## Evidence

**DDI minimum information models definitions**

<https://docs.google.com/spreadsheets/d/1dhUp496riwZ0AHqRP7I85oEvuP2jjEI0rcw1Fcm2zI8/edit#gid=0>

### Updated User-Centered Definition

**Evidence for a Suspected Drug-Drug Interaction:**

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

### Previous User-Centered Definition (Qualtrics)

**Evidence:**

The support given for the possible existence or nonexistence of a drug-drug interaction; it may be data resulting from clinical studies, clinical observation or physiological experiments, or it may be an extrapolation based on drug-drug interaction mechanisms.

**For example:** Evidence of an interaction between corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), and between aldosterone antagonists and NSAIDs:

* “Both corticosteroids and aldosterone antagonists have been shown to substantially increase the risk of UGIB in patients on NSAIDs, with relative risks of 12.8 and 11 respectively compared to a risk of 4.3 with NSAIDs alone”
* Results from a case series analysis (Masclee et al. *Gastroenterology*. 2014;147:784-92.)
  + **Source**: [Warfarin-NSAID Decision Table](https://pitt.co1.qualtrics.com/CP/File.php?F=F_29xiLSLtHky74vX), NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone, University of Arizona; John Horn, Philip Hansten, University of Washington

**Feedback Themes**

* The term “nonexistence”: removed
* Provenance/types of evidence: will be addressed in the future
  + Grading/strength of evidence: outside of scope
* Examples/source information: how to incorporate the decision trees
  + Amount of information to include; PICO: Participants, Interventions, Comparisons and Outcomes

**Background Information:**

* **DIDEO**:
  + **Evidence information content entity**: “An information content entity that is used to support or refute an assertion”
  + **Drug-drug interaction evidence**: “An information content entity that is about a drug co-administration and is intended to be specified input into the assessment of whether a drug-drug interaction exists or not."
  + **Drug-drug interaction**: "An information content entity that is about a drug-drug interaction."
  + **Potential drug-drug interaction**: "A potential drug-drug interaction (PDDI) is an information content entity that specifies the possibility of a drug-drug interaction based on either reasonable extrapolation about drug-drug interaction mechanisms or a data item created by clinical studies, clinical observation or physiological experiment.”
  + **Information content entity**: "A generically dependent continuant that is about some thing.”
* **DINTO:**
  + **Information Resource**: "A resource that provides data, knowledge or narrative."
* **DIKB** (as per comments):
  + The support for a particular assertion, such as the existence of an interaction or pathway.

**Standard sub-team Qualtrics Comments**

* **3 Agree** 
  + **Appropriate**
    - This is hard to read/understand due to the sentence structure, e.g. “The support given for the”
    - ’relative risks of 12.8 and 11 respectively compared to a risk of 4.3 with NSAIDs alone’ --> this needs a citation to the primary source, not the decision table. Does "Outcome of the decision pathway" mean something particular here?
  + **Less General**
    - Evidence should always be linked to provenance
    - Evidence can be very useful for mapping the PDDI with patient health records and help to reduce false alarms in decision support systems. We might extend the definition to capture a set of data items such as studied population (size and characteristics), primary outcome, etc.
    - Currently Cochrane develops PICO ontology which aims to specify Participants, Interventions, Comparisons and Outcomes for each evidence. Later this might help us to define the vocabulary.
    - If the evidence is generated at a clinical setting, the study design should be described.
    - For the source of evidence we give a publication. However same study might be reported in different publications. If same study reported more than once, this might create a bias regarding the strength of the evidence, and might become a issue for clinical decision support systems. I wondered in micropublication ontology do we have a solution for this problem ?
* **1 Somewhat agree**
  + **Appropriate**
* **1 Neither agree nor disagree**
  + **More general**
    - 1) Evidence can be used to support or to oppose to drug administration. Current definition sounds like only support is considered. / 2) "The support given for the possible nonexistence of a drug-drug interaction"--> nonexistence or unknown? As a reader, a more straightforward expression will be much appreciated. /
    - I think if we can add sample size of the case series analysis, that would be helpful for users to make a decision about this piece of evidence.
* **1 Somewhat disagree**
  + **Less General**
    - I would suggest to label the term 'evidence' to 'drug-drug interaction evidence'. This definition is for 'drug-drug interaction evidence'. It's not for the more general term 'evidence'. /
    - Maybe it would be better to remove the words "or nonexistence". Evidence to support nonexistence is very condition-specific. Given different conditions, the result may change. If we do want to say "or nonexistence", it would be better to list the detailed experimental or clinical conditions.
    - It may be good to provide a list of subclasses of this term, such as DDI evidence based on clinical observation, ...

**Content sub-team Qualtrics Comments**

* **2 Strongly agree**
  + **Appropriate**
* **3 Agree** 
  + **Appropriate**
    - Hard to say. It needs to be specific on the mechanism and probability of an interaction taking place.
* **1 Somewhat agree**
  + **Appropriate**
    - What if the term 'clinical observation' was replaced by 'observational studies'? I'm not sure what the term 'clinical observation' conveys.

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**Evidence:**

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**For example:** Evidence of an interaction between corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), and between aldosterone antagonists and NSAIDs:

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### Updated User-Centered Definition (Jodi’s Edits)

**Evidence:**

The support given for the possible existence or nonexistence of a drug-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”
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**Themes**: in their comments, task force members appear to be concerned about:

* trust/bias/provenance
* scope
* strength
* over-reliance on one "line" of evidence

**Jodi**: Acknowledging what the model is NOT trying to do (and that additional attributes might be processed by users of the evidence) might help in moving forward.

**Suggested User-Centered Definition (Google Sheets)**

* **Evidence is a type of information that is used to support an assertion and assertion method is defined as a means by which a statement is made about an entity.**
  + Comments
    - a set of symbols, letters, and/or numbers to communicate the evidence with clear explanations of the [strength of evidence] grading system
      * Using existing standards such as GRADE? Or...?
      * Should this not be more focused on the nature of the evidence - for instance, whether identified from prospective or retrospective studies, size and diversity of the studies, etc.? or perhaps it comes from the analysis of twitter feeds, or patient-centered posts?
    - I think we need to request an edit here. Evidence is IMO not a type of information. Any information can be used as evidence.
    - Evidence has different levels, systematic reviews and meta-analysis are on the top. If we can classify the different levels of evidence, users can decide what to do with the evidence easier.
      * Reference: <http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-Introduction-2.1.pdf>
      * Certainly, we need to differentiate evidence levels.
  + Reference: <http://www.evidenceontology.org/Welcome.html>
* **Evidence is the metadata for a particular assertion (knowledge) including the provenance of the statement; scope and limits of the statement; and the strength of the findings (analysis/study) indicating the assertion (knowledge).** 
  + Comments:
    - I think using the term 'metadata' in this context can only lead to obscuring the actual relationship between evidence and the assertion.
  + Additional Comments:
    - capturing the evidence is important for us from three aspects:
      * 1) Defining the trust level.
      * 2) Capture the relevance (limits, scope)
      * 3) conclude the strength of the evidence
    - For defining the trust level: in this level aim should do minimum interpretation, and just enable users to query source of the evidence. We can keep the provenance of the evidence with W3C PROV Ontology.
    - For the relevance: we need to identify components of the evidence in terms of its relevancy to the possible given situation (when user have a case, a specific patient, with a defined intervention much the evidence will match with the given situation. PICO (Population, Intervention, Comparator and Outcome) classification can help us to identify the relevant population for the evidence, and admission of drug. If we can represent relevant population -such as age groups, sex, genetic deviation, etc- automated clinical decision support systems can pull out this data for personalized recommendations.
    - For concluding the strength of the evidence we can use models like GRADE. But at the same time we can capture a set of data items (including type of the study, size and diversity of the population, was it primary outcome, were there any reported bias, etc. ) to enable others to develop their own independent conclusion about the strength of the evidence. For this we might need a vocabulary.
    - Example
      * For any pieces of represented knowledge, various evidences can be defined. There might be more than one study/systematic review investigating the interaction between drug X and drug Y. Each study might have different inclusion and exclusion criteria and admission protocol. Results might be different. Metadata for each study can be captured in three levels:
        + 1) provenance with PROV
        + 2)Coverage of the study with PICO
        + 3) Strength of the conclusion with predefined vocabulary plus there might be models such as GRADE .
* **Drug Interaction Knowledge Base Ontology: The support for a particular assertion, such as the existence of an interaction or pathway.** 
  + Usage: At least one of confidence, evidenceCode, or experimentalForm must be instantiated when creating an evidence instance. XREF may reference a publication describing the experimental evidence using a publicationXref or may store a description of the experiment in an experimental description database using a unificationXref (if the referenced experiment is the same) or relationshipXref (if it is not identical, but similar in some way e.g. similar in protocol). Evidence is meant to provide more information than just an xref to the source paper. Examples: A description of a molecular binding assay that was used to detect a protein-protein interaction. Definition: The support for a particular assertion, such as the existence of an interaction or pathway. Usage: At least one of CONFIDENCE, EVIDENCE-CODE, or EXPERIMENTAL-FORM must be instantiated when creating an evidence instance. XREF may reference a publication describing the experimental evidence using a publicationXref or may store a description of the experiment in an experimental description database using a unificationXref (if the referenced experiment is the same) or relationshipXref (if it is not identical, but similar in some way e.g. similar in protocol). Evidence is meant to provide more information than just an xref to the source paper.
  + Comments:
    - quality of evidence (with definitions), summarize the evidence briefly, and provide access to references from the primary literature when possible
    - evidence also be provided for adverse effects, frequency, risk factors, and management strategies
    - links to the primary evidence sources
  + Further comments:
    - Quality needs to be defined and characterized. Is this a controlled list of quality signals (e.g. GRADE)? Not clear whether "quality" is the same as "strength of evidence" or something else.
    - No mention of bias or provenance is given here. Does that belong somewhere?
  + Examples:
    - A description of a molecular binding assay that was used to detect a protein-protein interaction.
  + Reference: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3124652/>
* **Comments**
  + Another issue is multiple appearance of the same evidence (in various systematic reviews, or same study in multiple publications. ). It might be difficult to tackle, since our primary aim in not to improve the quality of overall evidence curation.
  + I think this is a new database for protein-disease relationships evidence that maybe could provide some ideas: <https://www.targetvalidation.org/>
  + DIDEO: Evidence information content entity: “an information content entity that is used to support or refute an assertion”