## Clinical Consequences

**DDI minimum information models definitions**

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

### User-Centered Definitions

**Clinical Consequences:**

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

**Clinical Consequences Suspected to be the Result of a Drug-Drug Interaction:**

Changes in patient health status that may be the result of co-administration of two or more drugs that may interact.

**For example:**

* An acute hypertensive reaction may be a clinical consequence of epinephrine given in the presence of beta-blockade.
  + **Support**: Outcome of the decision pathway, [Beta-blocker - Epi Decision Table](https://pitt.co1.qualtrics.com/CP/File.php?F=F_cZykzdoKFxi0b09), NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone, University of Arizona; John Horn, Philip Hansten, University of Washington
* An acute upper gastrointestinal bleed or other bleeding event may be a clinical consequence of NSAIDs taken in conjunction with warfarin.
  + **Support**: Outcome of the decision pathway, [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
* Boosting of the antiretroviral effect of darunavir is a clinical consequence of co-administration with cobicistat.
  + **Support:** “Darunavir is primarily metabolized by CYP3A. Cobicistat inhibits CYP3A, thereby increasing the plasma concentrations of darunavir.” Prezcobix® (darunavir and cobicistat) package insert. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2016 Mar.

**Adapted from:**

Scheife RT, Hines LE, Boyce RD, et al. Consensus Recommendations for Systematic Evaluation of Drug-Drug Interaction Evidence for Clinical Decision Support [supplemental appendix]. *Drug Saf*. 2015;38(2):197-206. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624322/bin/NIHMS732017-supplement-Appendices.docx>. Accessed 03 Jun 2016.

Scheuermann RH, Ceusters W, Smith B. Toward an Ontological Treatment of Disease and Diagnosis. *Summit on Translat Bioinforma*. 2009;2009:116-120.

**Content sub-team Qualtrics Comments**

**Comments re: “Clinical Consequences”**

* **2 Strongly agree**
* **4 Agree**
  + Remove "from baseline". What is baseline? I think simplifying will keep it focused on the real issue - "changes" that cause harm.

**Comments re: “Clinical Consequences Suspected to be the Result of a Drug-Drug Interaction”**

* **2 Strongly agree**
  + The term "known to interact" could be open to interpretation. For example, I would consider a substrate and inhibitor of the same enzyme to be known to interact even if there was no direct data on the drug pair. Others may not.
* **4 Agree** 
  + consider '...may be the result of co-administration of two OR MORE drugs that MAY interact.'
  + I think we could simplify by also deleting “that can be observed or measured by clinician or reported by a patient and that” All of these qualifiers are unnecessary in my opinion. They are self-evident.

**Comments re: Examples**

* **None**

### Prior Versions

**Clinical Consequences:**

Changes in patient status from baseline that can be observed or measured by a clinician or reported by a patient.

**Clinical Consequences Suspected to be the Result of a Drug-Drug Interaction:**

Changes in patient status from baseline that can be observed or measured by a clinician or reported by a patient and that may be the result of co-administration of two drugs that are known to interact.

### Previous Version

**Clinical Consequences:**

Changes in patient status from baseline that can be ~~objectively~~ observed or measured by a clinician, or ~~subjectively~~ reported by a patient, and that ~~are~~ may be the result of taking medication(s).

**For example:**

* A clinical consequence of epinephrine given in the presence of beta-blockade may be an acute hypertensive reaction.
  + **Support**: Outcome of the decision pathway, [Beta-blocker - Epi Decision Table](https://pitt.co1.qualtrics.com/CP/File.php?F=F_cZykzdoKFxi0b09), NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Contact PI: Daniel C. Malone, University of Arizona
* A clinical consequence of NSAIDs taken in the presence of warfarin may be an acute upper gastrointestinal bleed or other bleeding event.
  + **Support**: Outcome of the decision pathway, [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; Contact PI: Daniel C. Malone, University of Arizona

### Standard sub-team Qualtrics Comments

2 Strongly agree

6 Agree

2 Neither agree nor disagree

1 Disagree

1 Strongly disagree

**Comments re: Definition**

* **Neither agree nor disagree**
  + Not clear what "from baseline" means. Several grammar problems obscure the meaning: / --Is it the 'changes' or the 'baseline' that can be objectively observed or measured? / --Does 'objectively' modify just 'observed' or 'observed or measured'? / --Does 'by a clinician' modify just 'measured' or also 'objectively observed'?
* **Agree**
  + Do this include only clinical consequences that are proven, or does it include possible risk of that is not yet proven to be associated such as might have been seen in a couple of case reports. I am not sure that changes the definition, but "are the result of" is pretty definitive.
  + I am not sure "subjectively reported by a patient" should be in the definition. In my view the clinical consequence is a professional judgement made by specific trained personnel (e.g., physicians, nurses, etc.) . The judgement can be supported by detectable evidence, such as observable symptoms or lab test results. / Another suggestion: ....observed by a clinician or measured by a test...
* **Strongly Disagree**
* Suggest removing "and that are the result of taking medication(s)." / / If we ever publish these definitions with our work, other groups may want to reuse them. By adding this line, we limit the reuse of the definition, not to mention that it is incorrect as clinical consequences are not only the result of taking medications. / / Suggest changing the term that we are defining to something along the lines of "clinical consequences that are the result of taking medication(s)."
* **Disagree**
  + There are other non medication interventions (e.g. procedures) that can elicit a change in patient status.

**Comments re: Examples**

* **Neither agree nor disagree**
  + These examples ofevidence are not specific enough. Please reference at least 1 specific cell, row, or column (or multiple cells, rows, or columns) in the decision tables. / / These sentences are awkward due to their structure. It is unclear what words would be used if the sentence were to start with the symptom, i.e. what is the missing phrase in the following sentence? "Acute hypertensive reaction [XX rephrasing"a clinical consequence of"XX] when epinephrine is given in the presence of beta-blockade."
* **Agree**
  + These are two excellent tables. However clinical consequences are not labelled explicitly in the table.
  + It may be helpful to include an example of a "positive" clinical consequence, such as a drug working well (e.g., adequate pain management) or lack of an ADR (e.g., hypersensitivity).

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

* *Clinical observable or detectable deviations from patients’ common statuses (before taking medications) after taking medications.*
* *Clinical consequences can be favorable or unfavorable.*
* *Favorable clinical consequences are intended consequence of medications administration.*
* *Unfavorable clinical consequences are caused by unintended and unexpected drug-drug interactions.*
* *Unfavorable clinical consequences range from common symptoms (such as nausea) to death.*

#### Genus Differentia: To think about

* Favorable and unfavorable consequences.
  + Favorable consequences are the intended consequence of medication administration.
  + Unfavorable consequences may be the result of drug-drug interactions (or drug withdrawal events?)
* Observable (Signs) vs. Subjective (Symptoms)
* Signs/Symptoms by severity
* Signs/Symptoms by organ system
* Signs/Symptoms by lifestyle effects

**Suggested Genus Differentia Definition (Google Sheets)**

* *Clinical consequences can be classified into favorable and unfavorable consequences.*
* *Clinical consequences from drug-drug interactions mainly focus on unfavorable consequences.*
* *Theoretically unfavorable consequences can be any symptoms of entire human body, from mental to physical, the worst consequence will be death.*
* *Symptoms can be classified into different systems, such as neurological, respiratory, circular, digestive systems etc.*

**Notes re: User-Centered Definition (eag)**

* It can be important to keep in mind that stopping a medication can also have a clinical consequence, but I’m not sure if that belongs here
* OGMS (MB’s comments): clinical manifestation of a disease: “A representation that is either the output of a clinical history taking or a physical examination or an image finding, or some combination thereof.”
* Objective (signs) vs. subjective (symptoms) – really important in clinical activities

**Comments (Google Sheets)**

* For example, simply stating that ciprofloxacin may increase the blood levels of theophylline is insufficient. Clinical effects of theophylline toxicity such as nausea, vomiting, cardiovascular instability, and seizures should be provided with the decision support information
* Perhaps we should consider a separation of "pharmacological consequence" (e.g., increase in theophylline level), from “clinical consequence” (e.g., symptoms associated with increase in theophylline level). This would allow us to capture such details as, for example, DDI’s with a pharmacological consequence with no clinical consequence. This would lean towards an information model where DDI’s have only pharmacological consequences, and medications have clinical consequences. [C.Vitale]
* I would suggest not specifying "unexpected drug-drug interactions" because sometimes, although it is known that a DDI might occur, the combinations might be used under certain monitorization of the patient
* I agree with this separation between what could be denominated PK and PD consequences (or pharmacological consequences together), and clinical consequences, which are closely related to the adverse or toxic effects (or therapeutic effects if we include beneficial DDIs) of one or the two interacting drugs, and that I would define by having these two characteristics: (1) relevant for the patient clinical status or therapeutic outcome AND (2) observable (e.g. rash), measurable (e.g. elevated high pressure) or perceived and reported by the patient (e.g. abdominal pain). This allows to distinguish between clinical and nonclinical and unobservable consequences.
* Of course, each DDI will have several PK and/or PD consequences, but I think it is not possible to distinguish between DDIs having a pharmacological consequence and those non having it, since the occurrence of the clinical consequence will depend (most of the times) on other factors such as dose of the drugs and patient factors.
* Also, the distinction between DDIs having only pharmacological consequences and medications having clinical consequences is confusing to me. I would suggest considering that the DDI occurs between pharmacological substances, that are ingredients of drug products (medications), but the clinical consequence (relevant and observable) depends on other factors (as dose, administration route, age, renal function, …)
* The clinical consequence occurs as a consequence of the PK or PD consequences, that occur because of the occurrence of the DDI mechanism, which happens at the molecular level and involves therefore the pharmacological substances (which are administered to patient as drug products). Therefore, I think it is not possible to separate PK and PD consequences from clinical consequences as suggested.
* Here is the definition of 'clinical finding' (OGMS\_0000014) from OGMS, which is think is relevant to representing clinical consquence: "A representation that is either the output of a clinical history taking or a physical examination or an image finding, or some combination thereof." [MB]