Drug-drug Interactions - opportunities for improved standardization and interoperability of data

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Potential drug-drug interactions (PDDIs)

- Exposure two or more drugs that are known to interact
  - "potential" because exposure does not necessarily mean a clinically meaningful effect

Clues about the frequency of harm

- Clinically important events attributable to drug-drug interactions [1]:

  – 5.3% - 14.3% of inpatients

  – 231,000 US emergency department visits

- Hospital admissions associated with an adverse drug event attributable to drug-drug interactions [2]:

  – 22.2% (interquartile range 16.6 - 36.0%)

1. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. *Expert Opin Drug Saf*. 2012;11(1):83-94. doi:10.1517/14740338.2012.631910
2. Dechanont S, Maphanta S, Butthum B, Kongkaew C. Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2014;23(5):489-497. doi:10.1002/pds.3592.

Key point

No broadly accepted standards exist on how to organize and present PDDI knowledge

PDDI clinical decision support (CDS) information needs

- Review and synthesis of:
  - 77 journal articles

  - 4 white papers from AHRQ-funded PDDI Working Groups

  - 6 semi-structured interviews

Romagnoli KM, Nelson SD, Hines L, Empey P, Boyce RD, Hochheiser H. Information needs for making clinical recommendations about potential drug-drug interactions: a synthesis of literature review and interviews. *BMC Med Inform Decis Mak*. 2017;17(1):21. doi:10.1186/s12911-017-0419-3

"there may be 3 or 4 pharmacokinetic case studies... there may be a bunch of case reports.. So then we add up all that information together.."
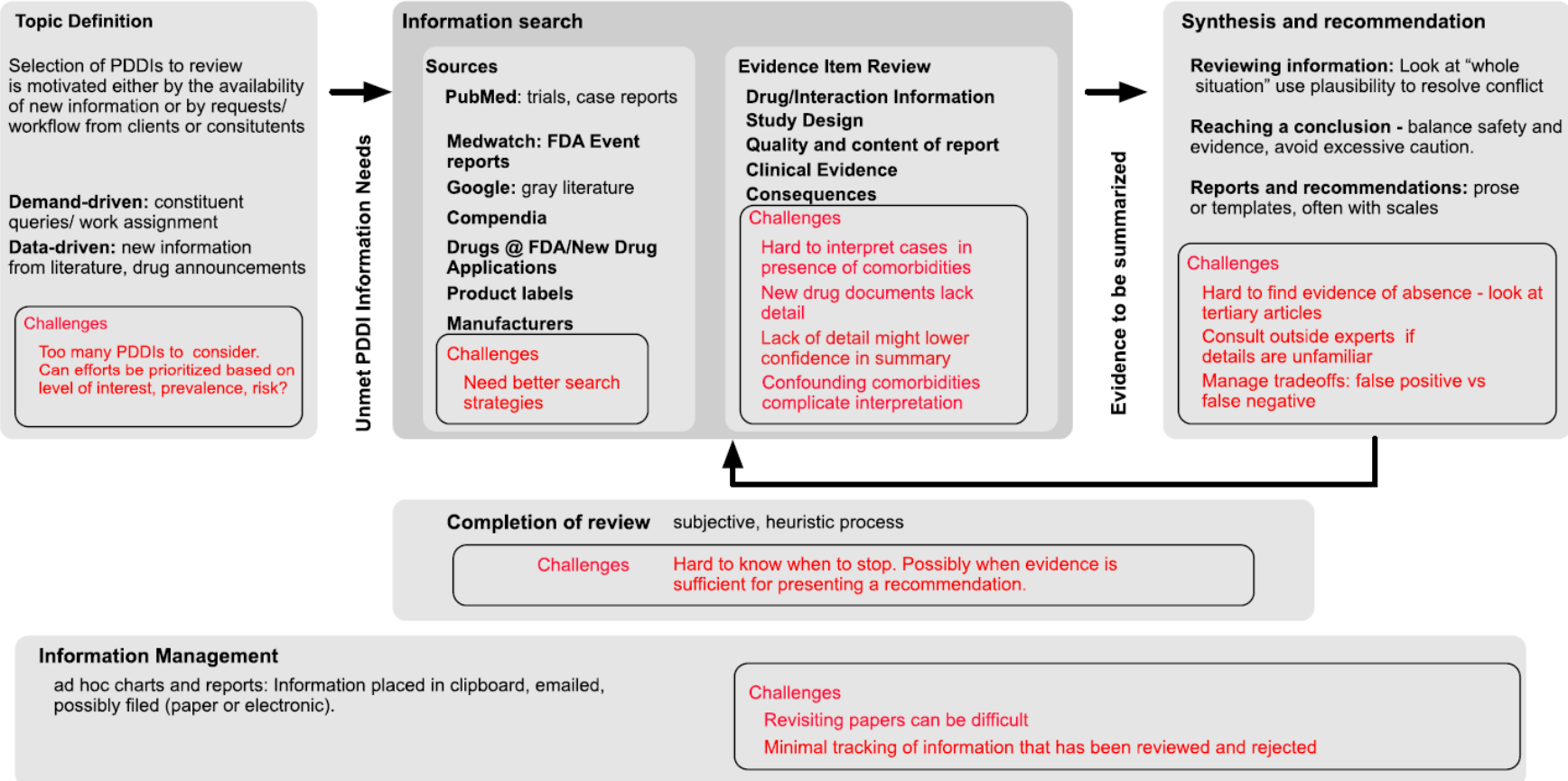
Topic Definition

Selection of PDDIs to review is motivated either by the availability of new information or by requests/ workflow from clients or consitutents

Demand-driven: constituent queries/ work assignment
Data-driven: new information from literature, drug announcements

Challenges
   Too many PDDIs to consider. Can efforts be prioritized based on level of interest, prevalence, risk?

Unmet PDDI Information Needs

Information search

Sources
   PubMed: trials, case reports
   Medwatch: FDA Event reports
   Google: gray literature
   Compendia
   Drugs @ FDA/New Drug Applications
   Product labels
   Manufacturers
   Challenges
      Need better search strategies

Evidence Item Review
   Drug/Interaction Information
   Study Design
   Quality and content of report
   Clinical Evidence
   Consequences
   Challenges
      Hard to interpret cases in presence of comorbidities
      New drug documents lack detail
      Lack of detail might lower confidence in summary
      Confounding comorbidities complicate interpretation

Evidence to be summarized

Synthesis and recommendation

Reviewing information: Look at "whole situation" use plausibility to resolve conflict

Reaching a conclusion - balance safety and evidence, avoid excessive caution.

Reports and recommendations: prose or templates, often with scales

Challenges
   Hard to find evidence of absence - look at tertiary articles
   Consult outside experts if details are unfamiliar
   Manage tradeoffs: false positive vs false negative

Completion of review   subjective, heuristic process
   Challenges   Hard to know when to stop. Possibly when evidence is sufficient for presenting a recommendation.

Information Management
   ad hoc charts and reports: Information placed in clipboard, emailed, possibly filed (paper or electronic).
   Challenges
      Revisiting papers can be difficult
      Minimal tracking of information that has been reviewed and rejected

Fig. 2 Potential Drug-Drug Interaction information evaluation and synthesis workflow

PDDI CDS Information needs…

Mechanism of action

- Pharmacology
- Formulation
- Timing
- …

Context

- Modifying and mitigating factors
- Time of onset
- Manageability
- Frequency
- …

Evidence

- Study design
- Reporting information (e.g., funding agency)
- Causality assessment (case reports)
- …

Clinical Consequences

- Adverse effect(s)
- Seriousness
- Severity
- …

Recommended actions

- Monitor, change drugs, modify strength, adjust timing, etc
- Strength of recommendation

What have we done to address this gap?

The PDDI Minimum Information Model Task Force:

- volunteer-based – ~40 participants

  – W3C, AMIA Pharmacoinformatics, WorldVista, academics

- broad stakeholder involvement

  – NLM, industry, academic institutions, individuals

- Open public participation

  – formed within the Health Care and Life Sciences Interest Group that operates publicly through the World Wide Web Consortium (W3C)

Task force objective and deliverables

- **Objective**: Develop a minimal information model for drug interaction evidence and knowledge as part of an HIT standard like HL7

- **Deliverables:** using an interesting and non-trivial set of potential drug-drug interactions:

  - A minimum information model for potential drug interaction knowledge and evidence

  - A precise vocabulary describing/defining the information model

  - Demonstration of how the information model can support medication reconciliation

The deliverables as a W3C Community Group Report

- Available here: https://w3id.org/hclscg/pddi

- 10 core information items

- 8 detailed best practice recommendations related to the 10 core information items

- 2 exemplar PDDIs (narrative and prototype JSON artifacts using the information model)

- 12 User stories with related goals

The minimum information model and related vocabulary

Drugs involved
(R1)

→

Value sets:
RxNorm
ATC
Other

R1 - Explicitly state the drugs involved, ideally using value sets

Mechanism
(R2)

R2 – Report a mechanism if known (or state "not known")

Frequency of harm
vs exposure (R3)

R3 – State the frequency of harm relative to frequency of exposure if known
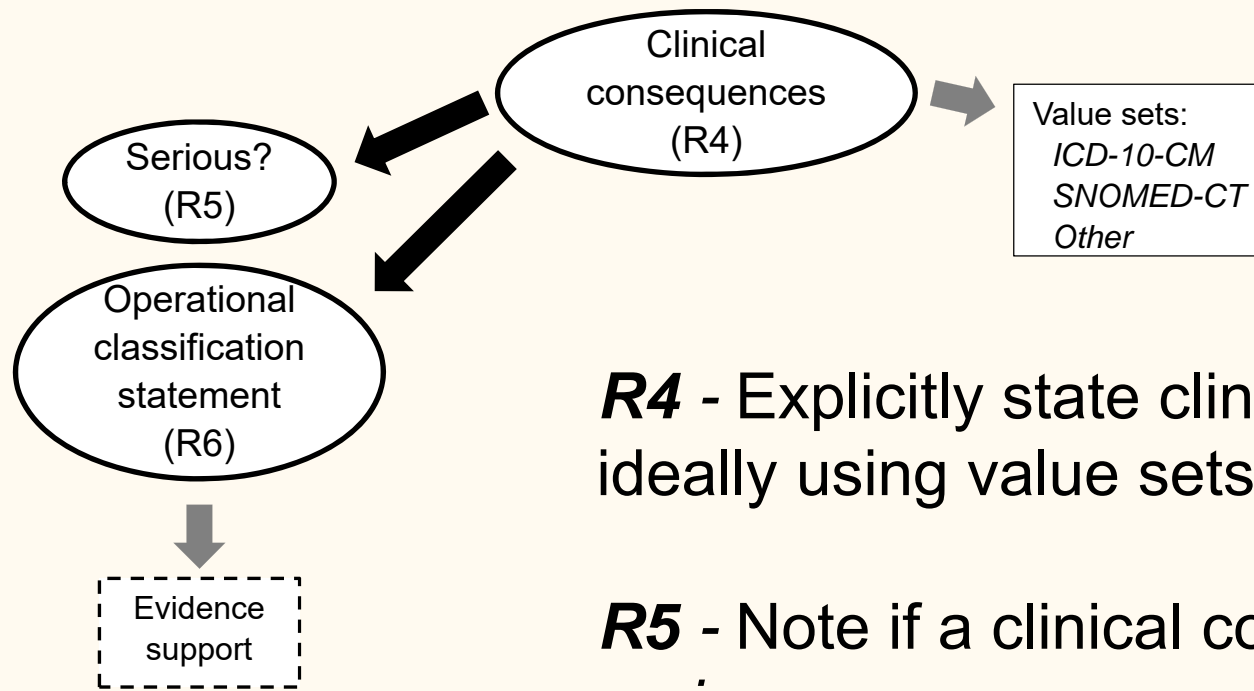
R4 - Explicitly state clinical consequences, ideally using value sets

R5 - Note if a clinical consequence is *serious*

R6 - Include an operational classification statement
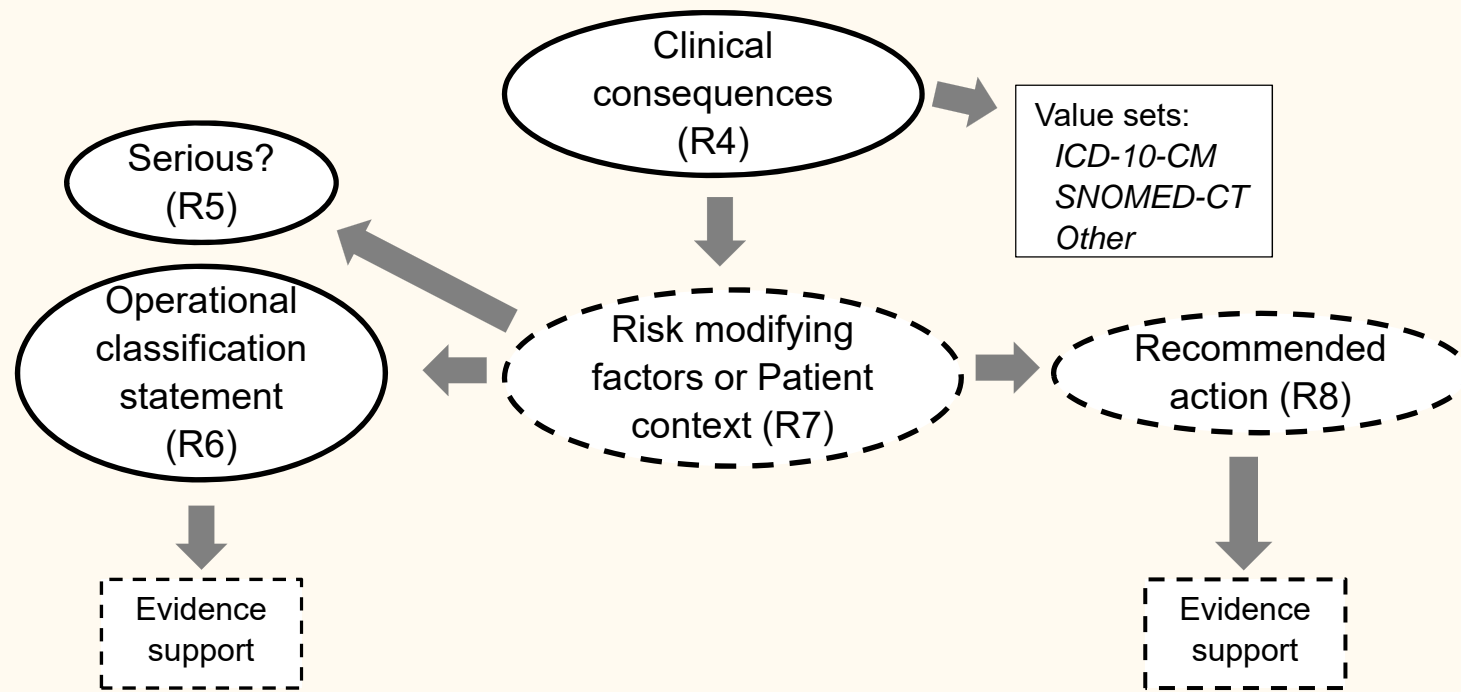
R7 - State each known risk modifying factor or patient context

R8 - State a recommended action if one is known
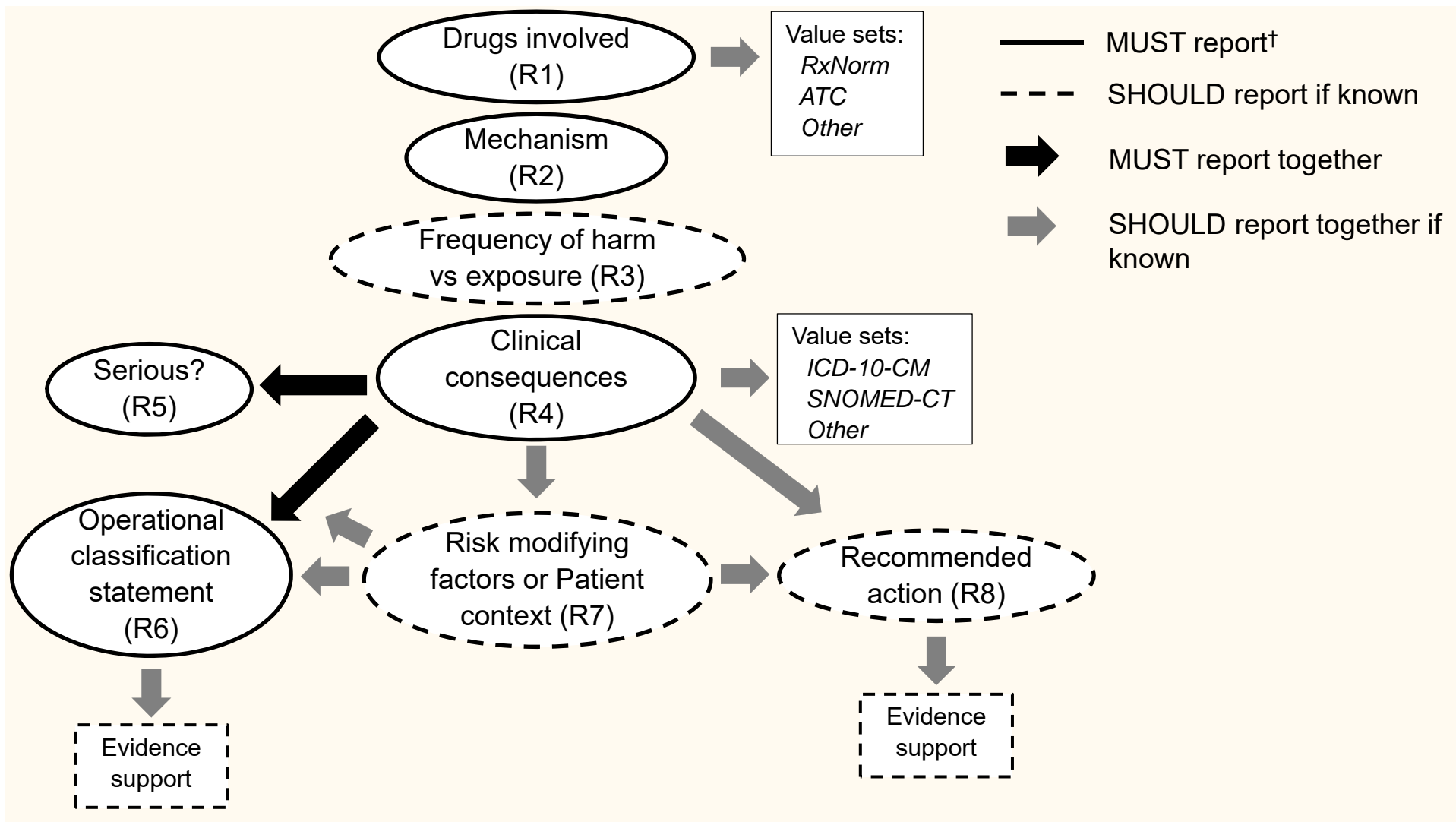
The envisioned role for a PDDI minimum information model

- Link to the report: https://w3id.org/hclscg/pddi
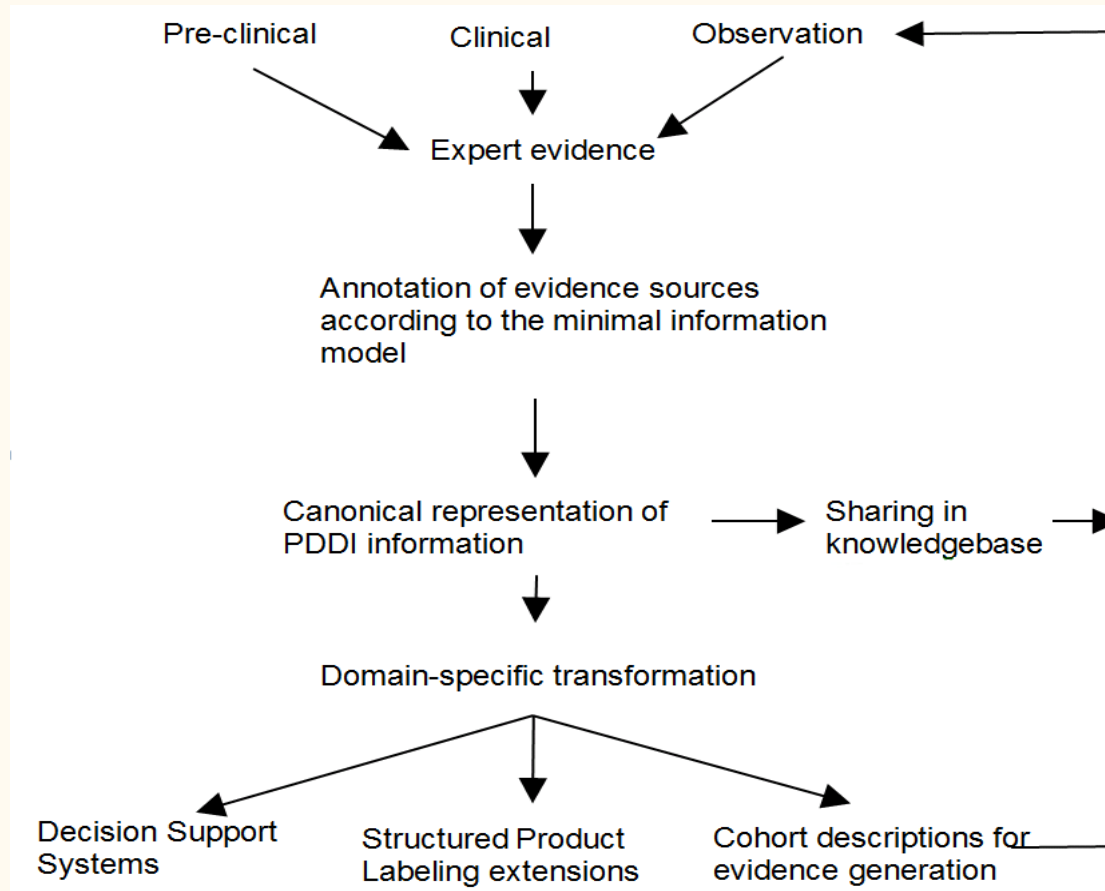
- There are multiple ways to provide feedback:

  – Anonymously provide feedback via this qualtrics survey: https://pitt.co1.qualtrics.com/jfe/form/SV_brNsZtD8vHwPoLX

  – email your comments to Rich Boyce at rdb20@pitt.edu

  – add an issue on the Note's github site:

    • https://github.com/w3c/hcls-drug-drug-interaction/issues

  – reply to the forums.dikb.org topic:

    • https://forums.dikb.org/t/final-comment-periods-for-the-pddi-information-model-community-group-note/211

The information model as part of PDDI CDS as a service

- An HL7 project within the CDS workgroup
  - Create an *implementation guide that* shows how to do PDDI CDS as a service:
    - The minimum information model, FHIR, CDS Hooks, and CQL
  - Join us!
    - http://wiki.hl7.org/index.php?title=PDDI_CDS

Acknowledgements

Discussion