et al., 2009; Atkins et al., 2004; Guyatt et al., 2008). The modifications to the GRADE approach that have been introduced by

AHRQ are in wide use by Evidence-Based Practice Centers in the United States and include a distinct rating for the applicability of the studied intervention (AHRQ, 2012). Such ratings are particularly valuable when assessing evidence on EHRs, since the study findings and applicability could vary with the specific EHR being used, the clinical setting, the patient population or other clinical parameters. Together these strengths make the AHRQ approach of particular applicability in developing recommendations to promote EHR-related patient safety.

CHAPTER 3

RESULTS

An overview of the literature search process and results are shown in Figure 1. In brief, titles and abstracts for 39952 citations were screened for relevance to the topic of EHRs and patient safety by the project author. On the basis of the previously defined inclusion and exclusion criteria, 1704 articles were identified for further review; full text was not available for 301 articles, but the remaining 1403 articles were reviewed for relevance. Of these references, 49 examined the effects of a modification to an existing EHR that was intended to have a direct or indirect benefit for patient safety. A systematic search was not done for the years 2011 or 2012; however, while the project was being completed, 8 additional relevant studies from those years were identified. No studies were found that addressed ways to minimize new risks associated with EHRs.

Of the 49 articles that were identified in the comprehensive search, all were present in MEDLINE. In terms of the representation of these articles in the searches from the other databases, 37 were present in Scopus, 21 in ISI Web of Science, 14 in the Cochrane database, 8 in the EBSCO Host database and 1 in the Engineering Village database. Information extracted from individual studies and assessments of the quality of individual studies and bodies of evidence are presented in Appendices C and D, respectively.

CHAPTER 4

DISCUSSION

Systematic review findings

This systematic review of safety-related modifications of EHRs searched a large number of medical, scientific and technological databases to optimize the sensitivity of the search. As with any literature search that is intended to be comprehensive, a substantial number of the citations did not appear to have direct relevance to the aim of the review. Even with duplicate references removed, only 0.12% of the screened citations were found to have direct relevance to safety-related modifications in EHR systems. In terms of the relative work effort, this means that on average 815 citations were screened for every one that was included in the final review. Best practice for systematic reviews requires that multiple databases be searched to maintain the search sensitivity (Institute of Medicine, 2011b). In this instance, all of the articles in the final review could have been identified through a search of PubMed alone. This would have led to a significant reduction in the work effort for the project as only 373 citations would have needed to be screened on average for each included article.

In the process of screening the titles, abstracts and a portion of full text articles, a number of factors contributed to the low specificity of the search. First, the initial strategy was intentionally developed to err on the side of being comprehensive. It seemed likely that important information about potential patient-safety related

modifications might be found in qualitative studies, quasi-experimental studies, case reports of EHR technology failures, expert commentaries or consensus statements. In fact, an additional 289 articles were marked by the project author for potential reference in the future, although they were not included in the ultimate analysis for this project. Often such articles or documents commented upon observed or potential EHR hazards that suggested potential approaches for EHR improvements (e.g., Magrabi et al., 2011; Jones, et al., 2011). For example, Ash et al. (2007) noted the possibility of new juxtaposition errors with CPOE that occurred when users clicked on a neighboring item rather than the intended one. Although not directly stated, one might be able to postulate a host of interventions that might reduce such entry errors. Using larger font sizes, placing more space between pick-list choices, limiting choices to those that are truly relevant, and incorporating best-practices for usability could each have benefits (Leavitt and Schneiderman, 2006). Optimizing the display of information to align the user interface with the clinical context could also be helpful (Ash et al., 2004). Each of these approaches could be illuminated through heuristic testing or through more detailed research (Borycki and Keay, 2010; Kushniruk and Patel, 2004; Zheng et al., 2009; Carvalho et al., 2009).

Apart from limiting the search to a smaller number of literature databases, a number of other approaches could have reduced the screening load and enhanced specificity (Booth, 2010). One technique that is sometimes used is to restrict the search to particular study designs (e.g., randomized controlled trials) as part of the formal search strategy. As much of the current research in HIT is quasi-experimental and blinding can be impossible due to clearly perceivable software differences, using strict delimiters on

study methodology would eliminate much informative research from consideration. It is conceivable that the majority of key articles on EHRs and safety are localized to a small portion of journals or journals with higher impact factors. Limiting a search to these types of journals might retrieve the bulk of the relevant literature. For example, Montori et al. (2003) examined publication patterns for systematic reviews and found that 80% could be found in a subset of about one-tenth of the journals. There was a weak but statistically significant correlation between journal impact factor and systematic review publication ($R^2 = 0.075$, $P = 0.0035$). Similar types of analyses could be conducted for EHR-related publications. Limiting the search to articles with abstracts only would eliminate letters and commentaries with potentially helpful information but would minimize the need to screen multiple titles related to single page or side bar overviews of EHR related issues.

Improvements in literature tagging (e.g., MeSH nomenclature) might also be helpful for identifying safety related articles in the future. Although the search strategy used in this project included search terms for EHRs as text words, a significant number of retrieved articles studied other medical problems and EHRs were mentioned only incidentally as the source of the research data. In addition, the rate of growth of articles on HIT safety appears to be more rapid than the general explosion of information in the medical literature. This is shown in Figure 2, which compares numbers of annual citations to English language articles in PubMed to the annual distribution of articles identified as part of this systematic review. There appears to be a flat but increasing rate

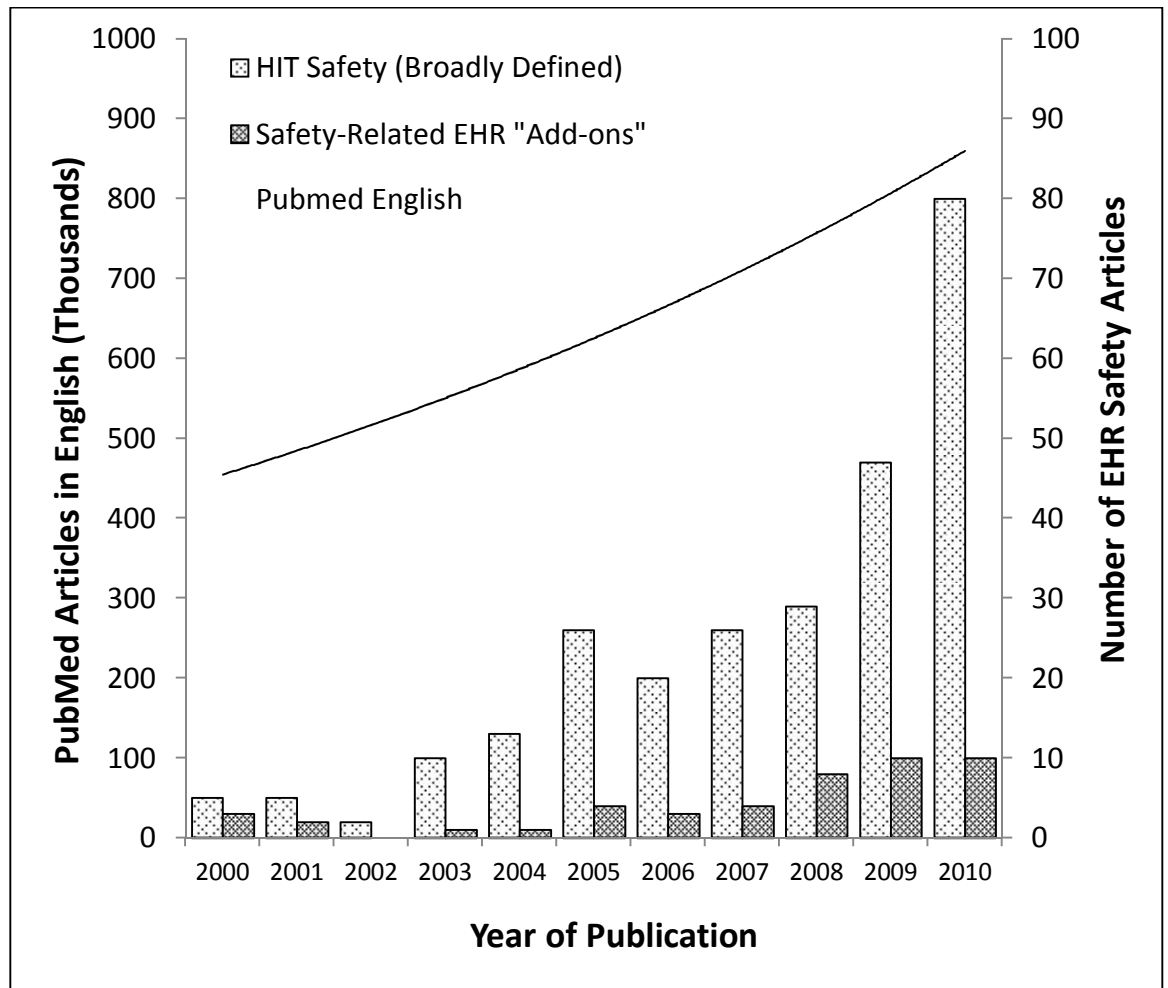


Figure 2. Comparison of annual publication rates of English language articles indexed in PubMed to rates of publication of HIT literature with direct or indirect relationships to patient safety. Light cross-hatched bars show the annual publication rates for articles on HIT safety as broadly defined. Dark cross-hatched bars show the annual publication rates for studies of modifications to EHR systems, aimed at enhancing patient safety. PubMed citations are indicated by the trend line.

of studies on EHR modifications to improve safety with a more rapid increase in broadly defined HIT safety literature. With such a growth in publications, compilations of relevant high quality references on HIT could provide important shortcuts for researchers, if updated on a regular basis. The Knowledge Library of the AHRQ National Resource Center for Health IT (AHRQ, 2012) is one example of such a literature repository.

In considering the results of this systematic review, a number of factors should be noted that are not consistent with detailed recommendations for systematic reviews (Liberati et al., 2009; AHRQ, 2012). A key limitation is that the screening of the literature was done by a single individual rather than by duplicate screeners. Having a single individual screening the literature introduces a greater risk of erroneously excluding relevant evidence than using duplicate screeners (Buscemi et al., 2006; AHRQ, 2012; Liberati et al., 2009). However, the time and effort required to do double screening of the literature would be extremely high for a project of this type. As a check on the adequacy of the screening process, the final results were compared against a recent systematic review of HIT safety (Institute of Medicine, 2011a) which was published after this project was begun and also included a systematic review of the literature. No articles were found that were cited in the evidence tables of the Institute of Medicine report and met the criteria for this review but had not already been identified. The likelihood of including an irrelevant reference is less problematic as the articles were read in detail prior to inclusion and the extracted information is included in Appendix C of this report as well as subsequent sections of the discussion. An additional limitation is that a portion of citations appeared to be of possible relevance from the title but it was not possible to locate the full text article despite searching the electronic journal collections at two major

university libraries and physically visiting the libraries of another major medical center and the National Library of Medicine. It seems unlikely that the author of an important study would choose to publish in a journal that is generally not accessible to readers. Nevertheless, it is possible that a relevant study was missed through lack of availability. A final limitation is that the information from each article was extracted by a single individual; summary tables and ratings of the body of evidence were also done by a single individual. As with the screening of the literature, duplicate extraction of data is a recommended best practice (AHRQ, 2012) but would have been difficult for a project of this type. However, the detailed evidence tables and summary ratings are included in appendices C and D and could be double-checked by an interested reader. Where indicated, these tables include a brief rationale for the chosen ratings. The likelihood of errors in ratings may also be reduced by the fact that the project author has some experience in applying the AHRQ methodology to evidence reviews in other contexts. In addition, the project author has extensive experience as an academic clinician and reviewer of scientific literature for guideline development and journal publication.

Interventions to improve patient safety with CPOE

Despite the comprehensive search and screening of the literature, no specific studies were identified that implemented a defined intervention aimed at minimizing "new errors" related to EHRs or CPOE. However, Bonnabry et al. (2008) examined the effect of CPOE implementation on patient safety from the vantage point of a Failure Modes, Effects and Criticality Analysis (FMECA) conducted before and after CPOE implementation. They also identified multiple criticality points that could benefit from

improvements to the CPOE system and recalculated the criticality indices based upon the anticipated benefits to safety. Based upon the sum of criticality indices, safety improved by 23% with CPOE implementation. Nevertheless, several indices were worsened by implementation of CPOE compared to the pre-CPOE state including inattention to vital signs, allergies or indicated drug monitoring and a greater risk of wrong date, wrong patient or wrong drug selection. The authors anticipated that multifactorial modifications in CPOE would result in an additional 43% reduction in the criticality indices. These planned modifications included alerts for omitted treatments, omitted allergies or antibiotic suggestions as well as integration of vital signs into the record and adjustments in printed prescriptions. In terms of specific patient safety related tasks, improvements in CPOE were expected to result in a lower risk of wrong patient selection, more appropriate treatment choices, and greater attention to vital signs, drug interactions/contraindications, allergies, and drug monitoring.

The use of a structured FMECA provides one mechanism for organizations to assess the potential risks associated with EMR implementation, but the judgments needed for determining criticality indices (Bonnabry et al., 2008) are subjective ones. In addition, the specifics of the software and hardware at a specific organization will have a sizeable effect on the risks identified by the FMECA and the potential for elements of EHRs to be improved, worsened or both by modifications. This makes it difficult to draw generalizable conclusions from a FMECA-based before-after study design. Nevertheless, this article suggests that systematic assessments of CPOE implementations can be helpful to organizations in making process improvements.

Interventions to improve computerized medication decision support

A number of studies have looked broadly at decision support added to an existing EHR or CPOE system in order to assess benefits on medication prescribing. Bates et al. (1999) compared the rates of medication errors (other than missed doses) across their sequential implementation of CPOE in which increasing amounts of decision support incorporated into the system. In the baseline phase, prescribers wrote orders on paper. During period 1, CPOE with basic decision support was implemented. Additional allergy checking was added in period 2 and enhanced drug-drug interaction checking was added along with improved ordering features for potassium during period 3. Over the course of the implementation, there was a statistically significant reduction in non-missed dose medication errors ($p=0.0001$), missed dose medication errors ($p=0.0001$), non-intercepted ADEs ($p=0.0006$), preventable ADEs ($p=0.05$), and non-intercepted serious medication errors ($p=0.0003$). However, these calculations include the effect of CPOE implementation as well as the effects of gradually increased decision support. From period 1 to period 2, the rate of non-missed-dose errors per admission was stable at 0.27 to 0.28 whereas with the addition of drug-drug interaction checking and enhanced potassium ordering it fell to 0.11 non-missed dose errors per admission. Non-intercepted potential ADEs per 1000 patient days fell from 1.5 in phase 1 to 0.6 in phase 2 and then to 0 in phase 3. Preventable ADEs per 1000 patient-days fell from 5.7 in phase 1 to 1.1 in phases 2 and 3 whereas non-intercepted serious medication errors per 1000 patient days fell from 7.3 in phase 1 to 1.7 and 1.1 in phases 2 and 3, respectively. Thus, across multiple measures, implementing robust CDSS as part of an existing CPOE system resulted in reductions in medication errors and adverse drug effects.

Scott et al. (2011) developed 30 clinical scenarios consisting of a clinical vignette, a prescribing task, and an e-prescribing alert intended to warn the prescriber about an error in prescribing that was built into the scenario. The scenario also described the point in the prescribing process when the alert would be presented. Nine of the scenarios were designated as “calibration scenarios” whereas the remaining 21 scenarios were used as testing scenarios. For the testing scenarios, 24 junior physicians were randomized to receive no alert, a non-modal alert that passively presented information to the prescriber without requiring a response and a modal alert that required a response by the prescriber. Using a mixed effects logistic regression analysis, the authors found that the type of alert presented to the prescriber had a highly significant effect on the prescribing error rate ($p < 0.0001$). Prescribing errors were reduced by modal and non-modal alerts (by 12 times and 3.6 times respectively) compared to a 51.8% prescribing error rate with no alert. The error rate with modal alerts was also significantly less than with non-modal alerts. There was also a shift in the distribution of errors per prescribing scenario, with a greater proportion of scenarios in the modal alert group that had no errors. This study suggests that modal and non-modal alerts are each effective in reducing prescribing errors but that modal alerts lead to more robust reductions in errors.

Tamblyn et al (2008) stratified active physician users of an electronic drug management system by clinic. Users were then randomly assigned to receive either computer-triggered or on-demand medication decision support and were blinded to outcome. Alerts were categorized according to 3 levels of severity and prescribers could adjust the category of alerts that would be shown. Prescribers could also override individual alerts but had to note their reasons for doing so. On demand alerts were

identical to computer-triggered alerts but could be accessed by the physician at any time in the prescribing process by clicking on a menu choice in the system. With the exception of therapeutic duplication for which a small but statistically significant decrease was seen in the computer-triggered group (4.3 % active vs. 5.4 % passive alert), there was no difference in the prevalence of specific types of prescribing problems, the severity of prescribing problems or the presence of any prescribing problem. Physicians receiving computer-triggered alerts were more likely to adjust their alert settings so that they were presented only with alerts of the highest severity (35.7% vs. 14.3 %). In addition, those receiving computer-triggered alerts were more likely to see an alert (668 alerts/6505 prescribing problems vs. 41 alerts/4445 prescribing problems) but also more likely to ignore an alert (87.8% vs. 24.4%). The authors concluded that prescribing problems persisted despite the use of two distinct approaches to medication related decision support. However, they favored customizing computer-triggered alerts as the best way to reduce prescribing errors.

Paterno et al. (2009) assessed whether rates of adherence to medication-related decision support differed at a site that received tiered decision support alerts (by severity) as compared to a site that did not receive tiered alerts. The two sites used the same CPOE and decision support systems and over 70,000 alerts were reviewed between the two sites. Patient demographics between the two sites were comparable. The use of tiered as compared to non-tiered alerts was associated with greater adherence to moderate and severe alerts (29% vs. 11% and 100% vs. 34%, respectively; $p > 0.001$ for each comparison). The interruptive low severity alerts at the non-tiered site were over-ridden more than 90% of the time and likely contributed to alert fatigue. The authors suggested

that a shift to non-interruptive low severity alerts at the tiered site made physicians more receptive to the more severe alerts.

This group of studies suggests that the addition of medication related decision support can reduce potential prescribing errors in prototype (Scott et al., 2011) and production EHR systems (Bates et al., 1999), although this is not invariably true (Tamblyn et al., 2008). In addition, these studies suggest that the way in which alerts are configured can have a significant effect on the proportion of alerts that are over-ridden or ignored (Scott et al., 2011; Tamblyn et al., 2008; Paterno et al., 2009). Unfortunately, they do not give a clear answer as to the most effective way to balance issues of alert severity and type (e.g., adjustable, interruptive versus non-interruptive) against the risks of "alert fatigue." (Kesselheim et al. 2011; McKibbon et al., 2011; Cash, 2009). Further research on ways to customize the alerting process would be valuable in enhancing usability for prescribers and safety for patients.

It is also not clear whether more effects approaches could be developed to allow users to visualize the clinically important aspects of medication alerts in a more usable fashion. For example, Duke et al. (2009) has developed an approach for displaying the relative likelihood of various drug side effects based upon the list of medications that a patient is receiving. Users can then "drill down" from a graphical display to learn more about a specific side effect. Other proposed models for alerts are unintended to give physicians more control over the alerting system while channeling knowledge in a way that better supports clinical decision making (Wipfli and Lovis, 2010). Existing web-based drug information resources (e.g., GeneMedRx, Genelex Corporation, Seattle, WA) provide detailed information about drug-drug interactions based on knowledge of

cytochrome P450 enzyme, UDP-glucuronosyltransferases and physiological transporters and gives clinicians an estimate of the effect of drug combinations on plasma drug levels. This type of knowledge can be very useful in identifying the magnitude of likely drug interactions and whether they are likely to be clinically relevant or theoretical. Existing decision support software also varies in its ability to detect important interactions (Saverno et al., 2011) and in user perceptions about the reliability and clarity of that information (Van der Sijs et al., 2009; Shah et al., 2006). Also, clinician responses to alerts are not typically integrated with chart documentation or available to other users to explain clinical thought processes. This adds to clinicians' tendency to deal with alerts in a reflexive fashion, minimizing their utility. Combining clinically useful information with more technologically usable alerts could also reduce alert fatigue while benefiting patient care.

Interventions to improve the ordering of appropriate laboratory monitoring of pharmacotherapy

A key aspect of medical practice involves ongoing assessments for side effects of prescribed medications. Some of these side effects can be observed by the clinician or reported by the patient, but others involve end organ effects that are best detected through laboratory testing. Although some of these side effects only appear with longer term medication use and may be considered as preventive interventions, others relate to more acute safety considerations. Thus, the body of this evidence was included in this project.

Lo and colleagues (2009) conducted a study of 366 providers in 21 clinics who were prospectively assigned based on a stratified randomization (by clinic) to use either

the standard EHR or the standard EHR with non-interruptive alerts, which advised prescribers of recommended laboratory monitoring in conjunction with specific medications. Over the 6 month study, there were 3673 prescribing events among 2765 patients that would have warranted consideration of laboratory monitoring. The authors found no significant differences between the rates of ordering of recommended laboratory studies between the two groups (odds ratio 1.048, 95% CI 0.753 to 1.457). This lack of an effect was observed when the data were considered overall, by drug class or by ordered test. Thus, this study provides no support for including non-interruptive alerts to increase ordering of appropriate baseline laboratory tests in relationship to pharmacotherapy.

Palen et al. (2006) implemented a non-intrusive decision support alert that suggested ordering of recommended laboratory studies when specific medications were prescribed. Primary care physicians practicing in an ambulatory setting as part of a managed care organization were randomized to either receive these alerts in conjunction with the standard CPOE system or to use the CPOE system without the alerts. Appropriate laboratory testing occurred for 56.8% of index medication orders (19451/34242 orders) and there were no differences in the receipt of laboratory tests in the intervention group as compared with the control group. There was a statistically significant difference noted for 3 medication classes (methotrexate, statins and gemfibrozil), but this may have been due to chance alone given the large number of medications and medication classes that were being studied.

Matheny et al (2008) stratified 20 primary care ambulatory clinics, including community health centers, hospital-based clinics and off-site practices and then randomly

assigned an equal number of sites to serve either as a control or receive electronic reminders for recommended laboratory monitoring in association with the use of specific medications. Over the 6 month study period, there were 21083 patients who were taking one of the targeted medications and were seen by one of 464 physicians. Approximately one-tenth of patients had overdue laboratory monitoring for which testing was recommended. Rates of appropriate monitoring varied depending upon the laboratory test, but were high in both the intervention and control groups. None of the rates of laboratory test ordering for a specific medication were influenced by the implementation of computer prompts. Thus, the findings of this study suggest that for chronically administered medications augmenting CPOE with computer alerts does not improve adherence with recommended monitoring.

Steele et al. (2005) assessed the proportion of orders for which prescribers adhered to medication-related laboratory monitoring before and after advanced decision support was added to an existing CPOE system. Although there was no significant difference in adverse drug events during the intervention period, recommended laboratory tests were more likely to be ordered during the intervention period as compared to the baseline period (51% vs. 39%, respectively). In addition, high risk medication orders were more likely to be cancelled in the presence of a laboratory abnormality during the intervention period (10.9 vs. 5.6% during the control period). The occurrence of adverse drug events was determined through retrospective chart review but implementation of the alert was not associated with any difference in adverse events.

Overhage et al. (1997) randomly assigned physician teams to a control group or to an intervention group that received suggestions for additional laboratory orders that were

indicated within the context of the initial medication order. Examples of such "corollary orders" included renal function tests prior to an intravenous pyelogram, serum levels with specific antibiotics, electrolytes in patients receiving potassium supplementation or hematologic studies in patients receiving warfarin. During the 30 week study period, physician teams treated a total of 2181 patients and, of these, 77.3% had at least one order written that triggered suggestions for "corollary orders." Altogether, the 7394 trigger orders generated 11404 additional ordering suggestions. Computer prompts were associated with clinically and statistically significant improvements in the ordering of appropriate corollary orders relative to the control condition, regardless of whether adherence was measured immediately (46.3% intervention vs. 21.9% control), at 24 hours (50.4% intervention vs. 29.0% control) or at the end of the hospital stay (56% intervention vs. 43.5% control). However, the absolute levels of adherence and the differences between the control and intervention conditions were highly variable depending upon the specific "corollary order that was being recommended. This suggests that computerized alerts can assist in enhancing adherence with recommended laboratory monitoring of pharmacotherapy but that other confounding factors may also influence adherence.

Galanter et al. (2004) examined the effect of a set of decision supports aimed at enhancing the safety of digoxin prescribing. Alerts were aimed at monitoring potassium and magnesium levels, maintaining normal potassium and magnesium levels, minimizing the potential for drug-drug interactions with digoxin, assessing for recent digoxin serum levels and maintaining therapeutic serum levels of digoxin. The alerts could be presented either synchronously at time of ordering or asynchronously at time of posting of relevant

laboratory abnormalities. The study used retrospective data on relative adherence to recommended best practices prior to the initiation of the alerts (when only a standard commercial CPOE system was in place) as well as data collected after the digoxin decision support was implemented. There were 310 patients' records examined and approximately 800 alerts during each study period. The control and intervention groups did not differ in their use of potassium or magnesium supplementation by 24 hours in response to a low potassium or magnesium level at the time of digoxin ordering. However, at 24 hours there were statistically significant effects of the intervention compared to the control condition in terms of ordering indicated digoxin (38% vs. 22%), potassium (81% vs. 49%) and magnesium levels (66% vs. 44%) and in terms of giving potassium (87% vs. 70%) or magnesium (93% vs. 77%) supplementation in response to an asynchronous alert about low electrolyte values. In discussing their findings, the authors note the differences in prescribers, responses to the different alerts as well as the fact that individuals receiving alerts were able to take recommended actions with less delay than those who did not receive alerts, even for those situations in which the overall adherence at 24 hours was comparable.

Stewart et al. (2003) implemented an interactive template as part of the Veteran's Administration Computerized Patient Record, which was presented at the time of amiodarone ordering. The template documents the justification for amiodarone use and gives links to appropriate monitoring orders. Amiodarone was ordered in 341 patients prior to template initiation and 316 patients afterwards, although the template was used in only 172 of the latter group. When the template was not used, there was no difference in the rates of laboratory monitoring as compared to the pre-template condition. However,

when the template was used, significant improvements in monitoring rates were noted (63.6% before vs. 88.9% after for liver function tests; 55.7% before vs. 84.9% after for thyroid function tests; 20.5% before vs. 29.1% after for pulmonary function tests; 34.6% before vs 75.3% after for chest radiography; and 34.6% before vs 68.6% after for ophthalmology examination). These results suggested that decision support approaches that facilitate ordering of indicated tests may better support adherence to monitoring recommendations than alerts alone.

In contrast, Abboud et al. (2006) found no effect of an alert that recommended aminoglycoside levels upon ordering of an aminoglycoside and also provided the option for placing serum level orders. Adherence with appropriate monitoring was assessed before and after implementation of this alert. Over the course of the 6 month study, 275 patients received 336 courses of an aminoglycoside. In 18.5% of these courses, there were no serum levels drawn and of the 548 levels that were obtained, 20.8% were neither a peak nor a trough level. There was no difference in the frequency or appropriateness of serum level monitoring and no differences in the proportion of patients with toxic or therapeutic levels during the after period as compared to the before period. Although this study was limited to a pediatric acute care setting, it did not show any effects of alerts for aminoglycoside monitoring.

Traugott et al. (2011) implemented decision support alerts aimed at improving the appropriateness of ordering serum vancomycin orders, including the timing of blood collection and the justification for obtaining vancomycin levels. A retrospective review examined charts from 100 individuals who had had vancomycin levels obtained before the alert was implemented. Findings on the appropriateness of vancomycin level orders

were compared with a similar group of 100 patients who had had vancomycin levels done after the alert implementation. With the vancomycin alerts, the appropriateness of orders for vancomycin levels was significantly improved (58% pre vs. 68% post) although a sizeable fraction of vancomycin levels continued to have incorrect timing relative to the prior dose (55% of inappropriate orders). Furthermore, the improvement in the appropriateness of orders for vancomycin levels was only observed with initial vancomycin orders and not with subsequent levels that were ordered later in the hospital course. Thus, decision support did seem to improve ordering of vancomycin levels but confounding factors may also be present and require further elucidation.

Two studies have assessed the effects of decision support on the required monitoring for treatment with retinoic acid derivatives. Koide et al (2000) conducted a before-after study at a Japanese teaching hospital, in which a computerized alert that advised physicians of the need for normal aminotransferase levels within 3 months of etretinate prescribing. Once the alert was presented, it could either be overridden or orders for aminotransferase levels could be placed. During the study, 1022 etretinate prescriptions were written and only about 5% were prescribed to inpatients.

Implementation of the alert was associated with a clinically and statistically significant increase in the appropriateness of etretinate prescribing (25.9% pre vs. 66.2% post; $p > 0.0001$). There was also a decrease in the number of individuals who received etretinate despite having abnormal liver function tests (32% pre vs. 13% post). Three individuals (11%) who received a prescription for etretinate had markedly abnormal aminotransferase levels before the alert was implemented in contrast to no such individuals after the alert was in place.

Tang et al. (2009) developed a charting template to advise physicians of recommendations including necessary laboratory monitoring in association with isotretinoin therapy. The template was implemented in an outpatient dermatological center in Singapore in which an electronic medical record was already in use. Compared to the control condition preceding template use, implementation of this decision support tool was associated with a significant improvement in overall adherence to prescribing recommendations (57.5% before vs. 97.8% after; $p < 0.05$). Rates of monitoring of liver function and lipid tests were already high at 96.2% before the template was initiated but were done in 100% of patients after the intervention. Together, these results suggest that for potentially toxic medications such as retinoic acid derivatives, that computerized decision support alerts can improve the appropriate use of laboratory monitoring.

Table 2 summarizes the body of evidence on the effects of adding decision support relating to laboratory monitoring to an existing CPOE or EHR system. Although the evidence includes multiple randomized trials and well-designed quasi-experimental studies of fair to good quality, the study findings are variable and range from positive to neutral. This may not be surprising given the heterogeneity in the design of decision support and alerts across studies. In addition, physicians may have differing responses to alerts depending upon the perceived likelihood of the abnormality with a specific medication and the perceived severity of the effect if it were to occur. Future research is needed to tease apart these types of confounding factors to optimize decision support for essential laboratory monitoring.

Table 2. Summary of evidence on adding laboratory monitoring decision support to existing EHRs

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Lo et al. (2009)	Outpatient; primary care; US	Non-interruptive; recommending baseline tests	Randomized controlled trial, prospective	Good	Rate of ordering of indicated baseline laboratory tests	Neutral
Palen et al. (2006)	Outpatient; primary care; managed care organization; US	Non-interruptive; recommending medication-related tests	Randomized controlled trial, not-blinded	Good	Proportion of medication orders for which appropriate laboratory testing was ordered within 180 days before or 14 days after medication dispensing	Neutral, but variable
Matheny et al. (2008)	Outpatient; primary care; US	Non-interruptive; recommending medication-related tests	Cluster randomized controlled trial, stratified	Good	Proportion of patients who received recommended laboratory monitoring within 14 days	Neutral
Steele et al. (2005)	Outpatient; primary care; US	Alerts recommending medication-related tests	Before-after study	Fair	Percent adherence with recommended laboratory orders, percent of cancelled orders, rates of adverse drug events	Improved

Table 2. Summary of evidence on adding laboratory monitoring decision support to existing EHRs (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Overhage et al. (1997)	Inpatient internal medicine service; academic center; US	Alerts recommending medication-related tests and allowing easy ordering	Cluster randomized controlled trial	Good	Rates of physician adherence to ordering recommended laboratory monitoring calculated based on immediate ordering, ordering within 24 hours or ordering during the hospital stay	Improved, but variable
Galanter et al. (2004)	Inpatient; academic center; US	Complex decision support related to digoxin prescribing	Before-after	Fair	1 hour and 24 hour adherence with recommended safe practices	Improved, but variable
Stewart et al. (2003)	Veteran's Health System; US	Interactive ordering template	Before-after	Poor	Rates of laboratory monitoring with template use	Improved
Abboud et al. (2006)	Inpatient; pediatric; academic center; US	Alerts recommending aminoglycoside-related tests and allowing easy ordering	Before-after	Fair	Date, time and results of aminoglycoside levels in association with orders for aminoglycosides	Neutral

Table 2. Summary of evidence on adding laboratory monitoring decision support to existing EHRs (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Traugott et al. (2011)	Inpatient; academic center; US	Alert recommending vancomycin-related tests and allowing easy ordering	Before-after	Fair	Percent change in appropriateness of orders for vancomycin levels	Improved
Koide et al. (2000)	Academic center; Japan	Alert recommending etretinate-related tests	Before-after	Fair	Proportion of prescriptions for etretinate for which appropriate hepatic function tests were assessed within 90 days	Improved
Tang et al. (2009)	Outpatient; dermatology; Singapore	Interactive ordering template for isotretinoin	Before-after	Fair	Rates of adherence to recommended laboratory testing	Improved

Interventions to improve prophylaxis of venous thromboembolism

Hospitalized patients who are immobilized are at elevated risk for VTE including deep vein thrombosis (DVT) and pulmonary embolus (PE); prophylactic treatment of high-risk individuals has therefore been recommended (Geerts et al., 2008; McLeod and Geets, 2011). Since the rates of adherence to such recommendations has typically been low among clinicians, much effort has focused on ways to leverage EHR decision support tools to increase rates of indicated VTE prophylaxis.

Kucher et al (2005) conducted a randomized controlled trial of computerized decision support in hospitalized medical and surgical patients who were at risk for DVT. Consecutively admitted patients were assessed for risk of VTE and the presence of existing orders for VTE prophylaxis. Patients who were at risk but had had no orders for prophylaxis (N=2506) were randomly assigned based on their medical record number to have an alert presented to the treating physician or be allocated to a control condition with no computerized alerting or guidance. There was a statistically significant increase in the proportion of patients who received prophylaxis (33.5% with alert vs. 14.5% without alert) and this was true for mechanical as well as for pharmacological prophylaxis (10% vs. 1.5% and 23.6% vs. 13.0%, respectively). There were statistically and clinically significant reductions of DVT or PE at 30 and at 90 days (4.9% with alert vs. 8.2% without alert), corresponding to a 41% reduction in the risk of VTE at 90 days. In terms of potential adverse effects of VTE prophylaxis, there were no differences in the rates of death (at 30 or 90 days) or hemorrhage (measured only at 30 days). These findings suggested substantial benefits of implementing alerts to provide clinicians with

reminders about the importance of VTE prophylaxis and the recommended options for prophylactic interventions.

Lecumberri and colleagues (Lecumberri et al., 2008; Lecumberri et al., 2011) implemented decision support for VTE prophylaxis at an academic hospital in Spain. The alert notified physicians of patients who were at high risk of VTE and provided links that described recommended VTE prevention options. The investigators assessed rates of VTE during a six month period before initiating the decision support as well as in corresponding 6 month periods during 4 successive years after beginning the VTE decision support. Each study period included data from approximately 6500 individuals, about half of whom were hospitalized on medical services and about half on surgical services. Overall, during the intervention periods, alerts were issued for 35.3% of patients and, of those, 79.9% of the alerts were accepted and led to the prescription of appropriate prophylaxis. However, among patients with medical conditions, alerts were presented in only 15% of patients as compared to 51% of surgical patients. Similarly, alerts that did occur for surgical patients were more likely to be accepted than in medical patients (87.1% vs. 71.5% respectively). Implementation of the VTE alerts was associated with a significant decrease in VTE events overall (odds ratio 0.5; 95% CI 0.28-0.84), but this was driven by a reduction in VTE events among the medical patients as there was no effect of the VTE decision support among surgical patients. There was also no change in overall mortality or bleeding in association with the addition of VTE decision support. Thus, these studies also showed evidence for the benefits of VTE prophylaxis and no increase in the risk of harms with intervention.

Novis et al. (2010) incorporated a standardized risk assessment for VTE into the pre-surgical admission assessment and also included an ability to place recommended orders as a subsequent step of the assessment. Overall, 800 patients were included in the study and there were no significant difference in the demographics or types of surgery received by the pre- and post-implementation groups. There were significant improvements in the proportion of patients who received recommended pharmacological prophylaxis pre-operatively (14% before vs. 36% after; $p < 0.001$) or who received both pharmacological and mechanical prophylaxis pre-operatively (5% before vs. 32% after; $p < 0.001$). Ordering of post-operative prophylaxis with sequential compression devices (50% before vs. 63% after; $p < 0.001$) and with combined mechanical and pharmacological prophylaxis (32% before vs. 49% after; $p < 0.001$) was also increased by the implementation of the VTE assessment. There was a trend for a reduction in the incidence of DVT but numbers were small. No increase in bleeding complications was noted, confirming the relative safety of prophylactic treatment.

Sobieraj (2008) developed a pilot computerized alert on a medicine unit that advised prescribers of the need to assess patients for VTE risk and order appropriate pharmacological and mechanical prophylaxis. Compared to the period of time before the alert was implemented, activation of the alert was associated with a significant improvement in the rates of appropriate VTE prophylaxis (49% before vs. 93 % after; $p < 0.001$). Although the overall sample of 101 patients was relatively small, improvement in pharmacological prophylaxis was particularly prominent.

Durieux et al. (2000) examined the effect of a computerized alert about VTE and preventive options on the rates of appropriate ordering of prophylaxis in 1971 orthopedic

surgery patients in a French urban academic hospital. They alternated intervention and control groups (4 control periods and 3 intervention periods) and separated each phase with a washout period. Overall, adherence to VTE prophylactic recommendations occurred in 82.8% of patients during the control period and 94.9% of patients during the intervention periods ($p < 0.001$). As compared to the intervention period, the relative risk of not receiving indicated prophylaxis during the control period was 3.8 (95% CI 2.7-5.4). The effect of the decision support was greatest for individuals at moderate risk of VTE as compared to those at low or high risk of VTE. This is likely due to the fact that many fewer individuals at moderate risk received an initial prescription of VTE prophylaxis that was appropriate. Overall, however, this study suggested that decision support can be successful in promoting appropriate prescribing of VTE prophylaxis.

Candelario et al. (2010) randomly selected the charts of 126 cancer patients who were hospitalized in the year after implementing a computerized decision support alert aimed at enhancing rates of prophylaxis for VTE. Of the 116 individuals who were eligible to receive prophylaxis, 90.5% received some form of prophylaxis and 76.7% received adequate prophylaxis. This contrasted with the rates of prophylaxis noted in the retrospectively reviewed charts of patients hospitalized before use of the alert. Of those 410 individuals, 48.5% received some form of prophylaxis and 26.3% received adequate prophylaxis. In the facility overall, VTE rates before initiating the alert were 4.2% with a rate of 2.8% in the year after the alert. For a group of comparison academic facilities, the corresponding rates of VTE in hospitalized cancer patients were 3.7% and 5.1%, respectively. The before-after nature of the study design may introduce some confounding of the observed effects, particularly since the authors note that other

interventions to enhance awareness of VTE were implemented over the same period that the computerized alerts were introduced. Nonetheless, patients with cancer are at particularly increased risk of VTE (Agnelli and Verso, 2011) and the benefits of computerized alerts for this patient population were promising.

Dexter et al. (2001) implemented decision support alerts that reminded physicians to order a number of preventive interventions on patients admitted to a general medicine service of an academic hospital. General medicine teams were assigned to either the intervention or control conditions. Although about half of the physicians were assigned only to the intervention condition, other physicians spent time on both intervention and control teams. The authors note that their results were unchanged when this latter group was excluded from the analysis. In terms of adherence to the recommendations for subcutaneous heparin prophylaxis (for venous thromboembolism), 17% of the 6371 patients were eligible for prophylaxis. Heparin was more likely to be ordered when indicated for patients in the intervention group as compared to the control group (32.2% vs. 82.9% respectively; $p < 0.001$). Some patients had more than one hospitalization and a similar improvement was found in the intervention group when calculated based on the rates per hospitalization rather than by patient. The other preventive reminders that the authors' studied also showed benefits of the reminders though their content was outside of the scope of this review.

Teich et al. (2000) describe a number of interventions designed to modify physicians prescribing habits in an inpatient academic setting. Of these interventions, one involved an alert to suggest ordering of subcutaneous heparin for patients placed on bed rest who are not already receiving heparin or warfarin. The authors showed a

significant improvement in the proportion of patients receiving subcutaneous heparin for prophylaxis for VTE after the alert was implemented (23.9% before vs. 46.9% after; $p < 0.001$ in a total sample of 6452 patients over the course of the study). At 1 and 2 year followup intervals, there was no diminution in the response to the alerts, suggesting an ongoing benefit of the alerts.

Galanter et al. (2010) included a computerized VTE risk assessment form in a commercial EHR. Although the form was not linked to specific orders, surveillance was done by hospital staff independent of the EHR. The authors used an administrative data base to retrospectively review charts for the presence of VTE or major or minor bleeding in association with VTE prophylaxis; they used blinded reviewers to determine these outcomes. As compared to rates of VTE prophylaxis before the risk assessment was initiated, use of the form led to an increase in prophylaxis rates (25.9% before vs. 36.8% after; $p < 0.0001$). Improvements in the proportion of patients receiving prophylaxis were statistically improved in all patient groups except orthopedic surgery. This latter finding may relate to the fact that the orthopedic surgery patients already exhibited high baseline rates of VTE prophylaxis. However, the intervention was not associated with any overall changes in the proportion of patients with hospital acquired VTE. There was no associated change in the rates of bleeding events with the intervention.

Baroletti et al. (2008) examined the effects of an electronic alert to a responsible physician for patients who were at high risk of VTE but not receiving prophylaxis. Such patients accounted for 9.1% of the 9527 patients hospitalized during the study period and were predominantly medical service patients. As compared to a historical control, there were no differences in the ordering of prophylactic treatment and no differences in rates

of DVT, PE, bleeding or mortality. However, the design of the trial includes multiple opportunities for confounding factors that could influence the study results.

Fiumara et al. (2010) developed an enhanced VTE alert with more screens of information than contained within the initial VTE decision support. These multi-screen alerts were presented to physicians who had not responded to a single screen recommendation to provide prophylaxis for VTE. Compared to a cohort that responded to a single recommendation screen, the physicians who received the three screen alert had a greater rate of prescribing prophylaxis (50.8% vs. 58.4%, respectively). There were no differences in the rates of DVT or PE in the two groups but mortality was greater in the group for whom physicians had received the three-screen alerts. However, interpretation of these results is confounded by significant differences in the medical, surgical and demographic characteristics of the patient groups.

Kucher et al., (2009) compared the effects of a flashing non-interruptive electronic alert to their prior rates of VTE prophylaxis with a different VTE alert type. They found an improvement in rates of prophylaxis (from 44% to 76%) over a 3 year period, however, detailed statistical comparisons were not provided. The primary focus of their study with the enhanced electronic alert related to analysis of possible alert fatigue as they found a reduced rate of prophylaxis in physicians caring for more than 20 patients as compared to those caring for fewer patients. As alerts were presented on all patients, the authors hypothesized that alert fatigue may have contributed to this difference.

Overall, research on reducing VTE through decision support has yielded mixed findings (see Table 3). This may related to differences in the types of alerts and decision

support that are presented to physicians, the variable quality of the research and study design, the differences in VTE risk in key patient subgroups, and the high baseline rates of VTE prophylaxis in some studies. In general, the studies that were of fair to good quality and had adequate sample sizes showed consistently positive findings that were statistically and clinically significant in terms of enhanced adherence to recommended VTE prophylaxis as well as reductions in rates of DVT and PE. There were no reported increase in patient harms (e.g., bleeding), except in one poorly designed study, in which many baseline demographic differences were present that could have influenced mortality. In terms of decision support design, it remains unclear whether a simple reminder for VTE prophylaxis is sufficient or whether there are independent contributions to adherence with integrated risk assessment tools or an ability to order directly from the alert. For these more complex risk assessment and ordering tools, it will be particularly important to update software prompts as knowledge of VTE prophylaxis progresses (Wright, et al., 2011). Indeed, for medical patients and those hospitalized for stroke, a recent systematic review suggested that the risks of VTE prophylaxis may outweigh the potential for benefit (Lederle et al., 2011).

Table 3. Summary of evidence on adding decision support to existing EHRs to improve VTE prophylaxis

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Kucher et al. (2005)	Inpatient medical and surgical patients, academic center; US	VTE risk assessment; prophylaxis recommendations	Randomized controlled trial	Good	Rates of prophylaxis DVT or PE at 90 days	Improved Improved
Lecumberri et al. (2008) & Lecumberri et al. (2011)	Inpatient; academic center; Spain	Recommend VTE prophylaxis by risk level; ordering options	Before-after, with 4 after periods	Fair	Incidence of VTE Mortality Bleeding	Improved Neutral Neutral
Novis et al. (2010)	Inpatient, surgical patients; Veterans Administration Hospital; US	VTE risk assessment; prophylaxis recommendations; ordering options	Before-after	Fair	Rates of prophylaxis DVT or PE at 90 days	Improved Neutral
Sobieraj (2008)	Inpatient; community hospital; US	VTE risk assessment; prophylaxis recommendations	Before-after	Fair	Rates of prophylaxis	Improved
Durieux et al. (2000)	Inpatient; orthopedic surgery patients; academic center; France	Recommend VTE prophylaxis by risk level	Alternating OFF-ON periods with washouts	Good	Rates of prophylaxis	Improved

Table 3. Summary of evidence on adding decision support to existing EHRs to improve VTE prophylaxis (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Candelario et al. (2010)	Inpatient; oncology; academic center; US	Recommend VTE prophylaxis	Before-after design with retrospective pre-intervention comparison	Fair	Rates of prophylaxis VTE rates	Improved Improved
Dexter et al. (2001)	Inpatients; medical service; academic center; US	Recommend subcutaneous heparin prophylaxis	Non-randomized parallel intervention and control groups	Fair	Rates of prophylaxis	Improved
Teich et al. (2000)	Inpatient; academic center; US	Recommend subcutaneous heparin prophylaxis	Before-after	Fair	Rates of prophylaxis	Improved
Galanter et al., 2010	Inpatient, adults, academic center, US	Computerized risk assessment form	Before-after	Fair	Occurrence of VTE Major/minor bleeding Rates of prophylaxis	Neutral Neutral Improved

Table 3. Summary of evidence on adding decision support to existing EHRs to improve VTE prophylaxis (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Baroletti et al., 2008	Inpatients, adult, academic center, US	Electronic alert to physician if high-risk VTE patient was not on prophylaxis	Cohort with historical control	Poor	VTE at 90 days Mortality Bleeding Physician response	Neutral Neutral Neutral Neutral
Fiumara et al. (2010)	Inpatients, adult, medical or surgical service, academic center, US	Enhanced VTE alert for clinicians who did not respond to initial alert	Cohort	Poor	Use of prophylaxis VTE rate at 90 days Mortality	Improved Neutral Worsened
Kucher et al. (2009)	Inpatients, adult, medical service, academic center, Switzerland	Flashing electronic alert for patients not receiving VTE prophylaxis; ordering options	Cohort with historical control	Poor	Rate of prophylaxis	Improved

Interventions to reduce rates of medication errors in pediatric patients with electronic prescribing

Pediatric patients form an important subgroup of patients for whom medication errors are relatively common and more likely to produce harm (Ghaleb et al., 2006; Miller et al., 2007; Leonard, 2010; McKibbin et al, 2011). Several factors can contribute to these observations, including the need to use weight based dosing (with increased risks of calculation errors and decimal point errors). Furthermore, medications are typically packaged in doses and volumes that are targeted to adults, making it easier to give and unintended overdosage to a child. When errors do occur, children and particularly neonates have a much smaller tolerance for increased medication doses or fluid volumes.

Accordingly, pediatric populations would be a logical focus for clinical decision support aimed at reductions in medication dosing errors (van Rosse et al., 2009). The introduction of CPOE has shown overall benefit in reducing errors but no clear benefit in reducing harms of such errors (van Rosse et al., 2009). In addition, an earlier study suggested that introducing CPOE without sufficient attention to unintended consequences could actually increase patient harms (Han et al., 2005). Thus, it is useful to take a closer look at the effects of pediatric dosing support when added to an existing CPOE or EHR system.

Kadmon et al. (2009) reviewed 1250 prescriptions that were consecutively written during a one month period in each of 4 phases of their EMR rollout. Phases 1 and 2 occurred 1 month prior to CPOE and 1 year after initiation of CPOE, respectively. In phase 3, a CDSS was implemented and in phase 4 physician authorization of medication orders became mandatory. Addition of CDSS to CPOE was associated with significant

reductions in total errors (7.8 before vs. 4.4% after; $p=0.0004$), potential adverse drug events (2.4% before vs. 0.8% after; $p=0.0014$) and incomplete prescriptions (5.3% before vs. 3.8% after; $p=0.04$). Further decreases were noted in total errors and incomplete prescriptions in phase 4, when physician involvement in ordering became mandatory. There was no difference in mortality rate across the periods of the study.

Kazemi et al (2011) studied the effects of implementing CPOE and then adding CDSS to CPOE on the frequency of medication errors in the neonatal unit of an Iranian teaching hospital. The CDSS included advanced features and presented recommendations based on factors such as age, GFR and weight for neonates who were receiving either antibiotics or anticonvulsant medications. Rates of medication prescription errors were not altered by the transition from paper-prescribing (876 errors/1688 prescriptions) to CPOE (749 errors/1489 prescriptions) but dropped significantly when CDSS was added to CPOE (442 errors/1331 prescriptions). The reduction in the proportion of errors with the addition of CDSS (from 50% to 33%) was highly significant ($p<0.001$). A similar pattern was seen with dose errors and frequency errors, each of which was unchanged by the addition of CPOE but showed significant decreases with the addition of CDSS (38% to 22% and 25% to 20%, respectively). Discussion with prescribers identified new types of errors in the course of the study, particularly in relationship to selecting a neighboring menu choice in lieu of the correct one. Miscalculations were also common but not unique to a computerized process. Overall, however, the study findings suggested that addition of patient-specific CDSS can reduce rates of prescribing errors in a particularly vulnerable population of acutely ill neonates.

Sard et al. (2008) did a retrospective comparison of changes in prescribing errors before and after introduction of a pediatric drug dosing decision support tool that lists doses of commonly used emergency department medications. Patient visits were randomly selected and included 420 visits before and 420 visits after the decision support tool was implemented. Overall, these visits were associated with 724 medication orders of which 21% contained an error. This corresponded to a rate of 19 errors per 100 overall visits and 42 errors per 100 visits in which at least one medication was ordered. The drug “quicklists” were only used in 30% of orders after they became available, but their use was associated with a significant decrease in errors (1.9 errors per 100 orders with the “quicklist” vs. 18.3 errors per 100 orders otherwise). Even with this relatively low use of the “quicklists”, their availability was also associated with significant reductions in the relative rates of errors (24 errors per 100 visits before vs. 13 errors per 100 visits after; 31 errors per 100 orders before vs. 14 errors per 100 orders after). In terms of the specific types of errors that were seen, significant reductions in wrong frequency, wrong route, and wrong formulation errors occurred following “quicklist” implementation. No differences in error rates appeared to be related to factors such as urgency of the patient’s problem, patient age group or extent of the prescriber’s medical training. The findings suggested that rates of prescribing errors can be significantly reduced in an acute pediatric setting by the use of medication order lists that are structured for rapid selection and appropriateness of doses, frequencies and administration route.

These studies are heterogeneous in their interventions (i.e., alerts, drug sentence quick pick lists) and settings (emergency department, pediatric intensive care unit, neonatal intensive care unit). Nevertheless, all three studies showed benefits of adding

medication related decision supports to a baseline electronic record or prescribing system and complements evidence that suggests reductions in medication errors with CPOE and electronic prescribing approaches (van Rosse et al., 2009; Reckmann, et al., 2009).

Interventions to reduce rates of specific medication interactions

Drug-drug interactions are a common cause of medication errors and toxicity (Strandell and Wahlin, 2011; Hines and Murphy, 2011) and, as such, also represents an obvious opportunity to leverage the strengths of HIT. Nevertheless, much of the literature on computerized drug interaction alerts has failed to show benefit (Wong et al., 2008). Thus, it is useful to determine whether modifying existing EHR systems with different types of alerts or targeted alerts for high-risk combinations would be more effective.

Humphries et al. (2007) inserted a hard stop alert into an order entry system, which prevented pharmacists from dispensing a drug that would result in a critical drug-drug interaction between prescribed medications. This intervention was compared in a before-after fashion to the existing system of passive pharmacist alerts. The authors included 20 months of data before the intervention and 37 months of data after the intervention with a total of 623 dispensings of critically interacting drugs in the entire study. Compared to the control condition, there was a significant reduction in concomitantly dispensed interacting drugs in the context of the intervention (11.8 per 10,000 prescriptions after vs. 24.7 per 10,000 prescriptions before). Significant decreases were also noted in the prescribing of particular drug combinations (i.e., carbamazepine with macrolide antibiotics, theophylline with macrolide antibiotics, theophylline with

cimetidine, theophylline with ciprofloxacin). Although this study involved alerting of pharmacists rather than physicians, the findings do appear relevant to the integration of real-time alerts for critical drug-drug interactions between the ordering and dispensing steps of the medication management process.

Strom et al (2010a) developed a customized alert that would advise prescribers of the risk of simultaneous treatment with warfarin and trimethoprim-sulfamethoxazole. When an order for warfarin or trimethoprim-sulfamethoxazole was attempted that would lead to simultaneous use, prescribers were randomly assigned to receive either the customized alert or post-order entry pharmacist intervention, which was the standard practice. The customized alert could only be overridden if the prescriber attested that the patient required treatment for *Pneumocystis carinii* pneumonia. Otherwise, the order would not be placed and a phone call to the pharmacist was needed to place the order. The study included a total of 1981 clinicians and a total of 8836 orders. Of these only 7 orders were exempted by the use of trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia treatment or prophylaxis. There were 194 unique events that triggered an alert in the intervention group and 148 comparable events in the control group. Of these, the proportion of individuals who reordered the drug despite the potential for interaction was 42.8% and 86.5% respectively (odds ratio 0.12, 95% CI 0.07 to 0.20), suggesting that the hard stop intervention was extremely effective in changing clinical practice. However, the relative effectiveness of the alert appeared to decline over several months. In addition, the study was stopped early due to unintended delays in necessary treatment.

Strom et al (2010b) also developed a customized alert that would advise prescribers of the risk of simultaneous treatment with warfarin and a non-steroidal anti-inflammatory agent (NSAID). Prescribers were randomly assigned to receive either a standard drug-interaction message box or a customized alert when attempting to place an order that would result in concomitant treatment with warfarin and an NSAID. With the customized alert, users were asked to select an alternative drug such as acetaminophen in lieu of the NSAID and were directed to another order window that facilitated this recommended change. During the 17 month study period, a total of 1963 prescribers were randomized and 1024 alerts occurred that related to a unique ordering event. Overall, the intervention and control groups did not differ in their prescribing patterns with the proportion of desired prescribing responses being 25% in the intervention group and 28% in the control group. In addition, there was a statistically significant reduction in the proportion of desired prescribing over time (odds ratio 1.09 per month, $p=0.007$).

Together these studies show an inconsistent effect of alerting physicians to specific high risk drug combinations. Inconsistencies were present in the effectiveness of the alerts with no differences in prescribing patterns being found by Strom et al (2010b) for the combination of warfarin plus an NSAID and multiple combinations showing no effect in the study of Humphries et al. (2007). This contrasts with the decreases noted by Humphries et al. (2007) for other drug combinations and the decrease in warfarin and trimethoprim-sulfamethoxazole co-prescribing noted by Strom et al (2010a). In fact, the effect in the latter study was sufficient to lead to treatment delays and potential for patient harm. In both of the studies by Strom and colleagues (Strom et al., 2010a; Strom et al., 2010b), the effect of the decision support decayed with time from implementation.

Consequently, further study of alerts for critical drug-drug interactions is needed to determine the key elements that contribute to prescriber acceptance of drug interaction alerts. Approaches are also needed to optimize alerts and achieve benefits without delaying needed medications.

Interventions to improve the appropriateness of medication use in patients with renal insufficiency

Impaired renal function is present in a clinically significant fraction of the populations and requires that medication dosages be adjusted accordingly (Breton et al., 2011, Hudson and Nyman, 2011; Tawadrous et al., 2011). Manual systems of alerting physicians to renal dosing adjustments have shown promise as have some early systems that use electronic decision support (Tawadrous et al., 2011).

Chertow et al. (2001) developed a decision support alert that provided information on default medication dosing and frequency based on the patient's renal function. This decision support alert was added to the baseline CPOE system in alternating 2 month intervals (ON-OFF-ON -OFFdesign). Over the course of the study, 7887 and 9941 hospital stays occurred during the intervention and control periods respectively.

Impairments in renal function were common with 24.9% of patients having mild renal insufficiency and 15% having moderate to severe insufficiency. Of 97151 orders, 15% resulted in a renally related recommendation for the prescriber. In comparison with the control period, the rates of inappropriate prescribing were significantly reduced ($p < 0.001$ for all comparisons) during the intervention period for orders with recommendations for altered dose (46% vs. 33%), altered frequency (65% vs. 41%) or overall orders (70% vs.

49%). Although no effects were noted in terms of length of stay or hospital related costs, provision of additional renal-specific support does appear to enhance the appropriateness of medication dosing.

Sellier et al. (2009) examined the appropriateness of dosing of 24 targeted drugs in relation to patient's kidney function (as measured by estimated glomerular filtration rate) during alternating periods of receiving computerized alerts versus no alerts. Overall, about one-fifth of the 700 first prescriptions were inappropriate. No significant difference was found between the control and the intervention periods in the appropriateness of prescribing. However, appropriateness of dosing was enhanced among residents (29.3%) and reduced among senior physicians (16.3%) during intervention periods relative to control periods. No other factors were associated with differences in the appropriateness of dosing between the control and intervention groups. Thus, this study differed from others in showing no substantial benefit of individualized drug dosing recommendations.

Rind et al. (1994) implemented a clinical decision support system that was aimed at minimizing the risk of renally excreted or nephrotoxic medications in adults admitted to an urban academic medicine service. Clinical decision support alerts notified the physician if the serum creatinine increased by 0.5 mg/dL or more in a patient receiving one or more nephrotoxic medications or if the serum creatinine increased by 50% or more to a value of 2.0 mg/dL or higher in a patient received a renally excreted medication. The intervention was applied in a time series fashion with 3 control periods of 3 months each alternating with 2 intervention periods of 3 months each. As compared to the control periods, the intervention periods were associated with a shorter time to discontinuation of

a renally excreted or toxic medication (97.5 hours vs. 75.9 hours; $p < 0.0001$) and lesser likelihood of developing serious renal impairment (relative risk 0.45, 95% CI 0.22 to 0.94). Patients in the control group had a slight increase in their creatinine levels at days 3 and 7 (+0.05 mg/dL and +0.19 mg/dL, respectively) whereas patients in the intervention group had a slight decrease (-0.11 mg/dL and -0.10 mg/dL, respectively). Mortality rates did not differ between the two groups.

Galanter et al. (2005) assessed the effect of decision support alerts aimed at reducing the use of contraindicated medications in patients with impairments in renal function as measured by an estimated creatinine clearance (determined using the Cockcroft-Gault equation). When rates of inappropriate prescribing with use of a standard commercial CPOE system were compared to rates after addition of the decision support alert, there was a significant reduction in the proportion of individuals who received at least one dose of a contraindicated medication (89% before vs. 47% after; $p < 0.0001$). Among housestaff, who received 70% of the alerts, greater alert adherence was found with more advanced training (greater than 1 year) as well as in male patients and those with higher values of estimated creatinine clearance. Although the values of estimated creatinine clearance were comparable for male and female patients, the measured serum creatinine values were less for females, suggesting that the housestaff may have incorrectly placed more weight on the serum creatinine levels in making determinations about discontinuing contraindicated medications.

McCluggage et al. (2010) studied the effects of a vancomycin nomogram order set on the proportion of patients who received initial optimal dosing of vancomycin. The nomogram included consideration of estimated creatinine clearance and body weight but

required that users obtain this information themselves and then select the correct order. It did not obtain the relevant variables from the EMR system and then present the user with a single recommended order. Overall, data was analyzed for 522 patients, with comparable numbers and demographic characteristics of patients before and after the nomogram was implemented. Following nomogram initiation more individuals received a recommended regimen of vancomycin (23.7% before vs. 35.8% after; $p=0.0028$). This included a greater proportion of individuals receiving a recommended dose (35.5% before vs. 46.9% after; $p=0.008$) or recommended dosing interval (64.9% before vs. 75.3% after; $p=0.009$). There were significant reductions in the proportion of individuals receiving lower than recommended doses (50.9% before vs. 39.9% after; $p=0.012$) or shorter than recommended dosing intervals (33% before vs. 23% after; $p=0.01$). However, these are only indirect measures of the adequacy of vancomycin dosing as the authors did not incorporate an assessment of vancomycin levels into their research design.

Taken together, this body of evidence (Table 4) supplements the findings of other studies in showing benefits of decision support for renal dosing (Tawadrous et al., 2011).

Table 4. Summary of evidence on adding decision support related to renal impairment to existing EHRs

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Chertow et al. (2001)	Inpatient; medical, surgical, neurological or obstetrics and gynecology services; academic center; US	Customized dosing alert based on renal function	ON-OFF-ON – OFF in 2 month blocks	Good	Rate of appropriate prescribing	Improved
Sellier et al. (2009)	Inpatients; geriatric or internal medicine service; academic center; France	Customized dosing alert based on renal function	Alternating control and intervention periods	Fair	Rate of appropriate prescribing	Neutral
Rind et al. (1994)	Inpatient; medical service; academic center; US	Alert for change in renal function in patients taking contributory medications	Alternating control and intervention periods, 5 total blocks, 2 months each	Good	Time from renal event to medication change Creatinine change after renal event Serious renal impairment occurred Mortality	Improved Improved Improved Neutral

Table 4. Summary of evidence on adding decision support related to renal impairment to existing EHRs (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Galanter et al. (2005)	Inpatient; academic center; US	Alerts about medications that are contraindicated with renal impairment	Before-after	Fair	Use of contraindicated medication	Improved
McCluggage et al. (2010)	Inpatients; academic center; US	Vancomycin nomogram based on renal function integrated into CPOE order set	Before-after	Fair	Use of initial optimal dosing regimen	Improved

With the exception of one study that showed no effect on the proportions of inappropriately dosed medications, the data is relatively consistent and of fair to good quality in suggesting improved prescribing. In addition, one study suggested that alerts could reduce the risk of more serious renal impairment, making a case for direct benefits to patients from adding renal dosing and related decision supports to existing EHRs.

Interventions to improve the appropriateness of medication choice and dosing for geriatric patients

Individuals over age 65 are another group of patients who are at increased risk of medication interactions and side effects (Fick et al., 2003, Buck et al., 2009; Marcum and Hanlon, 2012). In some instances these side effects contribute to injuries such as falls (Yourman et al., 2008). In an effort to minimize prescribing of drugs that are most likely to cause difficulties in the elderly (Thomsen et al., 2007), a number of different lists of potentially inappropriate medications have been developed (Marcum and Hanlon, 2012). Such lists and age-related dosing modifications have been used in electronic systems to optimize pharmacotherapy, with promising results. However, outcome measures and research comparisons have not been well-delineated in the past (Yourman et al., 2008).

Peterson et al. (2005) studied the effects of computerized prescribing guidance that was provided in the context of inpatient care of patients aged 65 or older. The system was turned on in an alternating fashion (ON-OFF-ON-OFF) and provided age adjusted dosing recommendations as well as guidance on choices of alternative medication that are regarded as safer in the elderly. As compared to the control periods, active intervention periods were associated with a statistically significant reduction in fall

rates (0.64 vs. 0.28 per 100 patient days) as well as in the prescription of non-recommended drugs (10.8% vs. 7.6%). In addition, the incidence of 10 fold dosing excesses was decreased (5.0% vs. 2.8%) and a greater proportion of individuals received recommended daily doses of medication (29% vs. 19%) during active intervention as compared to control periods. Meperidine orders in particular were more likely to be dosed appropriately during intervention periods, although increased adherence to prescribing recommendations was seen during intervention periods for all medication classes that were studied (i.e., benzodiazepines, opiates, neuroleptics). However, the number of days in which the patient experienced an altered mental state was comparable for the intervention and control periods (20.9 vs. 21.9 days per 100 patient-days).

Griffey et al. (2012) studied the effects of computerized prescribing guidance that was provided at an urban academic hospital in the context of emergency department care of patients aged 65 or older. The system was turned on in an alternating fashion (OFF-ON-OFF-ON) and provided age adjusted dosing recommendations as well as guidance on alternative medication choices that are regarded as safer in the elderly. During all study periods, 2398 orders were placed for 1407 patients; 115 of the orders were for non-recommended medications, primarily benzodiazepines. In response to the alerts about non-recommended medications, prescribers modified only 7.5% of the medication choices. There was somewhat greater use of recommended doses and frequencies during the period when the decision support was active as compared to the control condition (31% vs. 23%; $p < 0.001$). No differences were found in the occurrence of 10 fold dosing errors or the need for rescue medications. A retrospective review of patient charts showed that the proportion of adverse drug events (e.g., altered mental status,

hypotension, respiratory depression) was significantly less during the active intervention than during the control condition (3%vs. 7% respectively; $p<0.02$). In addition, three-quarters of the adverse drug events occurred in individuals for whom the dosing and drug choice recommendations were not followed. Recommendations related to NSAIDs and opiates showed a greater effect of the intervention whereas no significant effect of the alerts was seen for benzodiazepine or other sedative hypnotic medications. Taken together, the findings of this study suggest some benefits of CDSS alerts aimed at adjusting medication choices and doses to the needs of geriatric patients. Although prescriber adherence to the decision support was limited, indirect effects of the alerts included more appropriate dosing and medication choices whereas direct benefits included a reduction in adverse drug events.

Mattison et al. (2010) examined the effect of computerized decision supports targeted at the prescribing of medications in patients aged 65 and older. The decision support included recommendations about medications that confer an increased risk in the elderly as well as medications for which a reduction in dosing may be needed. With the initiation of the decision support, the rate of prescribing non-recommended medications showed a significant decrease (11.56 order per day before vs. 9.94 orders per day after; $p<0.001$). There was a trend for a reduction in high-risk but unflagged prescriptions for which no suitable alternative treatment was available. No changes were noted in the number of orders for medications for which dosing reductions were suggested, although there was no information given as to whether reduced doses were ultimately prescribed.

Smith et al. (2006) used interrupted time series analysis to examine the effects of adding an alert about the use of non-preferred medications. In this sample of primary care

ambulatory patients there was a rapid decrease in the use of non-preferred medications in elderly individuals after alert implementation as compared with baseline levels of use (21.9 per 10,000 before vs. 16.8 per 10,000 after). When the alert was active, use of preferred medications showed a 20% increase in non-elderly patients whereas no changes occurred in the use of preferred medications in the elderly and non-preferred medications in other patients. There was a striking reduction in the prescription of the non-preferred tricyclic antidepressant amitriptyline, which fell by 35% in elderly individuals after the alert was initiated. Although some inconsistencies are present, these findings suggested that CDSS alerts may lead to more appropriate medication choice particularly in elderly individuals.

Terrell et al. (2009) developed a decision support alert that advised against use of 9 medications for patients aged 65 and older. The alert also suggested other medication options that were felt to be safer in this population. Emergency physicians of an urban academic hospital were randomized (with stratification based on level of training) to an intervention group in which CPOE incorporated geriatric prescribing alerts (N=32) or a control group using the hospital's standard CPOE system (N=31). Approximately one-third of physicians in each group were faculty members. There were 5162 patient visits included in the study with relatively comparable numbers and patient demographic characteristics in each of the groups. Relative to the control group, alerts were associated with a reduction in the number of visits with an inappropriate prescription (3.9% control vs. 2.6% intervention; $p=0.02$, odds ratio 0.55) and the percentage of inappropriate prescriptions (5.4% control vs. 3.4% intervention; $p=0.006$, odds ratio 0.59).

Raebel et al. (2007b) implemented a hard stop system for alerting pharmacists to the prescription of a medication that was not recommended for use in geriatric patients. The alert blocked dispensing of the medication until communication with the prescribing physician could occur. As part of the study 59,680 individuals aged 65 and older were randomly assigned to the intervention or control condition. The hard stop alert was associated with a statistically significant reduction in the use of inappropriate medications with 1.85 dispensings per 100 geriatric patients in the intervention group vs. 2.2 dispensings per 100 geriatric patients in the control group ($p=0.002$). Specific medications for which dispensings were significantly and appropriately reduced were amitriptyline ($p<0.001$) and diazepam ($p=0.02$). It is possible that the magnitude of the alert's effect was diminished by the relatively low levels of inappropriate prescribing in the usual care group.

Peterson et al. (2007) integrated guided dosing alerts into an organizationally developed CPOE system to enhance the safety of medication prescribing in geriatric patients. The authors included guided dosing lists, with recommended doses and frequencies for geriatric patients, as well as other prescribing information on 88 medications. Overall, orders for 9111 study medications were entered for 2981 patients. Physicians who were assigned only to intervention patients ($N=103$) prescribed significantly lower doses than those assigned only to control patients ($N=117$). Those using guided orders were more likely to adhere to recommended dosing than controls (28.6% vs. 24.1%, $p<0.001$) and had a lower median ratio of actual to recommended doses prescribed (2.0 vs. 4.0; $p<0.001$). Although statistically significant the clinical impact of the alerts in improving adherence to recommended dosing was rather modest.

Tamblyn et al. (2012) investigated the effects of an advanced decision support tool aimed at reducing injury rates in patients who were prescribed psychotropic medications and were 65 year of age or older. Eighty one primary care physicians were stratified based on the number of applicable patients in their practice and were then randomized to use the baseline electronic prescribing system with or without an additional alert. The alert used a predictive model to estimate a patient-specific risk of injury, which was graphically displayed to the prescriber. During the study, 5628 patients participated under the care of 81 family physicians. The groups of patients for whom the alert did or did not display were comparable except for a somewhat higher number of recent ED visits and gait/balance problems in the control group. The bulk of injury risk alerts (86.3%) related to pre-existing medications and the patient's prescription was modified in 25.7% of these circumstances. In addition, a change in the prescription occurred in 17.7% of new prescriptions. Compared with the control group, the intervention group experienced a significant reduction in the risk of injury with a decrease of 1.7 injuries per 1000 patients (95% CI 0.2 to 3.2 per 1000 patients; $p= 0.02$). This reduction in risk was most striking among patients with the highest likelihood of injury. These data suggest that targeted CDSS alerts that provide information on safety associated effects of medication therapy can have significant indirect and direct benefits by encouraging more appropriate prescribing and reducing injury rates.

Table 5 summarizes the evidence on interventions that can be added to EHRs to

Table 5. Summary of evidence on adding decision support to existing EHRs to improve geriatric prescribing

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Peterson et al. (2005)	Inpatients; medical, surgical, neurological or gynecological service; academic center; US	Dosing; Non-recommended medications	Prospective, on-off-on-off	Good	Rates of recommended doses Rates of 10 fold excess dosing Rates of patient falls Days with altered mental status	Improved Improved Improved Neutral
Griffey et al. (2012)	Emergency department; academic center; US	Dosing; Non-recommended medications	On-off-on-off	Good	Agreement with suggested drug choice Agreement with suggested dose 10 fold excessive dosing rates Proportion of ADEs Number of rescue drugs required	Improved Improved Neutral Improved Neutral

Table 5. Summary of evidence on adding decision support to existing EHRs to improve geriatric prescribing (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Mattison et al. (2010)	Urban academic hospital in the US	Dosing; Non-recommended medications	Before-after	Good	Rates of higher risk medication use	Improved
Smith et al. (2006)	Outpatient; academic related; US	Non-recommended medications	Before-after	Fair	Dispensing of preferred and non-preferred medications	Improved
Terrell et al. (2009)	Emergency department; academic center; US	Non-recommended medications	Randomized controlled trial	Good	Rate of visits with inappropriate medication Rate of inappropriate prescriptions	Improved Improved
Raebel et al. (2007b)	Ambulatory; health maintenance organization; US	Non-recommended medications (alert to pharmacist)	Randomized controlled double-blinded trial	Good	Proportion of potentially inappropriate medications dispensed	Improved

Table 5. Summary of evidence on adding decision support to existing EHRs to improve geriatric prescribing (continued)

Citation	Population	Alert type	Design	Quality	Outcomes	Effect of intervention
Peterson et al. (2007)	Inpatient; academic center; US	Dosing	Randomized controlled trial	Fair	Ratio of prescribed to recommended medication doses	Improved
Tamblyn et al. (2012)	Outpatient; primary care; Canada	Graphical alert of predictive risk of injury model	Cluster randomized controlled trial, single blind	Good	Risk of injury Changes in the use and dose of medications	Improved Improved

improve the quality of pharmacotherapy in geriatric patients. Overall, these studies are of fair to good quality and add to prior work (Yourman et al., 2008) by showing consistent benefits from focusing CDSS on the needs of the elderly. Although most of the outcome measures are indirect ones, such as the rates of potentially inappropriate medication use, some studies have also shown reductions in adverse drug events, falls or other injuries (Tamblyn et al., 2012; Peterson et al., 2005; Griffey et al., 2012). Thus, existing EHR or CPOE systems would seem to benefit from the inclusion of CDSS related to geriatric prescribing.

Interventions to improve the appropriateness of medication dosing in special populations

Several other studies have examined computerized decision support to address other specific dosing considerations. For example, Seidling et al. (2010) developed enhanced CDSS for medication prescribing that used individualized alerts and calculated maximum recommended doses based on factors such as patient age, concomitant medications or renal or hepatic function. A total of 42,444 prescriptions were issued to 8892 patients over the course of the study. These were about equally divided between the pre- and post-phases of the study, but in about 17% of patients there was not enough information available to calculate an individualized dosing recommendation. When individualized dosing calculations were possible, the enhanced decision support was associated with a statistically significant 20% reduction in the proportion of excessive doses that were prescribed (4.5% before vs. 3.6% after; $p < 0.001$). Prescribers were more likely to respond to alerts that related to analgesic agents, psychotropic medications and

immune modulating or antineoplastic drugs. They were also more likely to respond to alerts that identified excessive plasma levels or duplicate prescribing. Patient age and the number of prescribed drugs were additional mediators of the likelihood of responding to an alert.

Ginzburg et al. (2009) implemented dosing and frequency suggestions into a commercial EMR system in order to improve the appropriateness of acetaminophen and ibuprofen dosing in patients less than 13 years. The algorithm incorporated weight based dosing and used ideal body weight for calculations in individuals who were at or above the 95th percentile by weight. Among the 315 patients who received an acetaminophen or ibuprofen prescription before the dosing support was initiated, 32.7% of prescriptions included a dosing error. This contrasts with a significantly lower rate of errors after implementing dosing decision support (20.6% of 224 patient visits; $p=0.002$). The decision support was most effective in reducing overdoses of medications based on dosing strength, but errors related to dosing frequency and instructions also were reduced by the decision support intervention.

Although these 2 studies were quite different in scope and heterogeneous in design, both showed benefits of the computerized intervention in terms of dosing. This supplements the findings of research that used CDSS to optimize dosing in the elderly and in those with renal impairment.

Interventions to improve computerized decision support in specific clinical circumstances

In addition to the apparent utility of CDSS in optimizing medication dosing, CDSS has been used to address potential prescribing hazards associated with medication-related side effects. For example, Riggio et al. (2009) used an alert to notify physicians that a heparin-treated patient met criteria for thrombocytopenia (either a 50% drop in platelet count over 3 weeks or a 30% drop to less than 150,000 platelets per cubic mm). As compared to the pre-alert period, the authors calculated the time to diagnosis and treatment of heparin induced thrombocytopenia in hospitalized patients. More specifically, they assessed the time from platelet count criterion being met to initial laboratory testing for heparin induced thrombocytopenia, heparin discontinuation, and initiation of treatment for heparin induced thrombocytopenia. Among the 100 patients who were diagnosed with heparin induced thrombocytopenia during the study, those in the intervention group had a delayed time to heparin discontinuation relative to controls (2.9 days vs. 1.3 days, respectively; $p=0.04$). In addition, the positive predictive value of the alert was only 2.3% with a negative predictive value of 99.9%.

In an effort to reduce the risk of gastrointestinal complications due to NSAID use on the hospital cardiology and cardiac intensive care service, Côté et al. (2008) studied the effect of 2 potential interventions, brief physician education and a computerized alert integrated into an EHR. The specific interventions that were studied were a control condition, brief education alone, a computerized alert alone and the combination of education and a computerized alert. Groups of residents spent 4 week blocks on the service and the interventions were introduced sequentially in 8 week blocks. During the

32 week study period, there were a total of 601 patients who met the researchers' inclusion criteria. Of these 45% received a once daily proton pump inhibitor whereas 5% received inappropriate treatment. When compared to the control group, neither the brief educational intervention nor the computer alert had any impact on the use of appropriate gastroprotection (43% vs. 42% vs. 39%, respectively). However, the combined intervention was associated with significant benefit as 61% of individuals received appropriate gastroprotective prophylaxis. A similar pattern of benefit was seen for patients with highest risk of gastrointestinal complications.

In another circumscribed patient population, pregnant women, Raebel et al. (2007a) used a complex decision support system to alert ambulatory pharmacists to the ordering of a potential category D or X medication. Communication with the prescribing physician before dispensing the medication was then able to clarify the appropriateness of the order. During the study, patients were randomized to either the CDSS intervention or usual care group and the dispensing of medication was tracked. The proportion of women who were dispensed a category D or X medication during pregnancy was significantly reduced by the intervention as compared to the control condition (2.9% vs. 5.5%, respectively; $p < 0.001$). However, the ongoing use of the CDSS was limited by a significant numbers of false positive alerts such as misidentification of pregnancy and incorrect information in the database on contraindications.

Finally, Yu et al. (2011) examined the effects of implementing decision support alerts related to FDA black-box warnings in 51 outpatient practices encompassing specialty and primary care for adult patients. The decision support alerts on the black-box warnings included information on factors such as drug-drug interactions, drug-

pregnancy interactions, and drug-disease interactions that have been highlighted in product labeling as conferring particularly increased risk to patients. Overall, alert implementation was associated with a paradoxical but statistically significant worsening of adherence to recommendations about medication use and indicated laboratory monitoring (4.8% pre vs. 5.1% post). However, after the alerts were implemented there was a significant improvement in adherence to recommendations about drug-drug and drug-pregnancy interactions (6.1% pre vs. 1.8% post and 5.1% pre vs. 3.6% post, respectively). The before-after study design may have introduced confounding factors into the study, particularly since patient demographics and the relative proportion of specialist physicians were substantially different after implementation as compared to the period before the alerts were initiated. The authors suggested that, in general, alerts on black box warnings should not be incorporated into CDSS but that alerts specific to drug-drug and drug-pregnancy interactions may be valuable to include.

Although the heterogeneity of clinical circumstances and types of alerts limits drawing an overall conclusion from this research, none of these studies showed a benefit from adding electronic decision support alone. Given the importance of these clinical circumstances, the lack of benefit is counterintuitive. It is possible that the potential benefits of the decision support are being "washed out" by unidentified aspects of clinical decision-making, such as a lack of confidence in the clinical importance of all black box warnings or the lack of a perceived need for gastroprotection with rare NSAID use. Further study is needed to determine whether the lack of benefits related to the design of specific decision support system or other factors specific to these individual studies.

Interventions to reduce inappropriate tablet splitting

Several other studies assessed aspects of CDSS with even more indirect relationships to patient safety. One of these studies (Quinzler et al., 2009) prospectively assessed the effects of adding decision support alerts to an existing electronic prescribing system with the aim of reducing the rates of inappropriate splitting of medication tablets, which can create dosing errors through changes in bioavailability. Prior to the intervention 2.7% of drugs (257 of 9545 total drugs) were prescribed in a way that involved inappropriate splitting. In the subsequent intervention period, in which prescribers received a computerized alert about inappropriate splitting, this frequency diminished to 1.4% (146 of 10486 total drugs), typically by adjusting the medication regimen. The effect of the intervention was highly significant (odds ratio 0.51, 95% CI 0.35-0.76, $p=0.0008$). No new prescribing hazards were noted after introducing the intervention and, in almost 90% of cases, the modifications improved prescribing practice. Although replication of these results would be important, the practical benefits of providing this information to prescribers may warrant early inclusion in EHRs' CDSS.

Interventions to reduce the use of unapproved abbreviations

The Joint Commission (Joint Commission Resources, 2005) and the Institute for Safe Medication Practices (ISMP, 2012) have identified multiple medical abbreviations that are often prone to confusion and contribute to medication errors, particularly in handwritten documents. Consequently, for safety and regulatory reasons, hospitals are charged with eliminating the use of unapproved abbreviations. This can be a difficult task since clinicians have already incorporated many of these abbreviations into their

reflexive lexicon. It is also difficult to recall which of the many medical abbreviations are "unapproved" and which alternative abbreviations are acceptable. Thus, an electronic approach to reducing or eliminating unapproved abbreviations would be valued by clinicians and beneficial to patients.

A single study (Myers et al., 2011) examined the effects of 2 enhancements to an EMR that were aimed at reducing the rates of unapproved abbreviations in physician documentation. Fifty-nine interns were randomly assigned to a control group or to one of two interventions aimed at reducing the rates of unapproved abbreviation use. Interns in all groups used the electronic documentation system for progress notes but used handwritten documentation for history and physical examinations. All participants received the hospital's standard education about unapproved abbreviations and all groups showed reductions in the use of unapproved abbreviations in handwritten history and physical examinations during the year-long study. The group that received a "hard-stop" computer alert, instructing them to correct unapproved abbreviations with electronic progress note documentation, showed a significantly fewer proportion of unapproved abbreviations in the handwritten notes than either the control group or the group in which unapproved abbreviations were automatically corrected in electronic documentation. In both intervention groups, there was a reduction in alert numbers over the course of the study suggesting a decrease in attempted unapproved abbreviations with electronic charting. There was a trend for greater reductions in the "hard-stop" group as compared to the auto-correct group. The authors suggest that the findings support having alerts for unapproved abbreviations as part of electronic documentation.

Based on this study, the evidence for including electronic decision support to recognize unapproved abbreviations is quite weak. The primary outcome, a measure of unapproved abbreviation use in handwritten charts, is not relevant to fully electronic systems. In addition, rates of unapproved abbreviation use are only indirectly linked to patient safety outcomes, particularly in EHRs. However, Joint Commission requirements would be another major motivator for aggressively addressing unapproved abbreviations and, in this regard, the measured outcome would be more direct. Using “hard stop” alerts that require user intervention were noted to be more effective in this study but would also contribute to “alert fatigue” when used in tandem with other types of CDSS. Since unintended consequences of these alerts were not examined as part of the research, it is not clear whether the benefits of the interventions would outweigh potential detriments. It is possible, though unstudied, that using auto-correction of unapproved abbreviations would strike a more appropriate balance between safety issues and alert fatigue.

Interventions to enhance communication about prescribers’ thought processes

As another approach to improving safety and supporting decision-making, Johnson et al. (2010) investigated the benefits of including additional information (such as calculations or responses to alerts) from the prescriber's order entry session on the prescriptions transmitted to pharmacies. On randomly assigned days, prescriptions transmitted to pharmacists either were sent in the usual format or sent with additional information (termed by the authors as a Show-Your-Work system). A total of 47,059 prescriptions were transmitted during the study. Of those transmissions that included additional Show-Your-Work information, about 40% of transmitted prescriptions

included dosing alerts that had been shown to the prescriber, 15% showed dose-related calculations and 6% showed information about allergy overrides. Of all of the transmitted prescriptions only 202 (<0.5%) were associated with a pharmacist call back. The number of prescriptions and callbacks were comparable in the control and intervention groups as were the relative proportions of reasons that pharmacists gave for calling the prescriber (e.g., errors, insurance related issues). In addition, no differences were noted in the rates of pharmacy clarification calls between the intervention days and the control days. Nevertheless, the majority of pharmacists felt that the additional information conveyed by the Show-Your-Work approach was helpful, particularly in the context of pediatric prescriptions.

Although the findings of this single study do not support the routine inclusion of additional prescribing information with transmitted prescriptions, the measured outcome was an indirect one and positive impressions of the pharmacists suggest that additional study of this approach may be warranted.

Practical implications of the systematic review findings

In prioritizing new additions to decision support tools within an EHR, it is useful to know which specific elements are most beneficial in terms of patient safety (Table 6). There are several approaches that can be taken to this question, one of which is to examine the evidence for each decision support element in a systematic fashion. The results of the present review suggest that the highest priority should be given to medication-related decision support that is aimed at geriatric patient populations. Within a decision support tool for geriatric pharmacotherapy, the key types of alerts should help

clinicians avoid inappropriate medications and make recommendation about indicated dosing adjustments. Evidence for dosing related decision support in other patient populations (e.g., pediatric patients, renal insufficiency) is less compelling but also shows considerable potential for direct and indirect benefits to patient safety. Other CDSS related to prescribing has even more limited evidentiary support.

There is a moderate degree of evidence for decision support to improve prophylaxis of VTE and direct benefits to patient safety have been shown in several studies. Nevertheless, organizational decision-makers may need to reassess computerized VTE alerts if national guidelines for VTE prophylaxis change (Lederle et al., 2011). In terms of prioritization, VTE prophylaxis alerts can be quite complex if they incorporate elements of risk assessment and then stratify prophylactic recommendations based on risk (Novis et al., 2010). If such CDSS is not readily available within the users' EHR software, it may be costly or even impossible to build.

Among other CDSS elements, which have more limited research support, other considerations may need to factor into decisions about prioritization. For example, some evidence suggests benefits for CDSS on medication-related laboratory tests and safety and medicolegal considerations may warrant earlier adoption of such decision support, particularly for high risk medications. By the same token, transmitting information from the prescriber to the pharmacist on dosing calculations and alert overrides may assist with clinical decision making independent of direct safety effects. Knowledge of tablet sizes and splitting options may facilitate prescribing and warrant implementation even without direct or indirect benefits for safety.

An additional consideration in interpreting the results of this systematic review is that many CDSS tools incorporate many interventions simultaneously. This makes it difficult to determine which elements are contributing to overall benefit. As with other complex interventions such as psychotherapy (APA, 2007), it may be possible to use "unbundling" research designs to isolate the most effective elements of a particular process. A more detailed understanding of the components of a particular effect may also be helpful when overall benefits seem limited as with studies of laboratory monitoring or FDA black box warnings. In these instances, an important positive effect for several drugs may be overwhelmed by an absence of CDSS efficacy for other medications. If alerts could be customized to display those that are most effective or most relevant to the clinical context, this could be useful in minimizing alert fatigue (Kesselheim et al. 2011; McKibbin et al., 2011; Cash, 2009).

Finally, the impact of a CDSS can vary according to the characteristics of the user (Galanter et al., 2005; Terrell et al., 2009; Kutcher et al., 2009) such as level of experience or patient load. These factors as well as the specific details of the EHR software need to be described in more detail in published reports. Having a standardized checklist for describing facility, user and system characteristics could be a useful advance for the field.

Table 6. Summary of systematic review findings on modifications to EHRs to improve patient safety

Issue addressed	Strength of Evidence	Relationship to Safety	Type of study outcomes	Comments
Medication prescribing, including tiered and on-demand alerting	Low	Direct and indirect	Direct and indirect	Heterogeneous studies and interventions suggesting some benefits of adding decision support to electronic prescribing in reducing errors rates; adjustments in alert presentation are associated with variations in alert acceptance and apparent "alert fatigue."
Laboratory monitoring of pharmacotherapy	Low	Indirect	Indirect	Multiple studies of fair to good quality, neutral to positive findings with specific medication-related laboratory monitoring within and between studies, suggestion that interruptive alerts may be more effective than non-interruptive alerts and that baseline levels of adherence with monitoring may limit further increases in adherence with alerts.
Prophylaxis of venous thromboembolism	Moderate	Direct	Direct and indirect	Multiple studies of fair to good quality as well as some studies of poorer quality, consistently positive findings in the higher quality studies that are statistically and clinically significant in terms of enhanced adherence to recommended VTE prophylaxis as well as reductions in rates of DVT and pulmonary embolus, no reported increase in patient harms (e.g., bleeding), except in one poorly designed study; unclear whether there are independent contributions to adherence with integrated risk assessment tools or an ability to order directly from the alert
Medication error rates in pediatric patients	Low	Direct and indirect	Indirect	Heterogeneous studies and interventions suggesting benefits of adding decision support to electronic prescribing in reducing errors rates among pediatric populations although studies focused on specialized acute care settings

Table 6. Summary of systematic review findings on modifications to EHRs to improve patient safety (continued)

Issue addressed	Strength of Evidence	Relationship to Safety	Type of study outcomes	Comments
Rates of specific medication interactions	Insufficient	Indirect	Indirect	Inconsistent effects and shifts in effects with time from implementation; potential for harm due to treatment delays noted in one study
Decision support to improve prescribing for patients with renal insufficiency	Moderate	Direct and indirect	Direct and indirect	Benefits of decision support use in patients with renal impairment were relatively consistent with the exception of one study that showed no effect on the proportions of inappropriately dosed medications. One study suggested that alerts could reduce the risk of more serious renal impairment.
Prescribing for geriatric patients	High	Direct and indirect	Direct and indirect	Strong and consistent body of evidence suggesting that incorporating decision support relating to dosing and choice of medications in geriatric patients is associated with clinically and statistically significant reductions in patient harms (e.g., falls, injury, adverse effects) as well as intermediate measures of safety.
Medication dosing for other patient subgroups	Moderate	Direct and indirect	Indirect	Benefits of decision support on appropriate medication dosing were seen in 2 additional studies, despite heterogeneity of settings, populations and research questions.

Table 6. Summary of systematic review findings on modifications to EHRs to improve patient safety (continued)

Issue addressed	Strength of Evidence	Relationship to Safety	Type of study outcomes	Comments
Other specific clinical circumstances	Insufficient	Direct	Indirect	Heterogeneity of clinical circumstances (i.e., prescribing of category D or X drugs during pregnancy, FDA black box warnings, recognition and treatment of thrombocytopenia during heparin treatment, gastroprotective treatment in patients on NSAIDs) limits drawing an overall conclusion but none of these studies showed a benefit from adding electronic decision support alone. Additional studies of each of these interventions may be warranted.
Advice on inappropriate splitting of tablets or capsules	Low	Indirect	Indirect	Evidence comes from a single well-designed quasi-experimental study with strongly positive findings. Practical benefits of providing this information to prescribers may warrant inclusion in EHRs even before findings are replicated.
Unapproved abbreviations	Insufficient	Indirect	Indirect	Weak effect noted for hard stop alerts but measured outcomes were indirect and associated with several possible confounding factors. May warrant further study given the Joint Commission focus on reducing rates of unapproved abbreviations.
Transmitting dose calculation and alert information to pharmacies	Insufficient	Indirect	Indirect	No effect was found on pharmacist call back rates in a single study although pharmacist's perceptions were positive. May warrant further study.

CHAPTER 5

SUMMARY AND CONCLUSIONS

The results of this systematic review provide strong support for incorporating alerts to improve prescribing for geriatric patients. A substantial number of well-designed studies also suggest that venous thromboembolism (VTE) related decision support is beneficial but data from weaker trials is less consistent. More limited support exists for alerts to improve prescribing in other subgroups of patients such as individuals with impaired renal function. Additional aspects of EHRs that are been widely assumed to contribute to patient safety have not been as well-studied and would benefit from further research. In addition, most of the available research has taken place in acute care settings within US academic centers. It remains unclear whether findings from these sites will be valid in non-academic centers, in less traditional settings (e.g., home care, long term care, hospice), with commercial software, or in other countries that have other models for health care delivery. Finally, if we are to optimize patient safety and realize the full potential of HIT, it will be crucial to identify the best approaches for addressing the new types of errors that have arisen with EHR use.

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APPENDICES

Appendix A. Detailed literature search strategies

Appendix B. Design of Microsoft Access database program for screening literature

Appendix C. Evidence tables for individual studies identified in the systematic review

Appendix D. Tables summarizing the body of evidence for topics in the systematic
review

Appendix A

Detailed literature search strategies

MEDLINE database (PubMed)

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String 3 → 18604 references

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Limiting String → 14757453 references

((("animal"[All Fields] OR "animals"[All Fields] OR "animals"[MeSH Terms]) NOT ("human"[All Fields] OR "humans"[All Fields] OR "humans"[MeSH Terms])) OR "biochemistry"[All Fields] OR "biochemistry"[MeSH Terms] OR "biofeedback"[All Fields] OR "biochemical phenomena"[MeSH Terms] OR "biochemical processes"[MeSH Terms] OR "biofeedback, psychology"[MeSH Terms] OR "data mining"[All Fields] OR "data mining"[MeSH Terms] OR "dental"[All Fields] OR "dentistry"[MeSH Terms] OR "dentistry"[All Fields] OR "Nucleic Acids, Nucleotides, and Nucleosides" [MeSH Terms] OR "dna"[MeSH Terms] OR "dna"[All Fields] OR genetic[All Fields] OR "genome"[MeSH Terms] OR "genome"[All Fields] OR "health insurance portability and accountability act"[MeSH Terms] OR "health insurance portability and accountability act"[All Fields] OR "hipaa"[All Fields] OR "Diagnostic Imaging" [MeSH Terms] OR "imaging"[All Fields] OR microarray[All Fields] OR "Microchip Analytical Procedures" [MeSH Terms] OR molecular[All Fields] OR pacs[All Fields] OR "picture archiving"[All Fields] OR "picture archiving and communication system"[All Fields] OR "picture archiving and communication systems"[All Fields] OR "radiology"[All Fields] OR "radiology"[MeSH Terms] OR "radiograph"[All Fields] OR "radiographic"[All

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Strings 1, 2 or 3 (non-duplicated) → 187014; with limiting string excluded → 23262

References limited to English → 21174; limited to the years 1990 to 2010 → 18285

CINAHL; Computer Source; Computers and Applied Sciences; Library, Information Science and Technology Abstracts (searched through EBSCO Host interface)

("electronic medical record") OR ("electronic medical records") OR ("computerized medical record") OR ("computerized medical records") OR ("EMR") OR ("EHR") OR ("order entry") OR ("electronic prescribing") OR ("e-prescribing") OR ("computerized patient record")) or ((MH "Computerized Patient Record") OR (MH "Electronic Order Entry")) → 7194 references (4404 in CINAHL; 826 in Computer Source; 1542 in Computers and Applied Sciences; 439 in LISTA)

ISI Web of Knowledge Science Citation Index

TS=electronic medical record* OR TS=electronic health record* OR TS=electronic patient record OR TS=computerized patient record OR TS=order entry OR TS=CPOE AND Language=(English) Timespan=1990-2010 → 10,738 references

With exclusion of articles with TS=radiology OR TS=radiogra* OR TS=tomogra* OR TS=PACS → 10063 references

Cochrane database (through Wiley interface)

MeSH descriptor Electronic Health Records OR MeSH descriptor Medical Records Systems, Computerized OR MeSH descriptor Medical Order Entry Systems OR "electronic medical record" OR "electronic health record" OR "electronic patient record" OR "computerized patient record" OR "order entry" OR "CPOE" OR "electronic medical records" OR "electronic health records" OR "electronic patient records" OR "computerized patient records" → 427 references of which 22 were Cochrane Reviews, 20 were other reviews, 267 were clinical trials, 16 methods studies and 18 were assessments. 83 were economic evaluations and 1 was a Cochrane group with the latter 2 sets excluded as being irrelevant to the topic of the systematic review.

Compendex – Engineering Village

"electronic medical record" OR "electronic health record" OR "electronic patient record" OR "computerized medical record" OR "CPOE" OR "order entry" OR "electronic prescribing" OR "e-prescribing" limited to English and publication years 1990-2010 → 1232 references

IEEE Xplore

("electronic medical record" OR "electronic health record" OR "electronic patient record" OR "computerized medical record" OR "CPOE" OR "order entry" OR "electronic prescribing" OR "e-prescribing") Limited to Journals, Conferences and Books in Publication Years 1990 – 2010 → 402 references.

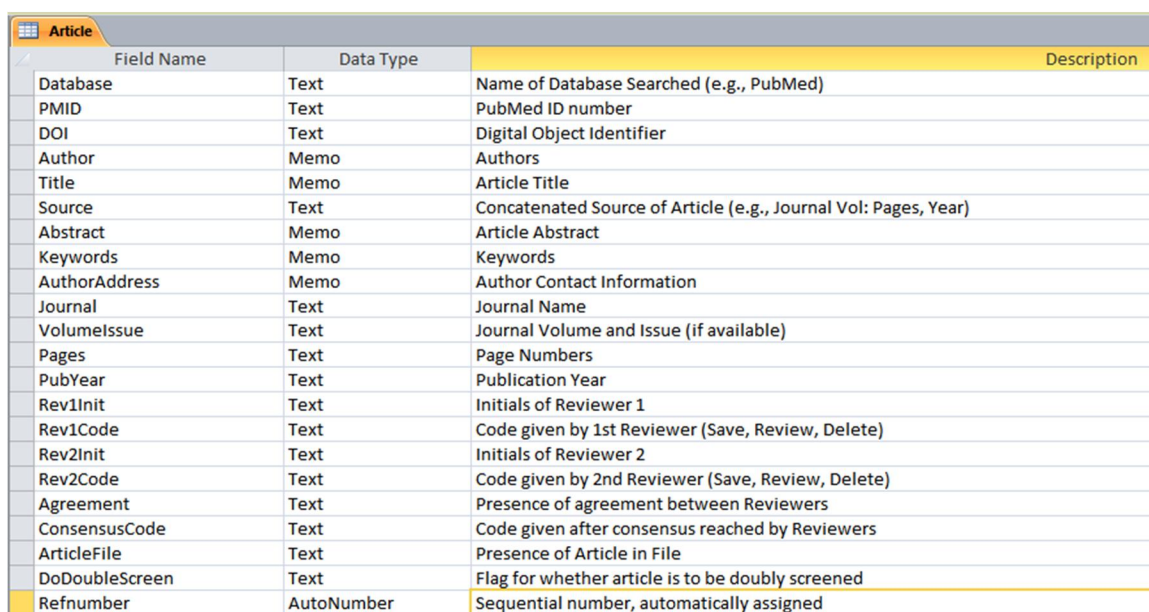
Scopus

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Appendix B

Design of Microsoft Access database program for screening literature

The database was constructed using a single table with the field names, data types and descriptions as shown in Figure 3. The fields were developed to be applicable for this project as well as for future systematic review efforts. Thus, not all fields were used in the screening of literature for this project.



Field Name	Data Type	Description
Database	Text	Name of Database Searched (e.g., PubMed)
PMID	Text	PubMed ID number
DOI	Text	Digital Object Identifier
Author	Memo	Authors
Title	Memo	Article Title
Source	Text	Concatenated Source of Article (e.g., Journal Vol: Pages, Year)
Abstract	Memo	Article Abstract
Keywords	Memo	Keywords
AuthorAddress	Memo	Author Contact Information
Journal	Text	Journal Name
Volumelssue	Text	Journal Volume and Issue (if available)
Pages	Text	Page Numbers
PubYear	Text	Publication Year
Rev1Init	Text	Initials of Reviewer 1
Rev1Code	Text	Code given by 1st Reviewer (Save, Review, Delete)
Rev2Init	Text	Initials of Reviewer 2
Rev2Code	Text	Code given by 2nd Reviewer (Save, Review, Delete)
Agreement	Text	Presence of agreement between Reviewers
ConsensusCode	Text	Code given after consensus reached by Reviewers
ArticleFile	Text	Presence of Article in File
DoDoubleScreen	Text	Flag for whether article is to be doubly screened
Refnumber	AutoNumber	Sequential number, automatically assigned

Figure 3. Table properties for Microsoft Access database.

The database program also included two forms for displaying information about each study and for entering a determination as to whether to exclude the article from further consideration. The design view of the form for displaying titles is shown in Figure 4.

The image shows the design view of a form titled "Reference Abstract Screening Program". The form is divided into three main sections: Form Header, Detail, and Form Footer. The Form Header section contains the title "Reference Abstract Screening Program" and a menu of reference coding choices: "D to Delete from list as unrelated to EHR safety", "S to Save as related to EHR safety", and "R to mark for later Review if relationship to EHR safety is unclear". Below the menu, there is a note: "Press A to show the Abstract for a given article." The Detail section contains two fields: "Rev2Code" and "Title". The Form Footer section contains a "Quit" button.

Figure 4. Design view of form to display and screen article titles.

This form includes an editable field (i.e., Rev2Code) for entering a screening determination. When the cursor is situated in this field, any key press will activate an Event Procedure, the code for which is included at the end of this appendix. Figure 5 shows an example of the screen display when populated with titles of articles retrieved from the literature search.

Reference Abstract Screening Program

Menu of reference coding choices:

- **D** to **Delete** from list as unrelated to EHR safety
- **S** to **Save** as related to EHR safety
- **R** to mark for later **Review** if relationship to EHR safety is unclear

Press **A** to show the **Abstract** for a given article.

Code	Title
<input type="text"/>	It vendor survey: Readers' choice
<input type="text"/>	New electronic system improves efficiency in pharmacist reviews: Problem medications quickly pop up
<input type="text"/>	Hci blog watch
<input type="text"/>	Method to rotate an endovascular device around the axis of a vessel using an external magnetic field
<input type="text"/>	Keeping up with technology: Your risks and responsibilities
<input type="text"/>	E-psychiatry: Uses and limitations
<input type="text"/>	Comparative structure and development of pollen and tapetum in pandanales
<input type="text"/>	The student editorial board of methods of information in medicine--an opportunity to educate tomorrow's peer reviewers
<input type="text"/>	Cyberpsychology in a clinical setting: Using virtual reality to treat storm phobia, a case report
<input type="text"/>	Artificial artificial intelligence: Surgeon intuition and computers to predict graft patency
<input type="text"/>	@neurist - chronic disease management through integration of heterogeneous data and computer-interpretable guideline services
<input type="text"/>	Enhance your technology and enrich your bottom line
<input type="text"/>	Confidentiality and security of information
<input type="text"/>	Moving from spatially segregated to transparent motion: A modelling approach
<input type="text"/>	Experience with computerized chemotherapy order entry
<input type="text"/>	Surveying acute care providers in the us to explore the impact of health information technology on the role of nurses and interdisci
<input type="text"/>	Group decision support system applied to the medical pluri-disciplinary decision group: Usability and efficacy




Figure 5. Form used to display and screen article titles.

The user can rapidly enter letter codes to categorize each title according to the instructions listed at the top of the display. The letters D, S, and R were specifically chosen for their meaning as well as their proximity on the keyboard, which facilitates rapid data entry. In addition, the Event Procedure code automatically corrects lower case letters to upper case letters, automatically moves the cursor to the next title upon entry of a viable letter code and prompts the user to re-enter a code if a non-viable letter is inserted.

In addition, if the title does not provide sufficient information about the article to permit a decision about appropriateness, the user can enter the letter A, which is also easily accessible on the keyboard and leads to the display of a popup window that contains the abstract and other citation details. The design of this popup window is shown in Figure 6 whereas an example of the popup window as displayed to the user is shown in Figure 7.

The image shows a web form with a grid-like border. At the top, there is a header section labeled 'Form Header' and a sub-section labeled 'Detail'. Below the header is a large, empty text area with the word 'Abstract' in the top-left corner. At the bottom of the form, there are four input fields: 'Author', 'Title', 'Source', and 'PMID'. The 'Source' field is a long, narrow box, while the others are shorter. The 'PMID' field is located on the right side of the bottom row.

Figure 6. Form used to display abstract and citation information.

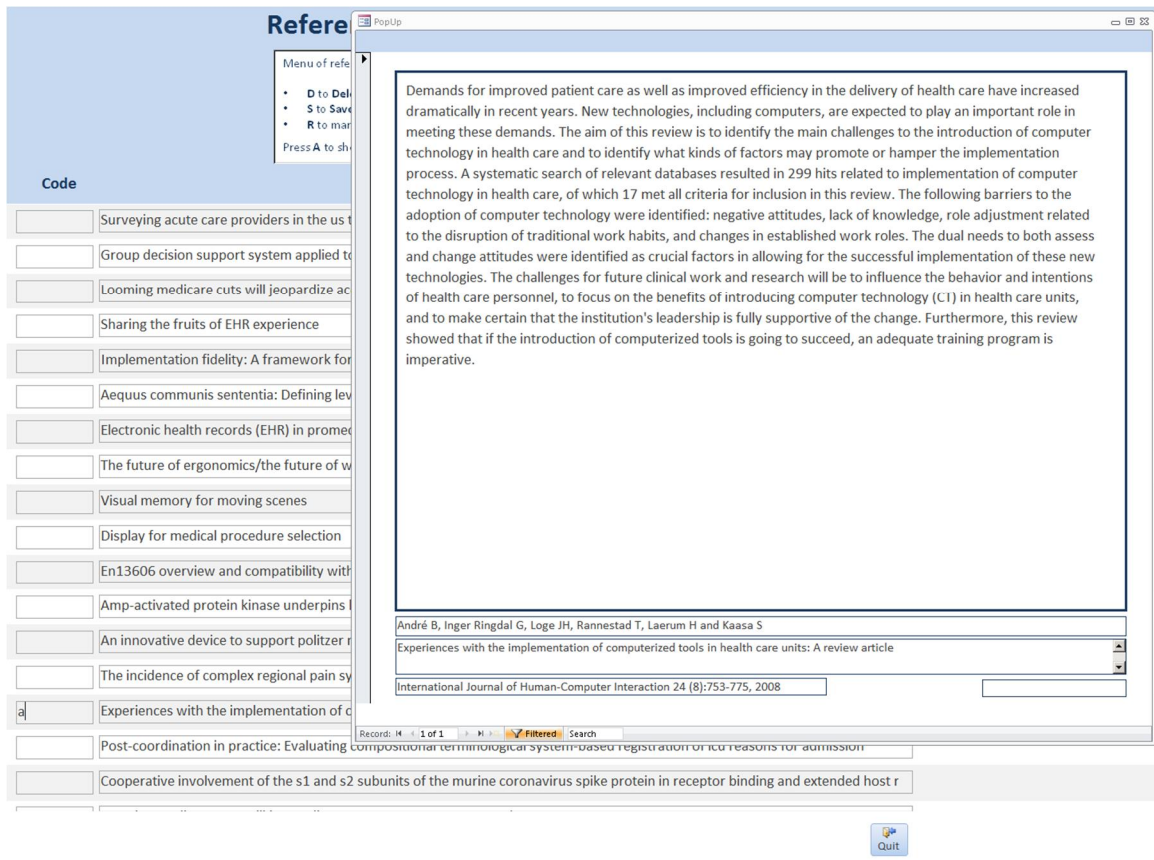


Figure 7. Example popup window that displays abstract and citation information.

During the display of the popup window, the cursor remains in the "code" field. This allows the user to enter the desired screening code after reading of the abstract. Entering a viable code, leads to the automatic closure of the popup window without a need for additional intervention by the user.

Entered data is saved immediately to the database table with each entry but at the end of a data screening session, the user is asked to enter his or her initials upon quitting the program (see Figure 8). The user's initials are added to the database in association with all items categorized during that session. This feature was not essential for the current project but was incorporated for situations in which multiple individuals are involved in screening. Entered data can be exported from Microsoft Access into Microsoft Excel or other programs using standard export/import tools if additional manipulation is required.

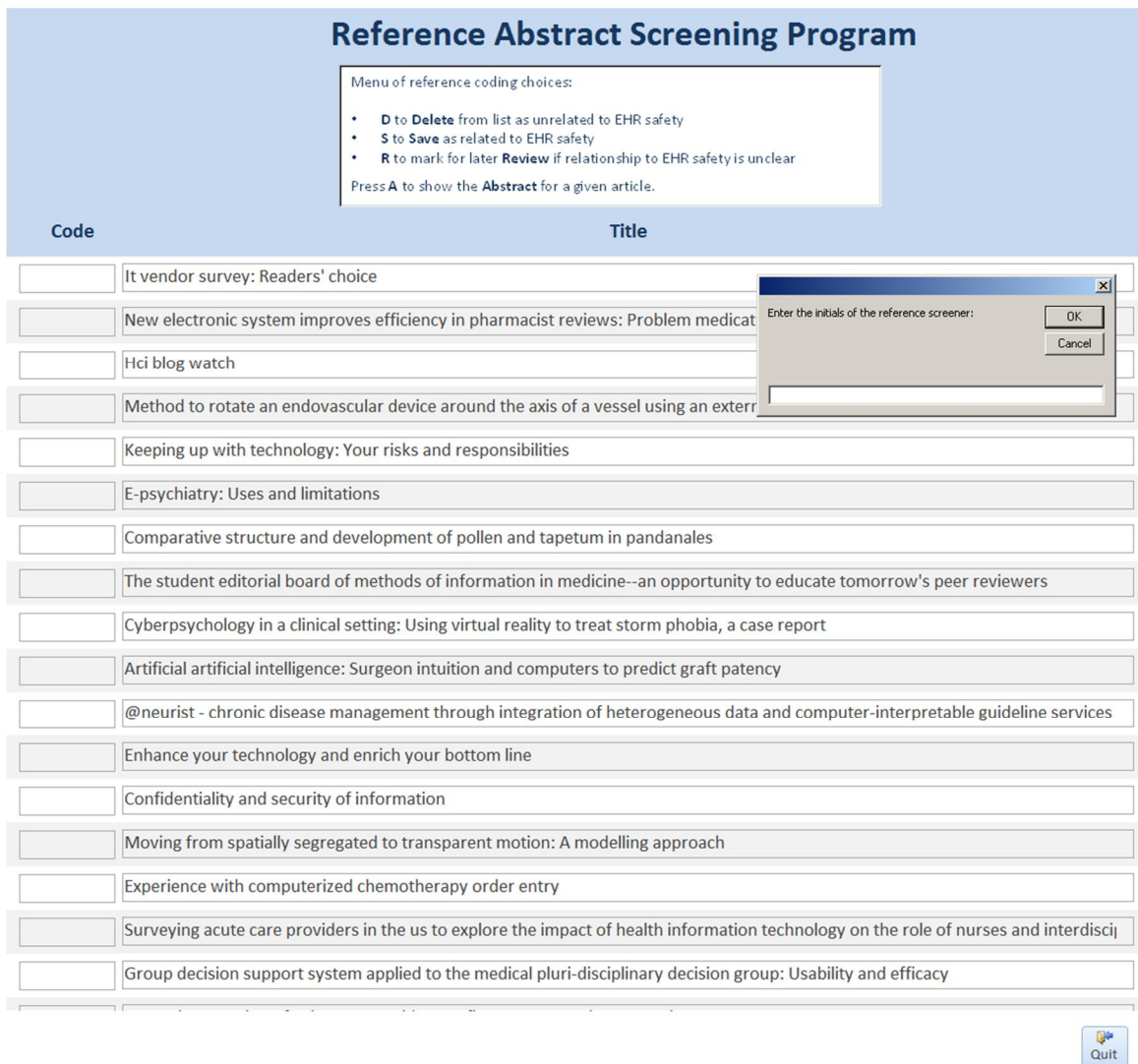


Figure 8. Example popup window requests user initials upon quitting.

Table 7. Event procedure code for Microsoft Access Database

```
Private Sub Rev2Code_KeyPress(KeyAscii As Integer)
    'Do While Loop determines if Abstract Popup is Open
    'If Abstract Popup is open, loop closes it
    Do While Forms.Count > 1
        DoCmd.Close acForm, "PopUp"
    Loop
    'Counter shows how many keystrokes have occurred
    'recsDoneCounter = recsDoneCounter + 1
    'Select case block determines the action to be taken
    'based on the most recent keystroke of the user
    Select Case KeyAscii
        'When user enters "A" or "a" abstract popup will open
        Case 65
            'User has entered "A"
            RefID = Me!Refnumber
            StrRefID = Str(RefID)
            RefIDStr1 = "[Refnumber]=" & StrRefID
            DoCmd.OpenForm "PopUp", , , RefIDStr1
            Forms!ReviewerForm.SetFocus
        Case 97
            'User has entered "a"
            RefID = Me!Refnumber
            StrRefID = Str(RefID)
            RefIDStr1 = "[Refnumber]=" & StrRefID
            DoCmd.OpenForm "PopUp", , , RefIDStr1
            Forms!ReviewerForm.SetFocus
        'When user enters other valid letters, capital form
        'of letter is entered in database and cursor moves
        'to next record
        'Case 67
        'User has entered "C"
        'Me.Rev2Code = ""
        'Me.Rev2Code = "C"
        'DoCmd.GoToRecord , , acNext
        'Case 99
        'User has entered "c"
        'Me.Rev2Code = ""
        'Me.Rev2Code = "C"
        'DoCmd.GoToRecord , , acNext
        Case 82
            'User has entered "R"
```

Table 7. Event procedure code for Microsoft Access Database (continued)

```
Me.Rev2Code = ""
Me.Rev2Code = "R"
DoCmd.GoToRecord , , acNext
Case 114
'User has entered "r"
Me.Rev2Code = ""
Me.Rev2Code = "R"
DoCmd.GoToRecord , , acNext
Case 68
'User has entered "D"
Me.Rev2Code = ""
Me.Rev2Code = "D"
DoCmd.GoToRecord , , acNext
Case 100
'User has entered "d"
Me.Rev2Code = ""
Me.Rev2Code = "D"
DoCmd.GoToRecord , , acNext
Case 83
'User has entered "S"
Me.Rev2Code = ""
Me.Rev2Code = "S"
DoCmd.GoToRecord , , acNext
Case 115
'User has entered "s"
Me.Rev2Code = ""
Me.Rev2Code = "S"
DoCmd.GoToRecord , , acNext
'If user enters tab or enter key, cursor
'moves automatically to next record with
'no further action needed.
Case 9
'User has pressed tab key -- no action needed
Case 13
'User has pressed enter key -- no action needed
'Otherwise User has pressed an invalid letter
'and is prompted to change it.
Case Else
Me.Rev2Code = ""
MsgBox "Please enter an allowable option."
End Select
End Sub
```

Table 7. Event procedure code for Microsoft Access Database (continued)

```
Private Sub QuitButton_Click()  
'When the user wishes to exit and clicks on the quit button, he or she will be asked to  
enter their initials  
strScrInit = ""  
'The initials box will continue to appear until something is entered.  
'This Do While Loop checks to see if the initials popup field is blank.  
'If so, it will instruct the use to enter the initials of the individual  
'doing reference screening.  
Do While strScrInit = ""  
strScrInit = InputBox("Enter the initials of the reference screener:", "")  
Loop  
'This converts the initials to upper case, regardless of what the enduser enters.  
strScrInit = UCase(strScrInit)  
'The following steps construct a string of SQL code to perform an update of the table  
'Following the table update the reviewers initials will be inserted into records  
'that have non-blank fields for the reference code.  
singleQuote = """"  
strSQL = "UPDATE Article SET [Rev2Init] = " & singleQuote & strScrInit &  
singleQuote & " WHERE [Rev2Init]=" & singleQuote & singleQuote & " AND  
[Rev2Code] <>" & singleQuote & singleQuote & ";"  
DoCmd.SetWarnings False  
DoCmd.RunSQL strSQL  
'After the table is updated, the table will be saved and the program will close.  
DoCmd.Save  
DoCmd.Quit  
End Sub
```

Appendix C

Evidence tables for individual studies identified in the systematic review

Interventions to improve patient safety with CPOE

Citation: Bonnabry et al. (2008)

Population/Setting: Pediatric service of a Swiss academic hospital; CPOE for total parenteral nutrition and cancer chemotherapy

Intervention: multifactorial modifications in CPOE: alerts for omitted treatments, omitted allergies or antibiotic suggestions; integration of vital signs into the record, adjustments in printed prescriptions

Comparators: CPOE, no CPOE

Outcomes: FMECA criticality index

Applicability: Moderate; FMECA and interventions were applied to a selected subset of pediatric orders but could be of relevance to other order types and populations, particularly in acute and critical care settings

Study design: non-standard design

Interventions to improve computerized medication decision support

Citation: Bates et al. (1999)

Population/Setting: Urban, academic center in the US

Intervention: Improved drug allergy checking; improved potassium orders; drug-drug interaction checking

Comparators: Paper orders, basic CPOE system

Outcomes: Medication errors (other than missed doses)

Applicability: General

Study design: Sequential

Study quality: Fair, non-randomized, non-blinded, confounds related to complexity of added features at each phase of implementation

Citation: Scott et al. (2011)

Population/Setting: Junior physicians using a prototype e-prescribing system in the UK

Intervention: modal alert to a prescribing error, non-modal alert to a prescribing error

Comparators: no alert to a prescribing error

Outcomes: rates at which a prescribing error was present

Applicability: Unclear, junior physicians are involved in the bulk of inpatient order entry, but a prototype system was used rather than a production e-prescribing system

Study design: Randomized controlled trial

Study quality: Good

Citation: Tamblyn et al. (2008)

Population/Setting: Ambulatory fee-for-service general practitioner or family medicine practices in Montreal

Intervention: On demand access to prescribing alerts, ability to customize alert display to limit alerts to definite/serious or display all 3 levels of alert severity

Comparators: Automatic computer triggered prescribing alerts, display of level 1 and level 2 alerts to identify definite/serious and likely adverse effects

Outcomes: prevalence of prescribing problems as identified by the drug knowledge database, including level of severity of prescribing problems; proportion of overridden alerts and associated override reasons; use of customization

Applicability: Generalizable

Study design: Cluster randomized controlled trial, single blind, with stratification by clinic

Study quality: Good

Citation: Paterno et al. (2009)

Population/Setting: Urban academic hospitals in the US

Intervention: Tiered drug decision support alerts with non-intrusive presentation of low severity alerts as part of CPOE

Comparators: Standard drug decision support (non-tiered) as part of CPOE

Outcomes: Alert adherence rates

Applicability: Generalizable

Study design: Non-randomized non-blinded controlled study

Study quality: Fair

Interventions to improve the ordering of appropriate laboratory monitoring of pharmacotherapy

Citation: Lo et al. (2009)

Population/Setting: 22 outpatient primary care practices in the Boston metropolitan area; mix of hospital clinics, women's clinics and community health centers; 366 study participants with a mix of professional background and experience

Intervention: Non-interruptive alert recommending baseline laboratory tests appropriate for prescribed medication

Comparators: Control condition with existing EMR

Outcomes: Rate of ordering of indicated baseline laboratory tests

Applicability: Ambulatory primary care settings; possible relevance to other settings

Study design: Prospective, randomized, controlled trial

Study quality: Good

Citation: Palen et al. (2006)

Population/Setting: Ambulatory primary care physicians practicing in a managed care organization

Intervention: Non-intrusive decision support alerts suggesting ordering of recommended laboratory studies when prescribing specific medications

Comparators: CPOE without laboratory order alerts

Outcomes: Proportion of medication orders for which appropriate laboratory testing was ordered within 180 days before or 14 days after medication dispensing

Applicability: Outpatient managed care setting, possible relevance to other settings and models of health care delivery

Study design: Randomized controlled trial, not-blinded

Study quality: Good, allocation via statistical program, randomized

Citation: Matheny et al. (2008)

Population/Setting: Primary care ambulatory clinics, including community health centers, hospital-based clinics and off-site practices

Intervention: Non-modal recommendations about laboratory monitoring in the context of chronic use of a specific medication

Comparators: Standard CPOE system without laboratory monitoring reminders

Outcomes: Proportion of patients who received recommended laboratory monitoring within 14 days

Applicability: Outpatient settings, possible relevance to other settings

Study design: Cluster randomized trial with stratification of sites to account for gender and socioeconomic status.

Study quality: Good

Citation: Steele et al. (2005)

Population/Setting: Primary care outpatient clinics

Intervention: Computerized alerts describing risks of specific medication related laboratory abnormalities and recommending monitoring of specific laboratory tests

Comparators: Control condition with standard CPOE without medication specific alerts

Outcomes: Percent adherence with recommended laboratory orders, percent of cancelled orders, rates of adverse drug events

Applicability: Outpatient, possible relevance to other settings

Study design: Before-after study

Study quality: Fair

Citation: Overhage et al. (1997)

Population/Setting: Inpatient internal medicine service of urban academic hospital

Intervention: Decision support alert that suggested and permitted easy ordering of recommended "corollary orders" for laboratory tests that were indicated in the context of prescribing a specific medication

Comparators: Control condition in which orders were entered using CPOE and lists of recommended "corollary orders" were available in hard-copy form

Outcomes: Rates of physician adherence to ordering recommended laboratory monitoring calculated based on immediate ordering, ordering within 24 hours or ordering during the hospital stay

Applicability: Inpatient settings, possible relevance to other settings

Study design: Cluster randomized controlled trial

Study quality: Good

Citation: Galanter et al. (2004)

Population/Setting: Urban academic hospital in the US

Intervention: Decision support alerts to enhance safe use of digoxin by maintaining normal potassium and magnesium levels, minimizing the potential for drug-drug interactions with digoxin and assessing for recent digoxin serum monitoring; alerts are presented at time of ordering or at time of posting of relevant laboratory abnormalities

Comparators: CPOE without enhanced digoxin alerts

Outcomes: 1 hour and 24 hour adherence with recommended safe practices

Applicability: Patients taking digoxin in any setting

Study design: Before-after

Study quality: Fair, non-randomized, non-blinded, used retrospective data for before period, used detailed "survival" curve methodology to track adherence to alerts over time

Citation: Stewart et al. (2003)

Population/Setting: Veteran's Health System in the US

Intervention: Interactive template presented at the time of amiodarone ordering that documents the justification for amiodarone use and gives links to appropriate monitoring orders.

Comparators: Standard Veteran's Administration Computerized Patient Record

Outcomes: Rates of laboratory monitoring with template use

Applicability: Patients taking amiodarone or other medications that require extensive laboratory monitoring

Study design: Before-after; with and without template comparisons after implementation

Study quality: Poor, non-randomized, some study details not available as it is published in abstract form, no figures for statistical significance were provided.

Citation: Abboud et al. (2006)

Population/Setting: Academic pediatric hospital, US

Intervention: Alert when ordering aminoglycosides that asked if the prescriber wished to order specific blood levels with links to potential orders embedded in the alert

Comparators: Standard CPOE condition

Outcomes: Date, time and results of aminoglycoside levels in association with orders for aminoglycosides

Applicability: Acute settings, pediatric population; possible relevance to other patient groups and settings

Study design: Before-after

Study quality: Fair, not randomized, not-blinded

Citation: Traugott et al. (2011)

Population/Setting: Academic hospital inpatient services

Intervention: Alert that fired upon ordering of a random or trough vancomycin serum level and gave information on monitoring criteria; default settings on the vancomycin orders were also adjusted

Comparators: CPOE without vancomycin related alert or adjustment of default ordering sentences

Outcomes: Percent change in appropriateness of orders for vancomycin levels

Applicability: Limited; relevant to drugs that require serum monitoring

Study design: Before-after study with retrospective chart review to determine pre-intervention data

Study quality: Fair

Citation: Koide et al. (2000)

Population/Setting: Ambulatory and inpatient services of a Japanese academic hospital

Intervention: Alert advising of the need for aminotransferase levels every 90 days in individuals being prescribed etretinate

Comparators: Control CPOE system without etretinate-related alerts

Outcomes: Proportion of prescriptions for etretinate for which appropriate hepatic function tests were assessed within 90 days

Applicability: Data relates to a single drug, but may be relevant to laboratory monitoring in relationship to other medication use

Study design: Before-after design

Study quality: Fair

Citation: Tang et al. (2009)

Population/Setting: Outpatient dermatological center in Singapore

Intervention: Computerized decision support template for enhancing the safety of isotretinoin prescribing

Comparators: Usual EMR without isotretinoin template

Outcomes: Rates of adherence to recommended laboratory testing

Applicability: Patients treated with isotretinoin, potentially applicability to other drugs that require extensive monitoring

Study design: Before-after

Study quality: Fair, non-randomized

Interventions to improve prophylaxis of venous thromboembolism

Citation: Kucher et al. (2005)

Population/Setting: Acute inpatient academic hospital, medical and surgical patients at risk of venous thromboembolism

Intervention: Electronic alert about VTE risk that provided options for mechanical and pharmacological prophylaxis

Comparators: Control group that received no VTE alert

Outcomes: Clinical diagnosis of deep vein thrombosis or pulmonary embolus within 90 days

Applicability: High; venous thromboembolism is a common problem in acute care settings

Study design: Randomized controlled trial

Study quality: Good

Citation: Durieux et al. (2000)

Population/Setting: Orthopedic surgery service of an urban academic hospital in France, 1971 patients

Intervention: Decision support alert advising about VTE prophylaxis, structured according to patient's level of VTE risk

Comparators: Standard CPOE

Outcomes: Proportion of individuals in whom appropriate VTE prophylaxis is given

Applicability: Study limited to small group of patients but relevant to acute care settings in which VTE prophylaxis is indicated

Study design: Alternating OFF-ON periods separated by washout periods

Study quality: Good; Non-randomized, non-blinded, but use of multiple intervention and control periods separated by "washout" periods limits potential cohort-related confounds

Citation: Lecumberri et al. (2008) and Lecumberri et al. (2011)

Population/Setting: Academic hospital in Spain

Intervention: Decision support alert to determine relative risk of VTE and provide links to advise prescribers about recommended VTE prevention options

Comparators: Existing EMR without VTE alerts

Outcomes: Incidence of VTE

Applicability: Hospitalized patients at risk of VTE

Study design: Before-after, with 4 after periods

Study quality: Fair, non-randomized, used comparable periods before and after (to eliminate confounds of season or study duration) and also examined trends over time

Citation: Novis et al. (2010)

Population/Setting: Surgical patients admitted to a US Veterans Administration Hospital

Intervention: VTE risk assessment incorporated into an EMR

Comparators: Standard EMR without VTE risk assessment embedded in pre-surgical documentation and having order generating capabilities

Outcomes: Proportion of patients receiving recommended VTE prophylaxis, incidence of post-operative DVT at 30 and 90 days.

Applicability: Surgical inpatients, other patients at risk for VTE

Study design: Before-after

Study quality: Fair, non-randomized, non-blinded

Citation: Sobieraj (2008)

Population/Setting: 20 bed medical unit of an acute care, community-based teaching hospital

Intervention: Educational program plus alert displayed to prescribers to perform an assessment for VTE risk and consider appropriate pharmacological and mechanical VTE prophylaxis when appropriate prophylaxis had not already been initiated

Comparators: Usual CPOE system and usual care

Outcomes: Rates of adherence to VTE prophylaxis

Applicability: Inpatients with VTE risk

Study design: Before-after

Study quality: Fair, non-randomized, some additional confounding factors including pre-implementation education

Citation: Candelario et al. (2010)

Population/Setting: Patients with cancer hospitalized at an academic center

Intervention: Electronic alert advised physicians to order VTE prophylaxis or provide a reason for not doing so

Comparators: Pre-alert implementation vs. post-alert implementation; VTE rates facility wide vs. VTE rates at other comparable facilities

Outcomes: Provision of adequate prophylaxis, provision of any prophylaxis, before-after VTE rates at the facility

Applicability: Moderate, although the study was limited to cancer patients in an acute care setting, such individuals represent a significant group of admitted patients who are at particularly high risk of VTE and related complications; use of overall facility rates for VTE rates makes patient-related outcome comparisons less specific

Study design: Before-after design with retrospective pre-intervention comparison

Study quality: Fair

Citation: Dexter et al. (2001)

Population/Setting: Academic hospital in the US, 6371 patients admitted to a general medicine service

Intervention: Preventive intervention reminders, including a prophylactic heparin reminder, as part of CPOE

Comparators: Standard CPOE system

Outcomes: Adjusted rates of ordering the preventive intervention

Applicability: Primarily applicable to acute settings, but may have some relevance to ambulatory preventive reminders as well

Study design: Non-randomized assignment of physicians to parallel intervention and control groups

Study quality: Fair, non-random, non-blinded, some physicians (13.9%) overlapped in the two conditions

Citation: Teich et al. (2000)

Population/Setting: Urban academic hospital in the US

Intervention: Alert to suggest ordering of subcutaneous heparin for patients placed on bed rest who are not already receiving heparin or warfarin

Comparators: Usual EMR without heparin alert

Outcomes: Adherence with placing of heparin order in same ordering session that bedrest is initiated

Applicability: Inpatients at risk of VTE

Study design: Before-after

Study quality: Fair, non-randomized, non-blinded

Citation: Galanter et al., 2010

Population/Setting: Inpatient, adults, academic center, US

Intervention: Computerized risk assessment form

Comparators: CPOE without computerized form

Outcomes: Occurrence of VTE; Major or minor bleeding; Rates of VTE prophylaxis

Applicability: Hospitalized patients at risk of VTE

Study design: Before-after

Study quality: Fair, used blinded raters to identify outcome measures

Citation: Baroletti et al., 2008

Population/Setting: Inpatients, adult, academic center, US

Intervention: Electronic alert to physician if high-risk VTE patient was not on prophylaxis

Comparators: Standard EHR system

Outcomes: VTE at 90 days, mortality, bleeding, physician response, prophylaxis choice

Applicability: Inpatients at risk for VTE

Study design: Cohort with historical control

Study quality: Poor

Citation: Fiumara et al. (2010)

Population/Setting: Inpatients, adult, medical or surgical service, academic center, US

Intervention: Enhanced VTE alert for clinicians who did not respond to initial alert

Comparators: Unenhanced VTE alert in standard EHR

Outcomes: Use of VTE prophylaxis, VTE rate at 90 days, mortality

Applicability: Inpatients at risk for VTE

Study design: Cohort

Study quality: Poor, multiple potential confounding factors including differences in patient baseline risks between the two groups and presentation of both alerts to the physicians in the intervention group

Citation: Kucher et al. (2009)

Population/Setting: Inpatients, adult, medical service, academic center, Switzerland

Intervention: Flashing electronic alert for patients not receiving VTE prophylaxis with options to order appropriate treatment

Comparators: Standard EHR with interruptive VTE alert

Outcomes: Rate of prophylaxis

Applicability: Inpatients at risk for VTE

Study design: Cohort with historical control

Study quality: Poor

Interventions to reduce rates of medication errors in pediatric patients with electronic prescribing

Citation: Kadmon et al. (2009)

Population/Setting: Pediatric intensive care unit in an academic hospital in Israel

Intervention: CDSS for medications

Comparators: EMR without CDSS

Outcomes: Rates of medication errors, incomplete prescriptions and adverse drug events

Applicability: Relevant to acute pediatric settings as well as adult acute care

Study design: Sequential periods with increasing addition of CPOE and later CDSS

Study quality: Fair, non-randomized, potential for cohort related confounds as well as effects of multiple simultaneous interventions

Citation: Kazemi et al. (2011)

Population/Setting: Patients in a neonatal intensive care unit of an Iranian teaching hospital who received treatment with either an antibiotic or an anticonvulsant

Intervention: Addition of medication-related decision support to CPOE

Comparators: CPOE alone, pre-CPOE ordering on paper

Outcomes: Rates of medication prescription errors

Applicability: Limited, used a small subset of orders as well as a circumscribed patient population

Study design: Before-after study, non-blinded

Study quality: Fair

Citation: Sard et al. (2008)

Population/Setting: Urban pediatric emergency department at an academic center in the US

Intervention: Option to use a “quicklist” for selecting pediatric specific medication orders

Comparators: Standard practice using the EMR with selection of medication orders using order sets or manually entering detailed information for each medication order

Outcomes: Rates of medication errors per 100 orders

Applicability: Moderate, with highest applicability to pediatric settings or acute care settings with some applicability to adult and non-acute settings

Study design: Retrospective, before-after study

Study quality: Fair

Interventions to reduce rates of specific medication interactions

Citation: Humphries et al. (2007)

Population/Setting: Ambulatory primary care health maintenance organization in the US

Intervention: Hard stop alert for critical drug interactions related to 8 pairs of co-prescribed medications that precluded dispensing without physician communication

Comparators: Passive drug interaction alert system

Outcomes: Changes in rate of critically interacting drug prescriptions

Applicability: Outpatient, pharmacist-based intervention; possible relevance to other settings and physician alerting

Study design: Before-after

Study quality: Fair, non-randomized, non-blinded

Citation: Strom et al. (2010a)

Population/Setting: academic center inpatient service in the US

Intervention: hard stop alert for an order that would lead to simultaneous treatment with warfarin and trimethoprim-sulfamethoxazole

Comparators: CPOE without immediate alert but with post-order pharmacist intervention to suggest prescribing changes

Outcomes: proportion of instances in which the alerting drug was not reordered within 10 minutes; monitoring for unintended discontinuation or lack of initiation of crucial treatment

Applicability: Inpatient; Patients treated with warfarin; Possible relevance to other settings

Study design: Randomized controlled trial, prescribers not blinded to intervention

Study quality: Good

Citation: · Strom et al. (2010b)

Population/Setting: academic center inpatient service in the US

Intervention: alert for an order that would lead to simultaneous treatment with warfarin and NSAID noting that the combination is contraindicated and directing the prescriber to a screen for ordering an alternative agent

Comparators: standard drug-interaction message box

Outcomes: Rates at which desired ordering behavior occurred and patient did not have a simultaneous order of warfarin and an NSAID

Applicability: Inpatient; Patients treated with warfarin; Possible relevance to other settings

Study design: Randomized controlled trial, prescribers not blinded to intervention

Study quality: Good

Interventions to improve the appropriateness of medication use in patients with renal insufficiency

Citation: Chertow et al. (2001)

Population/Setting: Urban academic hospital, sample of 17828 adults admitted to the medical, surgical, neurological or obstetrics and gynecology services

Intervention: Alerts of customized dosing recommendations for which the default varied with the patient's renal function

Comparators: Standard CPOE without customized dosing alerts

Outcomes: Fraction of prescriptions with appropriate dose and frequency

Applicability: Generalizable

Study design: ON-OFF-ON –OFF in 2 month alternating periods

Study quality: Good, non-randomized and non-blinded but multiple sequential OFF-ON periods rather than simply Before-after intervention

Citation: Sellier et al. (2009)

Population/Setting: Patients hospitalized on the internal medicine or geriatrics service of a large academic hospital in France

Intervention: Alert that provided recommendations for dosing adjustments based on the patient's renal function

Comparators: Standard order entry with pharmacist interventions

Outcomes: proportion of inappropriate prescriptions among first prescriptions that required dosage adjustment, proportion of inappropriate prescriptions among all prescriptions that required dosage adjustment

Applicability: Applicable to acute medical settings, with potential relevance to patients with renal impairment in other acute and ambulatory settings

Study design: Alternating control and intervention periods

Study quality: Fair, non-randomized, non-blinded but prospective with more than one intervention and control period

Citation: Rind et al. (1994)

Population/Setting: Urban academic hospital in the US; adult patients on the medical service with serum creatinine of 3.0 mg/dL or less

Intervention: Alert to physician if the serum creatinine increased by 0.5 mg/dL or more in a patient receiving one or more nephrotoxic medications or if the serum creatinine increased by 50% or more to a value of 2.0 mg/dL or higher in a patient received a renally excreted medication

Comparators: Usual EMR without renal-specific alert

Outcomes: Time from renal event to change in medications; change in serum creatinine at 3 and 7 days after renal event, development of serious renal impairment, mortality

Applicability: Generalizable to inpatients with some relevance to outpatients receiving potentially nephrotoxic medications

Study design: 3 control periods of 3 months each alternating with 2 intervention periods of 3 months each

Study quality: Good, non-randomized, but potential confounding factors addressed in part through the time series design

Citation: Galanter et al. (2005)

Population/Setting: Urban academic hospital in the US

Intervention: Decision support alerts to advise prescribers of medications that were contraindicated in individuals with impairments in renal function

Comparators: CPOE without alerts

Outcomes: Proportion of patients receiving at least one dose of a contraindicated medication

Applicability: Patients with renal impairment across settings of care

Study design: Before-after

Study quality: Fair, non-randomized, non-blinded, differing lengths of before period (4 months) as compared to after period (10 months)

Citation: McCluggage et al. (2010)

Population/Setting: Adult patients in an urban academic hospital who were treated with vancomycin

Intervention: Vancomycin nomogram integrated into CPOE using an order set

Comparators: CPOE without vancomycin order set

Outcomes: Proportion of patients with an initial optimal vancomycin dosing regimen

Applicability: Patients being treated with vancomycin, potential applicability for similar medications with complex dosing considerations

Study design: Before-after

Study quality: Fair, non-randomized, non-blinded

Interventions to improve the appropriateness of medication choice and dosing for geriatric patients

Citation: Peterson et al. (2005)

Population/Setting: Inpatients aged 65 years or older admitted to a medical, surgical, neurological or gynecological service

Intervention: Use of customized alerts that provide age-appropriate dosing suggestions for geriatric patients as well as offering suggestions for an alternative medication when an order is begun for a medication that is associated with lesser tolerability in the elderly.

Comparators: Existing CPOE system with standard alerts intended for adults of all ages

Outcomes: Proportion of doses that are at or less than the recommended dose in geriatric patients, proportion of doses that are at least 10 fold greater than the recommended dose in geriatric patients, rates of patient falls, number of hospital days associated with an alteration in mental status

Applicability: Geriatric patients in acute settings; possible applicability to other settings

Study design: Prospective, on-off-on-off

Study quality: Good; although not a randomized trial, the study is well designed and prospective. In addition, the use of an on-off-on-off design provides greater protection against confounding factors than a before-after design

Citation: Griffey et al. (2012)

Population/Setting: Individuals age 65 or older who were seen in an urban academic emergency department and had a medication order written

Intervention: Decision support alerts that give prescribing suggestions for geriatric patients including changes to doses and safer medication choices

Comparators: Standard CPOE system

Outcomes: agreement with suggested choice of drug, agreement with suggested choice of dose, 10 fold excessive dosing rates, proportion of ADEs (determined based on retrospective chart review), number of rescue drugs required

Applicability: Geriatric patients in acute settings; possibly applies to other settings

Study design: Prospective, on-off-on-off

Study quality: Good; although not a randomized trial, the study is well designed and prospective. In addition, the use of an on-off-on-off design provides greater protection against confounding factors than a before-after design

Citation: Mattison et al. (2010)

Population/Setting: Urban academic hospital in the US; patients aged 65 and older

Intervention: Alert to consider safer medication or reduced medication dose for a list of medications noted to have increased risk in the elderly

Comparators: Standard EMR without alerts

Outcomes: Daily number of medications in each higher risk class as a proportion of either the total number of hospitalized geriatric patients or the number of newly admitted geriatric patients; change with intervention determine based on the change in slope of smoothed splines

Applicability: Geriatric patients; acute settings; possibly applies to other settings

Study design: Before-after

Study quality: Good, non-randomized, but analysis included spline analysis to look at ordering trends over time that could suggest the presence of specific confounding factors

Citation: · Smith et al. (2006)

Population/Setting: Adult patients treated in a primary care setting in the US

Intervention: Decision support alert providing advice about preferable medications when the prescriber enters an order for a medication that is not preferred for use due to safety concerns

Comparators: Electronic prescribing without decision support alert

Outcomes: Dispensing of preferred and non-preferred medications

Applicability: Geriatric patients in outpatient settings; possible applicability to other settings and age groups as authors assessed medication use in elderly and non-elderly populations

Study design: Before-after

Study quality: Fair

Citation: Raebel et al. (2007b)

Population/Setting: Ambulatory health maintenance organization, 59,680 individuals aged 65 and older in the US

Intervention: Hard stop alert that precluded dispensing of non-recommended medication without physician communication

Comparators: Usual EMR without alerts for non-recommended medications in geriatric patients

Outcomes: Proportion of dispensing of potentially inappropriate medications

Applicability: Geriatric patients in outpatient settings involving pharmacist review of medications; possible applicability to other settings and physician alerts regarding non-recommended medications

Study design: Randomized controlled with patients, physicians and pharmacists were noted to be blinded to group assignment

Study quality: High, although it is hard to understand how pharmacists receiving intervention group alerts would be able to remain blinded to group assignment

Citation: Terrell et al. (2009)

Population/Setting: Emergency department of an urban academic hospital in the US; adult patients aged 65 years or older

Intervention: Decision support that advised against use of 9 medications for geriatric patients and suggested other medication options that are felt to be safer in this population

Comparators: Usual CPOE system

Outcomes: Proportion of visits associated with prescribing of an inappropriate medication; proportion of medication prescriptions that were inappropriate

Applicability: Geriatric patients in acute settings; possible applicability to other settings

Study design: Randomized controlled trial

Study quality: Good

Citation: Peterson et al. (2007)

Population/Setting: Academic health center in the US, inpatients ages 65 years or older

Intervention: Standard CPOE system with decision support related to geriatric specific dosing recommendations

Comparators: Standard organization developed CPOE system

Outcomes: Ratio of prescribed to recommended medication doses

Applicability: Applicable to geriatric patients in inpatient as well as outpatient settings

Study design: Randomized controlled trial

Study quality: Fair, reported as a randomized trial but exact randomization procedure is unclear and some physicians are noted to have been part of both the intervention and the control groups.

Citation: Tamblyn et al. (2012)

Population/Setting: Older patients being treated in an ambulatory setting by family physicians in Canada

Intervention: Graphical alert that used a predictive model to estimate a patient-specific risk of injury based on underlying risk factors and prescribed medication type and dose

Comparators: Use of electronic prescribing without a patient-specific injury risk alert

Outcomes: Risk of injury at the end of the followup period, changes in the use and dose of medications

Applicability: Geriatric patients in outpatient settings; possible applicability to other settings

Study design: Cluster randomized controlled trial, single blind (outcome)

Study quality: Good

Interventions to improve the appropriateness of medication dosing in special populations

Citation: Seidling et al. (2010)

Population/Setting: Academic hospital in Germany with inpatient and outpatient services

Intervention: Alerts that provided feedback on medication dosage based on a dosing algorithm that incorporated patient specific factors

Comparators: CPOE without patient-specific dosing alerts

Outcomes: Proportion of doses that were greater than the individual maximum recommended therapeutic dose; alert adherence

Applicability: General

Study design: Prospective before-after design

Study quality: Fair

Citation: Ginzburg et al. (2009)

Population/Setting: Pediatric visits in an ambulatory family medicine multi-site practice in the US

Intervention: Weight-based dosing support for acetaminophen and ibuprofen prescriptions in patients less than 13 years

Comparators: Standard commercial CPOE system

Outcomes: Proportion of patients who received an appropriate dose of acetaminophen or ibuprofen

Applicability: Children and infants regardless of setting

Study design: Before-after

Study quality: Fair, non-randomized

Interventions to improve computerized decision support in specific clinical circumstances

Citation: Riggio et al. (2009)

Population/Setting: Urban academic hospital in the US

Intervention: Decision support alert suggesting evaluation for heparin induced thrombocytopenia on the basis of an active heparin order and either a 50% drop in platelet count over 3 weeks or a 30% drop to less than 150,000 platelets per cubic mm

Comparators: Usual EMR with no heparin induced thrombocytopenia alert

Outcomes: Time from platelet count criterion to heparin discontinuation; time from platelet count criterion to initiation of treatment for heparin induced thrombocytopenia; time from platelet count criterion to initial laboratory testing for heparin induced thrombocytopenia

Applicability: Inpatients treated with heparin

Study design: Before-after

Study quality: Fair

Citation: Coté et al. (2008)

Population/Setting: Cardiology telemetry and intensive care unit at an academic hospital

Intervention: Brief education about risks of NSAID gastrointestinal ulceration and recommended prophylaxis, computerized alert recommending prophylaxis to reduce risk of gastrointestinal complications with NSAID, combination of brief physician education and computerized decision support alert

Comparators: Standard CPOE without alerts

Outcomes: Rates of provision of appropriate gastroprotection

Applicability: Acute care settings, particularly in patients with risk factors for gastrointestinal problems; potential relevance to other settings (e.g., ambulatory, long term care) in patients at increased risk for gastrointestinal problems

Study design: Prospective study with sequential observation periods for the 4 interventions and stratification of patients by their extent of gastrointestinal risk

Study quality: Good, non-randomized but incorporates multiple observation periods and appropriate stratification to minimize potential for bias

Citation: Raebel et al. (2007a)

Population/Setting: Ambulatory clinics of a managed care organization; women receiving treatment with medication

Intervention: Decision support that incorporated EMR data on the medication and identifiers of possible pregnancy to alert pharmacists to category D or X medications

Comparators: Standard EMR system

Outcomes: Proportion of patients who were dispensed category D or X medications while pregnant

Applicability: Limited given unique nature of pharmacist intervention

Study design: Randomized trial, non-blinded

Study quality: Fair

Citation: Yu et al. (2011)

Population/Setting: Adult patients from 51 outpatient practices encompassing specialty and primary care in a metropolitan area

Intervention: Computerized decision support alerts that provided information about relevant FDA black-box medication-related warnings

Comparators: Standard electronic prescribing system without Black-box warning alerts

Outcomes: Frequency of prescriptions that did not adhere to relevant Black-box warnings

Applicability: General, black box warnings are of relevance regardless of setting, but findings seem to vary depending upon the drug class and are potentially altered by prescriber and patient characteristics based on differences between hospital and non-hospital based clinic settings

Study design: Before-after

Study quality: Fair

Interventions to reduce inappropriate tablet splitting

Citation: Quinzler et al. (2009)

Population/Setting: Ambulatory practice of an academic center in Germany

Intervention: Display of icons noting form of oral drug (i.e. capsule vs. tablet), presence of score lines, number of possible fragments as well as alerts for doses that were not possible with splitting of available tablet/capsule sizes

Comparators: Standard electronic prescribing system without icons and alerts for tablet splitting

Outcomes: Fraction of inappropriately split tablets, changes in medication regimens, appropriateness of medication changes

Applicability: General

Study design: Before-after, prospective

Study quality: Fair, some possible confounding factors were present but well-designed for a quasi-experimental study

Interventions to reduce the use of unapproved abbreviations

Citation: Myers et al. (2011)

Population/Setting: Internal medicine units at an academic hospital; 59 interns participated

Intervention: Autocorrection of unapproved abbreviations, Alert forcing the user to manually correct the unapproved abbreviation

Comparators: Control condition with existing electronic record

Outcomes: Unapproved abbreviation percentage in up to 15 handwritten history and physical documents

Applicability: Acute care settings, physician users (residents); may also be relevant to other settings and users

Study design: Randomized, single-blind (unaware of outcome)

Study quality: Fair, potential confounding effects of concomitant educational interventions and indirect nature of primary outcome (i.e., use of unapproved abbreviations in handwritten documentation)

Interventions to enhance communication about prescribers' thought processes

Citation: Johnson et al. (2010)

Population/Setting: Ambulatory practices affiliated with an academic center in the US

Intervention: Transmission of prescription with prescription related annotations regarding information such as dose calculations, prescribing alerts presented during ordering and prescriber responses to alerts

Comparators: Transmission of prescription alone

Outcomes: Rates of pharmacist callbacks to prescriber, pharmacist perceptions of receiving annotated prescriptions

Applicability: Outpatient settings across patient ages and diagnoses; potential relevance to other settings in which prescribing occurs

Study design: Randomized controlled trial, prescribers blinded with respect to information transmission

Study quality: Fair, data collection on call backs depended upon voluntarily collected pharmacist logs introducing potential for bias

Appendix D

Summaries of the body of evidence for topics in the systematic review

Interventions to improve patient safety with CPOE

Risk of bias: High; criticality index calculations are subjective

Consistency: Not applicable, single study

Directness: Indirect; criticality indices are thought to reflect patient safety related failure points but no direct outcomes were assessed.

Precision: Imprecise

Risk of confounds: High, due to clinical judgment involved in rating criticality indices

Strength of association: Low

Applicability: Inpatients; possible relevance to EHRs in other settings

Interventions to improve computerized medication decision support

Risk of bias: Medium,

Consistency: Low

Directness: Indirect, although one study does include direct evidence of reductions of adverse drug events in patients

Precision: Imprecise, substantial heterogeneity in effects of decision support alerts depending upon alert configurations

Risk of confounds: Present, due to complex interventions and lack of randomization in some of the studies

Strength of association: Low

Applicability: General

Interventions to improve the ordering of appropriate laboratory monitoring of pharmacotherapy

Risk of bias: Low, substantial number of randomized trials and well-designed quasi-experimental trial

Consistency: Inconsistent, effects are neutral to positive but variability within and between studies is present

Directness: Indirect, outcomes relate to rates of recommended laboratory testing with specific medications and not patient health outcomes

Precision: Imprecise, due to variability in outcomes across studies; studies with positive outcomes typically had high degrees of statistical significance.

Risk of confounds: Present, heterogeneity in design of alerts across studies, variable importance of medication monitoring with specific agents

Strength of association: Weak, due to limited consistency, heterogeneity of alert design

Applicability: General

Interventions to improve prophylaxis of venous thromboembolism

Risk of bias: Moderate, multiple studies with good design as well as additional quasi-experimental studies and some poorly designed studies

Consistency: Consistent, improved provision of appropriate VTE prophylaxis in well-designed studies across multiple at-risk patient populations, reductions in rates of DVT or pulmonary embolus were reduced in several studies, though not all

Directness: Direct, some evidence for reductions in DVT and pulmonary embolism as well as corroborating indirect evidence

Precision: Precise, significant differences in results of well-designed studies

Risk of confounds: Present in a portion of studies

Strength of association: Moderate

Applicability: Inpatients at risk for VTE; possible relevance to other settings (e.g., long term care, bedbound patients in the community)

Interventions to reduce rates of specific medication interactions

Risk of bias: Medium; One before-after trial and two trials that were randomized but in which prescribers were not blinded to the intervention

Consistency: Inconsistent, some benefits in reducing concomitant prescription of some combinations but not all, decline in effectiveness over time in two studies, potential for harm due to treatment delays noted in one study

Directness: Indirect; outcome measures assess desired prescribing patterns and not patient-specific outcomes such as adverse events

Precision: Imprecise, two studies with temporal shift in findings

Risk of confounds: Present, due to lack of blinding of prescribers

Strength of association: Weak overall due to inconsistencies in effect within and between the studies

Applicability: General

Interventions to improve the appropriateness of medication use in patients with renal insufficiency

Risk of bias: Medium, all studies are before-after or alternating on-off periods, with some potential for bias

Consistency: Consistent benefits in improving prescribing to patients with renal impairment with the exception of one study that showed no effect

Directness: Indirect, with the exception of a direct relationship to development of serious renal impairment in one study

Precision: Precise

Risk of confounds: Present

Strength of association: Weak, due to some inconsistency in findings and heterogeneity of alert types

Applicability: Inpatients with renal impairment, possibly relevant to patients with renal impairment in other settings

Interventions to improve the appropriateness of medication choice and dosing for geriatric patients

Risk of bias: Low, multiple studies of fair to good quality

Consistency: Consistent benefits of interventions across studies despite heterogeneity in settings, geography, approach to enhancing prescribing and measured outcomes

Directness: Direct, although some measures are indirect, several studies include direct measures of patient safety such as falls, risk of injury and adverse drug events

Precision: Precise

Risk of confounds: Present in some of the studies, but consistency of findings across multiple sites and methods suggest that confounds in individual studies are unlikely to affect the overall findings

Strength of association: Strong

Applicability: Geriatric patients in acute and outpatient settings, with likely relevance to geriatric patients in other settings (e.g., long term care) and other patients (e.g., those with renal or hepatic impairment) who may require patient-specific medication dosing adjustments or restrictions on use of specific medications

Interventions to improve the appropriateness of medication dosing in special populations

Risk of bias: Medium

Consistency: Consistent, despite the heterogeneity of the studies in scope, both showed benefits of the intervention in terms of dosing. The findings of the geriatric specific dosing modification studies also were consistent in showing a benefit of dosing related decision support.

Directness: Indirect, dosing errors are presumed to relate to adverse outcomes but no patient specific harms were measured

Precision: Precise

Risk of confounds: Present, due to quasi-experimental nature of these studies

Strength of association: Strong, due to highly significant changes in both studies as a result of the intervention

Applicability: General

Interventions to improve computerized decision support in specific clinical circumstances

Risk of bias: Medium

Consistency: Consistent in showing no effect although the heterogeneity of interventions should be noted.

Directness: Indirect

Precision: Not applicable as no effect was found

Risk of confounds: Present

Strength of association: Not applicable as no effect was found

Applicability: Limited to specific patient subgroups for each intervention

Interventions to reduce inappropriate tablet splitting

Risk of bias: Medium, before-after study with possible confounding factors

Consistency: Not applicable, single study

Directness: Indirect effect on safety, split tablets would be expected to have differing pharmacokinetic properties with associated difficulties in efficacy and/or adverse effects

Precision: Precise, narrow confidence intervals, significant statistical effects

Risk of confounds: Present, other factors (e.g., educational efforts to enhance awareness) could have led to a similar reduction in inappropriate tablet splitting without being recognized due to before-after design

Strength of association: Strong

Applicability: General

Interventions to reduce the use of unapproved abbreviations

Risk of bias: Medium

Consistency: Not applicable, single study

Directness: Indirect; authors examine effects of electronic intervention on handwritten documentation; use of unapproved abbreviations has been linked to increased potential for medication errors when using handwritten charts but effects in electronic charts are unclear

Precision: Imprecise; reductions in handwritten unapproved abbreviations decreased as much as the difference between the control and intervention groups during any single quarter.

Risk of confounds: Present, due to concomitant educational interventions

Strength of association: Weak

Applicability: General, given the ubiquitous use of abbreviations in clinical documentation

Interventions to enhance communication about prescribers' thought processes

Risk of bias: Medium, data collection on call backs depended upon voluntarily collected pharmacist logs

Consistency: Not applicable, single study

Directness: Indirect, an increased potential for prescribing errors (and adverse effects) could occur when a prescription is unclear as would be reflected by changes in pharmacy callback rates

Precision: Not applicable

Risk of confounds: Present

Strength of association: Not applicable, no association was found

Applicability: Outpatient settings across patient ages and diagnoses; potential relevance to other settings in which prescribing occurs