

**A Minimum Representation of Potential Drug- Drug Interaction Knowledge and Evidence - Technical and User-centered Foundation**

## Draft Community Group Report 26 April 2018

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[Commit history](https://github.com/W3C-HCLS/w3c-ddi/commits/gh-pages) [Pull requests](https://github.com/W3C-HCLS/w3c-ddi/pulls/)

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## Abstract

Ensuring medication therapy occurs safely and to the maximum benefit for any given patient is of great interest to clinicians [[*institute-medicine-2006*](#_bookmark172)]. 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), and could therefore lead to a clinically observable effect on the patient (i.e., an actual drug-drug interaction). The purpose of this Community Group Note is to provide a technical and user-centered foundation for a minimum information model for PDDI information. New information regarding PDDIs is published every day in primary sources such as drug product labeling and the scientific literature. 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 clinical decision support. These shortcomings suggest the need for harmonized approaches for documenting and sharing PDDI information. The resulting common representation of PDDI summaries would facilitate curation and information exchange. Downstream applications would process these representations into forms amenable for clinical decision support, drug product label enhancement, cohort identification, and other pharmacovigilance activities.

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## Introduction

Ensuring medication therapy occurs safely and to the maximum benefit for any given patient is of great interest to clinicians [[*institute-medicine-2006*](#_bookmark172)]. 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), and could therefore lead to a clinically observable effect on the patient (i.e., an actual drug-drug interaction). While the effects that may occur due to exposure to some PDDIs can benefit patients (e.g., some HIV therapies use a low-dose of ritonavir to increase plasma concentrations of co-administered protease inhibitors by inhibiting their metabolism), 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-2012*](#_bookmark173)][*[cdc-faststats](#_bookmark161)*]. 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-2014*](#_bookmark164)]. The potential for harm from PDDIs is an international concern reflected in guidance documents of regulatory agencies around the world [[*rekic-2017*](#_bookmark182)][*[european-medicines-2012](#_bookmark166)*][[*usdhhs-2017*](#_bookmark194)]. Moreover, in the United States, PDDI alerting is a criteria included in the so-called Meaningful Use criteria for Electronic Health Records [[*cms-2013*](#_bookmark162)][[*ridgely-2012*](#_bookmark184)]), and population-based strategies for tracking exposure are promoted by organizations such as the Pharmacy Quality Alliance [*[ahrq-drug-drug](#_bookmark154)*].

Clinicians often face barriers to the effective and appropriate management of PDDI exposures [*[nabovati-](#_bookmark176)* [*2017*](#_bookmark176)]. Barriers include PDDI alerts with poor specificity and incomplete personal PDDI knowledge [*[abarca-](#_bookmark153)* [*2004*](#_bookmark153)][*[van-der-sijs-2006](#_bookmark196)*] . An awareness of the need for PDDI decision support prompts clinicians to use various drug knowledge resources including print or online drug information references, drug interaction checking tools, and alerting systems. Unfortunately, poor specificity leads clinicians to be overwhelmed by PDDI information that is “difficult to retrieve, sort and digest into clinical decision making” [[*bottiger-2009*](#_bookmark158)]. PDDI alerts are often criticized for “over-alerting” that obfuscates the most important information, hinders the usability of the decision support system, and leads to alert fatigue and clinician dissatisfaction [*[bottiger-](#_bookmark158)* [*2009*](#_bookmark158)][[*payne-2015*](#_bookmark180)]. Moreover, while many compilations of PDDI evidence exist to help improve prescriber and pharmacist knowledge, they are not concordant in their coverage, accuracy, and agreement [[*wang-2010*](#_bookmark197)] [[*saverno-2011*](#_bookmark187)][[*ayvaz-2015*](#_bookmark156)][[*fung-2017*](#_bookmark167)]. Together, these shortcomings suggest the need for harmonized approaches for documenting and sharing PDDI information.

### 1.1 Need, envisioned workflow, and high-level requirements

New information regarding PDDIs is published every day in primary sources such as drug product labeling and the scientific literature. 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 through 2016. This suggests that the body of evidence about PDDIs is overwhelming and dynamic. As it is impossible for clinicians to keep up with the PDDI evidence base, drug experts generate summaries of PDDI evidence from primary sources. These summaries bring PDDI knowledge to clinicians in the form of published drug information compendium, clinical decision support rules, and interaction checking applications. **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 clinical decision support.

[Figure 1](#_bookmark70) provides an overview of the roles envisioned for a PDDI minimal information model. Drug experts would generate summaries of PDDI evidence from primary sources using the information elements from the PDDI minimal information model. The information elements would cover the minimum set of information required for the effective clinical management of PDDI exposure. The resulting common representation of PDDI summaries would facilitate curation and information exchange. Downstream applications would process these representations into forms amenable for clinical decision support, drug product label enhancement, cohort identification, and other pharmacovigilance activities. To achieve the envisioned roles, the minimal information model must be flexible and computable. Where possible, model elements should draw upon accepted biomedical taxonomies and ontologies to represent medications, diagnoses, and descriptions of potential adverse reactions. Preferring the use of ontologies over free-text descriptions will reduce ambiguity associated with free-text, thus supporting comparison and computational analyses.

Representations in commonly-used formats (JSON,XML/RDF ,etc.) will support ease of construction and parsing of models, particularly through shared libraries and APIs.

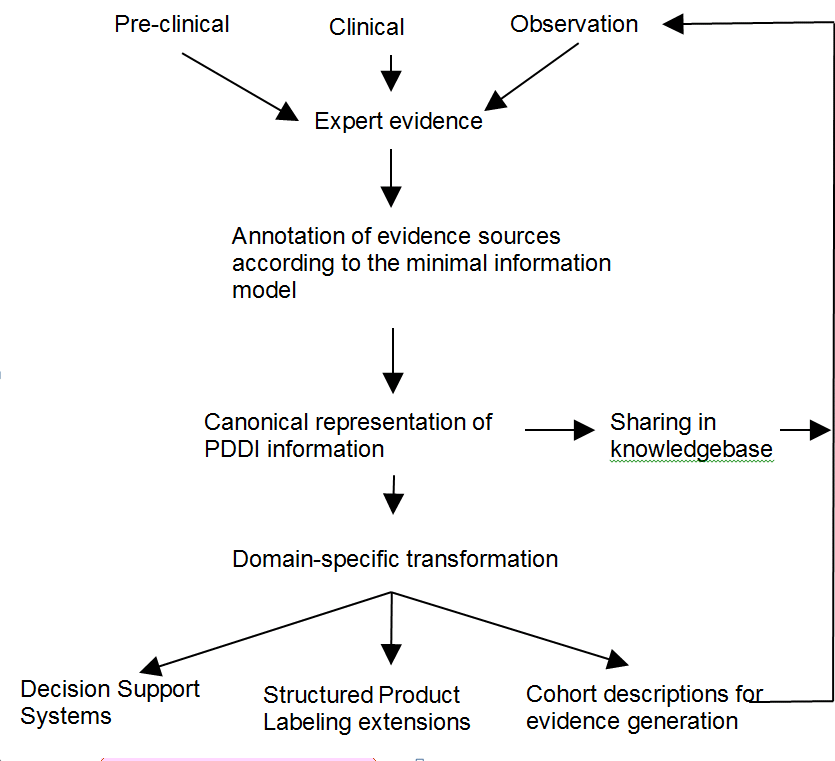


Figure 1 An overview of the role envisioned for a PDDI minimal information model.

The purpose of this Community Group Note is to provide a technical and user-centered foundation for a minimum information model for PDDI information. The principle contributions include:

* 1. definitions for the model's core information items, examples of using the definitions to represent two PDDIs, and a set of additional PDDIs selected as case studies for future work on the information model;
  2. clarification on the intended users of the information model along with use cases and specific information needs; and
  3. a statement on the appropriate scope of knowledge representation for the information model.

The following section discusses each of these contributions. Then follows a discussion of specific demonstrations that are the subject of future work.

## Definitions for the Core Information Items of the Minimum Information Model

The Task Force participants finalized user-centered definitions for a total nine core information items (see [A.1.4 Workflow for arriving at user-centered definitions](#_bookmark71)). An additional core information item *drugs involved* was considered non-ambiguous and was not included in the user-centered definition development process.

Each user-centered definition was developed by first creating a document with one or more candidate definitions along with supporting background information and examples. The documents were reviewed by the task force and iteratively refined until arriving at a consensus definition. The final definition creation documents are available for download from the project’s GitHub code repository ( [https://github.com/W3C-](https://github.com/W3C-HCLS/w3c-ddi/tree/master/User-centered-definitions) [HCLS/w3c-ddi/tree/master/User-centered-definitions](https://github.com/W3C-HCLS/w3c-ddi/tree/master/User-centered-definitions)). The definitions are listed below in alphabetical order:

* **Clinical Consequences** (<http://purl.obolibrary.org/obo/MPIO_0000002>): Changes in patient health status from baseline that can be observed or measured by a clinician or reported by a patient.
* **Contextual information/modifying factors** (<http://purl.obolibrary.org/obo/MPIO_0000000>): Factors

such as patient age, patient health conditions, route of administration, product formulation, or concurrent medications that might alter the risk of a drug-drug interaction clinical consequence or its seriousness.

* **Evidence for a Suspected Drug-Drug Interaction** (<http://purl.obolibrary.org/obo/MPIO_0000004>):

The support for or refutation of a drug-drug interaction in humans, potentially including data resulting from clinical studies, clinical observation, physiological experiments, or it may be an extrapolation based on drug-drug interaction mechanisms.

* **Mechanism of Interaction** (<http://purl.obolibrary.org/obo/MPIO_0000005>): The process(es) by

which a drug-drug interaction with clinical consequence occurs.

* **Frequency of Exposure to the PDDI** (<http://purl.obolibrary.org/obo/MPIO_0000007>): 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** (<http://purl.obolibrary.org/obo/MPIO_0000006>): The number of individuals within a cohort that experience a clinical consequence of a drug-drug interaction clinical consequence divided by the total number of patients co-exposed to the drugs involved.
* **Recommended Action** (<http://purl.obolibrary.org/obo/MPIO_0000008>): 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.*

* **Seriousness** (<http://purl.obolibrary.org/obo/MPIO_0000009>): The degree to which a drug-drug interaction clinical consequence may result in harm thereby determining the type and speed of clinician intervention.
* **Severity** (<http://purl.obolibrary.org/obo/MPIO_0000010>): The intensity of a drug-drug interaction clinical consequence.

The interested reader can review details on each user centered definition in the aforementioned definition documents downloadable from GitHub ([https://github.com/W3C-HCLS/w3c-ddi/tree/master/User-centered-](https://github.com/W3C-HCLS/w3c-ddi/tree/master/User-centered-definitions) [definitions](https://github.com/W3C-HCLS/w3c-ddi/tree/master/User-centered-definitions)). In the interest of space, we provide here only a limited discussion of the definitions in the form of two example PDDIs. These two are chosen from the set of 14 exemplar potential drug-drug interactions for which the Task Force developed comprehensive decision trees (see [A.1.2 Decision Trees Created for the](#_bookmark79) [Minimum Information Model Domain Analysis](#_bookmark79)).

### Applying the Minimal Information Model definitions to the PDDI between warfarin and non-steroidal anti-inflammatory drugs (NSAIDs)

We illustrate here the application of the Minimum Information Model definitions to representing the PDDI involving warfarin and non-steroidal anti-inflammatory drugs (NSAIDs). Task Force drug experts created the PDDI description and decision tree shown in [A.1.2.1 Example PDDI - Warfarin + NSAIDs (Draft)](#_bookmark80). The PDDI description and decision tree is shown below annotated with Minimal Information Model definitions and discussion comments. Note that the capitalized keywords (*MUST*, *MUST NOT*, *REQUIRED*, *SHALL*, *SHALL NOT*, *SHOULD*, *SHOULD NOT*, *RECOMMENDED*, *MAY*, AND *OPTIONAL*) are defined in RFC 2119 [[*RFC2119*](#_bookmark183)].

**Drugs involved**: [Warfarin](#_bookmark82) and [non-steroidal anti-inflammatory drugs (NSAIDs)](#_bookmark81)

**Comment:** The drugs involved in a PDDI *MUST* be explicitly stated. To support a computable representation of the PDDI, the drugs involved *SHOULD* be listed as sets of terms from a terminology such as [RxNorm](https://www.nlm.nih.gov/research/umls/rxnorm/) or the [Anatomical Therapeutic Chemical Classification System (ATC)](https://www.whocc.no/atc/structure_and_principles/). Such so called *value sets MAY* be referenced by a URI to a public repository such as the [Value Set](https://vsac.nlm.nih.gov/) [Authority Center](https://vsac.nlm.nih.gov/) that is maintained by the [United States National Library of Medicine](https://www.nlm.nih.gov/).

[Clinical Consequences](#_bookmark72): Increased risk of bleeding including [gastrointestinal bleeding](#_bookmark85), [intracranial](#_bookmark84) [hemorrhage](#_bookmark84), and [cerebral hemorrhage](#_bookmark83)

**Comment:** The clinical consequences associated with a PDDI *MUST* be reported if known. Clinical consequences *SHOULD* refer health outcomes as specific as possible. To support a computable representation of the PDDI, clinical consequences *SHOULD* be represented as one or more sets of terms from a terminology such as [ICD-10](http://www.who.int/classifications/icd/en/) or [SNOMED-CT](https://www.snomed.org/snomed-ct). Such so called *value sets MAY* be referenced by a URI to a public repository such as the [Value Set Authority Center](https://vsac.nlm.nih.gov/) that is maintained by the [United States National Library of Medicine](https://www.nlm.nih.gov/).

[Seriousness](#_bookmark77): Bleeding is a serious potential clinical consequence because it can result in death, life-

threatening hospitalization, and disability.

**Comment:** A PDDI clinical consequence *MUST* be noted as *serious* if it can result in death, life- threatening hospitalization, congenital anomaly, disability, or if it requires intervention to prevent permanent impairment or damage. This recommendation is in accordance with the World Health Organization [[*who-umc-glossary*](#_bookmark198)], the United States Food and Drug Administration [[*usdhhs-2011*](#_bookmark193)], and other organizations that conduct pharmacovigilance.

[Severity](#_bookmark78): While bleeding is a serious potential clinical consequence, severity can vary from easily tolerated to incapacitating

**Comment:** The severity of a PDDI clinical consequence *MUST* be reported if known. The severity of a PDDI clinical consequence *MUST* be noted using non-ambiguous terms or phrases. Any of the existing terminologies for adverse event severity, such as Common Terminology Criteria for Adverse Event (CTCAE) [*[ctcae-wiki](#_bookmark163)*], *MAY* be used for describing a PDDI clinical consequence.

[Mechanism of Interaction](#_bookmark75): [Non-steroidal anti-inflammatory drugs (NSAIDs)](#_bookmark87) have antiplatelet effects which increase the bleeding risk when combined with oral anticoagulants such as [warfarin](#_bookmark86). 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).

**Comment:** The mechanism of a PDDI *MUST* be reported if known. The description *SHOULD* be written for a clinician audience and include details that help the clinician decide what course of management action to take. To reduce ambiguity, the description *MAY* refer to specific drugs or health conditions using codes from terminologies.

[Recommended Action](#_bookmark76): 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.

**Comment:** Any recommended actions that apply to all patient exposures *SHOULD* be stated using clear and concise language. The recommended action statement *SHOULD* also provide citations to [evidence for a suspected drug-drug interaction](#_bookmark74) (not provided in this example). Recommendations that depend on [contextual information/modifying factors](#_bookmark73) *SHOULD* be mentioned separately to support context-specific presentation of such information.

[Contextual information/modifying factors](#_bookmark73):

* + 1. The [NSAIDs](#_bookmark89) is [topical diclofenac](#_bookmark88)
       - **Recommended Action:** No special precautions
       - **Evidence for a Suspected Drug-Drug Interaction:** [Topical diclofenac](#_bookmark90) 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. The NSAID is NOT [topical diclofenac](#_bookmark92) but the patient is concomitantly taking a [proton pump inhibitor](#_bookmark91) or [misoprostol](#_bookmark93)
       - **Recommended** **Action:** Assess risk and take action if necessary
       - **Evidence for a Suspected Drug-Drug Interaction:** [Proton pump inhibitors](#_bookmark95) and [misoprostol](#_bookmark94) may reduce the risk of UGIB in patients receiving NSAIDs and warfarin.
    3. The NSAID is NOT [topical diclofenac](#_bookmark98), the patient is NOT concomitantly taking a [proton pump inhibitor](#_bookmark97) or [misoprostol](#_bookmark96), and the patient has one or more of the following risk factors:
       - History of [upper gastrointestinal bleeding (UGIB) or peptic ulcer](#_bookmark99) or age > 65 years old
         * **Recommended Action:** Use only if benefit outweighs risk
         * **Evidence for a Suspected Drug-Drug Interaction:** 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.
       - Concomitantly taking [systemic corticosteroids](#_bookmark101), [aldosterone antagonists](#_bookmark100), or high dose or multiple [NSAIDs](#_bookmark102)
         * **Recommen****ded Action:** Use only if benefit outweighs risk
         * **Evidence for a Suspected Drug-Drug Interaction:** 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-2014*](#_bookmark174)]

**Comment:** [Contextual information/modifying factors](#_bookmark73) are necessary for alerts that are both sensitive and specific. Like clinical consequences, each known factor *SHOULD* be stated as specifically as possible. The factors *SHOULD* be amenable to implementation as executable logic using value sets from clinical terminologies such as [RxNorm](https://www.nlm.nih.gov/research/umls/rxnorm/), the [Anatomical Therapeutic Chemical Classification](https://www.whocc.no/atc/structure_and_principles/) [System (ATC)](https://www.whocc.no/atc/structure_and_principles/), [ICD-10](http://www.who.int/classifications/icd/en/), and [SNOMED-CT](https://www.snomed.org/snomed-ct). As is used in this example, a decision tree *SHOULD* relate each factor to a specific [recommended action](#_bookmark76) that is supported by the [evidence for a suspected](#_bookmark74) [drug-drug interaction](#_bookmark74)

**Frequency of Exposure to the PDDI:** Unknown

**Comment:** Frequency of exposure and frequency of harm information is rarely available but can help a clinician assess the risk/benefit trade-off of exposure to PDDI. Such information *SHOULD* be provided if available.

**Frequency of Harm for persons who have been exposed to the PDDI:** Unknown

**Comment:** Frequency of exposure and frequency of harm information is rarely available but can help a clinician assess the risk/benefit trade-off of exposure to PDDI. Such information *SHOULD* be provided if available.

### Applying the Minimal Information Model definitions to the PDDI between BCR- ABL Tyrosine Kinase Inhibitors (TKI) and Proton Pump Inhibitors (PPI)

We illustrate here the application of the Minimum Information Model to representing the PDDI involving BCR-ABL Tyrosine Kinase Inhibitors (TKIs) + Proton Pump Inhibitors (PPIs). Task Force drug experts created the description and decision tree shown in the Appendix [A.1.2.2 Example PDDI - BCR-ABL](#_bookmark103) [Tyrosine Kinase Inhibitors (TKI) + Proton Pump Inhibitors (PPI)](#_bookmark103). Here is the Task Force description annotated with Minimal Information Model definitions and discussion comments where different than for the previous example:

Drugs involved: [Tyrosine Kinase Inhibitors (TKIs)](#_bookmark104) and [Proton Pump Inhibitors (PPIs)](#_bookmark105)

**Comment:** The same comments about stated in the previous example about drugs involved apply to this example. Note that in the previous example the drugs involved are specified using RxNorm while this example uses ATC. This is to emphasize that, while the drugs involved *SHOULD* be listed as sets of terms from a terminology such as [RxNorm](https://www.nlm.nih.gov/research/umls/rxnorm/) or the [Anatomical Therapeutic Chemical Classification](https://www.whocc.no/atc/structure_and_principles/) [System (ATC)](https://www.whocc.no/atc/structure_and_principles/), the implementer *MAY* choose any terminology they think appropriate. To promote broader accessibility to PDDI knowledge, it is *RECOMMENDED* that the chosen terminology be one that is actively maintained and freely accessible to the public.

**Clinical Consequences:** Decreased efficacy relative to treatment for [chronic myeloid leukemia](#_bookmark106)

**Comment:** The same comments about stated in the previous example about the clinical consequences associated with a PDDI. Note that in the previous example the clinical consequences involved are specified using [ICD-10](http://www.who.int/classifications/icd/en/) while this example uses [SNOMED-CT](https://www.snomed.org/snomed-ct). This is to emphasize that, while the clinical consequences *SHOULD* be listed as sets of terms from a terminology such as ICD-10 or SNOMED-CT, the implementer *MAY* choose any terminology they think appropriate. To promote broader accessibility to PDDI knowledge, it is *RECOMMENDED* that the chosen terminology be one that is actively maintained and freely accessible to the public.

**Seriousness:** A decrease in chronic myeloid leukemia treatment efficacy is a serious potential clinical consequence because it can result in death, life-threatening hospitalization, and disability.

**Comment:** The same comments about stated in the previous example about the seriousness of a PDDI clinical consequence.

**Severity:** There is no intensity scale relevant to describing a decrease in chronic myeloid leukemia treatment efficacy

**Comment:** If there is no relevant description of intensity for the clinical consequence of a given PDDI, this *SHOULD* be explicitly stated.

**Mechanism of Interaction:** BCR-ABL Tyrosine Kinase inhibitors demonstrate pH dependent absorption for oral administration which may result in decreased efficacy when given concomitantly with medications that increase gastric pH.

**Comment:** The same comments about stated in the previous example about the mechanism of a PDDI. A limitation of this example is that it refers to 'medications that increase gastric pH' without reference any specific drugs or codes from a drug terminology.

**Contextual information/modifying factors:**

* The TKI is [imatinib](#_bookmark107) or [ponatinib](#_bookmark108)
  + **Recommended Action:** No special precautions
* **Evidence for a Suspected Drug-Drug Interaction:** Imatinib and ponatinib AUCs are not appreciably decreased by PPI co-administration
  + Iclusig [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc. 2016., and
  + 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.)
* The TKI is [nilotinib](#_bookmark109)
  + **Recommen****ded Action:** Assess risk and take action if necessary
  + **Evidence for a Suspected Drug-Drug Interaction:**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.
    - 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.
* The TKI is [bosutinib](#_bookmark110) or [dasatinib](#_bookmark111)
  + **Recommended Action:** Use only if benefit outweighs risk
  + **Evidence for a Suspected Drug-Drug Interaction:**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.
    - Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015
    - Bosulif [package insert]. New York, NY: Pfizer Labs; 2015.
    - Tasigna [package insert]. East Hanover, NJ: Novartis; 2015.

**Comment:** The same comments about stated in the previous example about the contextual information/modifying factors. As for other information items, reference to coded terms for drugs and other relevant entities *SHOULD* be used to reduce ambiguity. Notice that this example could be improved because it references coded terms for TKIs but not for antacids and H2 antagonists. The implementer *MAY* choose any terminologies they think appropriate. To promote broader accessibility to PDDI knowledge, it is *RECOMMENDED* that the chosen terminologies be one that is actively

maintained and freely accessible to the public.

**Frequency of Exposure to the PDDI:** Unknown

**Comment:** The same comments about stated in the previous example about the frequency of exposure to the PDDI.

**Frequency of Harm for persons who have been exposed to the PDDI:** Unknown

**Comment:** The same comments about stated in the previous example about the frequency of harm for persons who have been exposed to the PDDI.

## Background and Use Cases

### Stakeholder suggested core PDDI information items

The need for a standard representation of PDDI information was one of the topics addressed at two multi- stakeholder conference meetings/series [[*hines-2011*](#_bookmark170)][*[scheife-2015](#_bookmark188)*][[*payne-2015*](#_bookmark180)][[*tilson-2016*](#_bookmark192)]. Attendees at both conferences included stakeholders from drug information content providers, regulatory agencies, and academic organizations. 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-2015*](#_bookmark180)]:

* + - Drugs Involved
    - Clinical consequences
    - Frequency of exposure to the PDDI
    - Frequency of harm for person exposed to PDDI
    - Contextual information/modifying factors
    - Evidence
    - Mechanism of the Interaction
    - Recommended Actions
    - Seriousness Rating

These core information elements are consistent with the results of a separate international Delphi study on how to improve the delivery of medication alerts within computerized physician order entry systems (Riedmann et al. 2011). 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-2016*](#_bookmark169)]. However, there is little commonality across the conceptual models on those elements that are included and no single conceptual model covers all 9 of the information elements. 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 and 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) use considerably different information elements. For example, the National Drug File - Reference Terminology (NDF-RT) produced by the U.S. Department of Veterans Affairs [[*olvey-2010*](#_bookmark178)] includes detailed information about pharmacokinetic mechanisms but does not discuss clinical consequences. In contrast, the system reported by Mille, Degoulet, and Jaulent [[*mille-2007*](#_bookmark175)] provided details on the clinical consequences, including risk increasing and mitigating factors, but supplied only a limited structure for mechanism.

### The overarching use case for the minimum information model

The overarching use case for a minimum information model for representing PDDI information in a clinical context is **to provide a technical foundation for effective PDDI clinical decision support**. Unfortunately, existing drug information sources systems generally organize information into a more or less narrative format includes only some of the core PDDI information elements. 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*](#_bookmark155)] shown in [Figure 2](#_bookmark112).

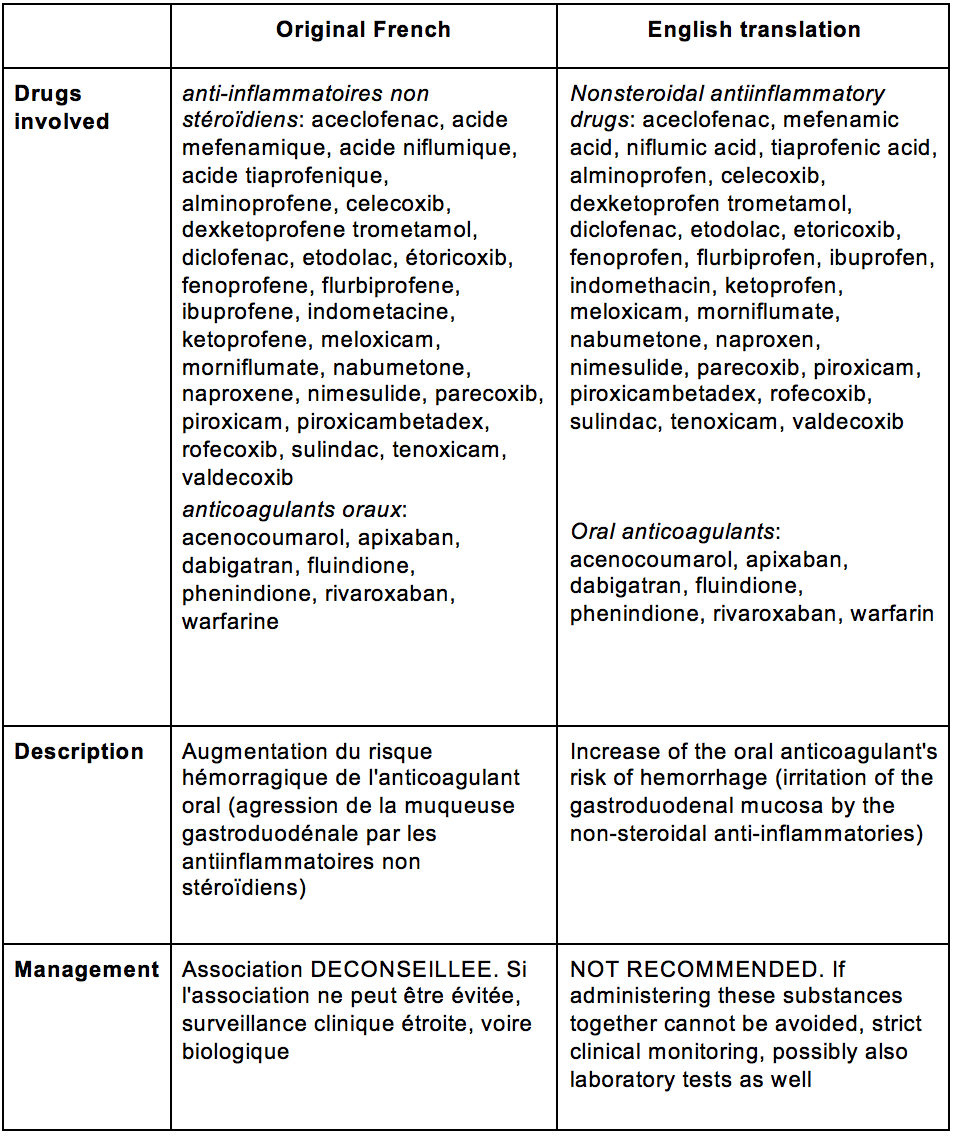


Figure 2 PDDI example from a French compendium

The PDDI narrative shown is structured into short and easy-to-read description and management sections. However, much of the information in the proposed minimum information model is either not structured or not provided:

* + - *Drugs Involved* - textual, non-standardized, non-coded lists of ingredients that have been classified as either NSAIDs or as oral anticoagulants
    - *Clinical consequences* - textual, non-standardized, 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* - textual, non-standardized, mention of gastroduodenal irritation by the NSAID
    - *Recommended actions* - avoidance if possible, monitoring otherwise
    - *Seriousness rating* - not explicit. However, the statement “not recommended” would suggest a risk of clinically significant consequence

As is evident from the listing above, there are four minimum information items that are not provided in the narrative (contextual information, frequency of exposure, frequency of harm, and evidence). Contextual information would include drug and patient characteristics 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 exposed persons who have been exposed). Together, these information items help to inform the clinician about the risk-benefit trade-off of PDDI exposure. In fact, it has been shown that effective clinical decision support that improves patient outcomes can be built using such information. For example, Tamblyn et al. found that a novel medication clinical decision support 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-2012*](#_bookmark190)]. Conversely, when a PDDI summary provides no context about risk and no frequency information, only clinical decision support alerts based on simple exposure to the drug combination can be built. This leads to highly sensitive but unspecific alerts and is a primary cause of alert fatigue and clinician dissatisfaction [[*van-der-sijs-2006*](#_bookmark196)].

Further, the PDDI narrative in [Figure 2](#_bookmark113) provides information without citing supporting evidence. Attendees of the 2015 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-2016*](#_bookmark192)]. Evidence in supporting PDDIs includes 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 [[*utecht-2017*](#_bookmark195)][*[brochhausen-](#_bookmark160)* [*2014*](#_bookmark160)]. Evidence may be useful for establishing the existence of an interaction without providing information about the potential clinical effect. Other evidence can help to answer questions about the associated clinical effects and their magnitude, variability, and estimated frequency [[*scheife-2015*](#_bookmark188)]. A PDDI representation should cite specific supporting evidence items and provide some acceptable appraisal of the total body of evidence [[*tilson-2016*](#_bookmark192)].

Unstructured narratives may also fail to provide critical information in computable form suitable for creation of personalized decision support presentation. The interaction described above notes that the mechanism of the interaction involves gastroduodenal irritation by the NSAID, suggesting gastrointestinal hemorrhage as a possible consequence. Such an occurrence would seem unlikely to occur for NSAIDs administered topically rather than orally. However, this constraint on the applicability of this PDDI is not stated implicitly: the formulation of the NSAID being described is ambiguous, and the importance of the means of administration is implied, but not stated directly. Describing PDDI evidence in terms of drugs in established drug terminologies, such as RxNorm (<https://www.nlm.nih.gov/research/umls/rxnorm/>), will reduce ambiguity and enable computation through rules and inference used to turn the PDDI descriptions into actionable content for clinical decision support.

The elements of the minimum information model demonstrate that, despite the readability of the example PDDI narrative, the information provided lacks both the structure and semantics necessary for effective decision support. Problems like these are not unique to the French Interactions médicamenteuses. For example, a search for the same Oral Anticoagulant / NSAID interaction executed at the drug ingredient level in the freely accessible database DrugBank returns a single statement that vaguely describes the clinical

effect but with no other information from the core items mentioned above:

“Ibuprofen may increase the anticoagulant activities of Warfarin.”

As [Figure 3](#_bookmark114) shows, slightly more information is provided in United States drug product labeling than in DrugBank but there are still many information gaps relative to the core PDDI information items suggested by conference series attendees (Bristol-Myers Squibb 2017).

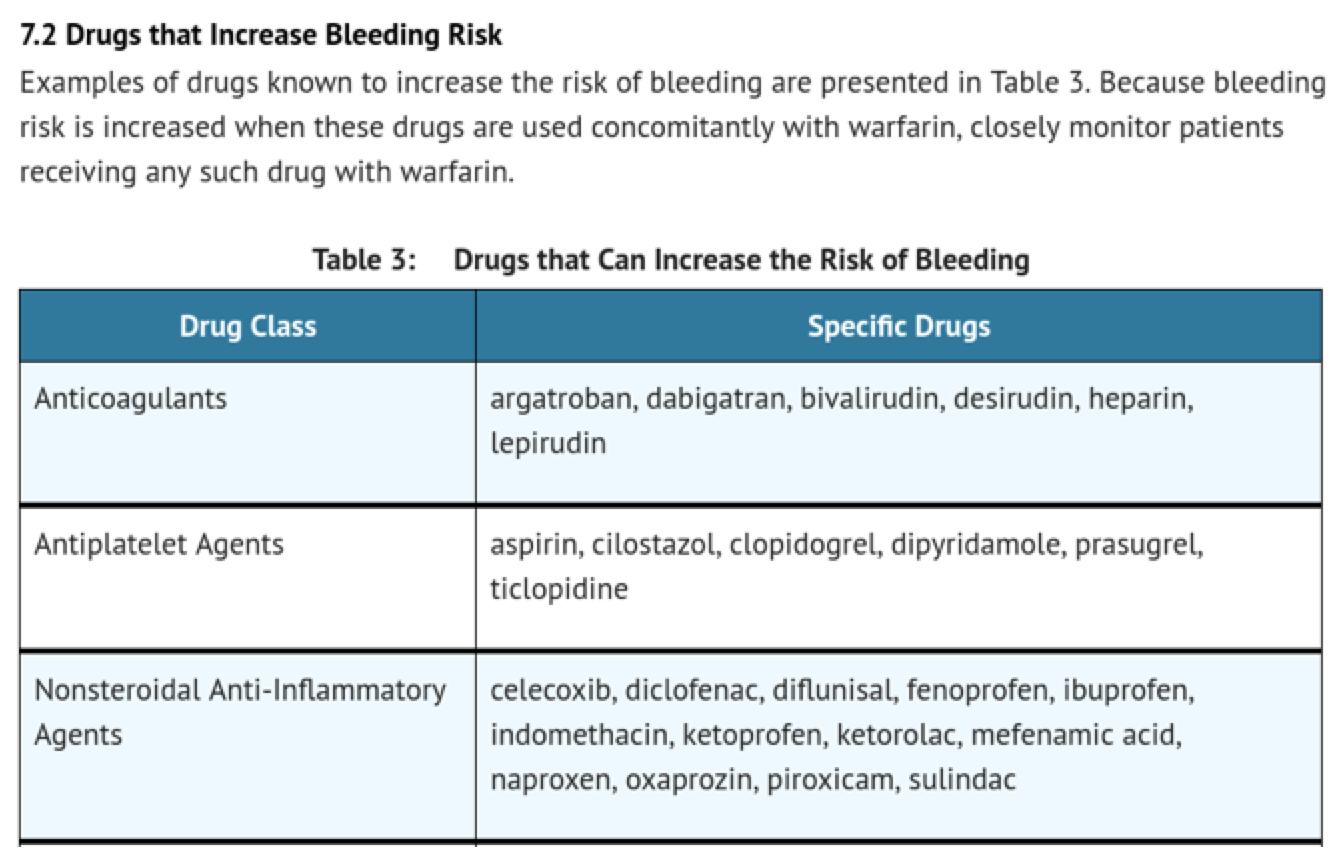


Figure 3 An oral Anticoagulant / NSAID PDDI shown at the drug ingredient level from the United States drug product label for COUMADIN- warfarin sodium tablet (Bristol-Myers Squibb 2017).

Although missing information is the primary concern for the examples discussed, the minimum information model would also increase the utility of narratives that are abundant with information. For example, a search for oral anticoagulant / NSAID in the online interaction checking tool provided by Drugs.com returns a very detailed narrative that 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 to best enable clinical decision support systems through the use of coded drugs names, clinical consequences, and contextual information and modifying factors. The provision of these details in a standardized, computable form will facilitate integration of PDDI information with data in a patient's

electronic health record, thus enabling patient-specific alerting and decision support.

### End-users of the minimum information model

User stories and goals were developed by the Task Force in order to show how the PDDI minimum information model would support various users. The Task Force began by developing stakeholder description and the user scenarios documents in order to identify key users. These 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.

Nine user stories with related goals were finalized by the Task Force force. Each user story was color coded for mention of core information items in the minimum information model (see [A.1.6.1 Color-coding Key](#_bookmark116)). The final set of user stories is located in [A.1.6.2 User Stories](#_bookmark115). User stories include the following:

* + - [A physician conducting treatment planning](#_bookmark117) (3 distinct user stories)
    - [A physician evaluating management options](#_bookmark118)
    - [A pharmacist evaluating management options](#_bookmark119)
    - [A nurse screening for PDDIs](#_bookmark120)
    - [A drug compendium editor synthesizing PDDI evidence for dissemination](#_bookmark121)
    - [A health science librarian assisting in the synthesis of PDDI evidence for dissemination](#_bookmark123)
    - [A systems analyst and content specialist translating a synthesizes of PDDI evidence into a clinical decision support tool](#_bookmark122)

The user types considered “out of scope” are listed in Appendix [A.1.6.3 Out of scope user stories](#_bookmark124).

### A set of use cases focused on medication reconciliation

Medication reconciliation use cases were created by the Task Force as a way to highlight the potential clinical applicability of the minimum information model. 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 and 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 force’s selected PDDIs were incorporated. Draft use cases were sent to the interviewed pharmacists for feedback and edits, and then presented during a full Task Force meeting involving all participants. Suggestions from this meeting were incorporated into the use cases. 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](file:///\\vmware-host\home\rdb20\Downloads\www.qualtrics.com)). This approach was chosen to allow for additional, anonymous feedback.

Three detailed medication reconciliation use cases are provide in the following sub-sections. Each use case is color coded for mention of core information items in the minimum information model (see [A.1.6.1 Color-](#_bookmark126) [coding Key](#_bookmark126)). One use case is for a Hospital Pharmacist dealing with medication reconciliation upon admission. Another use case is for a hospital pharmacist completing a dealing with medication reconciliation upon discharge. A third use case is 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 (see [A.1.2 Decision Trees Created for the Minimum Information Model Domain Analysis](#_bookmark125)).

#### Medication Reconciliation Use Cases

* + - 1. **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 as 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.

* + - 1. **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.

* + - 1. **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.

## Setting the Knowledge Representation Scope

The wide range of potential use cases for the information model require flexibility in certain aspects of the knowledge representation. Moreover, the number of pre-existing ontologies relevant to this domain clearly demonstrates the richness of the domain [[*herrero-zazo-2015*](#_bookmark168)]. 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:

* How should terms related to the core information items (see [2. Definitions for the Core Information Items of the Minimum Information Model](#_bookmark127)) be modeled?
* What is the role of an upper ontology?
* What is the relationship between the core information items and other existing ontologies?
* Should terms from other resources, such as medical terminologies, be reused?

The following list provides the strategies accepted by the PDDI Task Force (see [A.1.8 The Process Used by](#_bookmark128) [the Task Force for Setting the Knowledge Representation Scope](#_bookmark128)) based on recommendations from a sub-team of domain experts, biomedical informatics specialists, and knowledge representation experts:

* 1. The task force has developed an open source ontology called the Minimum PDDI Information Ontology ([MPIO](https://github.com/MPIO-Developers/MPIO)) for the core information items relevant to the PDDI domain (see Section [2. Definitions for the Core Information Items of the Minimum Information Model](#_bookmark130)). The ontology is limited in its semantic richness by design, but remains compatible with semantically rich models such as [DIDEO](http://purl.obolibrary.org/obo/dideo.owl) and [DINTO](http://purl.obolibrary.org/obo/dinto.owl). The minimal semantic richness of MPIO is motivated by the Task Force's domain analysis and resulting uses cases (see Section [3. Background and Use Cases](#_bookmark129)).
  2. The MPIO is written in the [Web Ontology Language (OWL 2)](http://www.w3.org/TR/owl2-primer/) [[*owl2-overview*](#_bookmark179)]. The individual classes in the MPIO are sub-classes of classes provided by the [Basic Formal Ontology (BFO)](https://github.com/bfo-ontology/BFO/wiki) upper ontology. This enables integration with numerous other ontologies written in OWL 2 that use the same upper ontology. This approach fosters integration with a number of existing formal ontology efforts including DIDEO, DINTO, [Ontology for Biomedical Investigations](http://obi-ontology.org/), and the [Ontology of Adverse Events](http://www.oae-ontology.org/).
  3. The core PDDI information items in the MPIO are all [information content entities](http://purl.obolibrary.org/obo/IAO_0000030). This approach is chosen because information in the PDDI domain can often be speculative or hypothetical and so it is important to distinguish between a description of a thing and the thing itself. Information content entities support this type of description and avoid the [existential fallacy](https://en.wikipedia.org/wiki/Existential_fallacy).
  4. One effect of defining the core PDDI information items as information content entities is that the OWL 2 entities do not refer to the actual material entities or processes. Rather, all properties of the

core information items are terminological in nature and refer to relations between the term and other terms. For example, the core term [Mechanism of Interaction](#_bookmark75) does not represent an entity that has participants or is preceded by another biological process. Those would be properties of material processes that are the actual realized mechanisms of the interaction. The MPIO term [Mechanism of](#_bookmark75) [Interaction](#_bookmark75) is an information content entity provides information about those material processes. It is up to other ontologies, such as DIDEO or DINTO, to provide a detailed representation of the underlying biomedical processes, qualities, and material entities. These representations will be complementary to the core information items in MPIO.

* 1. An important requirement of the PDDI minimum information model is that it allow for integration of terms from existing biomedical terminologies such as ICD-10, SNOMED-CT, RxNorm, and LOINC. This presents a challenge since relevant terminologies can come with different levels of semantic richness, methodological rigor, and semantic commitments. While it is highly unlikely that it would be possible to unify all external terms semantically at an upper level with the core PDDI information items (see Section [2. Definitions for the Core Information Items of the Minimum Information Model](#_bookmark131)), terms for which a human understandable, non-circular, definition exist, *MAY* be re-used in the MPIO. Re-use *SHALL* be accomplished by representing an information content entity about the object referenced by the term. For example, the diagnosis referred to by a diagnostic code from ICD 10 would be reused in the MPIO by representing an information content entity corresponding to the ICD 10 code.

## Discussion

The information provided in this Community Group Note provides a concrete, user centered, basis for design and implementation activities for the PDDI minimum information model. Nine user stories with related goals show how the PDDI minimum information model would support various users (see [3.3 End-users of the](#_bookmark138) [minimum information model](#_bookmark138)). Detailed descriptions of more than a dozen PDDIs were written by the task force along with decision trees that represent specific clinical contexts (see [A.1.2 Decision Trees Created for](#_bookmark137) [the Minimum Information Model Domain Analysis](#_bookmark137)). Non-ambiguous definitions were created for PDDI core information items and implemented in a new an open source ontology (see Sections [2. Definitions for the](#_bookmark136) [Core Information Items of the Minimum Information Model](#_bookmark136) and [4. Setting the Knowledge Representation](#_bookmark135) [Scope](#_bookmark135)). Two example PDDIs were annotated with the core information items along with detailed discussion of Task Force recommendations (see Sections [2.1 Applying the Minimal Information Model definitions to the](#_bookmark134) [PDDI between warfarin and non-steroidal anti-inflammatory drugs (NSAIDs)](#_bookmark134) and [2.2 Applying the Minimal](#_bookmark133) [Information Model definitions to the PDDI between BCR-ABL Tyrosine Kinase Inhibitors (TKI) and Proton](#_bookmark133) [Pump Inhibitors (PPI)](#_bookmark133). A subset of the user stories and selected PDDIs were integrated into three medication reconciliation use cases (see Section [3.4.1 Medication Reconciliation Use Cases](#_bookmark132)).

The next sub-sections provide a discussion of three potential applications of the minimum information that are shown in [Figure 1](#_bookmark139).

### Shareable PDDI Clinical Decision Support Using HL7 Standards

The creation and maintenance of PDDI clinical decision support (CDS) generally requires considerable time and energy from highly trained domain experts. An additional need is to standardize the electronic health records context that is used to trigger CDS services. This can include context parameters that currently might not available but that, if present, would be useful for increasing the specificity of the PDDI CDS alerts.

Achieving this sort of standardization is important to ensure that PDDI decision support can be implemented across a variety of systems.

Fast Health Interoperability Resources (FHIR) provides a possible solution to the challenge of seamless information exchange and data interoperability of information resources in health care related environments (Bender and Sartipi 2013; Mandel et al. 2016). [FHIR](https://www.hl7.org/fhir/overview.html) is a standard created by the [Health Level Seven (HL7)](https://www.hl7.org/)

organization. The standard provides a collection of specifications for resources in healthcare settings for the purpose of overcoming the data exchange challenges in healthcare. FHIR defines a set of standardized data models for health care covering key areas including Clinical information, Diagnostics, and Medications. For instance, the Medication resource contains medication codes, ingredient details, packaging information and related information. FHIR resources are API-based, making it possible for third party systems to access electronic health records data for the purpose of supporting new use cases.

FHIR encodings of PDDI information could form the basis of information exchange for more standardized PDDI clinical decision support. Indeed, a new [HL7 project related to PDDI decision support](http://wiki.hl7.org/index.php?title=PDDI_CDS) has been recently approved by the HL7 [Clinical Decision Support](http://wiki.hl7.org/index.php?title=Clinical_Decision_Support_Workgroup) and [Pharmacy Workgroups](http://wiki.hl7.org/index.php?title=Pharmacy_WG). The project seeks to develop an implementation guide for PDDI CDS that will specify both a knowledge representation format for PDDI logic and CDS services for PDDI with electronic health record (EHR) systems. Specifically, the implementation guide will include specifications for:

* + 1. How to represent PDDI logic in the HL7 [Clinical Quality Language](http://wiki.hl7.org/index.php?title=Clinical_Quality_Language) (CQL) using the FHIR Clinical Reasoning module.
    2. How to use the emerging [CDS Hooks](https://cds-hooks.org/) standard as a mechanism for electronic health records to request PDDI CDS from CDS services.

As is stated in the [project's scope statement](https://github.com/HL7/PDDI-CDS/blob/master/Documents/ProjectScopeStatement/PDDI%20CDS%20PSS%2002-15-2018.docx?raw=true), the HL7 PDDI CDS project will draw from the technical foundation, PDDI information, and user centered design artifacts reported in this Community Group Note. It is anticipated that the project may raise the need to create new FHIR resource(s) (e.g., a resource to represent drug interactions) and/or FHIR profile(s) (e,g, for PDDI context representation). At the time of this writing, participation in the PDDI CDS project is open to public participation. Persons interested in participation can find more information on the [HL7 PDDI CDS project wiki](http://wiki.hl7.org/index.php?title=PDDI_CDS).

### Enhancing the Drug-drug Interaction Section of Structured Product Labeling

Serious consequences for patients could result if information about known drug interactions is missing from a drug’s product labeling. To address this potential risk, the United States Food and Drug Administration (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).

Similar requirements have been enacted by the European Medicine's Agency for their equivalent of product labeling called [Summary of Product Characteristics](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248251/).

As mentioned in a previous section (see [3.2 The overarching use case for the minimum information model](#_bookmark140)), 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 drug labels [[*boyce-2013*](#_bookmark159)]. This problem is not unique to United States labeling. For instance, Pfistermeister et al. reported that critical drug–drug interaction warnings are frequently missing, or are mentioned inconsistently in the United States, United Kingdom, and German labels of the involved drugs [[*pfistermeister-2014*](#_bookmark181)].

As is shown [Figure 1](#_bookmark141), the PDDI minimum information model could help address this issue by making PDDI information reported in product labeling more complete and clinically useful. In the United States and other parts of the world, the content of a drug's product label is written by the company that owns the drug as part of the drug approval process. There is currently no information model to guide product label authors as they write drug interaction information. The PDDI minimum information model could providing authors with clear guidance on the core information items that they should discuss.

This approach might require an annotation tool to help authors tag the core PDDI information items correctly and consistently. Once the PDDI information is authored using the minimum information model, it would

need to be published in a computer readable format. In the United States, this would currently be accomplished using the [Structured Product Label (SPL)](https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/) standard. Other standards, such as the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP) serve a similar function outside of the United States. Focusing on the United States as case study, SPLs are XML documents written using the HL7 SPL specification that the FDA requires industry to use when submitting drug product label content (FDA 2005). The HL7 [Biomedical Research and Regulation](https://www.hl7.org/Special/committees/rcrim/overview.cfm) developed and maintains the SPL standard. Currently, 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 30,000 prescription products.

It would be technically possible to publish PDDI information annotated using the minimum information model in a computer readable format using what is called an SPL *supplemental indexing file*. Supplemental indexing to SPLs are SPL files that provide additional useful information for official FDA drug SPLs.

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 PDDI minimum information model. 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, and character-delimited tables. The Task Force recommends that this idea and other possibilities be tested to determine how to best provide accurate PDDI information that is clinically useful for decision support by SPL consumers.

### Highlighting and Filling Gaps in Evidence Needed to Develop PDDI Decision Support

Existing PDDI knowledge is heterogeneous with respect to coverage of the core information elements. For example, frequency of exposure and frequency of harm evidence was not available for either of the two PDDI examples detailed in this Note (see Sections [2.1 Applying the Minimal Information Model definitions](#_bookmark144) [to the PDDI between warfarin and non-steroidal anti-inflammatory drugs (NSAIDs)](#_bookmark144) and [2.2 Applying the](#_bookmark143) [Minimal Information Model definitions to the PDDI between BCR-ABL Tyrosine Kinase Inhibitors (TKI)](#_bookmark143) [and Proton Pump Inhibitors (PPI)](#_bookmark143)). Other examples of knowledge gaps are mentioned in Appendix [A.1.2](#_bookmark142) [Decision Trees Created for the Minimum Information Model Domain Analysis](#_bookmark142), such as the poorly understood mechanism of the PDDI between warfarin and Ifosfamide/Etoposide.

Part of the reason that there are many knowledge gaps is that 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, gaps in knowledge can exist 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.

In order to realize the potential of the minimum information model to advance PDDI decision support, it is important that gaps in clinically useful PDDI knowledge be identified, prioritized, and addressed. The information model itself would help highlight research gaps by acting as an information template for a group of drug experts to use while PDDI synthesizing evidence. As the expert panel compiles evidence for each of the core information categories, critical gaps in knowledge would become apparent. The prioritized gaps could help clinical research community to make efforts to generate appropriate evidence to fill those gaps.

One activity that can help lay the foundation for broader efforts to address gaps in PDDI knowledge is the

development of computable cohort descriptions — serialized queries that combine concept sets with logical operations to extract specific patient sub-populations from a clinical data repository. Computable cohort descriptions are a cornerstone for research on PDDIs using real world data. A recent project showed the feasibility of converting the decision trees for PDDIs created as part of this Note to computable cohort definitions [[*rosko-2017*](#_bookmark186)]. The target for translation was the Atlas clinical research tool created by the Observational Data Health and Informatics collaborative. Atlas has a powerful interface for creating, running, and sharing cohort descriptions [*[ohdsi-atlas](#_bookmark177)*]. Once created, the cohort descriptions were executed over a clinical dataset for a simulated population stored in the OHDSI common data model. The code, concept sets, and cohort descriptions for the demonstration are stored in [a GitHub repository](https://github.com/dbmi-pitt/iDIA_Rules) and [Docker container](https://github.com/dbmi-pitt/docker-iDIA-Rules).

The Task Force recommends further research that builds on this preliminary work with the goal of developing a learning system that identifies gaps in PDDI knowledge about the frequency of PDDI exposure, frequency of clinical outcomes, and factors that modify the risk of harm, prioritizes the gaps, and the collect data from multiple sites to fill in those knowledge gaps in knowledge. If successful, such a system would help improve patient safety by making PDDI decision support more current and complete than is currently the case.

## Conclusion

This Community Group Note provides motivation and a detailed domain analysis for a minimum information model for PDDI information. The Note also suggests potential applications of the minimum information model that could lead to improvements in patient safety with respect to PDDIs. The overarching goal of these contributions is to provide a technical foundation for effective PDDI clinical decision support. A reference implementation of the information model is the subject of future work.

## Acknowledgments

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## Appendices

### Development Process

Toward the goal of developing such a model, a volunteer-based Task Force was formed by the Health Care and Life Sciences Interest Group, an interest group that operates publicly through the World Wide Web Consortium (W3C). This 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 stakeholders (i.e.,

individuals who edit drug information sources, various types of clinicians, and decision support system 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 of the information model.

#### 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. 1The algorithms are 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. Two sample decision trees illustrating the management options can be found in the appendix (see Appendix [DECISION TREES](#_bookmark145)).

1The 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 (AHRQ Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone, University of Arizona; John Horn, Philip Hansten, University of Washington).

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. Task Force drug experts selected the PDDIs and identified contextual information/modifying factors that would warrant any of three different recommended actions - *No special precautions, Assess risk and take action if necessary, and Use only if benefit outweighs risk*. 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.

The Task Force began with a discussion of how to select the PDDIs for developing decision trees. One option was to select 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 which follow from the aforementioned information categories suggested by attendees of the multi-stakeholder conference meetings/series mentioned in Section [3. Background and Use Cases](#_bookmark146):

* + - 1. The interaction could (and should) be contextualized for specific patients or clinical circumstances.
      2. The interaction applies at the drug class level.
      3. The interaction does not apply at the drug class level.
      4. The mechanism is known and is pharmacokinetic.
      5. The mechanism is known and is pharmacodynamic.
      6. The mechanism is poorly described, not well elucidated.
      7. The evidence supporting the interaction is strong.
      8. The evidence supporting the interaction is weak.
      9. The frequency of exposure data is available.
      10. The frequency of exposure data is not available.
      11. The frequency of adverse event data is available.
      12. The frequency of adverse event data is not available. M.The recommended action is “monitor” or “take note”.

1. The recommended action is “avoid”.
2. The recommended action is “a clear alternative drug and dose”.

#### Decision Trees Created for the Minimum Information Model Domain Analysis

The Task Force developed 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 1*.

***Table 1***

#### 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 CYP2D6 status on paroxetine will derive no benefit from tamoxifen. (Status: completed, see [the](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees) [project on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

Combination has known patient-specific risk factors.

Potassium (KCL)

Potassium- sparing Diuretics

#### (Status: Completed as part of the iDIA project -- need permission before releasing to this project's github)

Applies at the class level

Monoamine Oxidase Inhibitors (MAOIs)

Indirect Sympathomime tics

A class interaction involving all drugs in the class. (Status: completed, see [the project on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

Does not apply at the class level

Tyrosine Kinase Inhibitors

Proton Pump Inhibitors

Not all Kinase inhibitors 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). (Status: completed, see [the project](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees) [on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

The mechanism is known and is pharmacokinetic

Warfarin

CYP2C9

Inhibitors (ie. Bactrim)

A CYP-mediated pharmacokinetic interaction. **(Status: In Process)**

A transport protein (p-

Digoxin Cyclosporin

glycoprotein) mediated interaction. **(Status: In Process)**

The mechanism is known and is pharmacodynamic

Epinephrine Beta-Blockers

The interaction is different differentiates between selective and non-selective beta blockers. The clinical outcome is a; hypertensive crisis. **(Status: Completed as part of the iDIA project**

#### -- need permission before releasing to this project's github)

The mechanism is not well elucidated/known

Warfarin Ifosfamide/Eto poside

Drugs for treating cancers of the blood drugs. - Clinical effect is INR change buts no mention of what mechanism could be found. (Status: completed,

see [the project on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

The evidence supporting the interaction is strong

Epinephrine Beta-Blockers

Widely known interaction with considerable available evidence. **(Status: Completed as part of the iDIA project -- need permission before releasing to this project's github)**

Simvastatin, Atorvastatin, Lovastatin

Clarithromycin

Widely known interaction with considerable available evidence. **(Status: In Process)**

The evidence supporting the interaction is weak

Warfarin

Antibiotics that don't inhibit CYP2C9

Hard to find evidence for the interaction. **(Status: In Process)**

The frequency of exposure data is available

Warfarin

Non-steroidal anti- inflammatory drugs (NSAIDs)

Paper by Malone et al. - National sample. (Status: completed, see [the project](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees) [on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

The frequency of exposure data is not available

Simvastatin Fluconazole

Based on literature search. (Status: completed, see [the](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees) [project on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

The frequency of adverse event data is available

Spironolacton e

Potassium supplements

Associated with Risk of hospitalization. **(Status: Completed as part of the iDIA project (KCL and K- sparing diuretics) -- need permission before releasing to this project's github)**

The frequency of adverse event data is not available

Simvastatin Fluconazole

Literature search did not find frequency of adverse event data. (Status: completed, see [the project](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees) [on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

The recommended action is “monitor” or “take note”

Potassium (KCL)

Potassium- sparing Diuretics

#### See explanation above. (Status: Completed as part of the iDIA project -- need permission before releasing to this project's github)

The recommended action is “avoid”

Monoamine Oxidase Inhibitors (MAOIs)

Indirect Sympathomime tics

See explanation above. (Status: completed, see [the](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees) [project on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

The recommended action is a clear alternative drug and dose

Simvastatin Amiodarone

[http://www.fda.gov/Drugs/](http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm) [DrugSafety/ucm283137.ht](http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm) [m](http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm) (Status: completed, see [the project on github](https://github.com/W3C-HCLS/w3c-ddi/tree/master/Decision-trees)).

* + - 1. **Example PDDI - Warfarin + NSAIDs (Draft)**

#### AHRQ 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).

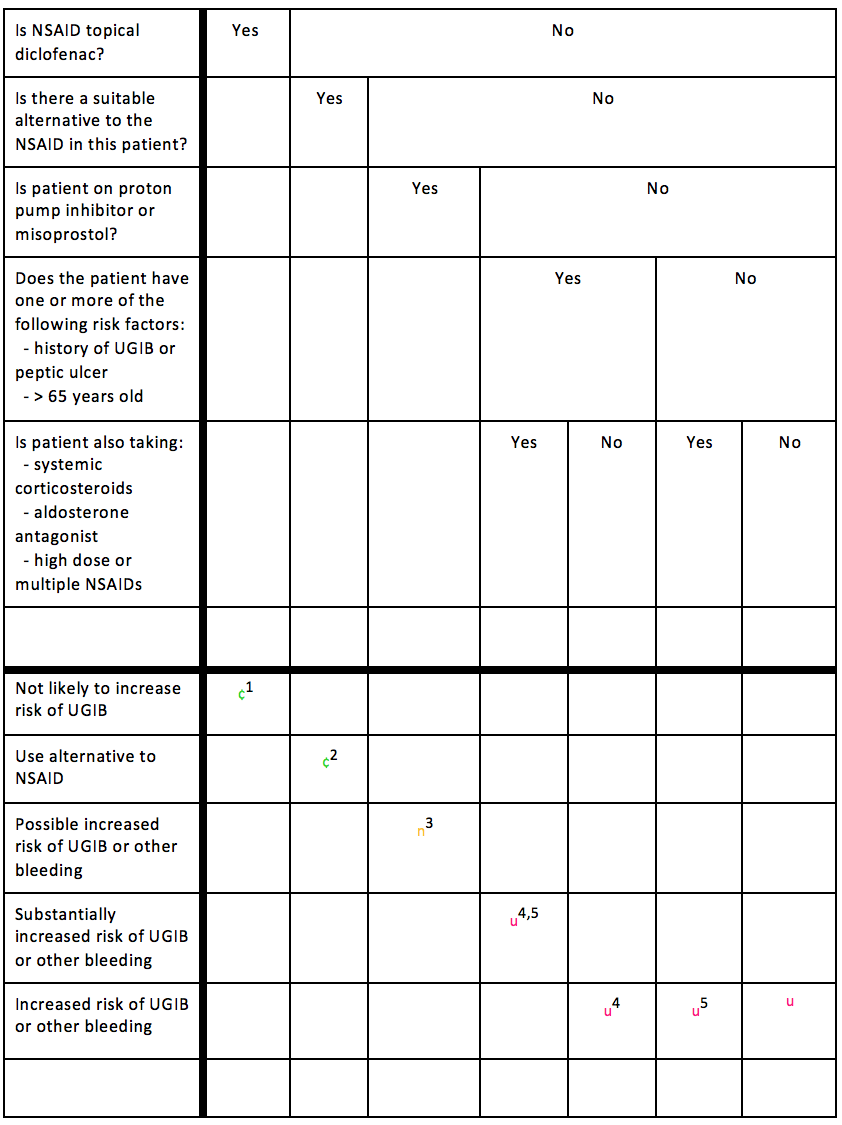


Figure 4 ¢ = No special precautions. n = Assess risk and take action if necessary. u = Use only if benefit outweighs risk

#### 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.

1. Proton pump inhibitors and misoprostol may reduce the risk of UGIB in patients receiving NSAIDs and warfarin.
2. 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.
3. 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-2014*](#_bookmark174)]
   * + 1. **Example PDDI - BCR-ABL Tyrosine Kinase Inhibitors (TKI) + Proton Pump Inhibitors (PPI)**

#### NIH Grant: "Addressing gaps in clinically useful evidence on drug-drug interactions" (R01LM011838); ; 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

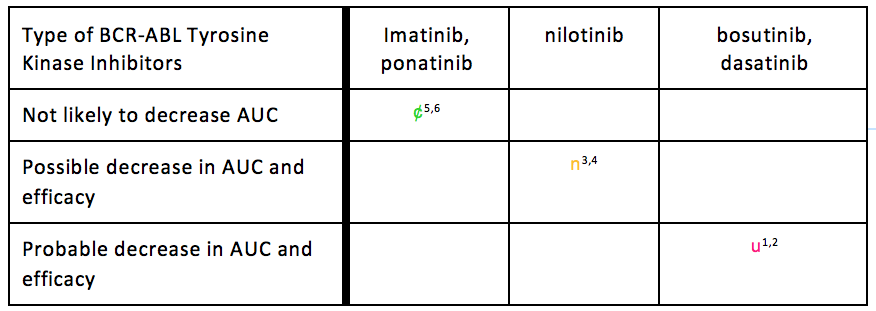


Figure 5 ¢ = No special precautions. n = Assess risk and take action if necessary. u = Use only if benefit outweighs risk

#### Footnotes:

1. [[*sprycel-2015*](#_bookmark189)]
2. [[*bosulif-2015*](#_bookmark157)]
3. [[*tasigna-2015*](#_bookmark191)] 4. [[*yin-2012*](#_bookmark199)]

5. [[*iclusig-2016*](#_bookmark171)] 6. [[*egorin-2009*](#_bookmark165)]

#### 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 [A.1.6.3](#_bookmark147) [Out of scope user stories](#_bookmark147).

In order to develop the user stories for the core user types, Task Force members created an initial information needs list and then was supplemented it with user interviews, interview transcripts collected as a part of a recently published manuscript on PDDI information needs of drug information compendium editors [[*romagnoli-2017*](#_bookmark185)], 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 minimum information model information item in question.

#### Workflow for arriving at user-centered definitions

We used the process shown in [Figure 6](#_bookmark150) to arrive at user-centered definitions for the core information items recommended by the prior drug interaction conference series (see Section [3. Background and Use Cases](#_bookmark149)). 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-2015*](#_bookmark168)] and DIDEO [[*brochhausen-2014*](#_bookmark160)] ontologies. We then solicited feedback from all Task Force force participants using a Qualtrics survey (see [A.1.5 Example of the survey used to](#_bookmark148) [arrive at final user centered definitions](#_bookmark148) ). The survey asked participants to rate their level of agreement with the definition and the 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, and 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.

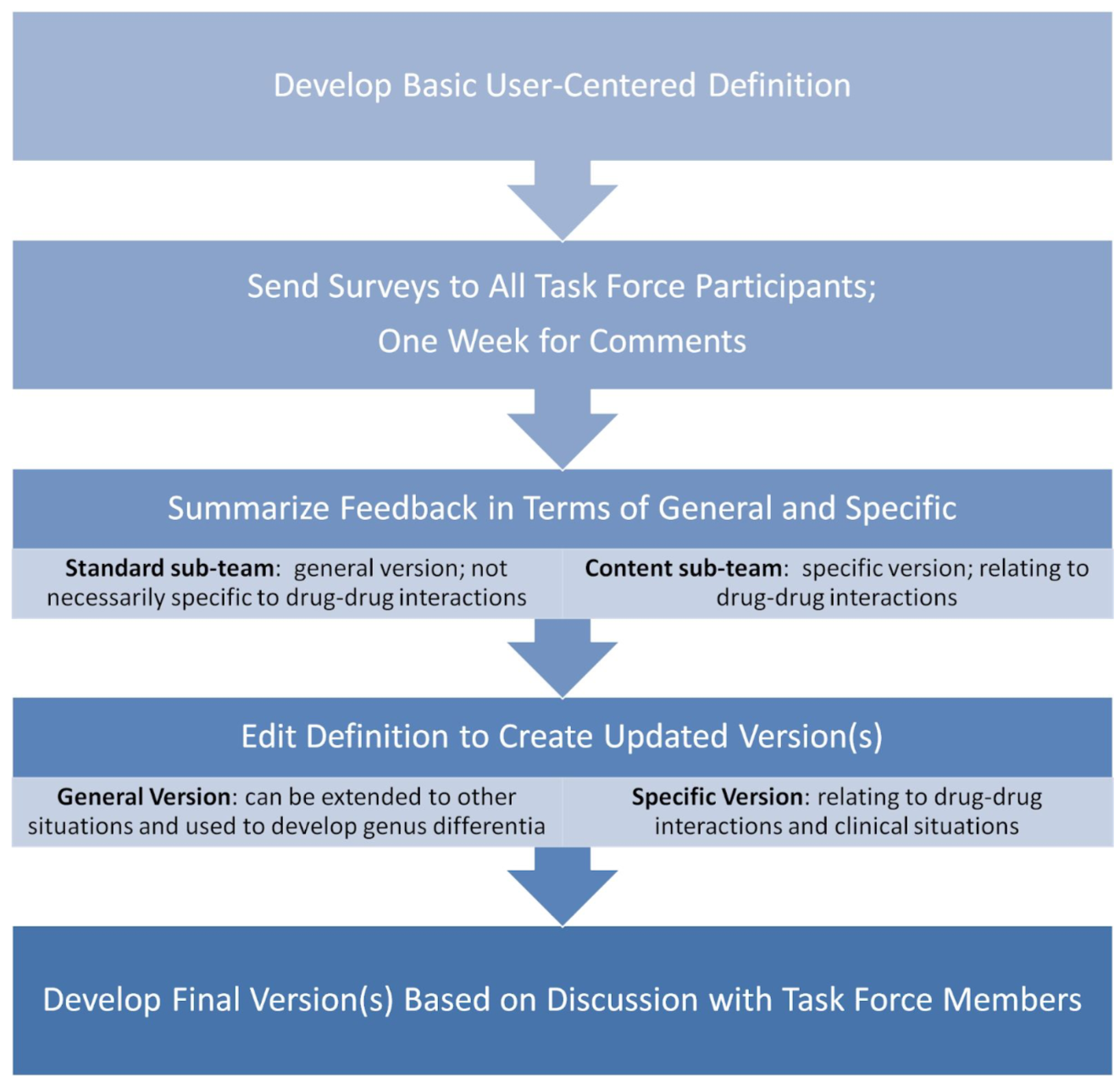


Figure 6 The process used by the Task Force to arrive at user-centered definitions for the core information items recommended by two multi-stakeholder conference meetings/series [[*hines-2011*](#_bookmark170)][*[scheife-2015](#_bookmark188)*][*[payne-](#_bookmark180)* [*2015*](#_bookmark180)][[*tilson-2016*](#_bookmark192)].

#### Example of the survey used to arrive at final user centered definitions

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-2014*](#_bookmark174)]
        + **Source:** Outcome of the decision pathway, [Warfarin-NSAID Decision Table](https://pitt.co1.qualtrics.com/CP/File.php?F=F_29xiLSLtHky74vX), AHRQ 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?

#### User stories for the minimum information model

* + - 1. **Color-coding Key**

The following three use cases presented below use the following color-coding to represent core information items defined for the minimum information model. A table summarizing the information needs exposed by these use cases is also presented in Appendix [A.1.7.2 Medication Reconciliation Information Needs Table](#_bookmark151).

Clinical Consequences

Evidence

Recommended Actions

Mechanism of Interaction

Contextual Evidence/Modifying Factors

Seriousness/Severity Rating

Frequency of Harm/Exposure

* + - 1. **User Stories**
         1. **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.

* + - * 1. **luation 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.

* + - * 1. **luation 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.

* + - * 1. **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.

* + - * 1. **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.

* + - * 1. **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.

* + - * 1. **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.

**A.1.6.3 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, since the goals of the user stories were to determine how healthcare providers use PDDI information in patient care, what PDDI resources healthcare providers use when making patient care decisions, and how those PDDI resources are developed.

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

#### Information Needs Tables

* + - 1. **User Information Needs Table**
      2. **Medication Reconciliation Information Needs Table**

#### The Process Used by the Task Force for Setting the Knowledge Representation Scope

A sub-team of the task force focused on setting the scope of knowledge representation for the minimum information model. A series of teleconferences bringing together domain experts, biomedical informatics specialists, and knowledge representation experts across the task force. Starting with a core set of questions, topics were discussed, arguments for different approaches were laid out and, agreement among the

participants was sought. Besides 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 was written into a draft document. The final version of the document was revised and written as Section of this document.

#### Value Sets to Support PDDI Examples

* + - 1. **aldosterone antagonists (RxNorm)**

298869 - eplerenone

9997 - Spironolactone

351256 - eplerenone 25 MG Oral Tablet 351257 - eplerenone 50 MG Oral Tablet

198224 - Hydrochlorothiazide 25 MG / Spironolactone 25 MG Oral Tablet 198225 - Hydrochlorothiazide 50 MG / Spironolactone 50 MG Oral Tablet 198222 - Spironolactone 100 MG Oral Tablet

313096 - Spironolactone 25 MG Oral Tablet 198223 - Spironolactone 50 MG Oral Tablet

* + - 1. **bosutinib (ATC)**

L01XE14 - bosutinib

* + - 1. **cerebral hemorrhage (ICD-10)**

**I61**.0 **- Nontraumatic intracerebral hemorrhage in hemisphere**, **subcortical I61**.1 **- Nontraumatic intracerebral hemorrhage in hemisphere**, **cortical I61**.2 **- Nontraumatic intracerebral hemorrhage in hemisphere**, **unspecified I61**.3 **- Nontraumatic intracerebral hemorrhage in brain stem**

**I61**.4 **- Nontraumatic intracerebral hemorrhage in cerebellum I61**.5 **- Nontraumatic intracerebral hemorrhage**, **intraventricular**

**I61**.6 **- Nontraumatic intracerebral hemorrhage**, **multiple localized I61**.8 **- Other nontraumatic intracerebral hemorrhage**

**I61**.9 **- Nontraumatic intracerebral hemorrhage**, **unspecified P10**.0 **- Subdural hemorrhage due to birth injury**

**P10**.1 **- Cerebral hemorrhage due to birth injury**

**P10**.2 **- Intraventricular hemorrhage due to birth injury P10**.3 **- Subarachnoid hemorrhage due to birth injury P10**.4 **- Tentorial tear due to birth injury**

**P10**.8 **- Other intracranial lacerations and hemorrhages due to birth injury P10**.9 **- Unspecified intracranial laceration and hemorrhage due to birth injury P52**.0 **- Intraventricular** (**nontraumatic**) **hemorrhage**, **grade** 1, **of newborn**

**P52**.1 **- Intraventricular** (**nontraumatic**) **hemorrhage**, **grade** 2, **of newborn P52**.2 **- Intraventricular** (**nontraumatic**) **hemorrhage**, **grade** 3 **and grade** 4, **of**

**newborn**

**P52**.3 **- Unspecified intraventricular** (**nontraumatic**) **hemorrhage of newborn P52**.4 **- Intracerebral** (**nontraumatic**) **hemorrhage of newborn**

**P52**.5 **- Subarachnoid** (**nontraumatic**) **hemorrhage of newborn**

**P52**.6 **- Cerebellar** (**nontraumatic**) **and posterior fossa hemorrhage of newborn P52**.8 **- Other intracranial** (**nontraumatic**) **hemorrhages of newborn**

**P52**.9 **- Intracranial** (**nontraumatic**) **hemorrhage of newborn**, **unspecified S06**.8 **- Other specified intracranial injuries**

* + - 1. **chronic myeloid leukemia (SNOMED-CT)**

415287001 - Relapsing chronic myeloid leukemia 277589003 - Atypical chronic myeloid leukemia 277587001 - Juvenile chronic myeloid leukemia

128826001 - Atypical chronic myeloid leukemia, BCR/ABL negative

* + - 1. **dasatinib (ATC)**

L01XE06 - dasatinib

* + - 1. **gastrointestinal bleeding or peptic ulcer (ICD-10)**

**k92**.2 – **Gastrointestinal hemorrhage**, **unspecified k25**.0 – **Acute gastric ulcer with hemorrhage**

**k25**.2 – **Acute gastric ulcer with hemorrhage and perforation k25**.4 – **Chronic or unspecified gastric ulcer with hemorrhage**

**k25**.6 – **Chronic or unspecified gastric ulcer with both hemorrhage and perforation**

**k26**.0 – **Acute duodenal ulcer with hemorrhage**

**k26**.2 **- Acute duodenal ulcer with hemorrhage and perforation k26**.4 – **Chronic duodenal ulcer with hemorrhage**

**k26**.6 – **Chronic duodenal ulcer with hemorrhage and perforation k27**.0 – **Acute peptic ulcer**, **site unspecified**, **with hemorrhage**

**k27**.2 **- Acute peptic ulcer**, **site unspecified**, **with hemorrhage and perforation k27**.4 – **Chronic peptic ulcer**, **site unspecified**, **with hemorrhage**

**k27**.6 – **Chronic peptic ulcer**, **site unspecified**, **with hemorrhage and perforation k28**.0 – **Acute gastrojejunel ulcer with hemorrhage**

**k28**.2 **- Acute gastrojejunel ulcer with hemorrhage and perforation k28**.4 – **Chronic gastrojejunel ulcer with hemorrhage**

**k28**.6 – **Chronic Acute gastrojejunel ulcer with hemorrhage and perforation k29**.01 – **Acute gastritis with bleeding**

**k29**.31 – **Chronic gastritis with bleeding**

**k29**.41 – **Chronic atrophic gastritis with bleeding k29**.51 – **Unspecified chronic gastritis with bleeding k29**.61 – **Other gastritis with bleeding**

**k29**.71 – **Gastritis**, **unspecified**, **with bleeding k29**.81 – **Duodenitis with bleeding**

**k29**.91 – **Gastroduodenitis**, **unspecified**, **with bleeding**

**k31**.811 – **Angiodysplasia** –**of stomach and duodenum with bleeding k31**.82 – **Dieulafoy lesion** (**hemorrhagic**) **of stomach and duodenum**

* + - 1. **imatinib (ATC)**

L01XE01 - imatinib

* + - 1. **intracranial hemorrhage (ICD-10)**

**I62**.0 **- Nontraumatic subdural hemorrhage I62**.1 **- Nontraumatic extradural hemorrhage**

**I62**.9 **- Nontraumatic intracranial hemorrhage**, **unspecified I69**.2 **- Sequelae of other nontraumatic intracranial hemorrhage P10**.0 **- Subdural hemorrhage due to birth injury**

**P10**.1 **- Cerebral hemorrhage due to birth injury**

**P10**.2 **- Intraventricular hemorrhage due to birth injury P10**.3 **- Subarachnoid hemorrhage due to birth injury P10**.4 **- Tentorial tear due to birth injury**

**P10**.8 **- Other intracranial lacerations and hemorrhages due to birth injury P10**.9 **- Unspecified intracranial laceration and hemorrhage due to birth injury P52**.0 **- Intraventricular** (**nontraumatic**) **hemorrhage**, **grade** 1, **of newborn**

**P52**.1 **- Intraventricular** (**nontraumatic**) **hemorrhage**, **grade** 2, **of newborn P52**.2 **- Intraventricular** (**nontraumatic**) **hemorrhage**, **grade** 3 **and grade** 4, **of**

**newborn**

**P52**.3 **- Unspecified intraventricular** (**nontraumatic**) **hemorrhage of newborn P52**.4 **- Intracerebral** (**nontraumatic**) **hemorrhage of newborn**

**P52**.5 **- Subarachnoid** (**nontraumatic**) **hemorrhage of newborn**

**P52**.6 **- Cerebellar** (**nontraumatic**) **and posterior fossa hemorrhage of newborn P52**.8 **- Other intracranial** (**nontraumatic**) **hemorrhages of newborn**

**P52**.9 **- Intracranial** (**nontraumatic**) **hemorrhage of newborn**, **unspecified S06**.5 **- Traumatic subdural hemorrhage**

**S06**.8 **- Other specified intracranial injuries**

* + - 1. **misoprostol (RxNorm)**

42331 - Misoprostol

* + - 1. **nilotinib (ATC)**

L01XE08 - nilotinib

* + - 1. **-steroidal anti-inflammatory drugs (NSAIDs) (RxNorm)**

1425 - Benzydamine

140587 - celecoxib

3355 - Diclofenac

24605 - Etodolac

24830 - fenbufen

4331 - Fenoprofen

4502 - Flurbiprofen

5640 - Ibuprofen

5781 - Indomethacin

6142 - Ketoprofen

35827 - Ketorolac

588003 - Meclofenamate

41493 - meloxicam

31448 - nabumetone

7258 - Naproxen

32613 - oxaprozin

8356 - Piroxicam

10237 - Sulindac

10255 - Suprofen

37790 - tenoxicam

10636 - Tolmetin

278567 - valdecoxib

1665675 - 1 ML Ketorolac Tromethamine 15 MG/ML Cartridge

860092 - 1 ML Ketorolac Tromethamine 15 MG/ML Injection

860113 - 1 ML Ketorolac Tromethamine 15 MG/ML Prefilled Syringe 1665679 - 1 ML Ketorolac Tromethamine 30 MG/ML Cartridge

1665461 - 1 ML Ketorolac Tromethamine 30 MG/ML Injection

860114 - 1 ML Ketorolac Tromethamine 30 MG/ML Prefilled Syringe

1367426 - 12 HR Naproxen sodium 220 MG / Pseudoephedrine Hydrochloride 120 MG Extended Release Oral Tablet

1665682 - 2 ML Ketorolac Tromethamine 30 MG/ML Cartridge

1665459 - 2 ML Ketorolac Tromethamine 30 MG/ML Injection

860115 - 2 ML Ketorolac Tromethamine 30 MG/ML Prefilled Syringe 855657 - 24 HR Diclofenac Sodium 100 MG Extended Release Oral Tablet 310245 - 24 HR Etodolac 400 MG Extended Release Oral Tablet

359500 - 24 HR Etodolac 500 MG Extended Release Oral Tablet 310247 - 24 HR Etodolac 600 MG Extended Release Oral Tablet 314059 - 24 HR Ketoprofen 100 MG Extended Release Oral Capsule 311230 - 24 HR Ketoprofen 150 MG Extended Release Oral Capsule 359697 - 24 HR Ketoprofen 200 MG Extended Release Oral Capsule 433845 - 24 HR Naproxen 1000 MG Extended Release Oral Tablet 1116320 - 24 HR Naproxen 375 MG Extended Release Oral Tablet 1116339 - 24 HR Naproxen 500 MG Extended Release Oral Tablet 1116349 - 24 HR Naproxen 750 MG Extended Release Oral Tablet

992420 - 8 ACTUAT Ketorolac Tromethamine 15.8 MG/ACTUAT Nasal Inhaler

1236089 - Benzydamine Hydrochloride 3 MG Oral Lozenge 205322 - celecoxib 100 MG Oral Capsule

205323 - celecoxib 200 MG Oral Capsule 349514 - celecoxib 400 MG Oral Capsule 686379 - celecoxib 50 MG Oral Capsule

1297390 - Chlorpheniramine Maleate 2 MG / Ibuprofen 200 MG / Pseudoephedrine Hydrochloride 30 MG Oral Tablet

1310503 - Chlorpheniramine Maleate 4 MG / Ibuprofen 200 MG / Phenylephrine Hydrochloride 10 MG Oral Tablet

1442116 - Diclofenac 18 MG Oral Capsule 1442128 - Diclofenac 35 MG Oral Capsule

859063 - Diclofenac Potassium 1.67 MG/ML Oral Solution 858342 - Diclofenac Potassium 25 MG Oral Capsule 857702 - Diclofenac Potassium 25 MG Oral Tablet

855942 - Diclofenac Potassium 50 MG Oral Tablet 855633 - Diclofenac Sodium 0.01 MG/MG Topical Gel 855642 - Diclofenac Sodium 0.03 MG/MG Topical Gel 1234493 - Diclofenac Sodium 100 MG Oral Capsule 857696 - Diclofenac Sodium 100 MG Rectal Suppository 857698 - Diclofenac Sodium 12.5 MG Rectal Suppository

855664 - Diclofenac Sodium 25 MG Delayed Release Oral Tablet 857703 - Diclofenac Sodium 25 MG Rectal Suppository

1599787 - Diclofenac Sodium 37.5 MG/ML Injectable Solution

857706 - Diclofenac Sodium 50 MG / Misoprostol 0.2 MG Oral Tablet 855906 - Diclofenac Sodium 50 MG Delayed Release Oral Tablet 857709 - Diclofenac Sodium 50 MG Rectal Suppository

1359105 - Diclofenac Sodium 75 MG / Misoprostol 0.2 MG Oral Tablet 855926 - Diclofenac Sodium 75 MG Delayed Release Oral Tablet

895664 - Diphenhydramine Citrate 38 MG / Ibuprofen 200 MG Oral Tablet

901814 - Diphenhydramine Hydrochloride 25 MG / Ibuprofen 200 MG Oral Capsule 1550957 - Diphenhydramine Hydrochloride 25 MG / Naproxen sodium 220 MG Oral

Tablet

994005 - Esomeprazole 20 MG / Naproxen 375 MG Delayed Release Oral Tablet 994008 - Esomeprazole 20 MG / Naproxen 500 MG Delayed Release Oral Tablet 197684 - Etodolac 200 MG Oral Capsule

197685 - Etodolac 300 MG Oral Capsule 197686 - Etodolac 400 MG Oral Tablet 199390 - Etodolac 500 MG Oral Tablet

1100066 - Famotidine 26.6 MG / Ibuprofen 800 MG Oral Tablet 199740 - fenbufen 450 MG Oral Tablet

197694 - Fenoprofen 200 MG Oral Capsule 858116 - Fenoprofen 400 MG Oral Capsule 310291 - Fenoprofen 600 MG Oral Tablet 197724 - Flurbiprofen 100 MG Oral Tablet

199749 - Flurbiprofen 200 MG Extended Release Oral Capsule 197725 - Flurbiprofen 50 MG Oral Tablet

859315 - Hydrocodone Bitartrate 10 MG / Ibuprofen 200 MG Oral Tablet 858770 - Hydrocodone Bitartrate 2.5 MG / Ibuprofen 200 MG Oral Tablet 858778 - Hydrocodone Bitartrate 5 MG / Ibuprofen 200 MG Oral Tablet 858798 - Hydrocodone Bitartrate 7.5 MG / Ibuprofen 200 MG Oral Tablet 310963 - Ibuprofen 100 MG Chewable Tablet

198405 - Ibuprofen 100 MG Oral Tablet

854183 - Ibuprofen 100 MG/ML Injectable Solution

1310487 - Ibuprofen 20 MG/ML / Pseudoephedrine Hydrochloride 3 MG/ML Oral

Suspension

197803 - Ibuprofen 20 MG/ML Oral Suspension

1369775 - Ibuprofen 200 MG / Phenylephrine Hydrochloride 10 MG Oral Tablet 1299018 - Ibuprofen 200 MG / Pseudoephedrine Hydrochloride 30 MG Oral Capsule 1299021 - Ibuprofen 200 MG / Pseudoephedrine Hydrochloride 30 MG Oral Tablet 310964 - Ibuprofen 200 MG Oral Capsule

310965 - Ibuprofen 200 MG Oral Tablet 204442 - Ibuprofen 40 MG/ML Oral Suspension

1049589 - Ibuprofen 400 MG / Oxycodone Hydrochloride 5 MG Oral Tablet 197805 - Ibuprofen 400 MG Oral Tablet

197806 - Ibuprofen 600 MG Oral Tablet 197807 - Ibuprofen 800 MG Oral Tablet

346508 - Indomethacin 1 MG/ML Injectable Solution 199549 - Indomethacin 100 MG Rectal Suppository 1490727 - Indomethacin 20 MG Oral Capsule

197817 - Indomethacin 25 MG Oral Capsule 1491529 - Indomethacin 40 MG Oral Capsule 310991 - Indomethacin 5 MG/ML Oral Suspension 197818 - Indomethacin 50 MG Oral Capsule 197819 - Indomethacin 50 MG Rectal Suppository

310992 - Indomethacin 75 MG Extended Release Oral Capsule 199321 - Ketoprofen 100 MG Oral Capsule

249482 - Ketoprofen 100 MG Oral Tablet

199553 - Ketoprofen 100 MG Rectal Suppository

431823 - Ketoprofen 150 MG Extended Release Oral Tablet 429192 - Ketoprofen 25 MG Oral Tablet

197855 - Ketoprofen 50 MG Oral Capsule 247630 - Ketoprofen 50 MG Rectal Suppository 197856 - Ketoprofen 75 MG Oral Capsule

834022 - Ketorolac Tromethamine 10 MG Oral Tablet

860096 - Ketorolac Tromethamine 30 MG/ML Injectable Solution 618552 - Meclofenamate 100 MG Oral Capsule

618557 - Meclofenamate 50 MG Oral Capsule 597406 - meloxicam 1.5 MG/ML Oral Suspension 152695 - meloxicam 15 MG Oral Tablet

311486 - meloxicam 7.5 MG Oral Tablet 311892 - nabumetone 500 MG Oral Tablet 311893 - nabumetone 750 MG Oral Tablet 245420 - Naproxen 125 MG Oral Tablet 311913 - Naproxen 25 MG/ML Oral Suspension 198013 - Naproxen 250 MG Oral Tablet

603103 - Naproxen 375 MG Delayed Release Oral Tablet 198012 - Naproxen 375 MG Oral Tablet

311915 - Naproxen 500 MG Delayed Release Oral Tablet 198014 - Naproxen 500 MG Oral Tablet

199490 - Naproxen 500 MG Rectal Suppository 1112231 - Naproxen sodium 220 MG Oral Capsule 849574 - Naproxen sodium 220 MG Oral Tablet 849398 - Naproxen sodium 275 MG Oral Tablet

849450 - Naproxen sodium 500 MG / Sumatriptan 85 MG Oral Tablet 849431 - Naproxen sodium 550 MG Oral Tablet

1653765 - Naproxen sodium 60 MG / Sumatriptan 10 MG Oral Tablet 312132 - oxaprozin 600 MG Oral Tablet

198107 - Piroxicam 10 MG Oral Capsule 199559 - Piroxicam 10 MG Oral Tablet

247066 - Piroxicam 10 MG Rectal Suppository 198108 - Piroxicam 20 MG Oral Capsule 199560 - Piroxicam 20 MG Oral Tablet

105942 - Piroxicam 20 MG Rectal Suppository 199279 - Sulindac 100 MG Oral Tablet

198238 - Sulindac 150 MG Oral Tablet 198239 - Sulindac 200 MG Oral Tablet 199516 - tenoxicam 10 MG Oral Tablet 105954 - tenoxicam 20 MG Oral Tablet

250197 - tenoxicam 20 MG Rectal Suppository 198295 - Tolmetin 200 MG Oral Tablet

198296 - Tolmetin 400 MG Oral Capsule 198297 - Tolmetin 600 MG Oral Tablet 349319 - valdecoxib 10 MG Oral Tablet 349321 - valdecoxib 20 MG Oral Tablet

* + - 1. **ponatinib (ATC)**

L01XE24 - ponatinib

* + - 1. **proton pump inhibitor (ATC)**

A02BC06 - dexlansoprazole A02BC05 - esomeprazole A02BC03 - lansoprazole A02BC01 - omeprazole A02BC02 - pantoprazole A02BC04 - rabeprazole

* + - 1. **proton pump inhibitor (RxNorm)**

816346 - Dexlansoprazole

283742 - Esomeprazole

17128 - Lansoprazole

7646 - Omeprazole

40790 - Pantoprazole

114979 - Rabeprazole

* + - 1. **systemic corticosteroids (RxNorm)**

1514 - Betamethasone

2878 - Cortisone

3264 - Dexamethasone

4452 - Fludrocortisone

5492 - Hydrocortisone

6902 - Methylprednisolone

8638 - prednisolone

8640 - Prednisone

10759 - Triamcinolone

1085795 - 100 ACTUAT Triamcinolone Acetonide 0.055 MG/ACTUAT Nasal Inhaler 833245 - 120 ACTUAT Triamcinolone Acetonide 0.05 MG/ACTUAT Nasal Inhaler 1085798 - 120 ACTUAT Triamcinolone Acetonide 0.055 MG/ACTUAT Nasal Inhaler 1493473 - 60 ACTUAT Triamcinolone Acetonide 0.055 MG/ACTUAT Nasal Inhaler 670084 - Betamethasone 0.12 MG/ML Oral Solution

308709 - Betamethasone 0.6 MG Oral Tablet

578803 - Betamethasone 3 MG/ML / Betamethasone acetate 3 MG/ML Injectable Suspension

197543 - Cortisone 10 MG Oral Tablet 197545 - Cortisone 5 MG Oral Tablet

828248 - cortisone acetate 25 MG Oral Tablet 309686 - Dexamethasone 0.1 MG/ML Oral Solution 197577 - Dexamethasone 0.5 MG Oral Tablet 854177 - Dexamethasone 0.7 MG Drug Implant 343033 - Dexamethasone 0.75 MG Oral Tablet 197579 - Dexamethasone 1 MG Oral Tablet

309684 - Dexamethasone 1 MG/ML Oral Solution 197580 - Dexamethasone 1.5 MG Oral Tablet

309696 - Dexamethasone 10 MG/ML Injectable Solution 197581 - Dexamethasone 2 MG Oral Tablet

197582 - Dexamethasone 4 MG Oral Tablet 197583 - Dexamethasone 6 MG Oral Tablet

1116927 - Dexamethasone phosphate 4 MG/ML Injectable Solution 313979 - Fludrocortisone 0.1 MG Oral Tablet

260192 - Hydrocortisone 0.01 MG/MG Rectal Ointment 310878 - Hydrocortisone 1.67 MG/ML Enema

197782 - Hydrocortisone 10 MG Oral Tablet 310868 - Hydrocortisone 10 MG/ML Rectal Cream 1494032 - Hydrocortisone 10 MG/ML Vaginal Cream

Cream

310899 - Hydrocortisone 2 MG/ML Oral Suspension 197783 - Hydrocortisone 20 MG Oral Tablet

1246528 - Hydrocortisone 25 MG/ML / Pramoxine hydrochloride 10 MG/ML Rectal

310879 - Hydrocortisone 25 MG/ML Rectal Cream 199320 - Hydrocortisone 4 MG Oral Tablet 197787 - Hydrocortisone 5 MG Oral Tablet

238755 - Hydrocortisone 50 MG/ML Injectable Solution

1012221 - hydrocortisone acetate 0.0055 MG/MG / Lidocaine Hydrochloride 0.028

MG/MG Rectal Gel

1012223 - hydrocortisone acetate 0.025 MG/MG / Lidocaine Hydrochloride 0.03 MG/MG Rectal Gel

1012229 - hydrocortisone acetate 10 MG/ML / Lidocaine Hydrochloride 30 MG/ML Rectal Cream

1235049 - hydrocortisone acetate 10 MG/ML / Pramoxine hydrochloride 10 MG/ML Rectal Cream

828362 - hydrocortisone acetate 10 MG/ML / Pramoxine hydrochloride 10 MG/ML Rectal Foam

1545172 - hydrocortisone acetate 100 MG/ML Rectal Foam

1114854 - hydrocortisone acetate 18.5 MG/ML / Pramoxine hydrochloride 11.5 MG/ML Rectal Cream

1012233 - hydrocortisone acetate 20 MG/ML / Lidocaine Hydrochloride 20 MG/ML Rectal Cream

1094443 - hydrocortisone acetate 23.5 MG/ML / Pramoxine hydrochloride 10 MG/ML Rectal Cream

1291082 - hydrocortisone acetate 25 MG Rectal Suppository

1294025 - hydrocortisone acetate 25 MG/ML / Pramoxine hydrochloride 10 MG/ML Rectal Cream

1291085 - hydrocortisone acetate 30 MG Rectal Suppository

1012235 - hydrocortisone acetate 5 MG/ML / Lidocaine Hydrochloride 30 MG/ML Rectal Cream

199771 - Methylprednisolone 100 MG Oral Tablet 328161 - Methylprednisolone 16 MG Oral Tablet 197969 - Methylprednisolone 2 MG Oral Tablet 197970 - Methylprednisolone 24 MG Oral Tablet 197971 - Methylprednisolone 32 MG Oral Tablet 259966 - Methylprednisolone 4 MG Oral Tablet

311659 - Methylprednisolone 40 MG/ML Injectable Solution 314099 - Methylprednisolone 62.5 MG/ML Injectable Solution 1357886 - Methylprednisolone 65.4 MG/ML Injectable Solution 197973 - Methylprednisolone 8 MG Oral Tablet

1358510 - methylprednisolone acetate 20 MG/ML Injectable Suspension 1358610 - methylprednisolone acetate 40 MG/ML Injectable Suspension 1358617 - methylprednisolone acetate 80 MG/ML Injectable Suspension 199343 - prednisolone 1 MG Oral Tablet

312614 - prednisolone 1 MG/ML Oral Solution

643123 - prednisolone 10 MG Disintegrating Oral Tablet 643125 - prednisolone 15 MG Disintegrating Oral Tablet 794979 - prednisolone 2 MG/ML Oral Solution

429199 - prednisolone 20 MG Oral Tablet 199967 - prednisolone 25 MG Oral Tablet 283077 - prednisolone 3 MG/ML Oral Solution 793099 - prednisolone 3 MG/ML Oral Suspension

643127 - prednisolone 30 MG Disintegrating Oral Tablet 702306 - prednisolone 4 MG/ML Oral Solution

198142 - prednisolone 5 MG Oral Tablet 249066 - prednisolone 5 MG/ML Oral Solution

1303125 - Prednisone 1 MG Delayed Release Oral Tablet 198144 - Prednisone 1 MG Oral Tablet

315187 - Prednisone 1 MG/ML Oral Solution 198145 - Prednisone 10 MG Oral Tablet

1303132 - Prednisone 2 MG Delayed Release Oral Tablet 198146 - Prednisone 2.5 MG Oral Tablet

312615 - Prednisone 20 MG Oral Tablet

1303135 - Prednisone 5 MG Delayed Release Oral Tablet 312617 - Prednisone 5 MG Oral Tablet

205301 - Prednisone 5 MG/ML Oral Solution 198148 - Prednisone 50 MG Oral Tablet 198301 - Triamcinolone 1 MG Oral Tablet

1085728 - Triamcinolone Acetonide 0.001 MG/MG Oral Paste

1085750 - Triamcinolone Acetonide 10 MG/ML Injectable Suspension 1085754 - Triamcinolone Acetonide 40 MG/ML Injectable Suspension 1085996 - triamcinolone hexacetonide 20 MG/ML Injectable Suspension 1085992 - triamcinolone hexacetonide 5 MG/ML Injectable Suspension

* + - 1. **topical diclofenac (RxNorm)**

1234735 - diclofenac epolamine 0.0129 MG/MG Topical Gel

* + - 1. **tyrosine kinase inhibitors (TKIs) (ATC)**

L01XE04 - sunitinib L01XC03 - trastuzumab

L01XC14 - ado-trastuzumab emtansine

* + - 1. **warfarin (RxNorm)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 855288 | - Warfarin | Sodium | 1 MG Oral Tablet |  |
| 855296 | - Warfarin | Sodium | 10 MG Oral Tablet |
| 855302 | - Warfarin | Sodium | 2 MG Oral Tablet |
| 855308 | - Warfarin | Sodium | 2 MG/ML Injectable | Solution |
| 855312 | - Warfarin | Sodium | 2.5 MG Oral Tablet |  |
| 855318 | - Warfarin | Sodium | 3 MG Oral Tablet |  |
| 855324 | - Warfarin | Sodium | 4 MG Oral Tablet |  |
| 855332 | - Warfarin | Sodium | 5 MG Oral Tablet |  |
| 855338 | - Warfarin | Sodium | 6 MG Oral Tablet |  |
| 855344 | - Warfarin | Sodium | 7.5 MG Oral Tablet |  |
| 11289 - | Warfarin |  |  |  |

#### Straw Man XML Examples

In this section we present straw man XML representations of the example PDDIs described in section [User-](#_bookmark152) [centered definitions](#_bookmark152).

* + - 1. **Example 1: warfarin and non-steroidal anti-inflammatory drugs (NSAIDs)**

Example 1: Warfarin and non-steroidal anti-inflammatory drugs (NSAIDs)

<MPIO:MPIO\_0000005 label=’mechanism of interaction information’>

‘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).’

</MPIO:MPIO\_0000005>

<MPIO:MPIO\_0000003

label=’information about clinical consequences suspected to be the result of a drug- drug interaction’> ‘Increased risk of bleeding’

</MPIO:MPIO\_0000003>

<MPIO:MPIO\_0000009 label=’seriousness’>

‘Bleeding is a serious potential clinical consequence because it can result in death, life-threatening hospitalization, and disability.’

</MPIO:MPIO\_0000009>

<MPIO:MPIO\_0000010 label=’severity’>

‘The intensity of a bleeding event may vary’

</MPIO:MPIO\_0000010>

<MPIO:MPIO\_0000008 label=’recommended action’>

‘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.’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000007 label=’Frequency of Exposure to the PDDI’> ‘Unknown’

<MPIO:MPIO\_0000007>

<MPIO:MPIO\_0000006 label=’Frequency of Harm for persons who have been exposed to the PDDI’>

‘Unknown’

<MPIO:MPIO\_0000006>

<MPIO:MPIO\_0000000 label=’modifying factors information’ expressionLogic=’human readable’ conceptSets=’None’>

<listOfModifyingFactors>

<it>

‘The NSAID is topical diclofenac’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘No special precautions’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’> ‘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.’

</MPIO:MPIO\_0000004>

</it>

<it>

‘The NSAID is NOT topical diclofenac but the patient is concomitantly taking a proton pump inhibitor or misoprostol’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘Assess risk and take action if necessary’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’> ‘Proton pump inhibitors and misoprostol may reduce the risk of UGIB in

patients receiving NSAIDs and warfarin.’

</MPIO:MPIO\_0000004>

</it>

<it>

‘The NSAID is NOT topical diclofenac, the patient is NOT concomitantly taking a proton pump inhibitor or misoprostol, and the patient has one or more of the following risk factors: history of UGIB or peptic ulcer or > 65 years old’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘Use only if benefit outweighs risk’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’> ‘Proton pump inhibitors and misoprostol may reduce the risk of UGIB in

patients receiving NSAIDs and warfarin.’

</MPIO:MPIO\_0000004>

</it>

<it>

‘The NSAID is NOT topical diclofenac, the patient is NOT concomitantly taking a proton pump inhibitor or misoprostol, and the patient has one or more of the following

risk factors: concomitantly taking systemic corticosteroids, aldosterone antagonist, or high dose or multiple NSAIDs’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘Use only if benefit outweighs risk’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’ references=’r1’>

‘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’

</MPIO:MPIO\_0000004>

</it>

<listOfReferences>

<reference id=’r1’>

‘Masclee et al. Gastroenterology 2014;147:784-92.’

</reference>

</listOfReferences>

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<MPIO:MPIO\_0000000 label=’modifying factors information’ expressionLogic=’CQL+FHIR’ conceptSets=’NLM Value Set Authority’>

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* QDM Logic

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* <LOGIC FOR DISTINGUISHING SITUATIONS WARRANTING 'No special precautions', 'Assess risk and take action if necessary.', AND 'Use only if benefit outweighs risk' GOES HERE>

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using FHIR

valueset "warfarin": '<code referencing that value set from National Library of Medicine Value Set Authority Center https://vsac.nlm.nih.gov/'

valueset "topical diclofenac": '<code referencing that value set from National Library of Medicine Value Set Authority Center https://vsac.nlm.nih.gov/'

valueset "proton pump inhibitor": '<code referencing that value set from National Library of Medicine Value Set Authority Center https://vsac.nlm.nih.gov/'

<OTHER VALUE SETS REQUIRED TO IMPLEMENT THE CLINICAL LOGIC>

<PARAMETERS AND DEFINITIONS REFERENCED IN THE QDM LOGIC>

]]>

</MPIO:MPIO\_0000000>

* + - 1. **Example 2: Tyrosine Kinase inhibitors and medications that increase gastric pH**

Example 2: Tyrosine Kinase inhibitors and medications that increase gastric pH

<MPIO:MPIO\_0000005 label=’mechanism of interaction information’>

‘These TKIs demonstrate pH dependent absorption for oral administration which may result in decreased efficacy when given concomitantly with medications that increase gastric pH.’

</MPIO:MPIO\_0000005>

<MPIO:MPIO\_0000003 label=’clinical consequences’>

‘Decreased efficacy relative to treatment for chronic myeloid leukemia’

</MPIO:MPIO\_0000003>

<MPIO:MPIO\_0000009 label=’seriousness’>

‘A decrease in chronic myeloid leukemia treatment efficacy is a serious potential clinical consequence because it can result in death, life-threatening hospitalization, and disability.’

</MPIO:MPIO\_0000009>

<MPIO:MPIO\_0000010 label=’severity’>

‘There is no intensity scale relevant to describing a decrease in chronic myeloid leukemia treatment efficacy’

</MPIO:MPIO\_0000010>

<MPIO:MPIO\_0000007 label=’Frequency of Exposure to the PDDI’> ‘Unknown’

<MPIO:MPIO\_0000007>

<MPIO:MPIO\_0000006 label=’Frequency of Harm for persons who have been exposed to the PDDI’>

‘Unknown’

<MPIO:MPIO\_0000006>

<MPIO:MPIO\_0000000 label=’modifying factors information’ expressionLogic=’human readable’ conceptSets=’None’>

<listOfModifyingFactors>

<it>

‘The TKI is imatinib or ponatinib’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘No special precautions’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’ references=’r1,r2’>

‘Imatinib and ponatinib AUCs are not appreciably decreased by PPI co-administration.’

</MPIO:MPIO\_0000004>

</it>

<it>

‘The TKI is nilotinib’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘Assess risk and take action if necessary’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’ references=’r3’>

‘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. However, for nilotinib a retrospective study has

shown no difference in cytogenetic response rates for patients taking PPIs.’

</MPIO:MPIO\_0000004>

</it>

<it>

‘The TKI is bosutinib or dasatinib’

<MPIO:MPIO\_0000008 label=’recommended action’> ‘Use only if benefit outweighs risk’

</MPIO:MPIO\_0000008>

<MPIO:MPIO\_0000004 label=’Evidence for a Suspected Drug-Drug Interaction’ references=’r4,r5’>

‘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.’

</MPIO:MPIO\_0000004>

</it>

<listOfReferences>

<reference id=’r1’>

‘Iclusig [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc. 2016’

</reference>

<reference id=’r2’>

‘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.’

</reference>

<reference id=’r3’>

‘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.’

</reference>

<reference id=’r5’>

‘Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015’

</reference>

<reference id=’r6’>

‘Bosulif [package insert]. New York, NY: Pfizer Labs; 2015.’

</reference>

</listOfReferences>

</MPIO:MPIO\_0000000>

<MPIO:MPIO\_0000004 label=‘suspected drug-drug interaction evidence’>

<listOfEvidence>

<it references=’r1’>

‘Dasatinib area under the curve (AUC) is decreased when co-administered with antacids, H2 antagonists, and PPIs.’

</it>

<it references=’r2,r3’>

‘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.’

</it>

<it references=’r4’>

‘However, for nilotinib a retrospective study has shown no difference in cytogenetic response rates for patients taking PPIs.’

</it>

<it references=’r5,r6’>

‘Imatinib and ponatinib AUCs are not appreciably decreased by PPI co- administration.5,6’

</it>

</listOfEvidence>

<listOfReferences>

<reference id=’r1’>

‘Sprycel [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015’

</reference>

<reference id=’r2’>

‘Bosulif [package insert]. New York, NY: Pfizer Labs; 2015.’

</reference>

<reference id=’r3’>

‘Tasigna [package insert]. East Hanover, NJ: Novartis; 2015.’

</reference>

<reference id=’r4’>

‘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.’

</reference>

<reference id=’r5’>

‘Iclusig [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc. 2016’

</reference>

<reference id=’r6’>

‘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.’

</reference>

</listOfReferences>

</MPIO:MPIO\_0000004>

<MPIO:MPIO\_0000000 label=’modifying factors information’ expressionLogic=’CQL+FHIR’ conceptSets=’NLM Value Set Authority’>

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* <LOGIC FOR DISTINGUISHING SITUATIONS WARRANTING 'No special precautions',

'Assess risk and take action if necessary.', AND 'Use only if benefit outweighs risk' GOES HERE>

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valueset "Type of BCR-ABL Tyrosine Kinase Inhibitors": '<code referencing that value set from National Library of Medicine Value Set Authority Center https://vsac.nlm.nih.gov/'

valueset "Imatinib": '<code referencing that value set from National Library of Medicine Value Set Authority Center https://vsac.nlm.nih.gov/'

<OTHER VALUE SETS REQUIRED TO IMPLEMENT THE CLINICAL LOGIC>

<PARAMETERS AND DEFINITIONS REFERENCED IN THE QDM LOGIC>

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</MPIO:MPIO\_0000000>

>>>>>>> master

## References

### Informative references

[abarca-2004]

[*Concordance of severity ratings provided in four drug interaction compendia*](https://www.ncbi.nlm.nih.gov/pubmed/15098847). Jacob Abarca; Daniel Malone; Edward Armstrong; Amy Grizzle; Philip Hansten; Robin Van, Bergen; Richard Lipton. Journal of the American Pharmacists Association: JAPhA. April 2004. URL: <https://www.ncbi.nlm.nih.gov/pubmed/15098847>

[ahrq-drug-drug]

[*Drug-drug interactions: percentage of patients who received a prescription for a target medication*](https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug%2Binteractions)[*during the measurement period and who were dispensed a concurrent prescription for a precipitant*](https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug%2Binteractions)[*medication. National Quality Measures Clearinghouse*](https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug%2Binteractions). AHRQ.URL: [https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-](https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug%2Binteractions) [patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-](https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug%2Binteractions) [who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug+interactions](https://qualitymeasures.ahrq.gov/summaries/summary/47511/drugdrug-interactions-percentage-of-patients-who-received-a-prescription-for-a-target-medication-during-the-measurement-period-and-who-were-dispensed-a-concurrent-prescription-for-a-precipitant-medication?q=drugdrug%2Binteractions)

[ansm-2016]

[*Thesaurus des interactions medicamenteuses*](http://ansm.sante.fr/var/ansm_site/storage/original/application/de444ea9eb4bc084905c917c902a805f.pdf). ANSM.2016. URL: [http://ansm.sante.fr/var/ansm\_site/storage/original/application/de444ea9eb4bc084905c917c902a805f.p](http://ansm.sante.fr/var/ansm_site/storage/original/application/de444ea9eb4bc084905c917c902a805f.pdf) [df](http://ansm.sante.fr/var/ansm_site/storage/original/application/de444ea9eb4bc084905c917c902a805f.pdf)

[ayvaz-2015]

[*Toward a complete dataset of drug-drug interaction information from publicly available sources*](https://www.ncbi.nlm.nih.gov/pubmed/25917055). Serkan Ayvaz; John Horn; Oktie Hassanzadeh; Qian Zhu; Johann Stan; Nicholas Tatonetti; Santiago

Vilar; Mathias Brochhausen; Matthias Samwald; Majid Rastegar-Mojarad; Michel Dumontier; Richard Boyce. Journal of Biomedical Informatics. Jun 2015. URL: <https://www.ncbi.nlm.nih.gov/pubmed/25917055>

[bosulif-2015]

*Bosulif* Pfizer Labs, New York, NY. 2015. [bottiger-2009]

[*{SFINX}-a drug-drug interaction database designed for clinical decision support systems*](https://www.ncbi.nlm.nih.gov/pubmed/19205683). Ylva Bottiger; Kari Laine; Marine Andersson; Tuomas Korhonen; Bjorn Molin; Marie-Louise Ovesjo; Tuire Tirkkonen; Anders Rane; Lars Gustafsson; Birgit Eiermann. European Journal of Clinical Pharmacology. Jun 2009. URL: <https://www.ncbi.nlm.nih.gov/pubmed/19205683>

[boyce-2013]

[*Dynamic enhancement of drug product labels to support drug safety, efficacy, and effectiveness*](https://jbiomedsem.biomedcentral.com/track/pdf/10.1186/2041-1480-4-5?site=jbiomedsem.biomedcentral.com). Richard Boyce; John Horn; Oktie Hassanzadeh; Anita De', u'Waard; Jodi Schneider; Joanne Luciano; Majid Rastegar-Mojarad; Maria Liakata. Journal of Biomedical Semantics. URL: [https://jbiomedsem.biomedcentral.com/track/pdf/10.1186/2041-1480-4-5?](https://jbiomedsem.biomedcentral.com/track/pdf/10.1186/2041-1480-4-5?site=jbiomedsem.biomedcentral.com) [site=jbiomedsem.biomedcentral.com](https://jbiomedsem.biomedcentral.com/track/pdf/10.1186/2041-1480-4-5?site=jbiomedsem.biomedcentral.com)

[brochhausen-2014]

[*Towards a foundational representation of potential drug- drug interaction knowledge*](http://ceur-ws.org/Vol-1309/paper2.pdf). Mathias Brochhausen; Jodi Schneider; Daniel Malone; Philip Empey; R. Hogan; Richard Boyce.URL: <http://ceur-ws.org/Vol-1309/paper2.pdf>

[cdc-faststats]

[*FastStats*](https://www.cdc.gov/nchs/fastats/emergency-department.htm). CDC. FASTSTATS.URL: <https://www.cdc.gov/nchs/fastats/emergency-department.htm> [cms-2013]

[*Eligible Professional Meaningful Use Core Measures, Measure 2 of 15*](http://www.opendental.com/manual/EHR%202011/2%20Drug%20Interaction%20Checks%202012-07%2027.pdf). CMS.2013. URL: [http://www.opendental.com/manual/EHR%202011/2%20Drug%20Interaction%20Checks%202012-](http://www.opendental.com/manual/EHR%202011/2%20Drug%20Interaction%20Checks%202012-07%2027.pdf) [07%2027.pdf](http://www.opendental.com/manual/EHR%202011/2%20Drug%20Interaction%20Checks%202012-07%2027.pdf)

[ctcae-wiki]

[*What is Common Terminology Criteria for Adverse Event (CTCAE)?*](https://wiki.nci.nih.gov/display/VKC/Common%2BTerminology%2BCriteria%2Bfor%2BAdverse%2BEvents). NCI.URL: [https://wiki.nci.nih.gov/display/VKC/Common+Terminology+Criteria+for+Adverse+Events](https://wiki.nci.nih.gov/display/VKC/Common%2BTerminology%2BCriteria%2Bfor%2BAdverse%2BEvents)

[dechanont-2014]

[*Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-*](http://www.ncbi.nlm.nih.gov/pubmed/24616171)[*analysis*](http://www.ncbi.nlm.nih.gov/pubmed/24616171). Supinya Dechanont; Sirada Maphanta; Bodin Butthum; Chuenjid Kongkaew.

Pharmacoepidemiology and Drug Safety. May 2014. URL: <http://www.ncbi.nlm.nih.gov/pubmed/24616171>

[egorin-2009]

[*Effect of a proton pump inhibitor on the pharmacokinetics of imatinib*](https://www.ncbi.nlm.nih.gov/pubmed/19740393). Merrill J. Egorin; Dhvani D. Shah; Susan M. Christner; Mara A. Yerk; Kristin A. Komazec; Leonard R. Appleman; Robert L. Redner; Brian M. Miller; Jan H. Beumer. British Journal of Clinical Pharmacology. 2009. URL: <https://www.ncbi.nlm.nih.gov/pubmed/19740393>

[european-medicines-2012]

[*Guideline on the investigation of drug interactions*](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf). European Medicines Agency.Jun 2012. URL: [http://www.ema.europa.eu/docs/en\_GB/document\_library/Scientific\_guideline/2012/07/WC500129606](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

[.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf) [fung-2017]

[*Comparison of three commercial knowledge bases for detection of drug-drug interactions in clinical*](https://www.ncbi.nlm.nih.gov/pubmed/28339701)[*decision support*](https://www.ncbi.nlm.nih.gov/pubmed/28339701). Kin Fung; Joan Kapusnik-Uner; Jean Cunningham; Stefanie Higby-Baker; Olivier Bodenreider. Journal of the American Medical Informatics Association: JAMIA. Jul 01, 2017. URL: <https://www.ncbi.nlm.nih.gov/pubmed/28339701>

[herrero-zazo-2015]

[*DINTO: Using OWL Ontologies and SWRL Rules to Infer Drug-Drug Interactions and Their*](https://www.ncbi.nlm.nih.gov/pubmed/26147071)[*Mechanisms*](https://www.ncbi.nlm.nih.gov/pubmed/26147071). Maria Herrero-Zazo; Isabel Segura-Bedmar; Janna Hastings; Paloma Martinez. Journal of Chemical Information and Modeling. Aug 24, 2015. URL: <https://www.ncbi.nlm.nih.gov/pubmed/26147071>

[herrero-zazo-2016]

[*Conceptual models of drug-drug interactions: A summary of recent efforts*](http://www.sciencedirect.com/science/article/pii/S0950705116303896). Maria Herrero-Zazo; Isabel Segura-Bedmar; Paloma Martinez. Knowledge-Based Systems. December 15, 2016. URL: <http://www.sciencedirect.com/science/article/pii/S0950705116303896>

[hines-2011]

[*Critical issues associated with drug-drug interactions: highlights of a multistakeholder conference*](https://www.ncbi.nlm.nih.gov/pubmed/21546646). Lisa Hines; John Murphy; Amy Grizzle; Daniel Malone. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists. May 15, 2011. URL: <https://www.ncbi.nlm.nih.gov/pubmed/21546646>

[iclusig-2016]

*Iclusig* ARIAD Pharmaceuticals, Inc., Cambridge, MA. 2016. [institute-medicine-2006]

[*Preventing Medication Errors*](https://www.nap.edu/catalog/11623/preventing-medication-errors). Institute of Medicine.July 2006. URL: <https://www.nap.edu/catalog/11623/preventing-medication-errors>

[magro-2012]

[*Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions*](https://www.ncbi.nlm.nih.gov/pubmed/22022824). Lara Magro; Ugo Moretti; Roberto Leone. Expert Opinion on Drug Safety. Jan 2012. URL: <https://www.ncbi.nlm.nih.gov/pubmed/22022824>

[masclee-2014]

[*Risk of upper gastrointestinal bleeding from different drug combinations.*](https://www.ncbi.nlm.nih.gov/pubmed/24937265). Preciosa Coloma; Gini Rosa; Ron Herings; Ernst Kuipers; Gwen Masclee; Giampiero Mazzaglia; Lars Pedersen; Gino Picelli; Silvana Romio; Martijn Schuemie; Lorenza Scotti; Miriam Sturkenboom; Vera Valkhoff; Maria de Ridder; Johan van der Lei. Gastroenterology. October 2014. URL: <https://www.ncbi.nlm.nih.gov/pubmed/24937265>

[mille-2007]

[*Modeling and acquisition of drug-drug interaction knowledge*](https://www.ncbi.nlm.nih.gov/pubmed/17911846). Frederic Mille; Patrice Degoulet; Marie- Christine Jaulent. Studies in Health Technology and Informatics. 2007. URL: <https://www.ncbi.nlm.nih.gov/pubmed/17911846>

[nabovati-2017]

[*A survey of attitudes, practices, and knowledge regarding drug-drug interactions among medical*](file:///\\vmware-host\home\rdb20\Downloads\www.ncbi.nlm.nih.gov\pubmed\28382584)[*residents in Iran*](file:///\\vmware-host\home\rdb20\Downloads\www.ncbi.nlm.nih.gov\pubmed\28382584). Ehsan Nabovati; Hasan Vakili-Arki; Zhila Taherzadeh; Mohammad Saberi; Ameen Abu-Hanna; Saeid Eslami. International Journal of Clinical Pharmacy. Jun 2017. URL: [www.ncbi.nlm.nih.gov/pubmed/28382584](file:///\\vmware-host\home\rdb20\Downloads\www.ncbi.nlm.nih.gov\pubmed\28382584)

[ohdsi-atlas]

[*OHDSI - Atlas: is an open source software tool for researchers to conduct scientific analyses on*](https://github.com/OHDSI/Atlas)[*standardized observational data*](https://github.com/OHDSI/Atlas). OHDSI. Observational Health Data Sciences and Informatics. URL: <https://github.com/OHDSI/Atlas>

[olvey-2010]

[*Comparison of critical drug-drug interaction listings: the Department of Veterans Affairs medical*](https://www.ncbi.nlm.nih.gov/pubmed/19890252)[*system and standard reference compendia*](https://www.ncbi.nlm.nih.gov/pubmed/19890252). E. Olvey; S. Clauschee; D. Malone. Clinical Pharmacology and Therapeutics. Jan 2010. URL: <https://www.ncbi.nlm.nih.gov/pubmed/19890252>

[owl2-overview]

[*OWL 2 Web Ontology Language Document Overview (Second Edition)*](https://www.w3.org/TR/owl2-overview/). W3C OWL Working Group.

W3C. 11 December 2012. W3C Recommendation. URL: <https://www.w3.org/TR/owl2-overview/> [payne-2015]

[*Recommendations to improve the usability of drug-drug interaction clinical decision support alerts*](https://www.ncbi.nlm.nih.gov/pubmed/25829460). Thomas Payne; Lisa Hines; Raymond Chan; Seth Hartman; Joan Kapusnik-Uner; Alissa Russ; Bruce Chaffee; Christian Hartman; Victoria Tamis; Brian Galbreth; Peter Glassman; Shobha Phansalkar; Heleen Sijs; Sheila Gephart; Gordon Mann; Howard Strasberg; Amy Grizzle; Mary Brown; Gilad Kuperman; Chris Steiner; Amanda Sullins; Hugh Ryan; Michael Wittie; Daniel Malone. Journal of the American Medical Informatics Association: JAMIA. Nov 2015. URL: <https://www.ncbi.nlm.nih.gov/pubmed/25829460>

[pfistermeister-2014]

[*Inconsistencies and misleading information in officially approved prescribing information from three*](https://www.ncbi.nlm.nih.gov/pubmed/25062063)[*major drug markets*](https://www.ncbi.nlm.nih.gov/pubmed/25062063). B. Pfistermeister; A. SaB; M. Criegee-Rieck; T. Burkle; M. Fromm; R. Maas.

Clinical Pharmacology and Therapeutics. Nov 2014. URL: <https://www.ncbi.nlm.nih.gov/pubmed/25062063>

[rekic-2017]

[*Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access*](https://www.ncbi.nlm.nih.gov/pubmed/28435142). Dinko Rekic; Kellie Reynolds; Ping Zhao; Lei Zhang; Kenta Yoshida; Madhav Sachar; Micheline Piquette', u'Miller; Shiew-Mei Huang; Issam Zineh. Journal of Pharmaceutical Sciences. Sep 2017. URL: <https://www.ncbi.nlm.nih.gov/pubmed/28435142>

[RFC2119]

[*Key words for use in RFCs to Indicate Requirement Levels*](https://tools.ietf.org/html/rfc2119). S. Bradner. IETF. March 1997. Best Current Practice. URL: <https://tools.ietf.org/html/rfc2119>

[ridgely-2012]

*Too Many Alerts, Too Much Liability: Sorting through the Malpractice Implications of Drug-Drug Interaction Clinical Decision Support Clinical Support Systems for Drug-Drug Interactions: Implementing Effective Systems, Limiting Malpractice Liability*. M. Ridgely; Michael Greenberg. Saint Louis University Journal of Health Law & Policy. 2011-2012. URL: [http://heinonline.org/HOL/Page?](http://heinonline.org/HOL/Page) handle=hein.journals/sljhlp5&collection=journals&id=271&startid=&endid=310

[romagnoli-2017]

[*Information needs for making clinical recommendations about potential drug-drug interactions: a*](https://www.ncbi.nlm.nih.gov/pubmed/28228132)[*synthesis of literature review and interviews*](https://www.ncbi.nlm.nih.gov/pubmed/28228132). Katrina Romagnoli; Scott Nelson; Lisa Hines; Philip Empey; Richard Boyce; Harry Hochheiser. BMC medical informatics and decision making. February 2017. URL: <https://www.ncbi.nlm.nih.gov/pubmed/28228132>

[rosko-2017]

*Toward shareable individualized drug interaction alerts.*Samuel C. Rosko; Philip Hansten; John R. Horn; Daniel C. Malone; Andrew Romero; Richard D. Boyce. AMIA Summit on Clinical Research Informatics. Mar 2017.

[saverno-2011]

[*Ability of pharmacy clinical decision-support software to alert users about clinically important drug-*](https://www.ncbi.nlm.nih.gov/pubmed/21131607)[*drug interactions*](https://www.ncbi.nlm.nih.gov/pubmed/21131607). Kim Saverno; Lisa Hines; Terri Warholak; Amy Grizzle; Lauren Babits; Courtney Clark; Ann Taylor; Daniel Malone. Journal of the American Medical Informatics Association: JAMIA. 2011 Jan-Feb. URL: <https://www.ncbi.nlm.nih.gov/pubmed/21131607>

[scheife-2015]

[*Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical*](https://www.ncbi.nlm.nih.gov/pubmed/25556085)[*decision support*](https://www.ncbi.nlm.nih.gov/pubmed/25556085). Richard Scheife; Lisa Hines; Richard Boyce; Sophie Chung; Jeremiah Momper; Christine Sommer; Darrell Abernethy; John Horn; Stephen Sklar; Samantha Wong; Gretchen Jones; Mary Brown; Amy Grizzle; Susan Comes; Tricia Wilkins; Clarissa Borst; Michael Wittie; Daniel Malone. Drug Safety. Feb 2015. URL: <https://www.ncbi.nlm.nih.gov/pubmed/25556085>

[sprycel-2015]

*Sprycel* Bristol-Myers Squibb Company, Princeton, NJ. 2015. [tamblyn-2012]

[*The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from*](https://www.ncbi.nlm.nih.gov/pubmed/22246963)[*drug side effects: a cluster randomized trial*](https://www.ncbi.nlm.nih.gov/pubmed/22246963). Robyn Tamblyn; Tewodros Eguale; David Buckeridge; Allen Huang; James Hanley; Kristen Reidel; Sherry Shi; Nancy Winslade. Journal of the American Medical Informatics Association: JAMIA. 2012 Jul-Aug. URL: <https://www.ncbi.nlm.nih.gov/pubmed/22246963>

[tasigna-2015]

*Tasigna* Novartis, East Hanover, NJ. 2015. [tilson-2016]

[*Recommendations for selecting drug-drug interactions for clinical decision support*](http://www.ncbi.nlm.nih.gov/pubmed/27045070). Hugh Tilson; Lisa Hines; Gerald McEvoy; David Weinstein; Philip Hansten; Karl Matuszewski; Marianne Comte; Stefanie Higby-Baker; Joseph Hanlon; Lynn Pezzullo; Kathleen Vieson; Amy Helwig; Shiew-Mei Huang; Anthony Perre; David Bates; John Poikonen; Michael Wittie; Amy Grizzle; Mary Brown;

Daniel Malone. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists. Apr 15, 2016. URL: <http://www.ncbi.nlm.nih.gov/pubmed/27045070>

[usdhhs-2011]

[*Guidance for Industry - Providing Regulatory Submissions in Electronic Format - Content of Labeling*](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072331.pdf).

U.S. Department of Health and Human Services.2011. URL: [https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07 2331.pdf](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072331.pdf)

[usdhhs-2017]

[*Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications*](https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf). U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research (CDER).Oct 2017. URL: <https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf>

[utecht-2017]

[*Formalizing Evidence Type Definitions for Drug-Drug Interaction Studies to Improve Evidence Base*](https://www.ncbi.nlm.nih.gov/pubmed/29295242)[*Curation*](https://www.ncbi.nlm.nih.gov/pubmed/29295242). Joseph Utecht; Mathias Brochhausen; John Judkins; Jodi Schneider; Richard Boyce. Studies in Health Technology and Informatics. 2017. URL: <https://www.ncbi.nlm.nih.gov/pubmed/29295242>

[van-der-sijs-2006]

[*Overriding of drug safety alerts in computerized physician order entry*](https://www.ncbi.nlm.nih.gov/pubmed/16357358). Heleen Van Der Sijs; Jos Aarts; Arnold Vulto; Marc Berg. Journal of the American Medical Informatics Association: JAMIA. 2006 Mar-Apr. URL: <https://www.ncbi.nlm.nih.gov/pubmed/16357358>

[wang-2010]

[*Black box warning contraindicated comedications: concordance among three major drug interaction*](https://www.ncbi.nlm.nih.gov/pubmed/20040698)[*screening programs*](https://www.ncbi.nlm.nih.gov/pubmed/20040698). Lorraine Wang; Maple Wong; James Lightwood; Christine Cheng. The Annals of Pharmacotherapy. Jan 2010. URL: <https://www.ncbi.nlm.nih.gov/pubmed/20040698>

[who-umc-glossary]

[*UMC - Glossary*](https://www.who-umc.org/global-pharmacovigilance/global-pharmacovigilance/glossary/). World Health Organizatoin.2017. URL: [https://www.who-umc.org/global-](https://www.who-umc.org/global-pharmacovigilance/global-pharmacovigilance/glossary/) [pharmacovigilance/global-pharmacovigilance/glossary/](https://www.who-umc.org/global-pharmacovigilance/global-pharmacovigilance/glossary/)

[yin-2012]

[*Concurrent use of proton pump inhibitors or H2 blockers did not adversely affect nilotinib efficacy in*](https://www.ncbi.nlm.nih.gov/pubmed/22623211)[*patients with chronic myeloid leukemia*](https://www.ncbi.nlm.nih.gov/pubmed/22623211). Ophelia Q.P. Yin; Frank J. Giles; Michele Baccarani; Philipp Le Coutre; Ovidiu Chiparus; Neil Gallagher; Giuseppe Saglio; Timothy P. Hughes; Andreas Hochhaus; Hagop M. Kantarjian; Richard A. Larson. Cancer Chemotherapy and Pharmacology. 2012. URL: <https://www.ncbi.nlm.nih.gov/pubmed/22623211>

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