Title Page

Title of Project: Meaningful Drug Interaction Alerts

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Structured Abstract

Purpose: Drug-drug interactions (DDIs) are responsible for 5-14% of adverse drug reactions in hospitalized patients. Individualizing DDI alerts to specific patient circumstances will result in a much greater proportion of alerts that physicians, pharmacists, and other healthcare providers will be more likely to heed.
Scope: To develop evidence to support, design, and implement novel alerting algorithms to reduce alert fatigue associated with DDIs.
Methods: Aim 1**:** To identify combinations that should be avoided, to identify drug and patient characteristics that would affect the likelihood of harm due to a DDI. Aim 2: We constructed artifacts using Drools and JBoss software to evaluate the ability to provide warnings based on contextual factors. Aim 3: Artifacts were created to disseminate to healthcare organizations and being implemented.
Results: Aim1: Numerous studies were conducted that quantified the evidence for various drug combinations. For example, reporting odds ratios (ROR) of adverse consequences due to colchicine-related interactions ranged from 35.4 (95% CI: 12.8-97.6) for atazanavir and rhabdomyolysis/myopathy.
Aim 2: A total of 8 DDIs were identified as high priority for contextual alerting. Both document-based decision trees and computable knowledge artifacts for these algorithms have been made available publicly at https://ddi-cds.org. Use of the 8 algorithms would result in filtering 1584 (52.4%) of these alerts.
Aim 3: Vanderbilt University Medical Center implemented a colchicine interaction app developed by the team. We also developed a custom drug interaction editor prototype and sought feedback from pharmacists and others about the usability of the tool.

Key Words: Drug Interactions; Cytochrome P-450 Enzyme System; Algorithms; Decision Support Systems, Clinical; Medical Order Entry Systems;

Purpose

Drug-drug interactions (DDIs) are preventable adverse events (AEs) that are responsible for 5–14% of adverse drug reactions (ADRs) in hospitalized patients, are a major risk factor for hospitalization, and occur in up to 13% of elderly ambulatory patients. Exposure to life-threatening DDIs continues to occur despite the widespread use of clinical decision support systems (CDS). Due to meaningful use requirements, most commercial drug knowledge-bases (KBs) and the electronic health records (EHRs) systems that utilize this knowledge have largely failed to implement meaningful DDI CDS due to liability concerns. Off-the-shelf systems generally use simple approach of triggering alerts based on the presence of potentially interacting drug pairs in a patient's medication regimen. The result is an overly sensitive trigger that more often than not generates inappropriate alerts, causing important alerts to be missed or ignored. The evolution of these systems to a more useful role in CDS has been hindered by the perceived risk of liability, competing customer needs, and legacy systems that cannot easily adapt to rapidly evolving science. The central hypothesis of this project is that individualizing DDI alerts to specific patient circumstances will result in a much greater proportion of alerts that physicians, pharmacists, and other healthcare providers will be more likely to heed. Therefore, to reduce excessive and irrelevant alerts, DDI alerts must be filtered and prioritized by contextual factors that increase or decrease the risk of a harmful interaction. The goals of this project were to: 1) use new and existing evidence related to exposure to DDIs to inform clinical decision systems (CDS); 2) construct and validate alert algorithms that incorporate relevant drug attributes and patient characteristics; and 3) widely implement and evaluate alerting algorithms across the continuum of care. These broad goals were supported by the following aims:

Aim 1: Assemble evidence for individualized DDI alerts and design DDI algorithms that draw on the wealth of data within electronic health records (EHR);
Aim 2: Validate the function of newly designed DDI algorithms using EHR data; and
Aim 3: Conduct a real-time evaluation of DDI algorithms in a variety of healthcare environments including ambulatory and institutional settings.

Scope

The primary scope of activities of this grant are outlined below under each specific aim.

Aim 1: Assemble evidence for individualized DDI alerts and design DDI algorithms that draw on the wealth of data within electronic health records (EHRs)

Problem: Evidence for most drug interactions is based on case reports and theoretical pharmacokinetic and pharmacodynamic considerations. The construction of CDS algorithms for DDIs to prevent over alerting are hindered by the lack of supporting evidence. This is especially true when determining laboratory values or dose limits that serve as triggers because these attributes are not studied or reported in the literature. *Solution:* We analyzed EHR and other healthcare data and other evidence from the literature to construct DDI alerting algorithms for 11 interactions that are frequently occurring in healthcare systems and institutions. When implemented, these algorithms could reduce warnings when patient characteristics, drug attributes, and contextual factors are taken into consideration.

Aim 2: Validate the function of newly designed DDI algorithms using EHR data

Problem: An important but often overlooked component of algorithm development is the need to validate that the specified approach is fit for the intended purpose. The ideal DDI alert algorithm should provide clinically meaningful information to healthcare providers when a patient is at risk but would not interrupt the workflow when the medications are not likely to cause harm.

Solution: We conduct a retrospective evaluation using both synthetic and de-identified data. To simulate implementation of the algorithms, and to test that the rules would run as expected, a synthetic patient population was created and loaded into the open-source common data model provided by the Observational Health Data Science and Informatics (OHDSI) collaborative.

Aim 3: Conduct a real-time evaluation of DDI algorithms in a variety of healthcare environments including ambulatory and institutional settings.
Problem: Numerous studies document high rates of "overridden" DDI alerts and extensive dissatisfaction with alerts that are perceived as inappropriate, insignificant, disruptive, or unnecessary. Receiving fewer but more specific alerts might increase clinicians' perceived benefits of DDI warnings. Healthcare organizations are keen on improving their systems to increase provider acceptance and satisfaction, as well as improving patient safety. *Solution:* We developed "apps" that can be implemented within EHRs to provide warnings and alternative approaches to address potential DDIs. After being reviewed by internal governance, information technology (IT) security, and various clinical teams, one of our apps was successfully implemented within a healthcare system.

Methods

Aim 1: Assemble evidence for individualized DDI alerts and design DDI algorithms that draw on the wealth of data within electronic health records (EHRs)

To identify combinations that should be avoided, the research team held multiple teleconferences involving experts in DDIs, obtained relevant publications associated with various interactions, and analyzed EHRs to identify drug and patient characteristics that would affect the likelihood of harm due to a DDI.

Drug pair selection: As unlimited and unknown DDIs exist, we did not aim to conduct an extensive search of all potential DDIs. To identify those interactions where potential algorithms could be developed, we first queried alerts and overrides from an academic healthcare system to identify DDI alerts that fired from 2,000 to 6,000 times/month. We also held a series of webinars to discuss the algorithms (discussed in aim 3 below), and through those webinars we received requests from clinicians to examine two potential interactions involving: 1) dexamethasone and direct acting oral anticoagulants; and 2) tizanidine and ciprofloxacin.

Evidence Generation: Among these DDIs, we identified a subset of interactions where there are modifying factors that may affect the risk of harm. For each DDI of interest, we conducted an extensive literature search to identify relevant studies and case reports. We also conducted analyses using the Food and Drug Administration's Federal Adverse Event Reporting System (FAERs). Because FAERs contains only "numerator" information, we conducted disproportionality analyses and estimated the reporting odds ratio of adverse events reports of combinations as compared to reports without such combinations. Within FAERs, each report contains a classification on the role played in the AEs by each drug mentioned: primary suspect (PS), secondary suspect (SS), interacting (I) or concomitant (C). All the reported AEs are mapped to MedDRA® (Medical Dictionary for Regulatory Activities) terminology. FAERS reports from 2004 quarter 1 through 2020 quarter 3 (dates of the FAERS data downloadable from the FDA's website) were downloaded from the FDA website and compiled for analysis using the process described by *Banda et al (2016).* This process included mapping drug mentions to the RxNorm terminology and collapsing duplicates reports to the latest submitted version. To remove duplicates, we extracted the most recent case version from all available cases based on the case id, the case event date, age, sex, reporter country, a concatenated alphabetic ordered

list of drug names, and outcomes. We kept the most current case version and removed all others.

We calculated disproportionality metrics for reports that each medication involved in a potential interaction and one or more of the suspected AEs. A contingency table was created for each combination to calculate the reporting odds ratio (ROR) and its corresponding 95% confidence interval (95% CI). RORs were calculated for those reports in which medication of interest was identify as having a PS, SS or I role and having any role (PS< SS< I and C). We defined a drug interaction safety signal as a ROR with a lower 95% CI above 2.0 and a minimum of 5 reports with the medications and AEs of interest. The disproportionality measure was also calculated for object drugs (medications affected by the interaction) having any role and each of the AEs without the requirement of a co-mentioned medication.

We also conducted a series of studies to identify risk of harm associated with various drug combinations and patient-level factors that mitigate or increase risk of harm. Because the project was conducted during the COVID-19 pandemic, we capitalized on the creation of the National COVID Cohort Collaboration (N3C), a national repository of patients who may have been infected with COVID-19 as well as non-infected individuals to investigate a potential interaction with dexamethasone and direct acting oral anticoagulants (DOACs). We used a retrospective, observational, nested case control design to study patients with or without a thromboembolic event to assess their previous exposure to the combination of apixaban or rivaroxaban (>= 10 days) and dexamethasone (equal to or more than 5 days of treatment after a patient has been taking a DOAC for at least 5 days). For every thromboembolic case, 2 controls were sampled with no replacement. Cases were matched to controls on data partner identifier, COVID+ based on laboratory or diagnostic criteria within 30 days prior to the index date, age (within 5 years), sex, duration of apixaban or rivaroxaban exposure binned into 90-day spans, and presence/absence of a thromboembolic event within 30 days prior to cohort entry date. Because the study treated COVID-19 as a covariate and was used for matching, the study period preceded the start of the COVID-19 pandemic going from Quarter 2 of 2018 to May 30th, 2021. Data were excluded prior to the study period start due to sparsity of data contribution prior to 2018. All data transformation and data analyses were performed in the N3C Enclave, which is a secure cloud-based platform developed by Palantir Technologies and hosted by NIH National Center for Advancing Translation Science (NCATS). The data in the N3C Enclave were contributed by over 40 participating data partners and include Electronic Health Records (EHR) of over 6.7 million patients who were tested for SARS-Co-V-2, had related symptoms, or had other similar diseases such as SARS 1, MERS, or H1N1.

We also used the CERNER Health Facts® (HF) database to investigate potential harm due to exposure to potential interactions. The Health Facts® database captures and stores de-identified, real-world, longitudinal EHR patient data, and contained data on almost 50 million patients, around 300 million encounters, and over 1.3 billion laboratory results from the participating medical institutes across the United States. HF contains detailed patient information including demographics characteristics, medical diagnoses based on the *International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10)* codes, and other related information like insurance status, location of service, laboratory tests and information on medications. We examined this database for evidence of harm associated with exposure to the following DDIs: potassium sparing diuretics and renin-angiotensin system (RAS) agents [this includes angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARBs); QTc prolonging agents; and thiazide diuretics and selective serotonin reuptake inhibitors]. For each of these studies, we created cohorts of patients with exposure to both medications, each medication alone, and control medications. Adverse events of interest

included laboratory values (i.e., serum potassium, serum sodium), diagnoses, and electrocardiogram results. Again, due to the COVID-19 pandemic, we also used the HF data to investigate potential QTc prolongation associated with hydroxychloroquine and other medications known to prolong the QTc interval using methods like those described above.

When the evidence regarding a particular interaction had not been summarized in previous systematic review, we conducted a review that included a meta-analysis to quantify the risk of harm. Such studies were conducted for interactions involving potassium sparing diuretics and angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) and the combination of warfarin with oral salicylates. For these studies, we conducted searches using PubMed and Embase, along with other databases such as Web of Science, Cochrane Collaboration, and Web of Science to identify relevant studies. For each study, we developed a project-specific protocol that specified inclusion and exclusion criteria. At least two individuals evaluated potential articles for inclusion. Data was extracted for each study and entered in a data file for analysis. We evaluated each included study for risk of bias. Summary effects were calculated to estimate the mean difference or odds ratio, depending on the outcome of interest. Analyses with random effects models were conducted, and heterogeneity was assessed using both Cochran's Q and I^2. We also examined funnel plots for publication bias and conducted subgroup analyses to explore various factors that may have affected the results, such as study design, reported outcomes, and medications of interest, and dose of medication.

Algorithm Design

For each drug combination of interest, a decision table was then developed consisting of modifiable risk factors such as: unique drug product, route of administration, dose, patient characteristics, contextual characteristics, and laboratory test values. This was then used to draft and refine the decision framework for each algorithm. Members of the research team met weekly to discuss the algorithms, including evaluating the evidence and defining criteria for alerting. Once draft algorithms were created, they were shared with the project's expert panel for review and comment. They were also shared with individuals from healthcare systems (hospital organizations), drug knowledgebase vendors, and other clinicians with expertise in DDIs.

Aim 2: Validate the function of newly designed DDI algorithms using EHR data

The algorithms developed in Aim 1 were operationalized using common coding systems for medications, laboratory values, and diagnosis codes. The expert-developed decision trees were converted into knowledge artifacts using both JBoss Drools and HL7 Clinical Quality Language. The rules were coded to enable a software program to identify patients that met inclusion criteria for the algorithm. To test if an algorithm would perform as expected, we created a synthetic patient population based on the Observational Health Data Science and Informatics (OHDSI) collaborative and implemented the OMOP on FHIR system to serve the synthetic patient data in the HL7 FHIR standard. The common data model was selected because of its ability to accommodate different observational data structures. Concept sets for unique medications and classes of medications using RxNorm were created. LOINC were used for laboratory values, and both SNOMED-CT and ICD was used for clinical conditions. The final set of concept sets were published on the National Library of Medicine's Value Set Authority Center. The value set authority is located at: https://vsac.nlm.nih.gov/. More details about the Value Set Authority can be found in the article: Bodenreider, Olivier, Duc Nguyen, Pishing Chiang, Philip Chuang, Maureen Madden, Rainer Winnenburg, Rob McClure, Steve Emrick, and Ivor D'Souza. "The NLM Value Set Authority Center." Studies in Health Technology and Informatics 192 (2013): 1224.

Implementation guides were developed to communicate the specific details of DDI rule implementation, the required terminology artifacts, and the testing and validation procedure. A sub-set of artifacts were submitted to the CDS Connect Repository and the ddi-cds.org website for dissemination. SMART on FHIR applications were developed for three high-priority DDIs and deployed to the Logica SMART app gallery and the Logica CDS sandbox.
We also evaluated the algorithms using data from a single healthcare academic medical center. Data were transformed into the OHDSI common data model. A Drools engine was used to execute the algorithms using this data. The results from the code were validated using SQL queries of the database (written independently). The research team manually validated the coding using simple drug exposure. Further analyses were conducted using output from the algorithms by analyzing various patient and drug attributes.

In another study we used the 15 high-priority DDIs identified by the Office of the National Coordinator (ONC) for Health Information Technology to examine the extent that contextual factors were available to customize alerts. This DDI list has been generally adopted by drug interaction knowledge sources. Each DDI was evaluated using three different drug interaction references: Lexicomp®, Micromedex®, and Hansten and Horn's Top 100 Drug Interactions©. We extracted the list of drugs in each interacting group and variables that can affect the risk or severity of the DDI. Variables were classified as either Order (i.e., *timing, dose*, and *route*) or Patient (i.e., *conditions, observations,* and *medications*. Similar to the ONC's list, the drug interaction references each provided drug groups. We measured the reliability of drugs in each group among the ONC's list and the three drug interaction references. The group reliability was calculated using Fleiss' Kappa for measuring nominal scale agreement among many raters. We identified variables that would affect the DDI risk or severity. These variables were placed in Order or Patient categories. Extracted Order variables were classified as *timing*, *dose*, and *route*. *Timing* variables are relevant when time between the administration of two interacting drugs can modify the risk that a DDI will occur. *Dose* variables are relevant when the dose of either interacting drug affects the potential severity/seriousness of harm due to the DDI. *Route of administration* (e.g., transdermal, oral, intravenous, etc.) can be important when the route can modify the risk of a DDI, usually due to lack of systemic absorption of topical, ophthalmic, or otic agents. Extracted patient variables were classified as *condition, observation,* and *medication*. *Condition* variables include patient comorbidities and/or acute problems that may affect the severity of DDI. *Observation* variables are any relevant measurements (e.g., laboratory test results and vital signs) that modify the risk or severity of a DDI. *Medication* variables include other medications the patient is taking that may increase or decrease the severity or risk of a DDI, including multiple interactions associated with single product. We identified the number of drug interaction references that provided a similar narrative and report these results descriptively.

Aim 3: Conduct a real-time evaluation of DDI algorithms in a variety of healthcare environments including ambulatory and institutional settings.

During the conduct of this project the COVID-19 pandemic swept the country making Aim 3 more challenging to accomplish. Resources that may have been available for implementation of algorithms were consumed with managing the day-to-day operations at healthcare institutions. Thus, interest in participating in the study significantly declined. Furthermore, resources and personnel within the Cerner organization changed dramatically over the duration of the grant, including a key contact that was a leader within Cerner. Hence, we shifted our planned activities to address the barriers limiting widescale implementation of the algorithms.

To generate interest for using the algorithms across the healthcare community we held a series of webinars, each focused on a separate algorithm or issue. Each webinar was promoted to previous attendees as well as posted on listservs for the pharmacoinformatic group within the American Medical Informatics Association and the pharmacy informatics and technology special interest group of the American Society of Health-Systems Pharmacy. We also sent information about the webinars to directors of pharmacy informatics residency programs. Each webinar was recorded and a link to the webinar was posted on our group website (ddi-cds.org).

After the pandemic situation started to stabilize, we started to reach out to various pharmacists and other persons with an interest in DDIs to identify possible sites to implement one or more of our algorithms. Via the webinars, we announced requests for information concerning modifications or implementations to DDI warning systems within participant's organizations.

To gain further insights on barriers to implement our DDI algorithms we conducted a series of interviews with pharmacy and medical informatics professionals. The purpose of this study was to examine how DDI clinical decision support systems (CDSS) are currently implemented and identify barriers and facilitative implementation strategies to foster implementation of third-party algorithmic DDI CDS support. Specifically, we sought to identify strategies and attributes needed to foster the algorithm adoption. A participant interview guide was framed based on the synthesis of the Learning Health System framework and informed by Proctor's taxonomy of implementation outcomes and Socio-technical Systems Theory. Areas of interest included feasibility of implementing external CDS, measuring alert performance, organizational culture and support of CDS, technical issues with implementing CDS, and CDS governance. A series of structured interviews were conducted with pharmacy and medical informatics with responsibility for medication safety, including DDI. Participants of interest included pharmacists with informatic roles within a hospital, chief medical informatics officers, and associate medical informatics directors/officers and were identified based on attendance at webinars related to DDI CDS. Each interview was recorded, and a transcript was created for analysis. Data analysis followed three phases of grounded theory coding.

We also developed a drug interaction customization editor (DICE), a prototype tool with an easy-to-use graphical interface to permit medication safety administrators to modify DDI warnings based on discrete coded data within the EHRs. These contextual attributes would be readily available in most EHR systems, and therefore DDI warnings could easily be customized by a medication safety committee or others responsible for such warnings. A team of pharmacists, physicians, and DDI experts identified attributes that were perceived to be useful for filtering DDI warnings. These attributes were then incorporated into DICE and grouped into 4 sections (general, medication, patient, and visit sections). A survey was constructed to evaluate attributes of DICE and to determine whether there were important missing attributes. Invited participants were asked to view a video explaining the DICE tool (12 minutes) and then answer questions about the tool, along with basic demographic information (10 minutes). The survey had 41 questions over 4 the DICE sections (general, medication, patient, and visits). For each section of DICE, a screen shot was provided, and respondents were asked about the perceived usefulness of that particular attribute using a scale of 0 "Not Useful" to 100 "Very useful", with a free response text question asking for additional comments at the end of each section. The general section contained 6 questions on DDI severity rating, DDI alert management, DDI documentation level, additional information, and interaction monograph. The medication section had a total of 6 questions about primary and secondary drug properties, route and frequency of administration, and ordering physician. The patient section included attributes such as age and weight. The laboratory section included attributes such as serum creatinine and other questions related to timing (e.g. 2 days, 1 week, last month, etc.). The visit section asked respondents to

rate the usefulness of the ability to change warnings based on encounter location (e.g. adult emergency department, observation, adult intensive care unit, etc.) and encounter type (e.g. ambulatory, inpatient, etc.). The final section asked respondents to rate their overall impression of the DICE tool and, its usefulness and to identify any other attributes they think would be useful for filtering DDI alerts. Comment boxes were provided in each section to capture respondents' opinions and thoughts.

Finally, we developed an "app" for our colchicine and cytochrome P-450 3A4 (CYP3A4) enzyme/ p-glycoprotein (P-gp) enzyme inhibitor algorithm. This app involved creating concept sets of known inhibitors of these enzymes and evaluating documentation of a patient's renal function using diagnosis information or laboratory data. The app is available via the DDI-CDS.org website. To test implementation of the app we worked with Vanderbilt University. Details on the implementation are provided below in the results section.

Limitations

There are several limitations that should be kept in mind when interpreting the findings from the above referenced studies. Data reported in FAERS represents only numerator data and determining the true incidence of harm from such voluntary reporting databases is not possible because of the lack of denominator data. Results from the CERNER Health Facts® database are largely based on inpatient stays and may not reflect the risk in ambulatory non-institutionalized settings. The evaluation of algorithms using both synthetic data and data from a single healthcare institution may not identify all issues that could arise when using one of the designed algorithms. Results from our structured interviews with pharmacists, CMIOs, and others responsible for medication safety is limited to those institutions included in the sample, and findings from the study are not generalizable to other organizations. The apps based on the algorithms have not been rigorously evaluated in production environments. As mentioned above, there were significant changes in personnel with the Cerner EHR software provider, limiting our ability to implement many of the DDI algorithms. Finally, the COVID-19 pandemic severely affected our ability to engage organizations to implement one or more apps/algorithms to evaluate their effectiveness in practice environments.

Results

AIM 1: Below are findings associated with the development of DDI evidence and associated algorithms. To conduct and disseminate all the research conducted with the grant and to achieve our aims we created a website: https://ddi-cds.org/about-us/ where more specific information and details on the results of the grant can be viewed. Algorithms for the following DDI pairs were developed: ACEIs or ARBs / Potassium Sparing Diuretic; Colchicine CYP3A4 / P-gp inhibitors; COVID-19 Therapies; KCL and K Sparing Diuretics; selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) / Thiazide-diuretics; Tizanidine / CYP1A2 Inhibitors; Warfarin / Non-steroidal anti-inflammatory drugs (NSAIDs); Warfarin / Antidepressants; and Warfarin / Salicylate. Details for each algorithm are available at: https://ddi-cds.org/ddi-algorithms/

Studies generating evidence for DDIs: A series of investigations were conducted to provide evidence for the various DDI algorithms. As described above, studies were conducted using the FDA's FAERs database, the CERNER Health Facts® (HF) database, and also the N3C data. We also conducted systematic reviews and meta-analyses. Summaries of results from these studies are provided below.

FAERS

- The disproportionality analysis for tizanidine interactions using FAERS showed a higher ROR when concomitantly mentioned with ciprofloxacin (ROR for hypotension 28.1, 95% confidence interval [CI] 19.2–41.2) or fluvoxamine (ROR for hypotension 36.9,95% CI 13.1–103.4), and also when reported in “any role” with zafirlukast (ROR for falls 16.0, 95% CI 6.1–42.1).
- For colchicine and CYP3A4, the strongest ROR signal observed occurred with colchicine + atazanavir and rhabdomyolysis/myopathy (ROR = 35.4, 95% CI: 12.8-97.6), and the strongest O/E signal was associated with colchicine + clarithromycin and agranulocytosis (O/E = 3.79, 95% credibility interval: 3.44-4.03).
- A descriptive analysis of colchicine and clarithromycin reports to FAERS identified 58 reported cases, 52% with a fatal outcome, and the most frequent adverse events reported were: diarrhea (31%), pancytopenia (22%), bone marrow failure (14%), and vomiting (14%).

CERNER Health Facts® (HF) database

- With over 70,000 encounters of patients on tizanidine across 221 hospitals, ciprofloxacin was co-administered with tizanidine in 2,487 encounters (3.6%). Compared to patients who did not receive ciprofloxacin, co-administration of tizanidine and ciprofloxacin was associated with an increased likelihood of hypotension (adjusted odds ratio: 1.43, 95% Confidence Intervals:1.25–1.63, p <0.001).
- A cohort study comparing colchicine plus a macrolide (2,199) and colchicine with an antibiotic no macrolide (12,670) found that heart failure was more frequent in the colchicine plus a macrolide cohort (n = 402, 18.3%) vs. the colchicine non-macrolide cohort (n = 1153, 9.1%) (p < 0.0001) and was associated with a higher mortality rate [(85 (3.87%) vs 289 (2.28%), p < 0.0001 macrolides vs. non-macrolides cohorts, respectively]. When the sample was limited to individuals exposed to either clarithromycin or erythromycin and colchicine, the adjusted OR for acute hepatic failure was 2.47 (95% CI 1.04–5.91) and 2.06 for death (95% CI 1.07–3.97).
- An analysis of 5,816 patients’ unique encounters were analyzed to investigate the risk of hyperkalemia after exposure to a KSD and a RAS agent. The prevalence rates of potassium serum levels ≥5.5 was 5.2%, with the KSD cohort showing the highest proportion (6.4%) and the KSD-ARB cohort having the lowest (3.7%). However, the difference between groups with respect to the proportion of the cohort with hyperkalemia was not statistically significant (p=0.12). Compared to APAP group, the KSD, concomitant use of KSD-ACEI, and KSD-ARB cohorts were associated with significant increases in serum potassium level (0.07, 0.10 and 0.09 millimoles per liter (mmol/L) respectively), but these differences are likely not clinically meaningful.
- The hydroxychloroquine plus a QTc-prolonging agent/drug cohort had the highest average Tisdale Risk Score compared with those without concomitant exposure (p < 0.05). A statistically significant increase in QTc interval from the last measurement prior to concomitant exposure of 18.0 ms (95% CI 3.5–32.5; p < 0.05) was found in the hydroxychloroquine monotherapy cohort.
- To investigate the relationship of exposure to QTc prolonging medications we examined a cohort of 1,698 patients with at least 2 QTc measurements. The risk of death among patients with a moderate Tisdale score was 2.61 (95%CI:1.25 – 5.47) or with high-risk Tisdale score OR 4.27 (95%CI:1.74 – 10.45) compared to those with a low Tisdale score. Patients with three or more QTc prolonging medications had risk of mortality of 1.70 (95% CI: 1.03- 2.78) compared to patients receiving only one QTc prolonging medication. Antipsychotics [OR = 2.98 (1.32-6.71)] and anesthetics [OR = 2.69 (1.35-5.37)] had the highest risk of mortality among the therapeutic classes of QTc prolonging medications.

- A study was conducted to examine risk of QTc prolongation after exposure to hydroxychloroquine and a medication known risk for QTc prolongation. Controls consisted of patients receiving other disease modifying rheumatic drugs. This study found that exposure to hydroxychloroquine is associated with a moderate increase in QTc interval compared to subjects receiving sulfasalazine and methotrexate. Surprisingly, there was no evidence that this effect is potentiated when hydroxychloroquine is given concomitantly with other drugs known to increase the QTc interval.

N3C Data

- A nested case control study of patients from a COVID-19 cohort assessing exposure for the drug interaction of direct oral anticoagulants and dexamethasone in patients with a thromboembolic event included a total of 172 cases who were matched to 344 controls. The analysis did not find a statistically significant increase in the risk of thromboembolic events when apixaban/rivaroxaban were administered with dexamethasone (OR (95% CI) = 1.15, (0.32, 4.18). While there is a theoretical concern of a pharmacokinetic drug-drug interaction between dexamethasone and oral anticoagulants, this case-control study did not observe a statistically significant increase in the risk of thromboembolism.

Systematic Reviews and Meta-Analyses

- A systematic review examining risk of bleeding after exposure to warfarin and NSAIDs identified 11 studies for inclusion. The estimated OR for gastrointestinal bleeding for the DDI exposure was 1.98 (95% confidence interval [CI]: 1.55–2.53). There was an increased risk of general bleeding with the combination of warfarin with NSAIDs (OR = 1.58, 95% CI: 1.18–2.12) or COX-2 inhibitors (OR = 1.54, 95% CI: 0.86–2.78) compared with warfarin alone.
- A systematic review to estimate the serum potassium changes when concomitant exposure to ACEI/ARB and spironolactone therapy identified 20 randomized controlled trials. Persons exposed to both medications compared to ACEI/ARB therapy alone had an increased serum potassium concentration by 0.19 mEq/L (95% CI, 0.12-0.26 mEq/L), with intermediate heterogeneity across studies (Q statistic = 46.5, P = 0.004; I^2 = 59). This study provides evidence of little risk of hyperkalemia with the combination of spironolactone and an ACEI/ARB.
- A systematic review and meta-analysis to examine the risk of bleeding in individuals exposed to a combination of oral anticoagulant (OAC) and aspirin, compared to those taking OAC or aspirin alone identified 43 studies. An analysis of 15 RCTs found an increase in the risk of bleeding with an OR=1.36 (95% CI 1.15, 1.59) when evaluating OAC plus aspirin versus OAC alone. This result was similar to findings from 19 observational studies (OR 1.42, 95% CI 1.09, 1.87). Similarly, when OAC plus aspirin was compared to aspirin alone, a higher rate of bleeding was found in the combination groups (OR 2.40 (95%CI 1.90, 3.0) in the analysis of 15 RCTs and (OR 3.18 (95% CI 1.53-6.65) among ten observational studies.
- A review of case reports associated with colchicine-related DDIs identified risk factors associated with colchicine toxicity. These factors included: colchicine dose; renal disease; and hepatic disease. The review also identified potential management strategies for the interaction.

AIM 2

A total of 8 DDIs were identified as high priority for contextual alerting. Both document-based decision trees and computable knowledge artifacts for these algorithms have been made available publicly at https://ddi-cds.org. The source code used to implement both the Drools and Clinical Quality Language knowledge artifacts is also available. Moreover, a Drools environment

containing the rules, rule execution environment, and synthetic data were made available via a Docker image and the CQL artifacts are available on GitHub (https://github.com/dbmi-pitt/ddi-cds/). Eight computable DDI algorithms were successfully validated. Almost all clinical entities required for the DDI rules were supported in the version 5 of the OHDSI common data model. Only 1 algorithm had a decision tree branch that was not possible to implement in the computable version. Specifically, the "Epinephrine/Beta-blocker" algorithm referenced the use of epinephrine for dermatology, dentistry, or plastic surgery. This could not be implemented in the computable rule because the OHDSI common data model does not directly link drug exposures with patient condition occurrences.

The real-world EHR dataset evaluation included 24,599 individual patients who had a healthcare encounter that overlapped with the study's 3-month period (January–March 2016). There were 31,332 distinct health encounters with 10,506 (33.5%) having a duration of at least 24 hours. We focused on encounters lasting 24 hours or more. The total number of alerts that would have triggered based on basic concomitant exposure was 3020. Use of the 8 algorithms would result in filtering 1584 (52.4%) of these alerts based on the operational classification of "No Special Precautions." Examining specific DDIs, the percentage of interruptive alerts that the algorithms suggest completely filtering ranged from 100% for citalopram/QT prolonging agent (N=849) and fluconazole/opioid (N=282) to <1% for warfarin/antidepressant (N=468). The algorithm that resulted in the most contextualized simulated alerts was warfarin/ antidepressants. In contrast to 468 basic concomitant exposures with no contextualization, the computable rule identified 368 (78.6%) situations classified as "Avoid Combination," 96 (20.5%) situations classified as "Usually Avoid Combination or Minimize Risk," and 4 (0.9%) situations classified as "No Special Precautions." The immunosuppressant/fluconazole algorithm also resulted in well contextualized output with 313 (89.4%) of the 350 basic concomitant exposures classified into 2 different situations warranting an "Avoid Combination" classification, and 37 (10.6%) classified as "No Special Precautions." The epinephrine/beta-blocker algorithm was the only algorithm that transitioned all basic concomitant exposures (N=176) to "Usually Avoid Combination or Minimize Risk."

For our study examining contextual factors that could be used to customize DDI warnings based on common drug compendia, the 15 DDIs included 682 unique medications and were grouped into 30 subclasses. The unique medications per subclasses was 23 (median = 13). Thirteen drug groups (43%) had statistically significant agreement (p <0.05) across the drug interaction references. Of these groups, three had perfect agreement (Kappa = 1), two had moderate agreement (Kappa = 0.41 - 0.60), four had fair agreement (Kappa= 0.21 - 0.40), and four had slight agreement (Kappa = 0.0 - 0.2). The perfect agreement groups consisted of less than two drugs (i.e., *irinotecan, tizanidine, azathioprine and mercaptopurine*). The median Kappa for all groups was 0.11 (slight agreement). Of the 23-drug average per group, an average of 3.8 drugs per group were the same across references. The majority of variables were order related (22/28, 79%). Timing variables were the most common with 10 of 15 DDIs (67%) having one or more variables. Furthermore, timing variables were consistent across references (i.e., 3/3 or 2/2) in 8 of the 10 DDIs (80%). The majority of timing variables were associated with MAOIs; the references provided recommendations to wait at least 14 days after stopping a MAOI before starting an interacting medication. *Dose* variables were available for 9 DDIs (60%). Compared to timing, *dose* of the medications was less consistent across the references. Two of the nine DDIs (22%) had *dose* considerations that were consistent across the references. Most *dose* recommendations were non-specific to increase or decrease doses when initiating a medication that changes metabolism. *Route* factors were mentioned in only one reference for three of 15 (20%). The three *route* issues were specific to the transdermal administration of the MAOI selegiline. Overall, there were 22 of 45 (49%) possible order variables. Patient variables were

available with 4 (27%) DDIs. High-risk QT prolonging agents had patient considerations in all three categories; however, only the *condition* attribute was consistent across all three drug interaction references. The *condition* factor for the atazanavir – proton pump inhibitors DDI included treatment experience (i.e., HIV treatment experienced versus naïve with atazanavir), age, sex, and heart disease. *Observation* variables included laboratory (e.g., hypokalemia) measures. The *medication* variable for high-risk QT prolonging agents was related to cytochrome P450 3A4 substrates. These substrates increase the blood concentration of certain QT prolonging agents and was an additive risk for prolonging QTc intervals.

AIM 3

Website: One of the major outputs of the project was the creation and updating of the website DDI-CDS.org. The website is a key component of our dissemination strategy and also a repository for work product from the grant. In addition to providing documentation for the various algorithms that were developed, the website contains links to the various webinar recordings and apps created by the project. We developed and tested three apps for DDI-CDS (https://ddi-cds.org/apps/), the first one, for the concomitant use of NSAIDS and warfarin and the potential of gastrointestinal bleed. The other two for tizanidine and cytochrome P450 1A2 inhibitors and for colchicine and cytochrome P450 3A4/p-glycoprotein inhibitors.

Dissemination
The presentation of 11 recorded webinars can be viewed via the webpage (https://ddi-cds.org/resources/). Each DDI webinar discussed the evidence and algorithm. Other webinars include other topics such as COVID-19 treatments, analyzing DDI data from the Epic system, and tools made available via vendors of drug information. See below for the list of webinars (reverse chronological order):

1. Tamoxifen Drug Interactions: A Critical Evaluation of the Evidence and Guidance for Patient Care (date 7/20/22)
2. Successful Deployment of Contextualized Drug-Drug Interactions CDS (date 2/23/2022)
3. Analyzing and Evaluating Drug-Drug Interaction Alert Data from Epic Electronic Health Records (date 10/27/2021)
4. Using existing Cerner tools to monitor and improve drug-drug interaction warnings (date 8/25/2021)
5. Tizanidine Drug-Drug Interactions (date 2/17/2021)
6. Drug interactions involving colchicine and CYP3A4 / P-gp inhibitors (date 1/20/2021)
7. Drug interactions involving ACE inhibitors or ARBs and potassium-sparing diuretics (date 9/23/2020)
8. Drug interactions involving SSRI or SNRI -Thiazide diuretics (date 7/22/2020)
9. Drug interactions involving drugs used to treat COVID-19 (date 5/13/2020)
10. Warfarin – NSAIDs (date 3/11/2020)
11. Warfarin – antidepressants (date 2/12/2020)

Algorithm Implementation: Two institutions, Vanderbilt University Medical Center (VMCU) and Northern Lights, implemented one or more of the algorithms that were developed. Both organizations focused on interactions with colchicine. At Vanderbilt University Medical Center, an EPIC user, the research team met with the CDS governance committee to review the app and discuss implementation. The review of the app included representatives from various operational groups within the medical center, and covered various topics such as medication identification, IT security, disaster recovery, programmers, product licensing, data use and integration, data retention, HIPAA/HITECH compliance, data encryption, data sharing, end-user

access, authentication, access, audit and access logging, and support. The colchcine-CYP3A4/P-gp inhibitors DDI SMART app is presently in the final stages of deployment within the Vanderbilt IT system with work ongoing to test and adapt it within the computerized provider order entry (CPOE) workflow.

At Northern Lights, a Cerner user, we worked with the pharmacy informatics team to ensure their system was correctly identifying medications that may interact with colchicine. Northern Lights is located in the northeastern part of the United States and comprises 9 hospitals and 250 ambulatory practices). Because of technical limitations of the Cerner system, integration of the app was not possible. However, they had previously implemented other DDI warning algorithms to limit unnecessary alerts. This included a review of all DDIs and reclassification of seriousness if necessary. Twelve pharmacists from six member hospitals reviewed a total of 103,486 DDIs with moderate, major, and major-contraindicated alert severity. The most common decision made for various DDI alerts was to suppress the warning. This included drug pairs of fentanyl-ondansetron and meperidine-ondansetron. No changes in severity were made for some DDI pairs where clinicians were of the opinion that the alerts were still relevant (e.g., diltiazem-metoprolol, warfarin-heparin, etc.). For other DDIs, such as ibuprofen-ketorolac, alert severity was downgraded from major-contraindicated to major-generally avoid. Some DDIs such as potassium chloride-spironolactone severity were upgraded from major-generally avoid to major-contraindicated. The hyperkalemia algorithm was also applied to the potassium chloride-spironolactone DDI such that the alert only showed when potassium level was high or missing. To limit unnecessary warning to clinicians the severity level was set to display major-contraindicated DDIs to all providers including inpatient, ambulatory providers, and pharmacists, whereas major severity would display the warning for pharmacists and ambulatory providers. Before making any of these changes to DDI alerts, pharmacist received the largest number of alerts, followed by physicians/providers, then nurses. For pharmacists, changes in warnings resulted in a spike followed by a drastic reduction following changes to the moderate to major alert threshold and alert customization changes. For clinicians, there was a significant reduction in warnings from a rate of approximately 17.1 DDI per 100 orders to approximately 1.8 DDIs per 100 orders, representing an 89% reduction in warnings shown to providers. The number of warnings for nursing followed a similar trend but with a lower volume of alerts. Each component for contextual filtering of DDI alerts resulted in varying results. For example, Inpatient/outpatient filtering was responsible for over 5448 alerts filtering during one week and filtered approximately 43% of DDIs alerts. Order detail filtering group 1-10 filtered around 0.2% of DDI alerts and filtered 19 alerts in 1 week. Discontinue on scratchpad filtering was responsible for approximately 77 alerts in 1 week and 0.6% of DDI alerts. The CERNER mCDS rule filter such as high/missing potassium filtered 468 alerts in 1 week and 3.7% of DDI alerts. Overall, DDI algorithms/filters reduced alerts for all providers. The percentage filtered was highest for pharmacists (52%) followed by physicians (42%), physician extender such as mid-level practitioners (34%), other (28%), nurses (22%), and medical assistants (8%).

Barriers to Implementation of DDI Algorithms: After recruitment via purposive snowball sampling from 14 diverse U.S. health systems including both inpatient and ambulatory services, 14 interviews were conducted with 17 participants. The coded interview transcripts generated 15 high-level barrier subthemes in 8 socio-technical themes. The barriers were grouped into three clusters (user, organization, and technical stakeholders), which revealed system dynamics that could stall the implementation of tailored DDI alerts. The study found it is essential to identify and demonstrate value metrics that healthcare organizations prioritize to enable implementation of tailored DDI alerts. A multi-faceted approach to promote adoption is needed. Important actions to overcome barriers include: partnering with healthcare organizations that have the capacity to adopt new DDI alert algorithms, identifying multidisciplinary specialists that

know users' needs; and working across organizations and vendors to facilitate implementation of customized DDI algorithms.

DICE Evaluation: A total of 54 individuals provided responses to the survey, although not all individuals answered every question (complete responses were available from 50 [92.6%] respondents). Among the 50 participants who provided information about their discipline, the vast majority (94%) were pharmacists. Almost two thirds of respondents (n=29, 67%) had roles as informatics pharmacists within their organizations. Most respondents (n=36, 88%) indicated their organization was a health system with both inpatient and outpatient clinics. Twenty-four respondents (59%) were associated with organizations that had more than 500 licensed beds. Overall, respondents rated the information in the general section of DICE as useful, with the ability to change severity ratings for DDIs rated 75.7 ± 22.2 and the monograph describing the interaction rated 69.3 ± 27.7 (See Table 2). There were several comments regarding the content and potential changes once implemented. For example, one participant mentioned, "*The DDI Alert Management Section could be of great value (scored as 100%) if it would result in a difference in alerting behavior, such as actively presenting a window requiring user interaction vs passively presenting an alert for a few moments that then auto-collapses vs DDI information available upon user initiated profile-level interaction check*", and *"For the interaction monograph, I think bullet formatting will be more readable"* or "*Instead of the interaction monograph, I would prefer to see a set of instructions*". One respondent thought it would be helpful for decision making "*I wish the content on the alert management was better because it would be great to be able to use a category like that for decision making*".

Discussion

Evidence of harm from specific drug combinations was evaluated by the research team through a series of investigations. In some instances, such as with colchicine-related interactions, the risk of harm was much greater than previously reported and that nearly 50% of reported cases in the FDA's FAERS database involving clarithromycin resulted in death. On the other hand, some theoretical DDIs, such as dexamethasone and OAC as well as KSD and ACEI/ABR combinations did not show significant changes in events or physiological measures, suggesting that warnings for these interactions are likely "not necessary" in the majority of instances.

The project was able to create artifacts for DDIs that could be implemented to reduce inappropriate warnings. Using both synthetic and actual patient encounter data, we demonstrated that it was possible to significantly reduce the number of warnings using rather simple alert filtering rules. The study was also successful in creating apps that could be implemented in healthcare organizations to improve warnings for certain drug combinations. However, implementing such algorithms was challenging due to a variety of issues. In general, hospitals and health systems are seeking "off-the-shelf" solutions to medication safety from compendia vendors and EHR software systems. Concerns about maintenance, competing priorities, governance, and lack of resources limits the ability to implement third-party DDI algorithms, such as the ones created by this project.

Conclusions

Inappropriate warnings related to DDI continue to plague healthcare systems despite our efforts to advance clinical decision support for these warnings. This project provides solid evidence for the risk of harm associated with many interactions that were lacking such evidence. The risk of serious harm from colchicine interactions with CYP3A4 and P-gp inhibitors is substantial, with nearly 50% of cases involving clarithromycin leading to death. In addition, we also investigated

drug combinations where there was concern but we found little evidence, suggesting any concerns were theoretical and that patients could safely use the medications concurrently. The project demonstrated that implementation of a relatively modest number of artifacts could have a dramatic decrease in potentially inappropriate warnings. However, implementing artifacts was challenging, in part due to the COVID-19 pandemic, but also because of the limited resources within healthcare organizations to implement third-party software. Pharmacy informatics professionals are seeking off-the-shelf solutions from their drug compendia and EHR vendors to provide artifacts to reduce over alerting.

Significance

There is keen interest in the healthcare community to increase the specificity of DDI warnings and reduce over alerting. Furthermore, some drug combinations the risk of harm can be mitigated through appropriate monitoring and highlighting patients with predisposing risk factors. Meaningful CDS for DDIs is possible using available data within EHRs, and over time may reduce provider alert fatigue.

Implications

Implementing third-party artifacts for DDI in hospitals and health systems is challenging due to a variety of factors, including lack of resources, concerns about maintenance, and IT security. Local governance of third-party artifacts is a barrier for widespread adoption of DDI alert filtering rules. Future studies should consider partnering with drug compendia vendors to increase adoption and implementation of medication safety artifacts. In addition, EHR software developers should incorporate end-user tools that would permit easy modification and maintenance of DDI warnings to limit alert fatigue and target patients at greatest risk of harm.

List of Publications and Products

a) Published literature supported by the grant:

1. Villa Zapata L, Hansten PD, Panic J, Horn JR, Boyce RD, Gephart S, Subbian V, Romero A, Malone DC. Risk of bleeding with exposure to warfarin and nonsteroidal anti-inflammatory drugs: a systematic review and meta-analysis. Thrombosis and Haemostasis 2020; 120(7): 1066-1074. PMID: 32455439 PMCID: PMC7665225 DOI: 10.1055/s-0040-1710592
2. Villa Zapata L, Hansten PD, Horn JR, Boyce RD, Gephart S, Subbian V, Romero A, Malone DC. Evidence of clinically meaningful drug-drug interaction with concomitant use of colchicine and clarithromycin. Drug Safety 2020; 43(7): 661-668. PMID: 32274687 PMCID: PMC7592308 DOI: 10.1007/s40264-020-00930-7
3. Chou E, Royce RD, Balkan B, Subbian V, Romero A, Hansten PD, Horn JR, Gephart S, Malone DC. Designing and evaluating contextualized drug-drug interaction algorithms. JAMIA Open 2021 Mar 19;4(1):ooab023 PMID: 33763631 PMCID: PMC7976224 DOI: 10.1093/jamiaopen/ooab023.
4. Villa Zapata L, Carhart BS, Horn JR, Hansten PD, Subbian V, Gephart S, Tan M, Romero A, Malone DC. Serum potassium changes due to concomitant ACEI/ARB and spironolactone therapy: A systematic review and meta-analysis. Am J Health Syst Pharm 2021 May 20;zxab215 PMID: 34013341 PMCID: PMC8194784 DOI: 10.1093/ajhp/zxab215
5. Reese T, Wright A Liu S, Boyce RD, Romero A, Del Fiol G, Kawamoto K, Malone DC Improving the specificity of drug-drug interaction alerts: Can it be done? American Journal of Health System Pharmacy 2022 79(13):1086-1095. PMID: 35136935 DOI: 10.1093/ajhp/zxac045.
6. Hochheiser H, Jing X, Garcia EA, Ayvaz S, Sahay R, Dumontier M, Banda JM, Beyan O, Brochhausen M, Draper E, Habiel S, Hassanzadeh O, Herrero-Zazo M, Hocum B, Horn J, LeBaron B, Malone DC, Nytrø Ø, Reese T, Romagnoli K, Schneider J, Zhang LY, Boyce RD. A Minimal Information Model for Potential Drug-Drug Interactions. Front Pharmacol. 2021 Mar 8;11:608068. PMID: 33762928; PMCID: PMC7982727. doi: 10.3389/fphar.2020.608068
7. Kravchenko OV, Boyce RD, Gomez-Lumbreras A, Kocis PT, Villa Zapata L, Tan M, Leonard CE, Andersen KM, Mehta H, Alexander GC, Malone DC; N3C consortium. Drug-drug interaction between dexamethasone and direct-acting oral anticoagulants: a nested case-control study in the National COVID Cohort Collaborative (N3C). BMJ Open. 2022 Dec 29;12(12):e066846. doi: 10.1136/bmjopen-2022-066846. PMID: 36581417; PMCID: PMC9806069.
8. Malone DC, Villa-Zapata L, Gómez-Lumbreras A, Horn J, Tan MS, Boyce RD. Authors' Response to Yoshihiro Noguchi's Comment on: "A Disproportionality Analysis of Drug-Drug Interactions of Tizanidine and CYP1A2 Inhibitors from the FDA Adverse Event Reporting System (FAERS)". Drug Saf. 2022 Dec;45(12):1553-1555. doi: 10.1007/s40264-022-01239-3. Epub 2022 Oct 12. PMID: 36223037.
9. Tan MS, Gomez-Lumbreras A, Villa-Zapata L, Malone DC. Colchicine and macrolides: a cohort study of the risk of adverse outcomes associated with concomitant exposure. Rheumatol Int. 2022 Dec;42(12):2253-2259. PMID: 36104598; DOI: 10.1007/s00296-022-05201-5
10. Giannouchos TV, Gómez-Lumbreras A, Malone DC. Risk of tizanidine-induced adverse events after concomitant exposure to ciprofloxacin: A cohort study in the U.S. Am J Emerg Med. 2022 May;55:147-151. PMID: 35325788. DOI: 10.1016/j.ajem.2022.03.008

11. Villa-Zapata L, Gómez-Lumbreras A, Horn J, Tan MS, Boyce RD, Malone DC. A Disproportionality Analysis of Drug-Drug Interactions of Tizanidine and CYP1A2 Inhibitors from the FDA Adverse Event Reporting System (FAERS). Drug Saf. 2022 Aug;45(8):863-871. PMID: 35834155. DOI: 10.1007/s40264-022-01200-4
12. Villa Zapata L, Boyce RD, Chou E, Hansten PD, Horn JR, Gephart SM, Subbian V, Romero A, Malone DC. QTc Prolongation with the Use of Hydroxychloroquine and Concomitant Arrhythmogenic Medications: A Retrospective Study Using Electronic Health Records Data. Drugs Real World Outcomes. 2022 Sep;9(3):415-423. doi: 10.1007/s40801-022-00307-5. Epub 2022 Jun 5. PMID: 35665910; PMCID: PMC9167427.
13. Villa Zapata L, Subbian V, Boyce RD, Hansten PD, Horn JR, Gephart SM, Romero A, Malone DC. Overriding Drug-Drug Interaction Alerts in Clinical Decision Support Systems: A Scoping Review. Stud Health Technol Inform. 2022 Jun 6; 290:380-384. doi: 10.3233/SHTI220101. PMID: 35673040.
14. Gómez-Lumbreras A, Boyce RD, Villa-Zapata L, Tan MS, Hansten PD, Horn J, Malone DC. Drugs That Interact With Colchicine Via Inhibition of Cytochrome P450 3A4 and P-Glycoprotein: A Signal Detection Analysis Using a Database of Spontaneously Reported Adverse Events (FAERS). Ann Pharmacother. 2023 Jan 23:10600280221148031. doi: 10.1177/10600280221148031. Epub ahead of print. PMID: 36688283.
15. Hansten PD, Tan MS, Horn JR, Gomez-Lumbreras A, Villa-Zapata L, Boyce RD, Subbian V, Romero A, Gephart S, Malone DC. Colchicine Drug Interaction Errors and Misunderstandings: Recommendations for Improved Evidence-Based Management. Drug Saf. 2022 Dec 15:1–20. doi: 10.1007/s40264-022-01265-1. Epub ahead of print. PMID: 36522578; PMCID: PMC9754312.
16. Malone DC, Villa-Zapata L, Gómez-Lumbreras A, Horn J, Tan MS, Boyce RD. Authors' Response to Yoshihiro Noguchi's Comment on: "A Disproportionality Analysis of Drug-Drug Interactions of Tizanidine and CYP1A2 Inhibitors from the FDA Adverse Event Reporting System (FAERS)". Drug Saf. 2022 Dec;45(12):1553-1555. doi: 10.1007/s40264-022-01239-3. Epub 2022 Oct 12. PMID: 36223037.

b) Papers submitted:

1. Zhang T, Gephart SM, Subbian V, Boyce RD, Villa-Zapata L, Hansten PD, Horn JR, Romero A, Malone DC. Barriers and Facilitators to Adoption of Drug-Drug Interaction Clinical Decision Supporting US Healthcare Organizations. Applied Clinical Informatics (accepted pending revisions)
2. Syeed MS, Gomez-Lumbreras A, Tan M, Malone DC. Changes in serum potassium with concurrent administration of angiotensin-converting enzyme inhibitor / angiotensin receptor blocker and potassium sparing diuretics: an analysis of electronic health records data. JAPhA Pharmacotherapy (under review)
3. Guhle P, Panic J, Malone DC. Risk of bleeding with concomitant use of oral anticoagulants and aspirin: a systematic review and analysis. American Journal of Health-System Pharmacy (under review).

c) Presentations at scientific conferences that were supported by the grant:

1. Zapata L, Subbian V, Boyce RD, Hansten PD, Horn JR, Gephart S, Romero A, Malone DC. Overriding Drug-Drug Interaction Alerts in Clinical Decision Support Systems: A Scoping Review. MEDINFO'21 (IMIA) Sept. 26, 2021.
2. Subbian V, Villa Zapata L., Boyce RD, Horn JR, Hansten PD, Gephart SM, Romero AV, Malone DC. Overriding Drug-Drug Interaction Alerts in Clinical

Decision Support Systems: A Scoping Review. Proceedings of the 18th World Congress on Medical and Health Informatics (MEDINFO 2021), 2022 (Forthcoming). https://www.youtube.com/watch?v=4ftwLlkTIoY

3. Zhang T, Gephart S, Subbian V, Boyce RD, Villa Zapata L, Hansten PD, Horn JR, Romero A, Malone DC. Barriers and Facilitators to Adoption of Drug-Drug Interaction Clinical Decision Support in US Healthcare Organizations. Academy Health 2021 Dec. 15, 2021.
4. Drug interaction clinical decision support: mending the medication safety net. Science in the Desert - Feb 22, 2019.
5. Contextualized drug-drug interaction decision support. 19th General Meetings of HSPC/CIIC - Oct. 7, 2019.
6. Syeed MS, Gomez-Lumbreras A, Tan M, Malone DC. Changes in Serum Potassium with Concurrent Administration of Angiotensin-Converting Enzyme Inhibitor / Angiotensin Receptor Blocker and Potassium Sparing Diuretics. American Heart Association's annual Scientific Sessions 2021, Boston, MA, November 14, 2021.
7. Kravchenko OV, Gomez Lumbreras A, Kocis PT, Malone DC, Leonard CE, Boyce RD Using N3C Enclave for Drug-Drug Interaction studies: the case of DOAC-Dexamethasone Interaction and the risk of Thrombosis. AMIA Informatics Summit. Chicago Illinois. March 22, 2022.
8. Olga Kravchenko, Ainhoa Gomez-Lumbreras, Paul T. Kocis, Daniel Malone, Charles E. Leonard, Richard D. Boyce, "Using N3C Enclave for Drug-Drug Interaction studies: the case of DOAC-Dexamethasone Interaction and the risk of Thrombosis," Poster presentation at the NLM Informatics Training Conference, virtual, June 21-23, 2021.
9. Sibilla MA., Malone DC., Del Fiol G., Boyce RD. Testing a Novel Tool for the Development of Drug-drug Interaction Clinical Decision Support. Accepted to the 2022 AMIA Informatics Summit. Chicago, Illinois. March 24, 2022.
10. Kharat A, Tan M, Gomez-Lumbreras A, Zapata LV, Malone DC. An Evaluation of the Relationship between QTc Prolonging Medications, Tisdale Risk Scores and Mortality Using a Nationally Representative Electronic Health Records Database. ISPOR Annual Meeting, Washington DC, May 17, 2022.
11. A Gomez-Lumbreras, RD Boyce, L Villa Zapata, PD Hansten, DC Malone. Colchicine and CYP3A4/P-gp inhibitors interaction signal detection using FAERS. 37th ISPE virtual meeting. August 2021. Spotlight poster.
12. L Villa Zapata, RD Boyce, A Gomez-Lumbreras, J Horn, DC Malone. Detecting tizanidine and CYP1A2 inhibitor interaction signals using the FDA's Adverse Event Reporting System. 37th ISPE virtual meeting. August 2021.