

Drug-Drug Interaction Clinical Decision Support Conference Series

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Structured Abstract

Purpose: The purpose of this conference grant was to provide recommendations for evaluation of evidence for drug-drug interactions (DDIs), identify principles for including DDI alerts in clinical decision support, and establish preferred strategies for presenting DDI clinical decision support notifications.

Scope: A conference series was conducted, and three expert workgroups were assembled to improve the quality of clinical decision support (CDS) for DDIs. The Evidence Workgroup consisted of 19 experts; the Content Workgroup included 20 experts, and the Usability Workgroup represented 24 clinical, usability, and informatics experts representing academia, health information technology (IT) vendors, healthcare organizations, and individuals from the Office of the National Coordinator for Health IT.

Methods: Groups met monthly by webinar, and two in-person meetings were conducted to reach consensus on recommendations. Recommendations were presented at four national meetings for additional comments and considerations.

Results: The recommendations include the consistent use of terminology, visual cues, minimal text, formatting, content, and reporting standards to facilitate usability. Experts recommended a transparent, systematic, and evidence-driven process with graded recommendations by a consensus panel of experts and oversight by a national organization. The experts also recommended judicious classification of DDIs as contraindicated. Finally, more research to identify methods to safely reduce repetitive and less relevant alerts is needed.

Key Words:

clinical decision support, alerts, drug interactions, medication safety, CPOE

REPORT

1. Purpose

The purpose of this conference grant was to support a solution-oriented conference series aimed at improving implementation of meaningful DDI alerts within clinical decision support (CDS). The overarching goal of the conference series was to improve patient safety through the appropriate use of DDI alerts within CDS. The long-term goals were to develop an ongoing structured process to improve the quality of DDI alerting systems used by health providers to maximize the value of this technology and, ultimately, improve patient safety. Over the course of the project, experts, stakeholders, and public-private partnerships developed strategies for explicit, systematic evaluation of DDIs to improve knowledgebase data and the practical utility of electronic clinical decision aids. The specific aims of the conference series were to:

- 1) develop guidelines for systematic appraisal of DDI evidence;
- 2) recommend principles for including DDIs in drug safety alerts; and
- 3) establish preferred strategies for presenting DDI alerts to clinician end users.

This successful work will help to strengthen the DDI alerting process, enabling more informed decisions by healthcare providers. The work products from the conference series provide guidelines and best practices that can be supported and adopted by professional societies, healthcare organizations, quality alliances and entities, drug knowledgebase vendors, and software application vendors.

2. Scope

Medications are essential to prevent and treat many illnesses. Americans receive an average of 12, and those aged 65 years and older receive more than 30 prescriptions each year.¹ This degree of medication use creates an increased potential for drug-drug interactions (DDIs). Injury due to a known DDI is a preventable adverse drug event and constitutes a serious medication error.^{2,3} Evidence suggests that hundreds of millions of interacting drugs are co-prescribed and consumed each year, ultimately exposing millions of patients to these known hazards.^{4,5} One study reported an increased risk for drug toxicity-related hospitalizations among elderly residents treated with interacting drugs the previous week.⁶ In addition, a survey of 3,005 community-residing older adults found that 4% of individuals were potentially at risk for a major DDI.⁷ In 2010, 7.3% of Medicare Part D enrollees were exposed to a small subset of known and potentially clinically significant DDIs.⁸ Although the exact magnitude of harm associated with DDIs is not known, interactions do occur, resulting in potentially life-threatening consequences. Electronic prescribing (e-prescribing) and pharmacy information systems include DDI alerts as a form of clinical decision support (CDS) to warn prescribers and pharmacists of potentially harmful medication combinations and, ideally, provide documentation on how to avoid or mitigate the risk of patient harm.^{9,10} Today, every pharmacy and soon every physician's office and healthcare organization will employ some form of health information technology (HIT) that includes DDI alerts. Substantial evidence indicates that the current system of DDI alerts is broken because 1) it lacks a standard process for evaluating DDI evidence; 2) it is overinclusive of nonclinically meaningful interaction alerts; and 3) it lacks well-designed user interfaces.

Healthcare organizations as well as compendia and drug knowledgebase vendors use varying methods to evaluate and synthesize evidence on drug-drug interactions (DDIs). Inconsistencies in how evidence is evaluated and presented results in excessive alerts that are frequently ignored.

This situation can have a negative effect on usefulness of clinical decision support (CDS) and may result in patients receiving potentially harmful medication combinations. Injury due to a known DDI is a preventable adverse drug event and serious medication error.

This project addresses an important public health issue regarding improving health information technology as a healthcare safety net and will, ultimately, lead to improved medication use and patient safety throughout the nation.

3. Methods

This project was a conference series that was conducted over a period of 3 years. The specific aims, conference plan, and agendas were developed under the direction of three committees formed specifically for this conference series: Planning Committee, Scientific Steering Committee, and Industry Advisory Committee. These committees were established at the time of the project proposal. Each committee member received drafts of the specific aims, agenda, and proposed conference series prior to a teleconference call and provided constructive feedback orally and/or via email. Committee members also suggested names of additional members for each committee. Additionally, committee members received the conference plan to review and provide feedback on prior to submission of the proposal to the funding agency.

Once the project was funded, three expert works groups were created to address the three major foci of the conference series: 1) **evidence** evaluation; 2) **content**; and 3) **usability**. Nineteen individuals with expertise in DDIs, clinical pharmacology, drug information, evidence evaluation, biomedical informatics, and health IT were invited to participate as **Evidence** workgroup members. Members were Richard T. Scheife, Tufts University School of Medicine; Darrell R. Abernethy, Center for Drug Evaluation and Research, Food and Drug Administration; Clarissa Borst, Elsevier Clinical Solutions; Richard Boyce, University of Pittsburgh; Sophie Chung, Epocrates; Susan Comes, Epocrates; John Horn, University of Washington School of Pharmacy; Jeremiah Momper, University of California, San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences; Alissa Rich, Stephen J. Sklar, Medispan Drug Interaction/Allergy Products, Wolters Kluwer Health; Christine D. Sommer, First Databank; Jill Sutton, Truven Health Analytics; Tricia Lee Wilkins, Beacon Community Program, Office of the National Coordinator for Health Information Technology, Department of Health and Human Services; Michael A. Wittie, Office of the Chief Medical Officer, Office of the National Coordinator for Health Information Technology, Department of Health and Human Services; and Samantha K. Wong, Cerner Multum. No invited experts declined to participate; one individual was unable to contribute due to health reasons. Members represented diverse backgrounds, such as academia; journal, compendia, and knowledgebase editors; healthcare organizations; US Food and Drug Administration (FDA); and the US Office of the National Coordinator for Health IT (ONC). A member with recognized leadership skills and experience facilitated the meetings. The group followed a structured consensus-development process that included clarifying issues to be decided; open discussion and debate among all members; iterative aggregation and refinement of ideas leading to proposals that incorporated the best elements of members' ideas while addressing all key concerns; and active agreement on the final proposal. To ensure that the most pressing issues were addressed, a nonsystematic search of the literature was conducted for papers describing methods for evaluating DDI evidence. From these articles, the following key questions were then developed by the conference organizers and reviewed and agreed upon by consensus of the members of the Evidence Workgroup: (1) What is the best approach to evaluate DDI evidence? (2) What evidence is required for a DDI to be applicable to an entire class of drugs? (3) How should a structured evaluation process be vetted and validated?

Twenty individuals with expertise in DDIs, clinical pharmacology, CDS, and establishing healthcare quality initiatives were invited and agreed to participate in the **Content** Workgroup. Members were Hugh Tilson, University of North Carolina Gillings School of Global Public Health; David W. Bates, Harvard Medical School; Joseph Hanlon, University of Pittsburgh and Pittsburgh VAHS; Philip D. Hansten, Emeritus, University of Washington School of Pharmacy; Amy L. Helwig, HHS Office of the National Coordinator for Health Information Technology; Stefanie Higby-Baker, Cerner Multum; Shiew-Mei Huang, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration; David R. Hunt, Office of Health Information Technology Adoption, HHS Office of the National Coordinator for Health Information Technology; Marianne le Comte, Drug Information Centre, Royal Dutch Association for the Advancement of Pharmacy (KNMP); Karl Matuszewski, Clinical Editorial First Databank; Gerald McEvoy, American Society of Health-System Pharmacists; Anthony Perre, Cancer Treatment Centers of America; Lynn Pezzullo, Pharmacy Quality Alliance; John Poikonen, MedVentive; Kathleen Vieson, Elsevier Clinical Solutions; Michael A. Wittie, Office of the Chief Medical Officer, Office of the National Coordinator for Health Information Technology, Department of Health and Human Services; and David Weinstein, Lexicomp Inc., Wolters-Kluwer Health. Members represented diverse backgrounds, such as academia, drug knowledgebase vendors, drug information compendia vendors, clinicians, professional societies, the Office of the National Coordinator for Health IT (ONC), and the US Food and Drug Administration (FDA). A member with recognized leadership skills and experience facilitated the meetings. The following key questions were developed by the conference organizers and then reviewed and agreed upon by consensus of the members of the Content Workgroup: (1) What process should be used to develop and maintain a standard set of DDIs? (2) What information should be included in a knowledgebase of standard DDIs? (3) Can/should a list of contraindicated drug pairs be established? and (4) How can DDI alerts be more intelligently filtered?

The **Usability** workgroup consisted of 24 individuals representing clinical, informatics, and computer interface design experts with diverse backgrounds, including academia, health IT (EHR and drug knowledgebase) vendors, healthcare organizations, practicing clinicians, and the Office of the National Coordinator for Health IT (ONC). Members were Thomas H. Payne, University of Washington; Bruce W. Chaffee, The University of Michigan Health System; Raymond C. Chan, Sentara; Brian Galbreth, PeaceHealth Southwest Medical Center; Peter A. Glassman, Internal Medicine, Department of Veterans Affairs (VA), Greater Los Angeles Healthcare System; Christian Hartman, Pharmacy OneSource; Seth Hartman, Oregon Health & Science University; Joan Kapusnik-Uner, FDB (First Databank, Inc.); Gilad J. Kuperman, New York-Presbyterian Hospital; Gordon Mann, Epic; Shobha Phansalkar, Lexicomp/Medi-Span/Facts & Comparisons; Alissa Russ, Roudebush VA Medical Center; Chris Steiner, Gold Standard Drug Databases/Editorial Systems; Howard Strasberg, Wolters Kluwer Health – Clinical Solutions; Amanda Sullins, Cerner Corporation; Vicki Tamis, PeaceHealth Southwest Medical Center; Heleen van der Sijs, Erasmus Medical Center, Rotterdam; and Michael A. Wittie, Office of the Chief Medical Officer, Office of the National Coordinator for Health Information Technology, Department of Health and Human Services. A member with recognized leadership skills and experience facilitated the meetings. The following key questions were developed by the conference organizers and then reviewed and agreed upon by consensus of the members of the Usability Workgroup: (1) What, how, where, and when do we display DDI decision support? (2) Should presentation of DDI decision support vary by clinicians? and (3) How should effectiveness of DDI decision support be measured?

Workgroup members were provided access to articles that were deemed relevant for consideration. They also identified relevant studies, and copies were obtained for all workgroup members to review. Each key question was evaluated in light of the available evidence and the collective experience of the workgroup members. Responses to each key question were written and then modified to improve clarity or address issues or concerns. Workgroup recommendations were posted on a project internet site, and feedback was sought from other stakeholders via dissemination to professional societies and organizations. Consensus was achieved through an iterative process of drafting recommendations, collecting verbal or written comments from workgroup members and other content experts, and revising documents until no additional substantive comments were provided. Workgroup recommendations were presented at regional and national forums to solicit feedback from stakeholders such as healthcare providers, compendia and knowledgebase editors, professional and quality organizations, and government agencies. Members of the workgroup were informed of feedback during the regularly scheduled webinar meetings. No substantial changes were made to the recommendations based on comments and questions collected during this vetting process. Changes to the recommendations were editorial in nature to improve clarity.

The conference series held monthly webinar meetings for each workgroup from January 2013 through February 2014, including an invitational solution-oriented working meeting held at the United States Pharmacopeia Convention Headquarters in Rockville, MD, in May 2013 with 48 participants, including speakers. A subset of all experts participated in a smaller in-person working meeting held in Phoenix, AZ, in September 2013 with 22 attendees. The results of the expert processes were presented at four national meetings (Human Factors and Ergonomics Society conference, American Medical Informatics Association, American Society of Health-Systems Pharmacists midyear clinical meeting, and American Pharmacists Association annual meeting) open to a broader group of stakeholders.

A multipronged approach was utilized for dissemination and feedback. First, materials were posted for public comment on a University of Arizona website. Notice of proposed guidelines was also disseminated using a network of professional organizations and contacts identified by members of the workgroups. Second, the proposed guidelines and best practices were presented at four national meetings: a Human Factors and Ergonomics Society conference (March 2014), a pre-meeting symposia at the American Medical Informatics Association meeting (November 2014), the American Society of Health-System Pharmacy midyear clinical meeting (December 2014), and the American Pharmacists Association annual meeting (March 2015). Presenting the results of expert workgroups at these meetings leveraged the large numbers of attendees with specific interest in the content of the guidelines and engaging relevant stakeholders. Participants of the national meetings represented stakeholders, including 1) individual healthcare providers; 2) those responsible for salient policy and guidelines, standards, payment, regulation, and accreditation; 3) organizations responsible for delivering care; and 4) industry, such as developers of DDI compendia, knowledgebases, and CDS systems. Third, we partnered with the Pharmacy Quality Alliance (PQA) to inform an extensive stakeholder community about the proposed guidelines and how to comment on these documents. The partnership with PQA was important because of the role it plays in establishing medication-related standards and measures. PQA turns to its member organizations for subject matter experts and uses a similar process to achieve consensus. In addition to the above activities, consumers and other constituents had the opportunity to view and download the proposed guidelines and best practices and to submit comments via the web-based forum hosted by the University of Arizona. Received comments were reviewed by workgroups and integrated into revised guidelines and standards.

The work products of the conference series generated papers by each of the three workgroups: Evidence Workgroup, Content Workgroup, and Usability Workgroup. The Evidence Workgroup focused on developing guidelines for rigorous, balanced, and transparent assessment of DDI evidence. This workgroup considered evidence-based approaches used by other evidence assessment entities, such as AHRQ's Evidence-based Practices Centers (EPCs) and the Cochrane Collaboration.

The Content Workgroup focused on principles for including DDIs in drug safety alerts. This workgroup focused on developing guidelines and criteria for creating and maintaining a "common" set of DDIs that warrant DDI alerts for prescribers, pharmacists, or other healthcare providers. In contrast to the ONC initiative to develop a list of critical interactions, this workgroup established principles for inclusion of DDIs in CDS systems as well as how a common set of DDIs should be maintained. They also established the minimum data elements needed to effectively communicate DDI alerts (e.g., mechanism of action, management strategies, references, source for additional information, strength of evidence, patient risk factors, mitigating factors, etc.) and how alerts can be more intelligently filtered. Furthermore, the group considered the role of "use-case" scenarios, site- and healthcare provider-specific tailoring of alerts, and the need for documentation when clinicians "override" an alert.

The Usability Workgroup consisted of experts who established preferred strategies for presenting DDIs to end users, including such attributes as color, font size, screen placement, methods to differentiate types of alerts, and other human-computer interface issues. The group discussed how the classification of DDIs (e.g., with tiered alerts) should be communicated to end users.

4. Results

The recommendations for each workgroup are summarized briefly below.

Evidence Workgroup

The Evidence Workgroup examined issues surrounding the evaluation of drug-drug interaction evidence. The results are presented in the following order: 1) recommendations about terminology; 2) best approaches for evaluating DDI evidence (Key Question 1); 3) recommendations for evidence of drug-class interactions (Key Question 2); and 4) procedures to validate a structured process for DDI evidence evaluation (Key Question 3). Recommendations from the Evidence Workgroup were published in the journal *Drug Safety*.¹¹

Terminology

It was recommended that consistent use of relevant terminology for evaluation of DDI evidence be maintained. In the process of answering the key questions, several terms required clarification. A complete list of definitions agreed upon by the workgroup was published in supplemental materials in the journal *Drug Safety*.¹¹

Key Question 1: What is the Best Approach to Evaluate DDI Evidence?

A critical first step in evaluating DDIs is to determine if sufficient evidence that a DDI exists. The panel identify only one instrument, the Drug Interaction Probability Scale (DIPS),¹² to be developed specifically to evaluate individual case reports for DDIs. This 10-item scale assesses causality of an adverse event due to a DDI. The workgroup also identified two systematic approaches to evaluate the totality of drug interaction evidence.^{13, 14} One approach

was involved in creating a DDI knowledgebase called the Swedish and Finnish computerized CDS systems (SFINX).¹³ That approach categorizes level of documentation (0–4) and clinical relevance (A–D). The second approach described in the literature was a systematic assessment of DDIs for CDS systems in The Netherlands.¹⁴ That method uses four core parameters: 1) evidence supporting the interaction; 2) clinical relevance of the potential adverse reaction; 3) risk factors related to patient, drug, or disease characteristics; and 4) incidence of the adverse reaction. Given limitations of the available tools, the workgroup decided that a new assessment instrument was needed to objectively evaluate a body of evidence to establish the existence of a DDI.

The workgroup created a new tool, referred to as the DRug Interaction eVidence Evaluation (DRIVE) instrument, designed to (1) use simple evidence categories; (2) include causality assessment with DDI case reports (via DIPS); (3) apply reasonable extrapolation, including from *in vitro* studies; (4) address evidence/statements provided in product labeling; and (5) describe study quality criteria and interpretation in the context of DDIs. The overall purpose was to promote greater consistency and transparency when evaluating a body of evidence concerning a potential DDI.

The workgroup also considered the issue of clinical relevance of potential interactions. The magnitude of harm, frequency, and factors that may modify the risk were considered to be important attributes. Exposure to a clinically relevant DDI might warrant a change in therapy, increased monitoring, and/or patient education.

It was recommended that studies be conducted to help provide estimates of the frequency (incidence) of adverse outcomes from DDIs. Furthermore, a thorough evidence evaluation of DDI literature should include suggested approaches to minimize or eliminate harm (e.g., dosage adjustment, monitoring strategies, and therapeutic alternatives). The workgroup also recommended that modifying factors be considered when evaluating and reporting DDI evidence. These factors could include dose, duration, route of administration, order of administration, timing of dose, and co-medications. Other modifying factors may be patient related. CDS support algorithms may be developed based on modifying factors to reduce or eliminate alerts that are not relevant. Furthermore, CDS rules could also be constructed to request additional information to assess risk.

Key Question 2: What evidence is required for a DDI to be applicable to an entire class of medications?

The second key question considered by the Evidence Workgroup was how much evidence is needed to determine if a “class” effect exists with respect to a potential DDI. Nuisance alerts maybe generated when a class effect is inferred but not actually present. Understanding the mechanism of interaction and/or metabolic pathways can be crucial to determining whether there is basis for a class effect. The workgroup recognized that the magnitude of effect can vary considerably across medications in the same class. Thus, it was concluded that it is often necessary to consider each medication in the class separately.

To reduce the volume of irrelevant alerts, the workgroup recommended that DDIs should be class based only when the evidence (or reasonable extrapolation) applies to the entire pharmacological class of drugs.

Key Question 3: How should a structured evaluation process be vetted and validated?

Key Question 1 recommended use of a new instrument as a standard to evaluate DDI evidence. However, the workgroup recognized that any new DDI evidence evaluation instrument should undergo a validation. Therefore, it was recommended that an evaluation of the DRIVE tool be

conducted to determine if the instrument is easy to use and produces results that are generally concordant with other DDI evidence rating systems.

Content Workgroup

The Content Workgroup focused on issues concerning identifying and maintaining a standard list of medication interactions that should be included in CDS, recommendations concerning use of terminology, and issues related to making CDS notifications and alerts more specific. The specific questions addressed by the Content Workgroup were as follows: 1) What process should be used to develop and maintain a standard set of DDIs; 2) What information should be included in a knowledgebase of standard DDIs; and 3) Can/should a list of contraindicated drug pairs be established? A brief summary of findings from the Content Workgroup is presented below. Recommendations from the Content Workgroup have been accepted for publication in the *American Journal of Health-Systems Pharmacy*.¹⁵

Key Question 1: What process should be used to develop and maintain a standard set of DDIs?

A key component of improving the relevance of DDIs is identifying DDIs warranting notification of prescribers and other health professionals about potential harm. Due to a dynamic marketplace and evolving clinical knowledge, it is necessary to create an ongoing process to ensure that a standard set of DDIs involved in CDS is regularly updated. The Content Workgroup recommended the formation of a national consensus panel of experts to create and maintain a standard set of clinically relevant DDIs for CDS systems. The workgroup also recommended that a centralized organizer or convener with full-time staff convene the panel and disseminate the panel's findings. It was also recommended a standard set of DDIs for use in CDS should be created and maintained.

The workgroup also recommended a systematic process for assembling DDI evidence, similar to approaches used for systematic reviews and practice guideline development.¹⁶⁻²¹ A major challenge is defining the hierarchy of graded risk management recommendations. The panel acknowledged that it will be important to present risk management recommendations in a manner applicable to a wide range of users. It was also recommended that a process be established to gather input from various constituencies about the classification of DDIs and suggestions for additions or deletions from the nationally maintained list of DDIs

Key Question 2: What information should be included in a knowledgebase of standard DDIs?

The workgroup identified the following items that should be included in drug knowledgebases that include DDIs: (1) classification of seriousness; (2) clinical consequences; (3) frequency of harm and exposure; (4) modifying factors; (5) interaction mechanism; (6) recommended action (with strength of recommendations); and (7) evidence (with quality ratings). These are briefly discussed below.

Information on the criteria used to classify drug pairs should be readily accessible. The workgroup recommended that use of the term, "seriousness," defined as the extent to which an adverse reaction can or does cause harm,²² instead of the more common references to severity. Severity is more ambiguous and describes the intensity of an adverse reaction in an individual.

Another recommendation was that decision support systems should use no more than three categories of seriousness in order to simplify and increase the consistency of these classification systems. Alerts should also include the potential adverse clinical consequences for

the patient as a result of co-prescribing the interacting drugs. When available, the frequency or incidence of adverse outcomes associated with a specific DDI should be stated in numbers (e.g., 1/1,000). Risk factors that may decrease or increase the risk of harm associated with a DDI should be included when possible.

The workgroup recommended that clinically relevant information regarding interaction mechanisms be included with the standard set of DDIs. This information may be useful to assess patient risk and identify reasonable therapeutic alternatives. To maximize the potential of the CDS, it was recommended that systems provide actionable recommendations to mitigate or avoid the potential for harm. DDI alerts should also indicate the quality of evidence (with definitions), summarize the evidence briefly, and provide access to references from the primary literature when possible.

Key Question 3: Can/should a list of contraindicated drug pairs be established?

The workgroup noted that there has been inconsistent use of the term “contraindicated” with respect to DDIs. The phrase of “contraindicated” DDIs should be reserved to indicate no situations have been identified in which the benefit of the combination outweighs the risk.¹⁰ It was recommended that the classification of an interaction as “contraindicated” should be done judiciously.

Key Question 4: How can DDI alerts be more intelligently filtered?

Members of the workgroup all concurred that there is lack of evidence on what approaches should be used when trying to filter alerts to improve adherence to the most relevant notifications. Given this situation, it was recommended that healthcare organizations use an interprofessional committee to review frequently overridden alerts and suggest safe and effective ways reduce alert burden and increase relevance. It was also recommended that individual users be able to provide feedback to the committee.

As CDS systems become more sophisticated, the workgroup recommended that developers should take context into account when designing alerts. However, the workgroup did not support indiscriminately “turning off” alerts and recommend that modifications to DDI alerts be done cautiously. Furthermore, suggesting strategies to actively monitor for signs of harm for patients on concomitant therapies that may result in a DDI should be incorporated into CDS systems.

Usability Workgroup

The Usability Workgroup examined issues related to 1) what, how, where, and when do we display DDI decision support; and 2) should presentation of DDI decision support vary by clinician roles. Recommendations from the Usability Workgroup were published in the *Journal of the American Medical Informatics Association*.²³

Key Question 1: What, how, where, and when do we display DDI decision support?

The Usability Workgroup considered research from human factors engineering that indicates that visibility, color, and prioritization influence a clinician’s response to safety warnings.²⁴ However, the workgroup could identify few studies that have focused on designing drug-related warnings.²⁵ Software vendors display alerts using inconsistent presentation styles, which may lead to confusion by clinicians who often work with multiple systems. It therefore was recommended that computer systems use greater uniformity and consistency for DDI alerts.

The workgroup also considered what information to include in DDI alerts. Using data from the safety literature, it was recommended to include the following: (1) a *signal word* indicating the

seriousness of the DDI; (2) *hazard* information (e.g., clearly denoting the potentially harmful drug combination); (3) *instructions* or actions on how to reduce risk of injury; and (4) specific clinical *consequences* that may ensue if the hazard is not averted.^{24, 26} The workgroup also recommended seven components be integrated into alerting systems for DDI warnings including: (1) *drugs involved*, (2) *seriousness*, (3) *clinical consequences*, (4) *mechanism of the interaction*, (5) *contextual information/modifying factors*, (6) *recommended action(s)*, and (7) *evidence*. These issues are briefly discussed below.

The interacting drug pair(s) should be clearly identified, and there should be consistent terms and definitions to indicate the potential seriousness of the DDI. The potential adverse clinical outcome(s) for the patient taking interacting drugs should be clearly described to permit clinicians to balance the risks and benefits. The alert should describe the mechanism of the DDI, when known, allowing the clinician to gain understanding of the problem and to identify potential therapeutic alternatives. The adjudication of DDI alerts should be based on an assessment of patient-specific factors, such as age; predisposing diseases; pharmacogenomic phenotype; and the specific drug regimen(s), such as dose, route, duration of therapy, sequence of initiating co-therapy, and timing of co-administration.¹⁰ This information should be included in the alerting logic or presented within the alert display. The workgroup also recommended that, when presenting DDI alerts, it is important to provide guidance on strategies to mitigate potential harm.^{10, 27, 28} CDS systems should present multiple suggestions when appropriate to take into account a range of contextual situations in which medications may be used safely and otherwise. The final component that was recommended to be included into notifications regarding DDIs is the strength and source of the evidence.

The workgroup also recommended reserving interruptive alerts (i.e., those requiring action by clinicians before proceeding) for the most serious DDIs. It was not recommended that institutions eliminate or completely turn off clinically relevant alerts; instead, alerts could be diverted from interruptive to noninterruptive form with on-demand access.

The Usability Workgroup also considered physical factors on how to present DDI alerts, including the consistent use of color and visual cues, consistent use of terminology and phrases, and use of limited text and larger font size to enhance recognition and readability.

Clinicians' abilities to understand and respond to DDI alerts are influenced by information presented.²⁹⁻³¹ Recognizing that there is an inherent trade-off between providing too many details that risk overwhelming the clinician and too few details that fail to communicate the potential seriousness or the actions to be taken, the workgroup believes that the most critical information should be presented with linked information accessible on demand concerning background and secondary considerations. It was also recommended that further research with formal testing occur to determine the essential components for primary dialog box and the secondary components. Prototypes should include all seven recommended alert components, with the objective of unambiguous and intuitive design.

The Usability Workgroup evaluated when alerts should be presented, and it was decided that DDI alert information should be displayed at the point of decision making and that resolving alerts should be facilitated via on-screen operations. Clinicians should be able to select from a list of actionable choices when presented with a DDI alert. In general, there should be as few steps (e.g., keystrokes, mouse clicks, scrolling, window changes) as possible to resolve the potential alert.

CDS systems may require override reasons to be provided by clinicians to permit the ordering of medications that may interact. It was recommended that evaluation of DDI alerts be conducted based on a Bayesian framework to help system designers identify false-positive and false-negative alerts.

Key Question 2: Should presentation of DDI decision support vary by clinician roles?

The workgroup considered that DDI alerts are commonly presented in the context of healthcare being delivered, where multiple professionals may be alerted. For nonprescribing clinicians, DDI alerts may be deployed as a second check to help ensure that patients receiving interacting drug pairs are being monitored or assessed. Patient care and safety are best achieved when all members of the team have knowledge of what other members are doing.³² As such, the expert panel advocates for a team approach to managing DDIs.

Furthermore, it was recommended that general alert content be consistent among clinicians (e.g., physicians, pharmacists, nurses, etc.). What may differ, however, is *how* the information is presented to specific professionals. The message may be changed based on the context or functions, recognizing that professionals in different settings have different roles, responsibilities, and privileges.

Another important question that was considered is whether an alert display should change if an individual clinician has been exposed many times to an alert, yet there is no detectable behavior change. The workgroup experts were not aware of evidence that demonstrates that it is safe to eliminate DDI alerts for specialists. As a consequence, it was recommended that CDS system architecture allow institutions to easily make these changes based on clinician characteristics.

Key Question 3: How should effectiveness of DDI decision support be measured?

The final key question addressed by the Usability Workgroup concerned the issue of measuring the effectiveness of DDI alerting systems. It was noted that effectiveness of CDS can be defined as a product of both *measured* value as well as *perceived* value, because components of value include, but are not limited to, clinical outcomes, process efficiency measures, clinician satisfaction, heuristics, evidence, usability, and cost of ADEs. Alert override rates are not sufficient to determine effectiveness unless the actions were discreetly captured with the alert. Generally speaking, as alert effectiveness increases, alert value increases; thus, alert fatigue may decrease.

It was also noted that override rates alone cannot be used to assess the effectiveness of alerts, because alerts in and of themselves don't capture the thought process of clinicians and subsequent actions by current systems. Override rates provide a crude estimate of alert adherence. In the near term, override rates should be used to identify alerts that require a detailed evaluation process, including the incorporation of clinician feedback.

In the long term, the workgroup proposed that a professional group or trusted agency be established to standardize collection and analysis of DDI decision support/alert data. The creation of a central repository for submitting de-identified DDI alert data was recommended to permit continuous quality improvement to optimize the value of individual alerts. Aggregating de-identified alert data with override rates, patient predisposing factors, and actions taken could maximize the power of data and establish CDS feedback loops to knowledgebase and EHR vendors and healthcare organizations.

5. Conclusions

All workgroups emphasized that additional studies are needed to measure the impact of these suggested DDI alert recommendations and the next generation of DDI decision support. Additional research will be critical to evaluate the most effective DDI alert content and design. Evaluating outcomes (actual occurrence or avoidance of ADEs), and not just DDI override rates, is of high importance. Below is a table of additional research recommendations to determine the most effective methods to reduce alert fatigue and ultimately improve patient safety (Table 1). These recommendations focus on DDI alerts but may serve as a template for other types of drug safety alerts. Improving CDS systems is an iterative process, as knowledge about best practices for DDI alert design is dynamic and will evolve as systems become more sophisticated.

Table 1. Areas for Future Research to Improve DDI Decision Support

Area of Research	Description/Example
Alert Components	<ul style="list-style-type: none"> Identify essential information components to maximize DDI alert comprehension
Terminology	<ul style="list-style-type: none"> Most appropriate words, phrases, and definitions for DDI alert Most appropriate terms and definitions to indicate the potential seriousness
Information Placement	<ul style="list-style-type: none"> Identify the information that is essential to display on the primary alert interface vs. accessible via an embedded link Best methods to facilitate links to supplemental information or other screens to aid decision making
Contextual Alerting	<ul style="list-style-type: none"> Identification of predisposing risk factors (e.g., large-scale observational research) Optimal use and display of contextual data (e.g., patient age, lab results) to improve DDI alerts³³⁻³⁶
Patient-focused CDS and ADE Surveillance	<ul style="list-style-type: none"> How patients might be involved in DDI ADE surveillance
Noninterruptive CDS	<ul style="list-style-type: none"> How alternative interface designs for CDS tools can be deployed to reduce ADEs associated with DDIs, and under what circumstances they are superior or inferior to interruptive alerts
Decision Making	<ul style="list-style-type: none"> Elucidating the cognitive strategies that clinicians use to make decisions about DDIs
Filtering/Suppressing DDI Alerts	<ul style="list-style-type: none"> Safety and effectiveness of alert filtering and modifications (e.g., dynamic diversion from interruptive to noninterruptive)
Prototype Testing	<ul style="list-style-type: none"> Evaluation of prototypes incorporating these recommendations to determine what works best, including different settings, clinician types, and clinical contexts

ADE = adverse drug event; CDS = clinical decision support; DDI = drug-drug interaction

6. Significance

The project deliverables, specifically the workgroup white papers and accompanying recommendations, webinars, and meetings/conference proceedings, have the potential to provide meaningful improvement to DDI CDS and thereby reduce alert fatigue, improve workflow, reduce medication errors, and improve patient safety. The recommendations of the three workgroups can serve as guiding principles for (a) establishing a transparent and systematic process for evidence evaluation; (b) employing consistent terminology used by knowledgebase and e-prescribing vendors; (c) providing adequate and appropriate evidence to substantiate alerts; (d) selecting efficient and effective presentation of alert content; and (e) enhancing end-user experience by decreasing unnecessary workflow interruptions. A project website created by the University of Arizona team is the dissemination tool for providing information to advisory committees, facilitators, and workgroup members. The project website (<https://sites.google.com/site/ddiconferenceseriessite/home>) has provided a convenient forum for establishing, organizing, providing continuity, and promoting efficiency among groups of individuals working together, especially those who are geographically dispersed.

7. Implications

In summary, this conference series generated recommendations for incorporating DDI into CDS in a manner that will hopefully improve provider (e.g., physicians, nurse practitioners, pharmacists, etc.) recognition of harmful alerts and thereby improve patient safety.

8. List of Publications and Products

Tilson H, Hines LE, McEvoy G, Weinstein DM, Hansten PH, Matuszewski K, le Comte M, Higby-Baker S, Hanlon JT, Pezzullo L, Vieson K, Helwig AL, Huang S, Perre A, Bates DW, Poikonen J, Wittie MA, Grizzle AJ, Brown ML, Malone DC. Recommendations for Selecting Drug-Drug Interactions for Clinical Decision Support (accepted)

Payne TH, Hines LE, Chan RC, Hartman S, Kapusnik-Uner J, Russ AL, Chaffee BW, Hartman C, Tamis V, Galbreath B, Glassman PA, Phansalkar S, van der Sijs H, Gephart S, Mann G, Strasburg HR, Grizzle AJ, Brown M, Kuperman G, Steiner C, Sullins A, Ryan H, Wittie MA, Malone DC. Recommendations to improve usability of drug-drug interaction clinical decision support alerts. *Journal of the American Medical Informatics Association* 2015 Mar 30: pii: ocv011. doi: 10.1093/jamia/ocv011. [Epub ahead of print]

Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, Abernathy DR, Horn JR, Sklar SJ, Wong SK, Jones G, Brown ML, Grizzle AJ, Comes S, Wilkins TL, Borst C, Wittie MA, Malone DC. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. *Drug Safety* 2015; 38:197-206.

Products: website <https://sites.google.com/site/ddiconferenceseriessite/>

Priority Populations

Older individuals are vulnerable to DDIs because of age-related physiologic changes, an increased risk for disease, and the consequent increase in medication use.³⁷ Therefore, the elderly are the primary population for this conference series. Of particular interest are low-income elderly individuals, who typically have less access to care and/or coordination of care and who are more likely to represent a vulnerable population. Women are another priority population affected by DDIs; women are at greater risk for adverse interactions for physiologic reasons (e.g., increased risk QTc prolongation, smaller body mass)^{38, 39} and because

women are historically less likely to be represented in clinical trials yet tend to take more medications than men.^{40, 41} Furthermore, patients with an increased burden of disease (e.g., pediatric patients with chronic illnesses,⁴² African Americans with hypertension,⁴³ patients with HIV/AIDS,⁴⁴ and cancer patients⁴⁵) are more likely to experience DDIs and are indirectly addressed in this conference.

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