💬 A Minimum Information Model for Representing Potential Drug-Drug Interaction Knowledge and Evidence - Introduction, User Scenarios, Use Cases, and Scope of Knowledge Representation

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ABSTRACT

TODO -

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This Note was produced by the [Semantic Web in Health Care and Life Sciences Interest Group](part of the Data Activity) to build a meta-data standard for potential drug-drug interactions (PDDI) that can meet the information needs of pharmacists working in different care settings. The (archived) public mailing list public-semweb-lifesci@w3.org (see instructions) is preferred for discussion of this document. As of the time of publication no further work on this document is scheduled; however, submitted comments will be retained for future consideration.

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INTRODUCTION

Ensuring medication therapy occurs safely and to the maximum benefit of any given patient is of great interest to clinicians (Institute of Medicine 2007). One possible threat to patient safety comes from exposure to two or more drugs that are known to interact (i.e., potential drug-drug interactions or PDDIs) drug-drug interaction) While some PDDIs can benefit patients (e.g., by reducing the dose required for an expensive drug), PDDIs are more often a patient safety concern. Clinically important events that are attributable to PDDI exposure occur in 5.3% - 14.3% of inpatients, and are responsible for up to 231,000 emergency department visits that occur each year in the United States alone (Magro et al. 2012; CDC 2012). A recent systematic review and meta-analysis of 13 studies conducted on 3 continents found the median rate of PDDI associated hospital admissions to be 22.2% (interquartile range 16.6 - 36.0%)(Dechanont et al. 2014). The broad concern about harm from PDDIs is reflected in the fact that PDDI alerting is a criteria included in the so-called Meaningful Use criteria for Electronic Health Records (CMS 2013; Ridgley et al. 2012), and population-based strategies for tracking exposure are promoted by organizations such as the Pharmacy Quality Alliance (National Quality Measures Clearinghouse 2015).

Clinicians want to be effective at appropriately managing or avoiding PDDI exposure (Nabovati et al. 2017). However, they often face barriers to these goals such as incomplete personal PDDI knowledge and PDDI alerts with poor specificity (Abarca et al. 2004; Van der Sijs et al. 2006). An awareness of the need for PDDI decision support prompts clinicians to use various drug knowledge resources. However, poor specificity leads clinicians to be overwhelmed by PDDI information that is "difficult to retrieve, sort and digest into clinical decision making" (Bottiger et al. 2009). PDDI alerts are attributed to 'over-alerting' to such a degree that it often obfuscates the most important information, hinders the usability of the decision support system, and leads to clinician dissatisfaction (Böttiger, Ylva, et al. 2009; Payne et al. 2015). Moreover, while many sources of PDDI evidence exist to help improve prescriber knowledge, they are not concordant in their coverage, accuracy, and agreement (Wang et al. 2010; Saverno et al. 2011; Ayvaz et al. 2015; Fung et al. 2017).

Events that have led to the concept of a PDDI minimum information model

New information regarding PDDIs is published every day in primary sources such as drug product labeling and the scientific literature. Food and drug regulatory agencies in the United States, European Union, and Japan have issued guidances to industry which recommend to drug developers that they communicate each marketed drug's potential for involvement in drug interactions to clinicians through drug product labeling (Rekić et al. 2017). A PubMed search for publications indexed with the Medical Subject Headings keyword "Drug interactions" shows an average of 3,970 publications per year from 2000 to 2016. This means that the body of evidence about the PDDIs and the clinical implications of PDDI exposure is overwhelming and dynamic.

Drug information compendia organize and synthesize evidence from primary sources into summaries that are presented to clinicians as computerized decision support (CDS) alerts. Alternatively, Summaries can be made available to clinicians through various drug information products. Regardless of the source, PDDI information systems are carefully built, with drug information that is maintained by panels of experts who understand drugs and the clinical implications of drug interactions. However, there are currently no broadly accepted standards to guide these experts in the organization and presentation of PDDI information that would be most effective for CDS. This issue was one of the topics addressed at two recent conference series funded by the United States Agency for Healthcare Research and Quality (AHRQ) (Hines et al. 2011; Scheife et al. 2015). Attendees at both conference series included key stakeholders from organizations that provide drug information for use in clinical settings. Among the key recommendations was the following suggested set of core information that should be included for every PDDI mentioned in a clinically-oriented drug information resource (Payne et al. 2015):

1. *Drugs Involved*

2. *Clinical consequences*
3. *Frequency of exposure to the PDDI*
4. *Frequency of harm for persons who have been exposed to the PDDI*
5. *Contextual information/modifying factors*
6. *Evidence*
7. *Mechanism of the interaction*
8. *Recommended actions*
9. *Seriousness rating*

This suggested list of core information elements includes some that are present in one or more of the 15 PDDI conceptual models analyzed in a recent comprehensive review by Herrero-Zazo, Segura-Bedmar, and Martínez (Herrero-Zazo et al. 2016). However, no single conceptual model covers all 9 of the information elements, and there is little commonality across the conceptual models on those elements that are included. For example, the mechanism of the interaction and clinical consequences were present in multiple models but at different levels of granularity. Other information elements, such as frequency of exposure or frequency of harm are not present in any of the 15 sources. Even PDDI knowledge bases that are strongly clinically-oriented (as opposed to knowledge bases oriented toward use in bioinformatics or drug development) were considerably different in the information elements they used. For example, the NDF-RT (Olvey et al. 2010) was detailed about pharmacokinetic mechanisms but had no information on clinical consequences. In contrast, the system reported by Mille, Degoulet, and Jaulent (Mille et al. 2007) provided details on the clinical consequence, including risk increasing and mitigating factors, but supplied only a limited structure for mechanism.

The recommended core information elements are based on consensus from a wide range of clinical, academic, and commercial stakeholders. It is important to translate them into a new standard for representing and sharing PDDI knowledge and evidence as information artifacts -- what we refer to from here forward as a PDDI minimum information model. Such a standard will be an important contribution to medication safety by:

1) Clarifying the information that is necessary for effective PDDI decision support that satisfies what is known as the Five Rights of CDS -- the right information, communicated to the right person, using the right intervention format, delivered through the right channel, at the right time in the clinical workflow (Osheroff 2005); and

2) Highlighting for the clinical research community gaps that exist in the clinically useful evidence available for developing effective PDDI decision support.

These two potential contributions are discussed further in the next two sections.

The minimum information model will help PDDI decision support satisfy the Five Rights of CDS

Many drug information systems that include PDDIs, whether proprietary or free, organize the information into a more or less narrative format which does not easily translate to effective CDS. To illustrate, consider the PDDI between oral anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDs) reported in the well-curated French *Interactions médicamenteuses* PDDI dataset (ANSM 2016):

	Original French	**English translation**
Drugs involved	*anti-inflammatoires non stéroïdiens*: aceclofenac, acide mefenamique, acide niflumique, acide tiaprofenique, alminoprofene, celecoxib, dexketoprofene trometamol, diclofenac, etodolac, étoricoxib, fenoprofene, flurbiprofene, ibuprofene, indometacine, ketoprofene, meloxicam, morniflumate, nabumetone, naproxene, nimesulide, parecoxib, piroxicam, piroxicambetadex, rofecoxib, sulindac, tenoxicam, valdecoxib *anticoagulants oraux*: acenocoumarol, apixaban, dabigatran, fluindione, phenindione, rivaroxaban, warfarine	*Nonsteroidal antiinflammatory drugs*: aceclofenac, mefenamic acid, niflumic acid, tiaprofenic acid, alminoprofen, celecoxib, dexketoprofen trometamol, diclofenac, etodolac, etoricoxib, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, morniflumate, nabumetone, naproxen, nimesulide, parecoxib, piroxicam, piroxicambetadex, rofecoxib, sulindac, tenoxicam, valdecoxib *Oral anticoagulants*: acenocoumarol, apixaban, dabigatran, fluindione, phenindione, rivaroxaban, warfarin
Description	Augmentation du risque hémorragique de l'anticoagulant oral (agression de la muqueuse gastroduodénale par les antiinflammatoires non stéroïdiens)	Increase of the oral anticoagulant's risk of hemorrhage (irritation of the gastroduodenal mucosa by the non-steroidal anti-inflammatories)
Management	Association DECONSEILLEE. Si l'association ne peut être évitée,	NOT RECOMMENDED. If administering these substances

	surveillance clinique étroite, voire biologique	together cannot be avoided, strict clinical monitoring, possibly also laboratory tests as well

This PDDI narrative is structured into short and easy-to-read description and management sections. However, much of the recommended minimum information is either not structured or not provided:

- *Drugs Involved* - non-coded lists of ingredients that have been classified as either and NSAID or an oral anticoagulant
- *Clinical consequences* - non-coded mention of 'hemorrhage'
- *Frequency of exposure to the PDDI* - no mention
- *Frequency of harm for persons who have been exposed to the PDDI* - no mention
- *Contextual information/modifying factors* - no mention
- *Evidence* - no mention
- *Mechanism of the interaction* - gastroduodenal irritation by the NSAID
- *Recommended actions* - avoidance if possible, monitoring otherwise
- *Seriousness rating* - not explicit. However, the statement 'not recommended' would indicate a serious clinical consequence

As evident from the listing above, four minimum information items are not provided in the narrative (contextual information, frequency of exposure, frequency of harm, and evidence). Contextual information would include drug and patient factors that might increase or mitigate the risk of harm from exposure to the interaction drug pair. Such information often complements, and sometimes is based on, information on the frequency information items (frequency of exposure to the PDDI and frequency of harm for persons who have been exposed). Together, these information items help to inform the clinician about the risk-benefit tradeoff of PDDI exposure. While not always easy, intelligent CDS that improves patient outcomes can be built using such information. For example, Tamblyn et al. showed that a novel CDS system that provided patient-specific risk estimates of injury due to falls reduced fall-related injury by 1.7 injuries per 1000 patients (95% CI 0.2/1000 to 3.2/1000 p=0.02) (Tamblyn et al. 2012). Conversely, when a PDDI summary provides no context about risk and no frequency information, the only CDS alerts that can be built are those that trigger off of simple exposure to the drug combination. This leads to highly sensitive but poorly specific alerts and is one of the main reasons for alert fatigue (van der Sijs et al. 2006).

Further, the PDDI narrative above cites no evidence for the information that it provides. Attendees at the aforementioned AHRQ conference series concluded that "providing access to the evidence is a critical component of weighing the risks and benefits of co-prescribing drugs that have the potential to result in a drug-drug interaction." (Tilson et al. 2016). The informational bases of PDDIs includes numerous sources including physiological and pharmacological observations from clinical studies; mechanistic knowledge derived from pre-clinical and clinical studies; and observational data including case reports and various non-randomized studies

(Brochhausen et al. 2014). Some evidence may suggest the existence of an interaction, while other evidence can help answer questions about the associated clinical effects and their magnitude, variability, and estimated frequency (Scheife et al. 2015). Regardless, a PDDI representation should provide citations to the specific supporting evidence items and, if appropriate, some acceptable gradation of the total body of evidence (Tilson et al. 2016).

Another issue with the narrative above is that, as written, there would no way to filter the alert based on the drug formulation.
Because the lists of drugs for both classes are non-coded lists of ingredients rather than coded lists https://www.whocc.no/atc/structure_and_principles/). While the management section provides a strong recommendation to avoid the use of the combination if possible, the interaction description notes that the mechanism of the interaction involves gastroduodenal irritation by the NSAID. This implies that the clinical consequence of hemorrhage might be intended to mean gastrointestinal hemorrhage rather than all types. Such an occurrence would seem unlikely to occur for NSAIDs administered topically rather than orally.

Thus, the elements of the minimum information model shows that, in spite of the readability of the PDDI narrative, it might not be effective if used for a decision support alert. This is both because the narrative is missing important information, and lacks the semantics and structuring that would help decision support designers target alerts to the patients that are most likely to experience harm. Problems like these are not unique to the French *Interactions médicamenteuses*. A search for the same Oral Anticoagulant / NSAID interaction executed at the drug ingredient level in DrugBank returns only a single statement that mentions only vaguely the clinical effect but no other information from the core items mentioned above:

> "Ibuprofen may increase the anticoagulant activities of Warfarin."

As Figure XX. shows, slightly more information is provided in United States drug product labeling but there are still many information gaps relative to the core PDDI information items suggested by AHRQ conference series attendees (Bristol-Myers Squibb 2017).

7.2 Drugs that Increase Bleeding Risk

Examples of drugs known to increase the risk of bleeding are presented in Table 3. Because bleeding risk is increased when these drugs are used concomitantly with warfarin, closely monitor patients receiving any such drug with warfarin.

Table 3: Drugs that Can Increase the Risk of Bleeding

Drug Class	Specific Drugs
Anticoagulants	argatroban, dabigatran, bivalirudin, desirudin, heparin, lepirudin
Antiplatelet Agents	aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine
Nonsteroidal Anti-Inflammatory Agents	celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac

Figure XX. An oral Anticoagulant / NSAID PDDI shown at the drug ingredient level from the United States drug product label for COUMADIN- warfarin sodium tablet (Bristol-Myers Squibb 2017).

While missing information is the primary concern for the DrugBank and drug product label examples, the minimum information model would also provide a benefit for narratives that are abundant with information. For example, the same search in the online interaction checking tool provided by Drugs.com, a prescription drug information website for professionals and consumers, returns a very detailed narrative that also includes mention of clinical effect, mechanism, management options, some contextualized risk information, and specific citations of evidence (Drugs.com search 3/31/17). In this case, the minimum information model would be useful for suggesting how to provide structure and semantics to the description that would allow CDS systems to provide more effective alerts.

The minimum information model will help highlight research gaps that need to be filled to advance effective PDDI decision support

The PDDI knowledge space is heterogeneous with respect to coverage of the core information elements. While the oral Anticoagulant / NSAID PDDI used as an example in the above discussion is very well known, with information readily available across several core categories, this is only rarely the case. Many drug interactions are identified in case reports or observational studies that provide little or no indication of causal mechanisms. Other interactions, especially

pharmacokinetic interactions, are established based on small clinical studies that rarely suggest a clinical consequence. Still other interactions might be inferred from the pharmacodynamic properties of two drugs, leaving unanswered questions about contextual factors that might increase or mitigate patient risks. Moreover, there can exist gaps in knowledge about the risk factors or appropriate management options for a given interaction, even when solid evidence is available for its existence, the mechanism of its occurrence, and the likely clinical consequence from exposure.

This problem would be intractable if not for the fact that clinical research field as a whole is currently undergoing a massive change. New sources of data are becoming available that can be leveraged to generate evidence that fills in gaps in knowledge more rapidly than ever before. These include deeply interlinked longitudinal health-care datasets, web search log data, text mining of social media, and wearable real-time monitoring technology (Beninger 2016; Freifeld et al. 2017; Koutkias et al. 2016; Shang et al. 2014; Cameron et al. 2013; Yang et al. 2015; Harpaz et al. 2016). Large research networks have emerged that bridge multiple health systems and registries to enable innovative approaches to generating evidence to inform clinically actionable knowledge. Projects like the *All of Us Research Program* are seeking to gather health data from more than one million people for the purpose of accelerating research and improve health (https://allofus.nih.gov/). In the United States, the multiple government agencies have come together to form the National Medical Evidence Generation Collaborative ("EvGen Collaborative") with the goal of transforming evidence generation to support health and health care decisions (Califf et al. 2016). One of the initial use cases for EvGen is that of enabling decision support for clinicians:

> "EvGen can provide access to an integrated, comprehensive medical record. Incorporation of evidence-based tools and recommendations into the EHR and associated apps will expedite workflows. The broader access to actionable information supported by EvGen will enable public and private sectors to develop decision support applications that could be used by clinicians and patients to improve decision-making" (FDA 2017)

We think that these developments create potential to help advance PDDI decision support. However, the potential can only be realized if gaps in clinically useful PDDI knowledge are identified, prioritized, and then addressed using the most appropriate data and methods for evidence generation. One way the minimum information model helps to identify knowledge gaps would be to act as an information template for a group of drug experts to use while synthesizing evidence for PDDIs. As the expert panel compiles evidence for each of the core information categories, critical gaps in knowledge would become apparent. These gaps could be prioritized and reported to the clinical research community, which could then make efforts to generate appropriate evidence to fill those gaps.

A Task Force to create the PDDI minimum information model

The prior discussion motivates the need for a PDDI minimum information model. Toward the goal of developing such a model, a volunteer-based task force has been formed by the Health Care and Life Sciences Interest Group, an interest group that operates publicly through the World Wide Web Consortium (W3C). The task force seeks to develop the minimal information model for drug interaction evidence and knowledge that could eventually be adopted by an international health information technology standards organization like HL7. The results of these activities form a foundation from which the task force will create the following artifacts:

- Data Model: A data model (schema) for potential drug interaction knowledge and evidence.
- Vocabulary: A precise vocabulary describing/defining the data model.
- Serializations: One or more serialization formats of the abstract data model such as HL7 FHIR, FHIR RDF, Structured Product Labeling, JSON/JSON-LD.
- Demonstration of a use case: An interactive application that shows how the PDDI minimum information model can support a medication reconciliation.

The remainder of this W3C Interest Group Note explains how the task force has taken a user-centered design approach to designing the minimal information model through three main activities. A sub-team of drug experts on the task force selected more than a dozen PDDIs to represent using the new information model. In parallel, task force members initiated an iterative process that involved end-user stakeholders (i.e., compendia editors, various types of clinicians, and CDS developers), in the creation of user stories and use cases that define the requirements for the minimum information model. Also in parallel, a sub-team of knowledge representation experts developed guidelines for the information model's semantics. The remainder of this Note describes the methods and results of these user-centered design activities. A subsequent Note will provide a detailed account of the minimum information model, vocabulary, serializations, and use case demonstration.

METHODS

Selecting PDDIs to implement using the minimum information model

Prior work by some members of the task force has sought to develop evidence-based clinical algorithms that consider a patient's electronic health record information to provide a clinician with actionable information tailored to the patient's specific context.[1] The algorithms are

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[1] The initial decision trees were developed through the "Individualized Drug Interaction Alerts" AHRQ grant by task force members Dan Malone and John Horn, as well as Phil Hansten (NIH Project:

formulated as decision trees to provide concise information including the interaction description, the purported mechanism and possible effects, the evidence supporting the mechanism and effects along with citations listed in the footnotes. A sample decision tree illustrating the management options can be found in the appendix (see Appendix B).

The task force built on this prior work by selecting PDDIs to demonstrate the new minimum information model and then creating decision trees for each of the PDDIs that they selected. A sub-team of the task force with clinical drug expertise selected the PDDIs. Draft decision trees were presented during sub-team monthly meetings for thorough discussion. Revisions were made iteratively until the group reached consensus on the presented drafts and finalized the decision trees.

Early on, the task force discussed how to select the PDDIs for developing decision trees. One option was to choose the most serious PDDIs. However, it was noted that the seriousness of a PDDI depends a great deal on the patient characteristics context. This meant that it would be difficult to identify PDDIs that were considered the most serious in all clinical settings and for all patients. An alternative approach was to choose PDDIs that would allow the task force to demonstrate how the information model should be used when facing known issues with PDDI evidence and knowledge. Toward that aim, participants were requested to provide suggestions of PDDIs meeting at least one or more of the following criteria:
   A. The interaction could (and should) be contextualized for specific patients or clinical circumstances.
   B. The interaction applies at the class level.
   C. The interaction does not apply at the class level.
   D. The mechanism is known and is pharmacokinetic.
   E. The mechanism is known and is pharmacodynamic.
   F. The mechanism is not known.
   G. The evidence supporting the interaction is strong.
   H. The evidence supporting the interaction is weak.
   I. The frequency of exposure data is available.
   J. The frequency of exposure data is not available.
   K. The frequency of adverse event data is available.
   L. The frequency of adverse event data is not available.
   M. The recommended action is "monitor" or "take note".
   N. The recommended action is "avoid".
   O. The recommended action is "a clear alternative drug and dose".

Workflow for arriving at stories and goals

User stories and goals were developed in order to showcase how the PDDI minimum information model will support users. The task force began developing the Stakeholder Description document and the PDDI Minimum Information Model User Scenarios document in order to identify key users. These stakeholder descriptions and user scenarios were used as the basis for further brainstorming with the assistance of a user experience expert to develop a master list of tasks, users, information needs, information values, and barriers to drug-drug interaction based decision-making in a variety of situations. A core set of user types was selected for development of user stories based on the scope of the minimum information model. These will be presented in the Results section. The user types considered "out of scope" are listed in Appendix C.

In order to develop the user stories for the core user types, the initial information needs list was supplemented with user interviews, interview transcripts collected as a part of recently published manuscript on PDDI information needs of drug information compendia editors (Romagnoli et al. 2017), and the published literature. Where possible, user stories were based on PDDIs suggested by the task force's PDDI experts. All user stories were reviewed during team meetings to solicit feedback and comments. Based on task force member suggestions, the user stories were edited to make them more clinically relevant, accurate and appropriate. Information model items were highlighted based on a color-coded key to indicate the the minimum information model information item in question.

A set of use cases focused on medication reconciliation

Medication reconciliation use cases were recommended by a task force member as a way to highlight the task force information model elements. To obtain background information for the medication reconciliation use cases, a third year PharmD student conducted structured interviews with a hospital pharmacist and with a consultant pharmacist along with an observation of the hospital pharmacist medication reconciliation process. Detailed use cases were drafted based on points raised during the interviews and drug-drug interactions highlighted by the interviewed pharmacists. Where possible, the task force's selected PDDIs were incorporated. Draft use cases were sent to the interviewed pharmacists for feedback and edits, and then presented during a task force meeting involving all participants. Suggestions from this meeting were incorporated into the use cases. As with the user stories mentioned above, in order to tie the medication reconciliation use cases more closely to user-centered definitions, information model items were highlighted based on a color-coded key to indicate the user-centered definition in question. The modified use cases were then sent to members of the task force using a questionnaire custom built using Qualtrics software (www.qualtrics.com). This approach was chosen to allow for additional, anonymous feedback.

Workflow for arriving at user-centered definitions

We used the process shown in Figure XX to arrive at user-centered definitions for the core information items recommended by the prior AHRQ drug interaction conference series. We started with an initial definition of each item based on suggestions by members of the task force and review of the DINTO (Herrero-Zazo et al. 2015) and DIDEO (Brochhausen et al. 2014) ontologies. We then solicited feedback from all task force participants using a Qualtrics survey (see Appendix A). The survey asked participants to rate their level of agreement with the definition and evidence presented using a Likert scale (Strongly agree, Agree, Somewhat agree, Neither agree nor disagree, Somewhat disagree, Disagree, Strongly disagree), followed by questions about how to modify the definition in order to make it more general or specific. Feedback was collected and synthesized, then the proposed definition was modified based on task force recommendations. The task force sub-teams discussed and developed final versions. The definitions were finalized for use in the PDDI minimum information model.
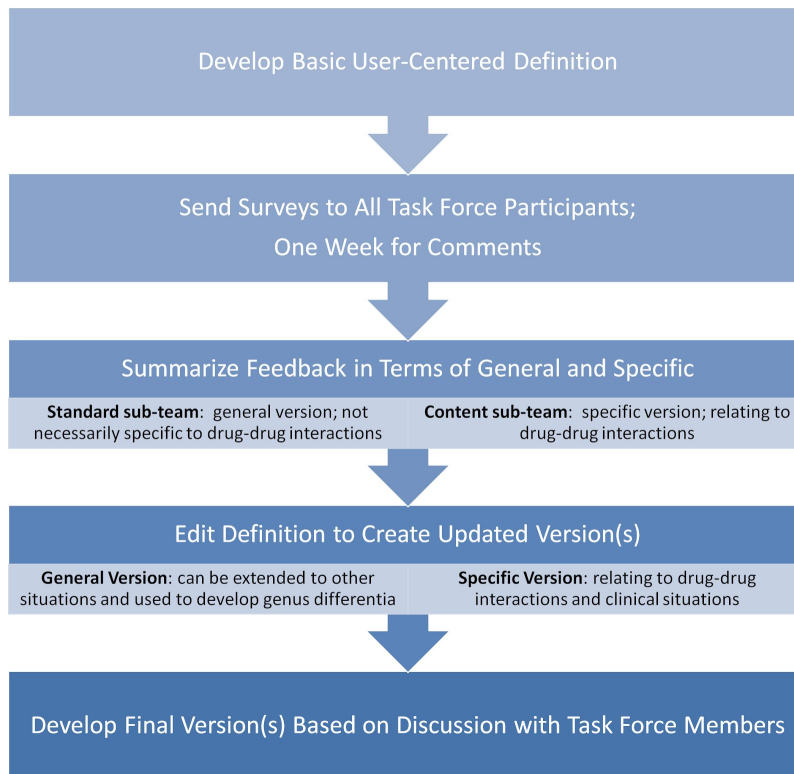
Setting the scope for knowledge representation

The task force recognized that the wide range of potential use cases for the information model require flexibility in certain aspects of the knowledge representation. The number of pre-existing ontologies relevant to this domain clearly demonstrates that richness of the domain. To keep the minimum information model lean and ensure its maintainability and usability, it was necessary to develop a clear scope for the knowledge representation including issues such as:

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a) Do we provide only the terms identified through the task force or do we aim to model terms relevant to those terms?

b) What is the relation to other, pre-existing ontologies?

c) Will we reuse terms from other resources?

d) Do we use an Upper Ontology?

The answers to these questions were determined through a series of teleconferences bringing together domain experts, biomedical informatics specialists, and knowledge representation experts across the task force. The topics were discussed, arguments for different approaches were laid out and, agreement among the participants was sought. In addition to the conversation during the teleconferences, participants had the opportunity to add comments and voice their opinion to the statements in the document. When the task force arrived at a consolidated version, the group voted by teleconference and through e-mail. The result of that vote is to be regarded the final version of the document and is provided in the results section.

RESULTS

Exemplar potential drug-drug interactions for Minimum Information Model and Decision Trees

The task force developed, as digital documents, 14 PDDI decision trees to be used for demonstrating the minimum information model. The PDDI decision trees cover 15 different situations identified by the task force as potentially affecting the search and syntheses of PDDI information. The potential interactions and the information situations they were selected for are listed in Table XX.

Table XX: Exemplar potential drug-drug interactions for which the task force developed comprehensive decision trees.

Exemplar potential drug-drug interactions	Drug or Drug Class 1	Drug or Drug Class 2	Explanation / Justification
can (and should) be contextualized for specific patients or clinical circumstances	Tamoxifen	Paroxetine	Patients with extensive 2D6 status on paroxetine will derive no benefit from tamoxifen
	KCL	K-sparing Diuretics	Combination has known patient-specific risk factors
applies at the class level	MAOI	indirect sympathomimetics	A class interaction
does not apply at the class level	Tyrosine Kinase Inhibitors	Proton Pump Inhibitors	Not all Kinase inhibs have pH dependent absorption. Imatinib, nilotinib, dasatinib, bosutinib, and ponatinib are BCR-ABL tyrosine kinase inhibitors. Imatinib and ponatinib do not have a significant interaction due to pH dependent absorption with proton pump inhibitors, whereas nilotinib, dasatinib, and bosutinib do (Lexi-comp and Micromedex).
the mechanism is known and is pharmacokinetic	Warfarin	2C9 inhibitors (ie. bactrim)	A CYP-mediated pharmacokinetic interaction
	digoxin	cyclosporin	A transport protein (p-glycoprotein) mediated interaction
the mechanism is known and is pharmacodynamic	Epinephrine	Beta-Blockers	differentiates between selective and non-selective beta blockers; hypertensive crisis
the mechanism is not known	Warfarin	Ifosfamide/Etoposide	cancer of the blood drugs - INR changes no mention of mechanism
the evidence supporting the interaction is strong	Epinephrine	Beta-Blockers	Widely known interaction with considerable available evidence
	simva, atorva, lovastatin	Clarithromycin	
the evidence supporting the interaction is weak	Warfarin	Antibiotics that don't inhibit CYP2C9	
the frequency of exposure data is available	Warfarin	NSAIDs	paper by Malone et al. - National sample
the frequency of exposure data is not available	Simvastatin	Fluconazole	
the frequency of adverse event data is available	Spironolactone	Potassium supplements	Risk of hospitalization

the frequency of adverse event data is not available	Simvastatin	Fluconazole	
the recommended action is "monitor" or "take note"	KCL	K-sparing Diuretics	
the recommended action is "avoid"	MAOIs	Indirect Sympathomimetics	
the recommended action is a clear alternative drug and dose	Simvastatin	Amiodarone	http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm

User-centered definitions

The task force participants finalized user-centered definitions for a total nine core information items. Severity was added to the core information items to distinguish it from seriousness. The nine definitions are listed here:

Evidence for a Suspected Drug-Drug Interaction:
The support for or refutation of a drug-drug interaction in humans; it may be data resulting from clinical studies, clinical observation or physiological experiments, or it may be an extrapolation based on drug-drug interaction mechanisms.

Mechanism of Interaction:
An assertion about the process(es) by which a drug-drug interaction clinical consequence occurs.

Recommended Action:
An evidence-based strategy to mitigate the potential clinical consequences of a drug-drug interaction; e.g., *use only if benefit outweighs risk*, *assess risk and take action if necessary*, *no special precautions*.

Frequency of Exposure to the PDDI:
The number of individuals within a cohort that are exposed to a drug-drug interaction over a specified time period divided by the total number of patients in the cohort.

Frequency of Harm for persons who have been exposed to the PDDI:
The number of individuals within a cohort that experience a drug-drug interaction clinical consequence divided by the total number of patients co-exposed to the drugs that are involved in the interaction.

Contextual information/modifying factors:
Factors such as patient age, patient health conditions, treatment dosage form, or concurrent medications that might alter the risk of a drug-drug interaction clinical consequence or its seriousness.

Clinical Consequences:
Changes in patient health status that can be observed or measured by a clinician or reported by a patient.

Seriousness:
The degree to which a drug-drug interaction clinical consequence may result in harm and that will determine the type and speed of clinician intervention.

Severity:
The intensity of a drug-drug interaction clinical consequence.

PDDI User Stories and Goals

Nine user stories with related goals were finalized by the task force. These cover four physician scenarios and one scenario each for a pharmacist, nurse, drug compendium editor, librarian, and a systems analyst & content specialist for a clinical decision support team. Each of these are listed in Appendix D: Final User Stories. Minimum information model elements are highlighted and color-coded to show information model user-centered definitions. Information needs related to different users are also listed. User information needs are summarized in Appendix E: User information needs summary table.

Medication reconciliation Use Cases

Three detailed medication reconciliation use cases were created by the task force to demonstrate the information needed in a clinical workflow. One use case is for a Hospital Pharmacist dealing with medication reconciliation upon admission, another for a hospital pharmacist dealing with medication reconciliation upon discharge, and a third for a consultant pharmacist performing medication reconciliation upon patient readmission. All three use cases include mention of PDDIs for which the task force has developed decision trees. The three use cases are shown in Appendix F: Medication Reconciliation Use Cases with the minimum information model core elements color-coded. A table summarizing the information needs exposed by these use cases is also presented in Appendix G: Medication Reconciliation Information Needs.

Knowledge Representation Core Considerations

The PDDI minimum information model taskforce, as a whole, seeks to create a minimum information model that contains the core common elements of any PDDI reporting system. The goal of the Knowledge Representation subgroup was to provide unambiguous representations for natural language expressions provided by the content group. The end result of this work is a core consensus ontology that entails a minimum information model.

This ontology can either be imported/reused/adoptedby other groups or it can be a mapping target for other groups. Different users may wish for additional information, and this model can be expanded to suit the specific needs of various users or use cases.The advantage of the minimal model is that the same core may be extended in different ways, with multiple terminologies or ontologies. The audience for this ontology are those who provide and implement DDI/PDDI knowledge representations or systems. The ontology will be provided in the Web Ontology Language (OWL) version 2(http://www.w3.org/TR/owl2-primer/). This

approach seems particularly promising because there is already a corpus of ontologies relevant to the domain, including specific ontologies representing drugs (e.g. the Drug Ontology), drug-drug interactions (e.g. DINTO, DIDEO), potential drug-drug interactions (e.g. DIDEO, DINTO). Building an OWL representation of a minimum information model for PDDIs fosters integration of existing formal ontology efforts. Individual classes from Basic Formal Ontologies (BFO) or from ontologies aligned therewith as our upper level (https://github.com/bfo-ontology/BFO/wiki) will be used. However, our aim is to not import the entirety of BFO, since that might hinder the adoption of the ontology we develop.

The basic strategies of knowledge representation followed by the PDDI Task Force's Knowledge Representation subgroup are as follows.

Aims and Strategies

1. Our aim is to create a core representation of the entities relevant to the PDDI domain.
2. Our goal is to provide a manageable resource in a relatively small amount of time.
3. Our plan is to provide this representation in form of an ontology.
4. A key question is how semantically rich the ontology needs to be. While both DIDEO (http://purl.obolibrary.org/obo/dideo.owl) and DINTO (http://purl.obolibrary.org/obo/dinto.owl) aim to provide a semantically rich representation of the domain, the PDDI Task Force needs to assess how much of that richness should go into the information model. The requirements regarding the semantic richness depend on the uses cases provided by the Content subgroup.
5. It is possible to create an ontology that is limited in its semantic richness, but is compatible with semantically rich models such as the ontologies mentioned above. The task force We aaims to integrate or use components such as multiple commonly used data schemata, terminologies and ontologies, by linking individual terms, data elements, and representations from them into our information model.
6. This presents certain challenges since the pre-existing resources can come with different levels of semantic richness, different methodological rigor and different semantic commitments.
7. It is highly likely that unifying all the resources semantically on the top level (based on the nine core terms: clinical consequences, frequency of exposure, frequency of harm, contextual information/modifying factors, evidence, mechanism of the interaction, recommended actions, seriousness rating, and severity) is either extremely complicated and time consuming.

Reusing terms

1. We agree to carefully consider the re-use of pre-existing representations in building our ontology, making sure they are well defined, not ambiguous and come with annotations regarding their provenance. If representations from pre-existing ontologies fulfill specified criteria (e.g. existence of a human understandable non-circular definition, etc.), they will be re-used. The ontologies we consider in this effort are mainly ontologies based on or linked to commonly used standards, such as ICD9, ICD10, RxNorm, etc.
2. We propose to create a small task force to formulate the strict rules and criteria of deciding which terms are ready to re-use.

General representation strategy

- We propose to represent the core terms (see #9 above) as information content entities (ICE; http://purl.obolibrary.org/obo/IAO_0000030). The aim of our ontology is to represent all triples about these information content entities and the relation to other information content entities.
- Information content entities (ICEs) distinguish between a description of a thing and the thing itself. For example, the process *mechanisms of the interaction* has participants and is preceded by another biological process.The information entity "Mechanisms of the interaction" just refers to processes of that time; it does not have participants and is not preceded by another biological process. The advantage of using ICEs is that these are descriptions of a process, which allows for them to be speculative and not necessarily true. All reports of PDDIs are individual findings. By using information content entities, we recognize that reports of PDDIs are statements made, have attributes and a life of their own.
- One effect of this is that the OWL representations of the minimum information model core terms do not refer to the actual material entities or processes, but do refer to the ICE. To clarify that: all properties of the core terms in our ontology will be terminological in nature and refer to relations between the term and other terms. E.g. the core term: "Mechanism of the interaction" in our model will not have participants or be preceded by another biological process. Those are properties of process that are *mechanisms of the interaction*, but not of the information entity "Mechanism of the interaction".
- Detailed development of the underlying biomedical processes, qualities and material entities will be done in other ontologies, for example the already mentioned ontologies, DIDEO and DINTO. However, these representations about the domain would be complementary to the level of the ontology we will provide. This means that, while those representation will be part of another ontology, they can and should be done in a way that is inline to our representation.
- We will still be able to re-use (See "Reusing terms" #10-11 above.) representations from data schemata, terminologies and ontologies that represent entities in the domain rather than information about the domain.
3. The re-use of those will be done by representing the information content entity only. For example, for a diagnostic ICD 9 or 10 code we would represent a specific ICD 9 or ICD 10 code as an information content entity.

DISCUSSION

The results provide a strong user-centered basis for proceeding with the remaining design and implementation activities for the PDDI minimal information model. A large set of information needs were derived from the use cases and user stories. Being a *minimum* information model, the tasks force's goal will not be to cover all of these information needs. For example, some information needs, such as patient lab results and clinician knowledge, are highly context dependant. However, the model *should* make it clear which specific local information (such as a patient lab value) would influence whether or not to trigger a PDDI alert. This is important so that implementers can easily adapt PDDI CDS to the local environment.

More than a dozen PDDIs are now represented using detailed decision trees. Three medication reconciliation use cases include mention of PDDIs for which the task force has developed decision trees. Combined, these artifacts provide a concrete focal point that will be useful for demonstrating how serializations of PDDIs written in the PDDI minimum information data model will support a clinically important task. While the specific demonstration cases will be described in an interest group note that follows this one, we can provide an overview here.

Demonstration example 1 : HL7 FHIR to support SMART on FHIR CDS

...TODO:

Demonstration example 2 : Structured Product Labeling Drug-drug Interaction Section indexing

If a drug's product labeling is missing information about known drug interactions it might have serious consequences for patients. To address this potential risk, the FDA mandated in 2006 that all product labels for FDA-approved prescription drugs include clinically significant interactions (c.f., CFR 21 201.57(c)(8)), as well as the results of pharmacokinetic studies that establish the absence of effect (c.f., CFR 21 201.57(c)(13)(C)) (Code of Federal Regulations Title 21). Structured Product Labels (SPLs) are XML documents written in an HL7 standard that the United States Food and Drug Administration (FDA) requires industry to use when submitting drug product label content (FDA 2005). The SPLs for all drug products marketed in the United States are available for download from the National Library of Medicine's DailyMed resource (National Library of Medicine 2017). At the time of this writing, DailyMed provides access to drug product labeling for more than 33,000 prescription products.

As was shown in a previous section (see The minimum information model will help PDDI decision support satisfy the Five Rights of CDS), drug product labeling can contain many gaps in information relative to the core PDDI information. Other prior work has shown that many known PDDIs are not mentioned in SPLs (Boyce et al. 2013). This is not a problem unique to United States labeling. Pfistermeister et al. reported that critical drug–drug interaction warnings

are frequently missing, or are mentioned inconsistently in the labels of the involved drugs (Pfistermeister et al. 2014).

The task force plans to represent PDDIs for which decision trees have been created as supplemental indexing data to the SPLs for the drugs involved. Supplemental indexing to SPLs are SPL files that provide additional useful information. Currently, supplemental indexing is used to specify pharmacologic classes, billing units, warning letter alerts, and other information (National Library of Medicine 2017). While a given supplemental indexing file is written in the same SPL document standard, it can include a detailed sub-model like the one planned for the PDDI minimum information model. While known to be difficult to use, a feature of the indexing files is that they can be used to both store the supplemental data in a computable format and, through the use of XSL and XSLT, render the data in various formats including HTML and PDF. The PDDIs supplemental indexing files will show a technical solution to enhancing SPL drug interaction content with information that could be used for decision support by SPL consumers.

Demonstration example 3 : JSON/JSON-LD Cohort descriptions

A prior section discussed that the minimum information model could help highlight research gaps that need to be filled to advance effective PDDI decision support (see The minimum information model will help highlight research gaps that need to be filled to advance effective PDDI decision support). A powerful method to accomplish this would be through the use of computable cohort descriptions — serialized queries that combine concept sets with logical operations to extract specific patient sub-populations from a clinical data repository. The Atlas clinical research tool created by the Observational Data Health and Informatics collaborative has a powerful interface for creating, running, and sharing cohort descriptions (OHDSI 2017; OHDSI 2016). The Atlas cohort definition tool can support using complex "and/or/not" relationships to develop alternative cohort definitions that yield counts and rates limited to specified times and specific populations. Once created, cohort descriptions can be executed over any clinical dataset that is stored in the OHDSI common data model. For the given project, this would be especially useful for acquiring data from multiple sites on the frequency of exposure to PDDIs and frequency of harm for those exposed.

The task force will show how a JSON/JSON-LD representation of PDDIs built using the minimum information model and the task force's decision trees can be translated to computable cohort definitions in Atlas. The translated cohort definitions will then be used by interested OHDSI sites to generate evidence on frequency of exposure and frequency of harm for each of the risk paths through each decision tree. Each site will run the cohorts within Atlas to query their dataset using the cohort definition and store the resulting patient de-ids for further analysis. Site leads will then run the Atlas cohort summarization and visualization tool (OHDSI Heracles 2017) which will generate counts of individuals who were exposed to the drug, experienced an adverse event, or both. The results will be fed back into the PDDI decision trees as generated evidence and metadata.

Conclusions

TODO: (after reading the MIAME papers again)
- What does all of this work do to help move the information model forward?
- Outline the next steps for the project
- Any code repositories set up for the project?
  - Tools

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APPENDICES

Appendix A: Sample user-centered definition survey

We would like your feedback regarding user-centered definitions. Please review the following user-centered definition(s) and example(s).

Q1
Here is our proposed user-centered definition of "evidence":

The support given for the possible existence of a drug interaction; it may include, but is not limited to, systematic reviews, randomized control trials, case reports, or study data.

For example: Evidence of an interaction between corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), and between aldosterone antagonists and NSAIDs:
- **"Both corticosteroids and aldosterone antagonists have been shown to substantially increase the risk of UGIB in patients on NSAIDs, with relative risks of 12.8 and 11 respectively compared to a risk of 4.3 with NSAIDs alone"**
- Results from a case series analysis (Masclee et al. *Gastroenterology*. 2014;147:784-92.)
    - **Source**: Outcome of the decision pathway, Warfarin-NSAID Decision Table, NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Contact PI: Daniel C. Malone, University of Arizona

Q2
Please select one of the following options to indicate whether you agree or disagree with this definition:
- Strongly agree
- Agree
- Somewhat agree
- Neither agree nor disagree
- Somewhat disagree
- Disagree
- Strongly disagree

Q3
How general do you think this definition should be?
- More General
- Appropriate

- ● Less General

Q4
What would you add to or remove from this definition in order to make it more general?

Q5
What would you add to or remove from this definition in order to make it more specific to drug drug interactions?

Q6
Do you have any additional comments, concerns, or suggestions about the definition?

Q7
Do you have any comments, concerns, or suggestions about the examples and evidence?

Appendix B: Sample Decision Trees

Warfarin + NSAIDs (Draft)

NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone , University of Arizona; John Horn, Philip Hansten, University of Washington

Non-steroidal anti-inflammatory drugs (NSAIDs) have antiplatelet effects which increase the bleeding risk when combined with oral anticoagulants such as warfarin. The antiplatelet effect of NSAIDs lasts only as long as the NSAID is present in the circulation, unlike aspirin's antiplatelet effect, which lasts for up to 2 weeks after aspirin is discontinued. NSAIDs also can cause peptic ulcers and most of the evidence for increased bleeding risk with NSAIDs plus warfarin is due to upper gastrointestinal bleeding (UGIB).

Is NSAID topical diclofenac?	Yes	No					
Is there a suitable alternative to the NSAID in this patient?		Yes	No				
Is patient on proton pump inhibitor or misoprostol?			Yes	No			
Does the patient have one or more of the following risk factors: - history of UGIB or peptic ulcer - > 65 years old				Yes		No	
Is patient also taking: - systemic corticosteroids - aldosterone antagonist - high dose or multiple NSAIDs				Yes	No	Yes	No
Not likely to increase risk of UGIB	c^1						
Use alternative to NSAID		c^2					

Possible increased risk of UGIB or other bleeding			n[3]				
Substantially increased risk of UGIB or other bleeding				u[4,5]			
Increased risk of UGIB or other bleeding					u[4]	u[5]	u

¢ = No special precautions.   n = Assess risk and take action if necessary. u = Use only if benefit outweighs risk

Footnotes:

1. Topical diclofenac has relatively low systemic absorption; in one study a topical gel (16 g/day) produced about 6% of the absorption seen with systemic administration of 150 mg/day. A higher than recommended dose of topical gel (48 g/day) produced 20% of a systemic dose of diclofenac.

2. If the NSAID is being used as an analgesic or antipyretic, it would be prudent to use an alternative such as acetaminophen. In some people, acetaminophen can increase the anticoagulant effect of warfarin, so monitor the INR if acetaminophen is used in doses over 2 g/day for a few days. For more severe pain consider short-term opioids in place of the NSAID.

3. Proton pump inhibitors and misoprostol may reduce the risk of UGIB in patients receiving NSAIDs and warfarin.
4. Patients with a history of UGIB or peptic ulcer may have an increased risk of UGIB from this interaction. The extent to which older age is an independent risk factor for UGIB due to these interactions is not firmly established, but UGIB in general is known to increase with age.

5. Both corticosteroids and aldosterone antagonists have been shown to substantially increase the risk of UGIB in patients on NSAIDs, with relative risks of 12.8 and 11 respectively compared to a risk of 4.3 with NSAIDs alone (Masclee et al. *Gastroenterology* 2014;147:784-92.)

BCR-ABL Tyrosine Kinase Inhibitors (TKI) + Proton Pump Inhibitors (PPI)

Authors: Evan Draper, Mayo Clinic; Daniel C. Malone , University of Arizona; John Horn, Philip Hansten, University of Washington

BCR-ABL Tyrosine Kinase inhibitors bosutinib, dasatinib, imatinib, nilotinib, and ponatinib are indicated for Philadelphia chromosome-positive chronic myeloid leukemia. Ponatinib is only approved in T315I-positive patients. These TKIs demonstrate pH dependent absorption for oral administration which may result in decreased efficacy when given concomitantly with medications that increase gastric pH. Dasatinib area under the curve (AUC) is decreased when co-administered with antacids, H2 antagonists, and PPIs.[1] Bosutinib and nilotinib AUCs are decreased with concomitant PPIs but antacids and H2 antagonists may be considered if TKI is given 2 hours before the antacid/H2 antagonist.[2,3] However, for nilotinib a retrospective study has shown no difference in cytogenetic response rates for patients taking PPIs.[4] Imatinib and ponatinib AUCs are not appreciably decreased by PPI co-administration.[5,6]

Type of BCR-ABL Tyrosine Kinase Inhibitors	Imatinib, ponatinib	nilotinib	bosutinib, dasatinib
Not likely to decrease AUC	¢[5,6]		
Possible decrease in AUC and efficacy		n[3,4]	
Probable decrease in AUC and efficacy			u[1,2]

¢ = No special precautions.   n = Assess risk and take action if necessary. u = Use only if benefit outweighs risk

Footnotes:

1.	Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015
2.	Bosulif [package insert]. New York, NY: Pfizer Labs; 2015.
3.	Tasigna [package insert]. East Hanover, NJ: Novartis; 2015.
4.	Yin OQ, Giles FJ, Baccarani M, et al. Concurrent use of proton pump inhibitors or H2 blockers did not adversely affect nilotinib efficacy in patients with chronic myeloid leukemia. Cancer Chemother Pharmacol. 2012;70(2):345-350.
5.	Iclusig [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc. 2016.
6.	Egorin MJ, Shah DD, Christner SM, et al. Effect of a proton pump inhibitor on the pharmacokinetics of imatinib. Br J Clin Pharmacol. 2009;68(3):370-374.

Appendix C: Out of scope user stories

The following user stories were considered as outside of scope of the task of developing the PDDI minimum information model.

Synthesis for Dissemination, Clinical Decision Support User Interface Designer
Synthesis for Dissemination, Data Scientist
Population Management, Pharmacoepidemiologist
Population Management, Insurance Companies
Population Management, P&T Committee (Formulary Development)
Population Management, Med Safety Department (Pharmaceutical Industry)
Passive Role, Patient

Appendix D: Final User Stories

Definitions Color-Coding Key

	Clinical Consequence
	Evidence
	Recommended Actions
	Mechanism of Interaction
	Contextual Evidence/Modifying Factors
	Seriousness Rating
	Frequency of Harm/Exposure

User Stories

Treatment Planning, Physician

Simvastatin + Amiodarone

- Kathleen is a physician who is treating a patient who has a ventricular arrhythmia. Kathleen would normally prescribe amiodarone for this particular patient, but he is being treated with simvastatin for dyslipidemia, and she knows that a potentially serious interaction may occur leading to rhabdomyolysis. Kathleen wants to know what the patient's risk factors are for rhabdomyolysis, what the benefits and risks would be to switching him to an alternative statin, and if amiodarone is not the best option for this patient, what alternatives to amiodarone exist for this patient, and what the available evidence shows in terms of ventricular arrhythmia patient outcomes.

(Pediatrics) Fluoxetine + Ondansetron

- Evelyn is a pediatric emergency medicine physician caring for an adolescent with a history of major depressive disorder treated with fluoxetine, who presents with acute onset of vomiting and diarrhea. Evelyn's usual first-line antiemetic for acute gastroenteritis is ondansetron, but Evelyn knows that both fluoxetine and ondansetron are listed as QTc-prolonging medications. Evelyn would like to know the likelihood of clinically significant QTc prolongation due to a brief course of co-administration of fluoxetine and ondansetron, and if there is a recommendation for dose adjustment or an alternate antiemetic.

(Pediatrics) Azole antifungals + Tacrolimus

- William is a pediatric hospitalist caring for a child with a history of liver transplant due to congenital liver disease, treated with tacrolimus to prevent organ rejection. The patient is admitted with a fever and starts broad anti-infective therapy, including vancomycin, piperacillin-tazobactam and fluconazole. William knows that azole antifungals can increase tacrolimus levels and wants to know if there is evidence to guide a decrease the patient's tacrolimus dose to prevent tacrolimus toxicity. He additionally wants to know the mechanism of interaction to avoid further interacting medications.

Evaluation of Management Options for Drug-Drug Interactions, Physician

Warfarin + Naproxen

- Melissa is a family physician whose patient called because he is experiencing noticeable bruising. Melissa knows that the patient is taking warfarin, but he has not experienced bruising before. She asks if the patient has taken any new medications recently, and he mentions that he visited a pain clinic for his chronic back pain and they prescribed the NSAID naproxen. Melissa knows that NSAIDs can increase the risk of bleeding when taken with warfarin, and she wants to know the best way to manage this interaction.

Evaluation of Management Options for Drug-Drug Interactions, Pharmacist

Atorvastatin + Clarithromycin

- James is a community pharmacist reviewing an electronic prescription that just came in for clarithromycin; an alert in his pharmacy's information system indicates that there is a potential interaction between the clarithromycin and the atorvastatin that the patient was prescribed a year ago by different physician. James calls the patient in order to discuss her medications; she tells him that she is taking the atorvastatin as prescribed, and cannot remember if she has ever taken clarithromycin in the past. In preparation for following up with the patient's physician, James would like to know the likelihood of an adverse drug event such as rhabdomyolysis occurring due to a potential interaction and how serious the interaction could be. He would also like to know if monitoring would be appropriate for this patient, or if a dose adjustment or temporary discontinuation of one of the drugs would be best.

Screening for Drug-Drug Interactions, Nurse

Glipizide + Lisinopril (Sulfonylureas + ACE Inhibitors)

- Nancy is a licensed practice nurse who works in a skilled nursing facility. She has noticed that her patient is experiencing symptoms of hypoglycemia. She sees that the patient was recently prescribed lisinopril, and is wondering if it interacts with one of the five medications that she is taking. Nancy remembers reading about a potential interaction with the glipizide that the patient is currently taking. She would like to know if the patient's symptoms are a possible consequence of an interaction between the glipizide and the lisinopril, or the lisinopril and one of the other

medications that the patient is taking, and if so, what information she should pass along to the registered nurse in charge in order to help treat the patient.

Synthesis for Dissemination, Drug Compendium Editor
Tyrosine Kinase Inhibitors + Proton Pump Inhibitors

- Olivia is a drug compendium editor who is reviewing the available literature for the potential interaction between tyrosine kinase inhibitors and proton pump inhibitors. She would like to review the most recent literature available surrounding the interaction, and would like to compare it against the existing entry in her drug compendium. She would like to understand more about the mechanism of the interaction, whether it applies to all drugs within the classes, whether certain populations are at greater risk, and the types and strength of the evidence available. She would also like to learn more about recommended management options.

Synthesis for Dissemination, Librarian

- Michael is a librarian who works for the medication safety unit in a regulatory agency. He has graduate training in library and information science, and has a good understanding of medical reference sources. When he is asked to locate information about a potential drug drug interaction, he wants to understand more about the terms used to describe the drugs so that he can develop search strategies to run daily, weekly, and monthly searches. He would like to find terms used to describe the specific drugs involved in the interaction, drug class concepts, clinical consequences of the interaction, and existing types of evidence of the interaction.

Synthesis for Dissemination, Clinical Decision Support Team - Systems Analyst & Content Specialist

- Richard is a systems analyst who is working with Joe, a content specialist, in order to design a new clinical information system which can provide personalized clinical knowledge and patient information for clinicians to improve healthcare quality. Richard is professionally trained in algorithms, databases, and programming. He also has some knowledge about electronic medical records. In order to help Richard design and implement the system, Joe would like to know about the evidence, clinical consequences, and mechanisms of interactions of potential drug-drug interactions so that he can develop rules for the most clinically relevant interactions. With that information, he can help Richard create linkages and designs algorithms based on electronic medical records. Joe can also help Richard prioritize what to display and how to display information or alerts for clinicians.

Appendix E: User information needs summary table

Tasks/Goals	Users	Info Needs	Aspects of Info Users Value to Make a Decision	Barriers
Evaluation of Management Options for Drug-Drug Interactions	General Practitioner (Physician)	• EHR/patient data 　○ Patient History 　○ Lab Results, Tests 　○ Patient Medications 　○ Potentially Interacting Drugs • Patient Assessment 　○ Signs/ Symptoms • Prescriber's Knowledge and Experience • Knowledgebase 　○ DDI Symptoms 　○ Mechanism of Interaction 　○ Potential Substitutes 　○ Indications 　○ Evidence	• Conciseness and Clarity • Timeliness • Accuracy • Grading of Evidence 　○ Type of Evidence 　○ Study Methods • Patient Context/ Relevance 　○ Disease States 　○ Risk Factors • Frequency 　○ Populations 　○ Demographics 　○ Risk Factors 　○ Comorbidities • Seriousness • Clinical Guidelines • How Colleagues Addressed Similar Scenarios	• Incomplete Medication List, Allergies • Irrelevant Alerts/ Lack of Evidence/ Not Graded • No Recommendations • Formulary Restrictions • Incomplete Information (e.g., Patient Report)
	Community Pharmacist	• EHR/patient data 　○ Patient History 　○ Lab Results, Tests 　○ Patient Medications 　○ Duration of Therapy 　○ Potentially Interacting Drugs • Pharmacist's Knowledge and Experience • Knowledgebase 　○ DDI Symptoms	• Conciseness 　○ Grading of Evidence 　○ Type of Evidence 　○ Study Methods • Accuracy • Frequency 　○ Populations 　○ Demographics 　○ Risk Factors 　○ Comorbidities • Seriousness • Patient Context/ Relevance	• Incomplete Medication List, Allergies • Delayed Information • Irrelevant Alerts/ Lack of Evidence/ Not Graded • No Recommendations • Incomplete Information (e.g., Patient Compliance)

		○ Mechanism of Interaction ○ Potential Substitutes ○ Indications ○ Evidence	○ Compliance ○ Disease States ○ Risk Factors ● Clinical Guidelines	

Screening for a Drug-Drug Interactions	Licensed Practical Nurse	● EHR/patient data
		  ○ Patient History
		  ○ Lab Results, Tests
		  ○ Patient Medications
		  ○ Potentially Interacting Drugs
		● Nurse's Knowledge and Experience
		● Patient Assessment
		  ○ Signs/ Symptoms
		● Knowledgebase
		  ○ Symptoms
		  ○ Potential Substitutes
		  ○ Evidence
			● Conciseness
			● Evidence (to support discussion with physician)
			● Patient Context/ Relevance
			● Recommendations
			● Institutional Protocols
				● Not Empowered to Confront Physician
				● Detecting Symptoms (e.g., nonverbal patients)
				● Irrelevant Alerts/ Lack of Evidence/ Not Graded
				● Incomplete Medication List, Allergies
				● No Recommendations

Treatment Planning (Source: Russ et al., *Health Informatics Journal*. 2010;16(4):287 –305)	<mark>Physician</mark>	● EHR/patient data
		  ○ Patient's Medical History and Allergies
		  ○ Patient's Medications
		  ○ Potentially Interacting Drugs
		● Patient Assessment
		  ○ Signs/ Symptoms
		● Prescriber's Knowledge and Experience
		  ○ Conditions
		  ○ Medication/ Class
		● Knowledgebase
		  ○ Mechanisms
		  ○ Potential Substitutes
			● Conciseness
			● Grading of Evidence
			● Patient Context/ Relevance
			● Timeliness
			● Accuracy
			● Recommendations
			● Clinical Guidelines
				● Lack of Guidelines/ Evidence
				● Incomplete Medication List, Allergies
				● Evidence Not Graded
				● Lack of Recommendations
				● Incomplete Information (e.g., patient report)

Synthesis for Dissemination (source: unpublished manuscript)	Drug Compendium Editorial Board	● Literature
		  ○ Patient Demographics
		  ○ Patient-Specific Clinical Characteristics
		  ○ Temporal Overlap in Drug Administration
		● Member Knowledge
		● Knowledgebase
		  ○ Evidence
		  ○ Information Quality
		  ○ Mechanism of Interaction
		  ○ Biological Plausibility of Interaction
		  ○ Treatment Comparisons
			● Grading of Evidence
			  ○ Type of Evidence
			  ○ Source of Evidence
			  ○ Study Methods
			● Relevance to DI Question
			● Study Results in Statistical Form
			● Result Magnitude
			● Statistical vs. Clinical Significance
			● Patient Populations
			  ○ Disease States
			  ○ Risk Factors
			● Frequency
			  ○ Populations
			  ○ Demographics
			  ○ Risk Factors
			  ○ Comorbidities
			● Seriousness
				● Difficulty of Showing Lack of Association
				● Lack of Evidence (e.g., RCTs) or Weak Evidence
				● Access to Newly Published Research
				● Comprehensiveness vs. Clinically Relevance

	Librarian	● Literature
		  ○ Drugs
		  ○ Patient Demographics
		  ○ Patient-Specific Clinical Characteristics
		● Librarian Knowledge
		● Knowledgebase
		  ○ Mechanism of Interaction
		  ○ Information Quality
			● Evidence Grading
			● Patient Populations
			● Summary of Study Results
			● Result Magnitude
			● Clinical Relevance
				● Lack of Evidence (e.g., RCTs)
				● Weak Evidence
				● Information Overload

	Clinical Decision Support Team (Systems Analyst & Content Expert)	● EHR/patient data
		  ○ Patient Baseline (lab results, tests, etc.)
		  ○ Patient Medical
			● Patient Context/ Relevance
			● Clinical Guidelines
			● Recommendations
			● Medicinal Effectiveness
				● No Personalized Recommendation
				● No Patient Improvement
				● No Personalized Alerts(Alerts

		History
		○ Patient
		  Medications
		○ Patient
		  Symptoms
		○ Family
		  History
		○ Genetics
		○ Historical
		  and
		  Geographica
		  l trends of
		  disease
		  occurrence
		○ Published
		  Clinical Data
		● EHR
		  Standards/Schema
		● Knowledgebase
		○ Schema
		○ Adverse
		  Drug Events
		● Algorithm
			● Accuracy
			● Consistency
			● Severity
			● Type of DDI
			● Specification of Data
			● Simplicity
			● Minimizing cognitive load
			● Efficient interactions
				should be personalized and identified with EHR)
				● Data is not been filtered before it was given to physicians

Appendix F: Medication Reconciliation Use Cases

Use Case 1: Hospital Pharmacist, Medication Reconciliation upon Admission

- **The modifying factors are unknown: Linezolid + SSRIs (sertraline)**

Beth is a hospital pharmacist who is reviewing the medications in the physician admission order for Bill. Bill is an 85-year-old male dementia patient who was transferred from a skilled nursing facility to the hospital after being diagnosed with a vancomycin-resistant *Enterococcus faecium* (VRE) infection. At the nursing home, Bill was prescribed sertraline to treat depression. Beth receives an alert that linezolid, which is being considered to treat the VRE infection, has a potential interaction with the sertraline that Bill is currently taking. Linezolid is a weak monoamine oxidase inhibitor, and has been shown to increase the risk of serotonin syndrome when taken concurrently with an SSRI such as sertraline. Beth would like to know the risks and benefits of continuing the sertraline and adding on the linezolid, the potential seriousness of the interaction's clinical consequence, and recommended management options, such a selecting an alternative medication or discontinuing the sertraline. She would like to see the current evidence behind the interaction, so that she can determine if Bill has an increased risk of serotonin syndrome. In order to gather this information, she reviews Bill's history, lab results, and allergies from the health records faxed by his skilled nursing facility, as well as his medication list upon admission. She reviews Lexicomp™ and the hospital's intranet resources for additional information, but is having trouble finding information that is relevant to Bill's situation. She does a literature search using PubMed in order to try to locate information about the frequency of adverse events in due to this potential interaction in other patients like Bill, but she does not have access to all of the articles in the search results.

Use Case 2: Hospital Pharmacist, Medication Reconciliation upon Discharge

- **Can (and should) be contextualized for specific patients or clinical circumstances: KCL (potassium chloride) + K-sparing Diuretics (spironolactone)**

Beth is reviewing the physician's discharge order for Maria. Maria is a 72-year old woman who was admitted to the hospital with acute decompensated heart failure. While reviewing Maria's medications, Beth sees that Maria is being discharged with spironolactone, a potassium-sparing diuretic that could potentially interact with the potassium chloride that Maria had been taking to treat low potassium levels. Spironolactone may increase potassium levels in Maria's blood, leading to hyperkalemia. Beth reviews Maria's electronic health record in order to view her lab results and her other medications. She sees that Maria is also taking the ACE inhibitor lisinopril

for heart failure, and since ACE inhibitors can also increase potassium levels, Beth would like to know how much this modifying factor has increased Maria's risk of hyperkalemia due to the interaction between potassium chloride and spironolactone. Beth would like to know how likely it is that Maria will experience hyperkalemia, how serious hyperkalemia may be, and how to manage the interaction, such as by discontinuing one of Maria's medications. Beth reviews the hospital's intranet, as well as Micromedex™, for recommendations. She would also like more information about the potassium chloride that Maria was taking as one of her home medications, so she will need to contact Maria's community pharmacy in order to find out the strength of the medication and if the prescription was still current.

Use Case 3: Consultant Pharmacist, Medication Reconciliation upon Readmission

- **The mechanism is known and is pharmacokinetic: Warfarin + 2C9 inhibitors (metronidazole)**

Patrick is a nursing home consultant pharmacist who is reviewing the medications of a readmitted patient, Nancy. Nancy is a 78 year-old woman who is being transferred back to her skilled nursing facility after a hospital admission for a *Clostridium difficile* (*C. diff*) infection; prior to the hospital admission, she was prescribed warfarin at the skilled nursing facility for deep vein thrombosis (DVT) treatment. Based on the hospital discharge summary, it appears that Nancy was taken off of the warfarin at the hospital due to an increased INR, and returned to the skilled nursing facility without an order for warfarin. Patrick sees that a potential interaction may occur with the warfarin that Nancy had been prescribed prior to her hospitalization, and the metronidazole now used to treat her infection, since metronidazole is a CYP2C9 inhibitor and may increase the plasma concentration of warfarin. A clinical consequence of this interaction would be an increased INR leading to an increased risk of bleeding. Patrick would like to gather management recommendations for this interaction prior to contacting Nancy's physician. He is interested in Nancy's duration of therapy for both the warfarin and the metronidazole, her current risk factors for a DVT, and if she is indicated for prophylactic therapy. Patrick also wants to know if and when warfarin should be restarted, and at what dose, in order to reduce the risk of bleeding due to the interaction. He would also like to know if metronidazole is the best option to continue treating Nancy's *C. diff* infection, or if there is an alternative option that may not interact with warfarin. In order to gather this information, he reviews Nancy's previous INR values, medication list, and history. He is also contacting the hospital in order to determine whether warfarin had been given at any point during Nancy's stay, if the dosage had been adjusted, what other medications she was given, and if any of her other medications were discontinued. He also reviews his company's intranet resources for additional information about the interaction and possible evidence-based recommendations. Patrick is also interested in the frequency of serious bleeding events in geriatric patients co-prescribed warfarin and metronidazole, and the literature surrounding the interaction.

Appendix G: Medication Reconciliation Information Needs

Tasks/Goals	User, Situation	Info Needs	Aspects of Info Users Value to Make a Decision	Barriers
Medication Reconciliation	Hospital Pharmacist, Upon Admission; Hospital Pharmacist, Upon Discharge; Consultant Pharmacist, Upon Readmission	EHR/patient data Patient History Lab Results, Tests Patient Medications (Drug, Dose, Frequency, Compliance) Duration of Therapy Potentially Interacting Drugs Pharmacist Knowledge Discontinuation Risks IV to PO Feeding Tube Interactions Patient Education and Counseling Knowledgebase DDI Symptoms Mechanism of Interaction Potential Substitutes Indications Evidence	Conciseness Grading of Evidence Type of Evidence Study Methods Reliability and Accuracy Frequency Populations Demographics Risk Factors Comorbidities Seriousness Patient Context/ Relevance Compliance Disease States Risk Factors Clinical Guidelines Benefit to Risk Ratio Medications to Continue Harm if Discontinued Potential Interactions	Incomplete Medication List, Allergies Delayed Information Irrelevant Alerts/ Lack of Evidence/ Not Graded No Recommendations Incomplete Information (e.g., Patient Compliance)