

Agency for Healthcare Research Quality Final Report

Health Information Technology Center for Education and Research on Therapeutics (HIT-CERT)

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Inclusive dates of subproject: September 30, 2011- August 31, 2016

Abstract

Purpose: The purpose of the BWH HIT-CERT was to leverage HIT for pharmacosurveillance, medication-related clinical decision support, and to identify new ways to utilize information coming from medication-related decision support. Moreover, we strove to advance our understanding of how providers are responding to medication-related decision support.

Scope: Within the three BWH HIT-CERT subprojects, our team examined questions relating to appropriateness, safety, and efficacy across diverse patient populations. The projects covered multiple settings including outpatients, inpatients and recently discharged inpatients.

Methods: We completed three research projects over a five-year period, each of which addressed one or more of the programmatic interest areas including patient safety, development and enhancement of tools, health care system interventions, and translation into practice or policy. The three subprojects involved: 1) leveraging new technologies to improve pharmacosurveillance; 2) using new sources of data from clinical decision support to identify physician-level variation and use these results to improve safety and efficiency; and 3) directly improving medication-related clinical decision support. The BWH HIT-CERT established two cores that supported the three projects and enhanced our ability to provide rapid response by our multidisciplinary team to requests by the AHRQ program staff and CERT steering committee. The cores included a methodology/data resources core, and a translation/dissemination core, which facilitated synergy. The Methodology and Data Resources Core focused on coordinating study design and analytic strategies across research projects. The Translational/Dissemination Core focused on promoting interchange and cross-fertilization across projects, the dissemination of research findings, and the translation of findings into practice through initiatives at the local, regional, and national levels together with our external partners.

Results: The BWH HIT-CERT made an important contribution to the existing CERT program by addressing key questions around therapeutics and HIT, and by contributing to advancement of the state of the art. Several of the studies were in the ambulatory setting, an important and understudied area. The BWH HIT-CERT worked closely with the existing CERT program, AHRQ, and partner organizations to translate research into improved clinical practices relating to medication safety, effectiveness, and cost.

Keywords: Patient safety, decision support systems, medication adherence

Project Purpose

The purpose of the BWH HIT-CERT was to leverage HIT for pharmacosurveillance, medication-related clinical decision support, and to identify new ways to utilize information coming from medication-related decision support. Moreover, we strove to advance our understanding of how providers are responding to medication-related decision support. The specific aims were as follows:

1. To leverage new technologies to improve pharmacosurveillance
2. To use new sources of data from clinical decision support to identify physician-level variation and use these results to improve safety and efficiency
3. To directly improve medication-related clinical decision support

Project Scope

Within the three BWH HIT-CERT subprojects, our team examined questions relating to appropriateness, safety, and efficacy across diverse patient populations. The projects covered multiple settings including outpatients, inpatients and recently discharged inpatients. The settings, participants, incidence and prevalence are described in the sub-reports included for each project. The BWH HIT-CERT aimed to address the key dimensions identified by the IOM's *Crossing the Quality Chasm* report in which today's health care system functions at far lower levels than it can and should. According to the IOM report, health care should be:

1. Safe—avoiding injuries to patients from the care that is intended to help them.
2. Effective—providing services based on scientific evidence to all who could benefit and refraining from providing services to those not likely to benefit.
3. Patient-centered—providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.
4. Timely—reducing waits and sometimes harmful delays.
5. Efficient—avoiding waste, including waste of equipment, supplies, ideas, and energy.
6. Equitable—providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomics.

The following table provides a summary of the three BWH HIT-CERT projects which included a number of priority populations.

Summary Table of BWH HIT-CERT Projects

#	Project Title	Project Leader(s)	Setting and Patient Population	Study Design	Outcomes/ Products	IOM Quality Domain
1	e-Pharmacovigilance	Gordon Schiff MD	Outpatients >18yrs old who receive a prescribed medication from their PCP	Prospective cohort study	Refinement and testing of the e-pharmacovigilance prototype	Safe Timely Patient-centered Equitable
2	Using new sources of clinical decision support data	David Bates MD, MSc	Outpatients with a primary care provider, inpatients at one hospital; no direct patient involvement	Two prospective cohort studies followed by randomized controlled trials	Description of physician-level variation in response to safety issues and efficiency suggestions in outpatients and inpatients; evaluation of impact of interventions to reduce this variation	Safe Effective Efficient
	Decision support rules	Shobha Phansalkar PharmD	All settings; no direct patient involvement	Prospective cohort study, direction observation	Unintended consequences), recommendations for prevention	Safe Effective Efficient

Project Methods

We completed three research projects over a five-year period, each of which addressed one or more of the programmatic interest areas including patient safety, development and enhancement of tools, health care system interventions, and translation into practice or policy. The study design, data sources, interventions, measures and limitations are included in the sub-reports for each of the three BWH HIT-CERT projects. The BWH HIT-CERT established two cores that supported the three projects and enhanced our ability to provide rapid response by our multidisciplinary team to requests by the AHRQ program staff and CERT steering committee. The cores included a methodology/data resources core, and a translation/dissemination core, which facilitated synergy.

Methodology and Data Resources Core. The goals of the Methodology and Data Resources Core (MDRC) were to ensure that the projects adhered to scientific principles and took full advantage of the available resources, including data, tools, and instruments. David Bates MD, MSc led the MDRC, which will included a core group of methodologists with expertise in

epidemiology, biostatistics, health services and educational and communications research. All project teams were represented in this core during the period of their active research.

Translation and Dissemination Core. The goals of the Translation and Dissemination Core (TDC) were to identify opportunities and implement strategies for disseminating key findings and translating them into practice and policy recommendations. The TDC oversaw all dissemination and educational activities of the HIT-CERT. Participants in the TDC included all project leaders in the program during the active period of their research. Participants met monthly face-to-face with teleconference capability for the investigators who are not on-site.

Project Results

The BWH HIT-CERT made an important contribution to the existing CERT program by addressing key questions around therapeutics and HIT, and by contributing to advancement of the state of the art. Several of the studies were in the ambulatory setting, an important and understudied area. The BWH HIT-CERT worked closely with the existing CERT program, AHRQ, and partner organizations to translate research into improved clinical practices relating to medication safety, effectiveness, and cost. The principal findings, outcomes, discussion, conclusions, significance and implications are discussed in the sub-reports for each of the three BWH HIT-CERT projects.

List of Publications and Products

The BWH HIT-CERT broadly disseminated its work. Key publications and products are included in the sub-reports for each of the three BWH HIT-CERT projects and a complete list of publications is available on CERT Central <https://certs.hhs.gov/articles/articles.htm>

Agency for Healthcare Research Quality Final Report**Health Information Technology Center for Education and Research on Therapeutics (HIT-CERT)****Subproject Title: E-Pharmacovigilance II - Surveillance for Safety and Effectiveness**

Subproject PI and Team Members: Gordon D. Schiff MD, Jennifer Haas MD, MSc, David W Bates MD, MSc. John Orav PhD, Enrique Seoane PhD, Alejandra Salazar Pharm D, Mary Amato Pharm D, Jeff Medoff BS, Walsh Lake BS, Theresa Fuller, BS.

Inclusive dates of subproject 9/1/2014- 8/21/2016

Abstract

Purpose/Scope: Test enhanced e-pharmaco-surveillance using interactive voice response (IVR) coupled with live pharmacist to detect patient-reported adverse drug-related symptoms. We implemented an electronic health record-linked, IVR tool for primary care patients newly prescribed medications for diabetes, hypertension, depression, or insomnia, and assessed effectiveness in detecting drug side effects. We targeted patients newly started on 104 medications started for these 4 target conditions in primary care practices.

Methods: Cluster randomized clinics (9 intervention, 9 control clinics) to receive intervention, and compared number of medication-related symptoms identified in 776 patients who responded to calls to propensity matched controls by chart review. We also measured total #'s and percentage of medications stopped for adverse effects vs. controls for entire cohort.

Results: We identified 11,128 patients newly started on the target medications whom we cluster randomized into control and intervention arms. After exclusions, calls were placed to 4,876 patients of whom 776 (16%) consented to participate and completed the call. A propensity matched cohort had similar number of medications, chronic problems, and co-morbidities. More than a third of patients reported symptoms and were transferred to our pharmacist who assessed these were evaluated for the likelihood and severity of their being related to the medication. Chart reviews, in progress, to identify total number of physician-noted symptoms related to target medications to examine hypothesis that the IVR calls and pharmacist intervention would significantly increase the numbers of medication-related symptoms identified by the physicians/prescribers.

Keywords: Adverse drug events, drug side effects, pharmacist monitoring, interactive voice response.

E-Pharmacovigilance II Subproject Purpose

Adverse drug events often go unnoticed, unreported or unaddressed. Moreover, patients are often confused or misinformed about the proper way to use newly prescribed medications and often are not aware of a wide range of side effects they may experience. Primary care physicians are frequently not notified by patients when the patients experience medication-induced adverse effects, or when the patient has chosen to discontinue the use of the medication due to perceived side effects. It is important for patients to have a structured system and opportunity to speak with a pharmacist about concerns or confusion they may have about their newly prescribed medication.

Thus the project had the following specific aims:

1. To develop and implement an electronic health record-linked, interactive voice response (IVR) e-pharmacovigilance system for patients who are newly prescribed medications for the treatment of diabetes, hypertension, depression, or insomnia.
2. To assess the efficacy and dissemination of this system, including data collection from both patients and providers.

Subproject Scope

More than half of the United States population reports use of a prescription medication in the last year, and medications dominate medical encounters with two thirds of adult ambulatory care visits resulting in prescription or continuation of a medication. Three quarters of clinician notes refer to one or more medications, with 34% of these being a new or changed prescription.

Prior work from our group demonstrated that up to one in four patients prescribed a new medication experience an adverse drug event (ADE) and recent studies have shown that the burden of outpatient ADEs on patients and health systems is substantial, resulting in more than one million emergency room visits each year annually. Timely identification of ADEs is important to minimize harms, but unfortunately many ADEs go undetected. While clinicians often ask about potential ADEs during follow-up encounters, systematic proactive approaches for monitoring and detecting ADEs are nonexistent in most clinical settings.

We have deployed a variety of approaches to proactively monitor patients for ADEs. Given the large numbers of medications initiated, manual monitoring efforts such as patient outreach by telephone should be replaced by more automated approaches. One such approach is interactive voice response (IVR) technology, ¹⁴ a tool programmed to make automated telephone calls.

In this study we have we deployed IVR to systematically reach out to patients being seen in primary care clinics who were newly started on medications for one of 4 conditions commonly seen in primary care (hypertension, diabetes, insomnia, or depression). Busy physicians do not have time to review each new medication to determine whether a patient is experiencing any side effects in a systematic way after starting the drug. Thus deploying IVR calls one month (for acute) and four months (for more chronic) adverse events/symptoms permits systematic surveillance without requiring additional clinician effort.

Because symptoms reported to an IVR system require additional confirmation (patients are at times confused in responding to the computer-delivered questions, symptoms reported may or may not be related to the drug) and consultation (to help patients assess their symptoms and appropriate next steps), we have coupled the IVR call with a "warm transfer" of the call to a live clinical pharmacist for any patient reporting a potential drug-related symptom.

Subproject Methods

The Calling for Earlier Detection of Adverse Reactions (CEDAR) project was a cluster randomized controlled trial (RCT) of adult primary care clinics with patients receiving care at Partners Brigham and Women's Primary Care Practice Network or North Shore Physician's Group clinics. Eligible intervention patients were called using IVR technology which asked patients questions about symptoms they were experiencing since starting the medications. Patients who reported symptoms were transferred in real time to a clinical pharmacist to assess whether the symptom was likely related to starting the new medication, as well as provide any needed telephone counseling. The pharmacist then filed a note in the electronic health record and notified the patient's physician if symptoms warranted further follow-up.

We identified 104 medications used for treating four common primary care conditions (hypertension, diabetes, depression, insomnia). We called all patients (who did not opt out after receiving a letter explaining the calls and the study) who received new prescriptions for one of these target medications 4-6 weeks and 4-6 months after receiving the prescription. Patients were included if they spoke either English or Spanish as we our IVR script was in these two languages and our pharmacist also was bilingual in English and Spanish.

Outcomes evaluated for this invention included the number of symptoms or adverse effects noted by MD in intervention patients compared to a carefully (using propensity scores) matched group of patients from the control clinics who did not receive the intervention. We also compared medication discontinued for the intervention vs. control patients using data downloaded from our electronic medical record.

Limitations in this study included: suboptimal response rate of patients picking up phone to interact with the IVR system and completing the calls (see below for response rates) which likely biased cohort to include disproportionate numbers/percentages of patients who were having problems or concerns, and some patient were confused in answering the IVR questions. Measurement limitations included: inability to blind chart reviewers as to whether patient was in intervention vs. control group, subjective judgments exercised by our pharmacist in assessing symptoms over the phone and research assistants in performing chart reviews.

Subproject Results

We identified 11,128 patients newly started on the target medications who we cluster randomized into control and intervention arms (based on which clinic they attended). After exclusions, calls were placed to 4,876 patients of whom 776 (16%) consented to participate and completed the call. A propensity matched cohort was found to have similar number of medications, chronic problems, and co-morbidities. More than a third of patients reported symptoms and were transferred to our pharmacist, who assessed the likelihood and severity of

their being related to the medication, and the majority of these symptoms were assessed by our pharmacist to be probably or possibly related to the newly started medication. Chart reviews have been completed and data is currently being analyzed to identify total number of physician-noted symptoms related to target medications to examine hypothesis that the IVR calls coupled with pharmacist phone counseling would significantly increase the numbers of medication-related symptoms identified in the notes of the physicians/prescribers. In addition we have collected the data on how often the clinician notes explicitly make reference to the pharmacist's note. An additional study outcome metric is total target medications for discontinuation with reason being listed as adverse effects, comparing the entire cohort of patients (those answering the phone as well as those who did not) in the intervention clinics vs. patients in the control clinics. Overall preliminary analysis suggests a positive impact of the intervention with final results being prepared for submission for publication.

Additional studies include a pharmaco-economic analysis of the overall cost of the intervention (development, hardware, software, and most importantly pharmacist labor time) to calculate what it cost in the study to identify these adverse medication symptoms. Finally based on the experience of the project we have developed a new conceptual model for attempting to better represent and understand adverse drug reactions and patient reported drug-related symptoms which we are preparing for publication.

Subproject List of Publications and Products

Previously reported publications and products can be found on CERT Central. Forthcoming publications (finishing data analysis, preparing for submission/publication):

1. Schiff GD, Klinger EV, Salazar A, Medoff J, Amato MG, Orav EJ, Shaykevich S, Seoane EV, Walsh L, Fuller TE, Bates DW, Hass JS. Screening for Adverse Drug Events: Automated Calls Coupled with Phone-Based Pharmacist Counseling (main results paper).
2. Schiff GD, Fuller TE, Klinger EV. Drug "side effects": Realizing a new shared decision making paradigm.
3. Klinger EV, Salazar A, Medoff J, Amato MG, Schiff GD. Implementing Interactive Voice Response Technology for Screening for Adverse Drug Symptoms: Benefits, Lessons, and Technical and Logistical Challenges.
4. Salazar A, Medoff J, Amato MG, Schiff GD. The Role of the Pharmacist in Monitoring and Evaluating Patients with Adverse Drug Events.

Agency for Healthcare Research Quality Final Report**Health Information Technology Center for Education and Research on Therapeutics (HIT-CERT)**

Subproject Title: Physician Level Variation in Medication Overrides of Computerized Decision Support

Subproject PI and Team Members: David W. Bates MD, MSc, Mary Amato Pharm D, Patrick Beeler MD, Insook Cho PhD, RN, Olivia Dalleur PhD, Patricia Dykes PhD, RN, Tewodros Equale MD, Julie Fiskio, Sabrina Fowler, Calvin Franz PhD, Qoua Her Pharm D, Nivethietha Maniam, Karen Nanji MD, Christine Rehr, Diane Seger Pharm D, Elizabeth Silvers, Sarah Slight PhD, Michael Swerdloff, Adrian Wong Pharm D

Inclusive dates of subproject: 9/30/2011 to 8/31/2016

Abstract

Purpose: Clinical Decision Support (CDS) systems are a valuable tool for improving safety and quality of care, and understanding how physicians respond to medication CDS alerts is critical to achieving meaningful use of electronic health records. The purpose of this study was to evaluate the override rates for medication clinical decision support alerts in the outpatient and inpatient settings as well as the reasons cited for overrides at the time of prescribing.

Scope: A key issue has emerged around physicians' desire for autonomy in decision-making and how much control they have over their responses to these alerts. Despite extensively modifying our decision support system to improve user acceptance, we continue to observe a high level of overrides for many prescription domains. Although some of these are undoubtedly warranted, many are not.

Methods: We evaluated the frequency and appropriateness with which physicians overrode these alerts and the override reasons provided. Data for drug-drug interaction, drug allergy, duplicate medication, renal, geriatric, and formulary alerts were obtained from the inpatient and outpatient setting at two Harvard teaching hospitals.

Results: More than half of the medication CDS alerts were overridden with reasons varying depending on the type of alert. Many alerts that were overridden inappropriately had the potential to cause patient harm. We hope to use data collected from this project to identify physician-level variations and use the results to improve patient safety and efficiency.

Keywords: Clinical decision support, electronic prescribing, decision-making, patient safety, medication alerts

Physician Level Variation in Medication Overrides of Computerized Decision Support

Subproject Purpose

The purpose of this subproject was to:

1. Evaluate how much clustering of medication alert overrides there is by provider for both safety and efficiency-related issues in the inpatient and outpatient settings.
2. Evaluate the appropriateness of medication alert overrides overall and among those with high override rates.
3. Characterize and understand the patterns and reasons for these override behaviors and decisions.
4. Intervene with providers who have high override rates, for the specific categories that appear inappropriate.

Subproject Scope

Using national data, Zhang, et al, found an association between lower-quality prescribing patterns and higher costs, which may be related to higher adverse drug event rates. Clinical decision support (CDS) is an important tool for promoting patient safety and quality of care, to avoid such detrimental events. Physicians can choose to accept or override most medication CDS alerts, and understanding how physicians respond to these alerts is critical to achieving meaningful use of electronic health records (EHRs). Although we have extensively modified the CDS system at our center to promote user acceptance, we continue to observe a high level of CDS alert overrides, and a recent study performed at our center found that only 66% of providers appeared to be meaningfully using EHR medication lists. In this study, we evaluated the override rates for CDS alerts in the outpatient and inpatient settings, the reasons cited for overrides at the time of prescribing, and their appropriateness.

Subproject Methods

With IRB approval, we obtained medication CDS alert override rates and the coded reasons for overrides cited by providers at the time of prescribing from both the outpatient and inpatient settings at a large academic healthcare center over a period of three years beginning in 2009. The overrides and reasons were obtained from data stored by the EHR. Provider types studied included attending physicians, house-staff, and non-physicians with prescribing authority. We evaluated the domains of drug-drug interactions (DDI), drug suggestions for geriatrics and patients with renal failure, drug-allergy interactions (DAI), and duplicate therapies. In addition, we evaluated the variation in rates for formulary decision support. Our primary outcome was the rate of CDS alert overrides, and our secondary outcome was the appropriateness of these overrides. After the rates were calculated, academic detailing was performed with providers who had especially high override rates and low rates of appropriateness.

Subproject Results

Principle Findings. We reviewed 157,483 outpatient CDS alerts (7.9% alert rate) on 2,004,069 medication orders during the study period. 82,889 (52.6%) of alerts were overridden. The most common alerts were duplicate drug (33.1%), patient allergy (16.8%), and drug-drug interactions (DDI) (15.8%). The most likely alerts to be overridden were formulary substitutions (85.0%), age-based recommendations (79.0%), renal recommendations (78.0%), and patient allergies (77.4%). An average of 53% of overrides were classified as appropriate, and rates of appropriateness varied by alert type ($p < 0.0001$) from 12% for renal recommendations to 92% for patient allergies. The rates of inappropriate overrides were highest for DDI, age-based, and renal substitutions, which had the greatest potential for causing patient harm. We found override rates for drug allergy and DDI alerts to be slightly higher in the inpatient setting, with

inappropriate override rates highest for age and renal based substitution alerts, and slightly lower for DDI overrides because of monitoring being done.

Table 1. Breakdown of alert overrides in the outpatient setting. Appropriateness based on a random sample of 100 alert overrides from each alert type domain.

Alert Type	Total Alerts		Alert Overrides		Override Appropriateness	Most common reason for override
	N	(%)	N	(%)	(%)	
Patient Allergy	26,408	16.8%	20,430	77.4%	92	Patient has previously taken without allergic reaction
Drug/Drug Interaction	24,849	15.8%	14,966	60.2%	12	Will monitor as recommended
Duplicate Drug	52,113	33.1%	14,917	28.6%	82	Patient requires different strengths of the same drug
Drug/Class Interaction	19,593	12.4%	4,782	24.4%	88	Transitioning from one drug to the other
Class/Class Interaction	4,184	2.7%	2,918	69.7%	69	Pt on long term therapy with combination
Age-based Substitution	10,501	6.7%	8,297	79.0%	39	Patient has tolerated this drug in the past
Renal Substitution	3,890	2.5%	3,035	78.0%	12	Patient has tolerated this drug in the past
Formulary Substitution	15,945	10.1%	13,554	85.0%	57	Intolerance/Failure of Suggested Substitution
Total	157,483	100	82,899	52.6%		

Outcomes. Of the 24,849 DDI alerts generated in the outpatient setting, the top 62 providers with the highest override rate were identified and eight overrides randomly selected for each (a total of 496 alert overrides for 438 patients, 3.3% of the sample) to further evaluate the appropriateness of the override. We found overall, 68.2% (338/496) of the DDI alert overrides were considered appropriate. Among inappropriate overrides, the therapeutic combinations put patients at increased risk of several specific conditions including: serotonin syndrome (21.5%, n=34), cardiotoxicity (16.5%, n=26), or sharp falls in blood pressure or significant hypotension (28.5%, n=45). A small number of drugs and DDIs accounted for a disproportionate share of alert overrides. Of the 121 appropriate alert overrides where the provider indicated they would "monitor as recommended", a detailed chart review revealed that only 35.5% (n=43) actually did. Providers sometimes reported that patients had already taken interacting medications together (15.7%, n=78), despite no evidence to confirm this.

For renal substitution alerts in the outpatient setting the most common drugs overridden were for Metformin, Glyburide, Hydrochlorothiazide and Nitrofurantoin. Almost half of the alerts were triggered by 40 providers and one-third was triggered by high-frequency overriders. Physicians' appropriateness rates were higher than the rates for nurse practitioners (32.9% vs. 22.1%). Physicians with low frequency override rates had higher levels of appropriateness for Metformin than the high frequency overriders (P=0.005).

The magnitude of variation between outpatient providers in overriding CDS alerts differed among the clinical domains of the warnings; more variation was observed in areas with more inappropriate overrides. Differences between 1717 providers accounted for 11% of the overall variability in override rates, so that while the average override rate was 45.2%, individual provider rates had a wide range with a 95% confidence interval (CI) (13.7%-76.7%). The highest variations between providers were observed in the categories: age-based (25.4% of total variability; average override rate 70.2% [95% CI, 29.1%-100%]) and renal recommendations (24.2%; average 70% [95% CI, 29.5%-100%]), and provider responses within these 2 categories were most often clinically inappropriate. Among providers who received at least 10 age-based recommendations, 64 of 238 (27%) overrode $\geq 90\%$ of the warnings and 13 of 238 (5%) overrode all of them. Of those who received at least 10 renal recommendations, 36 of 92 (39%) overrode $\geq 90\%$ of the alerts and 9 of 92 (10%) overrode all of them.

The providers' mean override rates per 100 prescriptions and per 100 alerts were 0.52 (95% confidence interval (CI), 0.46-0.58) and 0.42 (95% CI, 0.38-0.44) respectively. The physicians (n=422) on average overrode drug alerts with rates of 0.48 per 100 drugs and 0.44 per 100 warnings. Univariate analysis revealed that six physician characteristics (physician type, age, number of encounters, medical school ranking, residency hospital ranking, and acceptance of Medicaid) were significantly related to the override rate.

We collected 131,615 (83%) inpatient drug allergy interaction (DAI) alerts and 26,408 (17%) outpatient alerts for a total of 158,023 DAI alerts where 128,157 (81%) were overridden. A random sample of inpatient (n=200, 0.19%) and outpatient (n=50, 0.25%) alert overrides were screened for appropriateness, with >96% considered appropriate. Alerts for some drug classes, such as 'non-antibiotic sulfonamides', were overridden for >81% of prescriptions in both settings. The most common override reason was patient has taken previously without allergic reaction. In the inpatient setting alone, 70.9% of alerts that warned against the risk of anaphylaxis were overridden.

Review of the alert overrides of the top 11 (n = 206) most-utilized and highest-costing Non-Formulary medication (NFM) inpatient alerts from January 1 to December 31, 2012, were randomly selected for appropriateness evaluation. We found approximately 17.2% (n = 35.4/206) of NFM alerts were inappropriately overridden. Non-oral NFM alerts were more likely to be inappropriately overridden compared to orals. Alerts overridden with "blank" reasons were more likely to be inappropriate. The failure to first try a formulary alternative was the most common reason for alerts being overridden inappropriately.

Discussion and Conclusion. In this evaluation, more than half of medication CDS alerts in the outpatient and inpatient setting were overridden by providers. We also found many of the alert overrides to be appropriate, so refinement of the alerts has the potential to improve their relevance and reduce alert fatigue. A number of insights were identified through academic detailing sessions including that alert fatigue existed for warnings deemed irrelevant, and frustration that repetitive alerts cannot be disabled. The alerts were appreciated when the provider first saw the patient, however subsequent alerting was seen as frustrating and time consuming. Overall, clinicians were generally favorable towards the medication CDS alerts and felt that they were helpful in identifying possible adverse events. Providers were especially grateful for alerts informing them about the risk of drugs they infrequently use. By incorporating provider preferences, customizing alerts to the context of the visit and the setting, providers felt that CDS alerts would be less likely to be overridden providing more effective, efficient care.

Significance and Implications. Our results are consistent with existing literature, which reports override rates ranging from 50% to more than 90%, with DDIs being one of the most common alert types to be overridden. Although few previous studies have compared such a broad array of alert types, we believe these results may help organizations consider which ones to focus on. Our current higher overall rate of overrides suggests that the number of alerts that our clinicians experience has probably grown, which leads to alert fatigue. There are possible reasons for this increased number of alerts, one being we may have a lower threshold for alerting. The natural tendency is for committees that manage alerts to add alerts incrementally and, unless an aggressive approach is taken to eliminate unnecessary alerts, more are generally included over time.

Our study also provides some important additions to the existing literature. First, we assessed the override responses to a very broad range of medication alert types, such as age-based and renal recommendation, which most prior alert studies have not assessed. Second, we evaluated the appropriateness of alert overrides, and found that appropriateness varies dramatically by alert type. Few studies have evaluated the appropriateness of alert overrides and little prior data exist about the appropriateness of overrides by alert type. The results about the appropriateness of alert overrides may help identify a number of ways in which alerts can be improved. For example, in many instances alerts might be made more specific, with one example being suppressing alerts if a patient has been taking a combination of interacting drugs for some time, or bringing in additional factors such as the presence of laboratory tests or symptoms.

Subproject List of Publications and Products

We have 37 products (9 publications listed below and 28 abstract/presentations) along with 24 affiliated products/publications. These can all be found on Cert Central.

In addition we have 7 manuscripts in preparation for submission.

1. Nanji KC, Slight SP, Seger DL, et al. Overrides of medication-related clinical decision support alerts in outpatients. *J Am Med Inform Assoc* 2014 May;21:487-491. PMID: 24166725.
2. Slight SP, Seger DL, Nanji KC, et al. Are we heeding the warning signs? Examining providers' overrides of computerized drug-drug interaction alerts in primary care. *PLoS One* 2013 Dec;8(12):e85071. PMID: 24386447
3. Insook Cho, Slight SP, Nanji KC, et al. Understanding physicians' behavior toward alerts about nephrotoxic medications in outpatients: a cross-sectional analysis. *BMC Nephrol* 2014 Dec;15:200. PMID: 25511564.
4. Insook Cho, Slight SP, Nanji KC, et al. The effect of provider characteristics on the responses to medication-related decision support alerts. *Int J Med Inform.* 2015 Sep;84(9):630-639. PMID: 26004341.
5. Her QL, Amato MG, Seger DL, et al. Development of an algorithm to assess appropriateness of override non-formulary medication alerts in a computer provider order entry system. *Am J Health Syst Pharm* 2016 Jan;73(1):e34-45. PMID: 26683678.
6. Beeler PE, Orav EJ, Seger DL, et al. Provider variation in responses to warnings: do the same providers run stop signs repeatedly. *J Am Med Inform Assoc* 2016 Apr;23(e1):ee93-98. PMID: 26499104.
7. Slight SP, Beeler PE, Seger DL, et al. High override rates of drug allergy alerts in inpatient and outpatient settings. *BMJ Qual Saf* 2016 March;0:1-9. PMID: 26993641.

8. Her QL, Amato MG, Seger DL, et al. The frequency of inappropriate non-formulary medication alert overrides in the inpatient setting. *J Am Med Inform Assoc* 2016 Sep;23(5):924-33. PMID: 27002076.
9. Her QL, Amato MG, Seger DL, et al. Review of nonformulary medication approvals in an academic medical center. *Joint Commission Journal on Quality and Patient Safety* 2016 Nov. doi: 10.1016/j.jcjq.2016.10.003

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Health Information Technology Center for Education and Research on Therapeutics (HIT-CERT)

Subproject Title: Examining Human Factors Principles in the Design and Implementation of Decision Support Alerts

Subproject PI and Team Members: Shobha Phansalkar PhD, Pamela Garabedian MS, Jan Horsky PhD, Lisa Burdick MS, Alexandra Robertson BS

Inclusive dates of subproject September 30, 2011- August 31, 2014

Abstract

Purpose/Scope: The purpose of this subproject was to investigate and assess how the design of alerts may affect prescribing behavior impact decision support acceptance. We also wanted to understand the role of patient-specific information in the decision-making process about the risks and benefits of medication therapy

Methods: The methods employed in this subproject included quantitative analyses and, surveys and observational, scenario-based analyses of clinical reasoning.

Results: This study was able to show a negative correlation between alert design and alert override rates. We found that the higher the design scores the less likely were participants to override the alerts. Our survey also showed that the greater the alert volume the more likely were participants to override alerts and not pay attention to even clinically significant alerts. We were also able to show differences in perceptions related to DDI and DAI alerts. Declining an alert suggestion was preceded by sometimes brief but often complex reasoning, prioritizing different aspects of care quality and safety, especially when the perceived risk was higher

Keywords: Clinical decision support, EHR, alert design, I-MeDeSA, clinical decision making, risk assessment

Examining Human Factors Principles Subproject Purpose

The overall purpose of this study was to understand how human factors impact alert acceptance. We specifically assessed alert design and user behavior and its impact on alert acceptance in EHRs. We also used qualitative methods to understand decision making with medication-related decision support alerts.

The aims of the three projects undertaken under this subproject were as follows:

1. To determine whether employing human factors principles can have an impact on physician behavior in terms of the rates of overriding alerts.
2. To evaluate user- related outcomes (provider satisfaction with alerts and provider perceptions on system usability) on medication-related clinical decision support alerts for electronic health records (EHRs) that comply with human factors principles.
3. Describe and analyze reasoning patterns of clinicians responding to drug-drug interaction alerts in order to understand the role of patient-specific information in the decision-making process about the risks and benefits of medication therapy

Subproject Scope

Human factors play a substantial role in the design of decision support alerts. Their adoption in clinical information systems has been slow. Poor design has been attributed to alert fatigue and high override rates.

Previously this group of researchers has established the influence that alert design can have on alert acceptance. We developed an instrument, I-MeDeSA which defines human factors principles that should be considered when designing alerts for EHRs. We also conducted an evaluation comparing EHRs using the I-MeDeSA and found significant deficiencies in how EHRs implemented these design principles.

In this body of research we wanted to study the impact these design principles have on how alerts are accepted. Do EHRs that have better designed alerts show greater acceptance of alerts? We measured alert design as a function of the EHRs score on the I-MeDeSA instrument and override rate as a proxy for measuring alert acceptance. We then studied how these two variables correlated with one another. We also tried to understand if there were differences in the type of alert generated by studying two different types of alerts: drug-drug interactions (DDIs) and drug allergy alerts (DAIs). We also wanted to understand how user perceptions impact alert acceptance and conducted a survey to measure user perceptions on DDIs and DAIs.

Our goal was to investigate how medical context is used by clinicians responding to alerts to assess risk to the patient and to find safer treatment alternatives. We wanted to describe patterns of clinical reasoning about risk factors associated with drug interactions that include delayed or less effective treatment, care priorities and uncertainty. Our broader objective was to review assumptions about optimal CDS design by collecting empirical evidence and to contribute new insights.

Subproject Methods

Study Design. Our subproject utilized multiple methods depending on the question in focus. For evaluating whether alert acceptance was correlated with alert design we collected screenshots of how alerts were presented in EHRs. These were scored using the I-MeDeSA and then correlated with the override rate. Override rate was calculated as the proportion of alerts where an action by the provider indicated that the alert was not acted upon divided by the total number of alerts that were displayed to the provider.

Our survey assessed providers' perceptions on medication-related clinical decision support (CDS) alerts, specifically, drug-drug and drug-allergy interaction alerts received in the EHR and was an adaptation of a previously published instrument.

Participants in an observational study responded to high- and low-severity drug-drug interaction alerts while verbalizing their thoughts in a standard think-aloud protocol.

Data Sources/Collection. We collected screenshots from 12 EHRs (both US and International implementations) and assessed design principles on 9 constructs. Our survey was mailed to 1545 internal medicine clinicians across the 8 sites and 365 surveys were opened.

Forty eight of the surveys were partial responses (less than 50% complete) and were excluded from the analysis. Our analysis included 317 surveys that were more than 50% complete.

Thirty-two clinicians working with five EHRs in two countries completed sets of six medication orders each and responded to high- and low-severity drug-drug interaction alerts while verbalizing their thoughts in a standard think-aloud protocol. Tasks were recorded and analyzed to describe reasoning patterns about patient-risk assessment and strategies to avoid or mitigate it.

Intervention. The interventions studied were impact of alert design, user behavior and a qualitative assessment of end user information needs for decision making on medication related decision support alerts.

Measures. As specified above.

Limitations. Many EHRs do not yet have the capability to calculate alert override rates. This limited our EHR selection in evaluating the impact of alert design on alert acceptance. In addition, contractual obligations of hospitals with EHR vendors currently limit their ability to share screenshots for evaluation.

Subproject Results

The EHRs studied had override rates that ranged from 71.2 to 96.9%. In order to understand the best set of independent variables that predict the overriding of an alert we ran a stepwise multiple regressions. Our model showed that the variable that was, by far, the most significant in predicting override rates was the total number of alerts which explained over 50% of the variance of why alerts were overridden (R squared = 0.51, $p= 0.07$). Addition of the remaining independent variables in terms of the design score, whether the EHR was homegrown or a vendor system, and whether the alert was generated in an inpatient or outpatient setting, only increased the R squared by 8%. Inter- rater reliability to assess agreement yielded a global kappa $k= 0.78$ (0.74- 0.82), DAI kappa $k= 0.79$ (0.74- 0.85), and DDI kappa $k= 0.77$ (0.71- 0.82). Both home grown and vendor system s performed equally well on both types of alerts.

From the sites assessed, it is evident that human factors principles are applied inconsistently across alert design in EHRs.

The survey assessing providers' perceptions on medication-related clinical decision support (CDS) alerts, specifically, drug-drug and drug-allergy interaction alerts received in the EHR was mailed to 1545 internal medicine clinicians across the 8 sites and 365 surveys were opened. Forty eight of the surveys were partial responses (less than 50% complete) and were excluded from the analysis. Our analysis includes 317 surveys that more than 50% complete. Overall, participants estimated receiving a greater number of DDI (26.5) than DAI (16.4) alerts per week, but were more likely to override DAI than DDI alerts. A key finding of this study was that for both DAI and DDI alerts across all 3 groups, we found that as the number of perceived alerts increases, the percentage of providers who report reading, finding these alerts relevant, or changing prescribing behaviors, based on the information provided decreases, and as the volume of alerts increases the number of alerts correspondingly overridden increases.

Physicians who reported receiving greater than 50 DDI/DAI alerts per week also reported reading only 25.5/29.8%, finding only 23.6/7.4% clinically relevant, identifying only 11.1/9.4% as changing their prescribing behavior, and reported overriding 89.9/97%, respectively. Comparatively, those who reported receiving between 1-10 DDI/DAI alerts per week reported: reading 69.6/83% of those alerts, finding 40.3/54.8% clinically relevant, identified 34.2/46.9% as changing their prescribing behavior, and overrode 64.0/67.7%, respectively. For five of the survey constructs (performance expectancy, perceived ease of use, effort expectancy, perceived fatigue, and perceived use behavior) the difference in means between DDI and DAI was significant.

We observed decision making of clinicians responding to drug-drug interaction alerts in order to analyze patterns in their reasoning about the risks and benefits of medication therapy and use of patient-specific information. In total, 171 decisions were made. Clinicians actively sought to reduce risk when responding to high-severity alerts, mostly by monitoring patients and making dose adjustments. In contrast, they routinely left prescriptions unchanged after low-severity alerts when feeling confident that patients would tolerate the combination and treatment benefits outweighed risks. Clinicians used this reasoning strategy regardless of setting or EHR type. Participants tended not to follow advice they considered low value, similar to clinicians working in actual settings. They conceptualized risk as a complex set of interdependent tradeoffs specific to an individual patient. Omission of patient-specific data, which was not present in any alerts, may have contributed to the constancy of reasoning and to similarities in risk-control strategies we observed despite significant differences in interface design and function. Placing selected contextual data directly in the visual field of clinicians during prescribing may help them integrate patient-specific information into their assessment of risks and benefits and potentially improve this type of decision support.

Subproject List of Publications and Products

Previously reported publications and products can be found on CERT Central. Forthcoming publications (finishing data analysis, preparing for submission/publication):

1. Slight SP, Seger DL, Thomas S, Coleman J, Bates DW, Phansalkar S. An International Evaluation of Drug-Drug Interaction Alerts That Should be Non-Interruptive in U.K. and U.S. Settings. American Medical Informatics Association (AMIA) 2013 Annual Symposium, Washington, DC, US. Nov 2013
2. Phansalkar S, Robertson A, Seidling HM, Spry K, Cho I, Mendes C, van der Sijs H, Bates DW. An International Evaluation of Clinical Decision Support Alerts in EHRs for Compliance with Human Factors Principles. HFES, San Diego, October 2013
3. Slight SP, Seger DL, Thomas S, Robertson A, Coleman J, Bates DW, Phansalkar S. An International Evaluation of Drug-Drug Interaction Alerts That Should be Non-Interruptive in U.K. and U.S. Settings. SGIM, San Diego, April 2014
4. Robertson A, Neri P, Burdick E, Slight SP, Bates DW, Phansalkar S. An International Evaluation of User Perceptions of Drug-Drug and Drug-Allergy Interaction Alerts. SGIM, San Diego, April 2014
5. Slight SP, Cornu P, Robertson A, Seger, DL, Thomas S, Cho I, Coleman J, Bates DW, Phansalkar S. An International Evaluation of Clinically Significant Drug-Drug Interaction Alerts in Electronic Health Records. AMIA, Washington DC, Nov 2014
6. Robertson A, Neri P, Burdick E, Slight SP, Bates DW, Phansalkar S. An International Evaluation of User Perceptions of Drug-Drug and Drug-Allergy Interaction Alerts. AMIA, Washington DC, Nov 2014
7. Phansalkar S, Zachariah M, Seidling H, Mendes C, Volk LA, Bates DW. Evaluation of Medication Alerts in Electronic Health Records for Compliance with Human Factors Principles J Am Med Inform Assoc 2014 doi:10.1136/amiajnl-2013-002279
8. Horsky J, Aarts J, Verheul L, Seger DL, van der Sijs H, Bates DW. Clinical reasoning in the context of active decision support during medication prescribing. International Journal of Medical Informatics. 2017;97:1-11.