

Reviewer 1:



1. There are so many different terms that describe drug safety profiles, such as adverse events (AE), drug adverse reactions, and drug adverse events. The authors are suggested to provide a consistent term in the revised version.

2. The authors integrated FAERS in current LAERTES. However, current FAERS is too old (2012 version based on ref 44). There are huge updated data from 2012 to 2015 in FAERS 2015 version.

3. All super links in Table 3 cannot work.

4. There are so many existing tools, such as MetaADEDB, CTD, and FAERS, that can link drug side effects or adverse events information. The authors are suggested to provide possible advantages or disadvantages compared to the existing tools or databases.

Response: There are many different sources of information that can provide evidence about drug side effects, each of which currently acts independently and have their own advantages and disadvantages. LAERTES does not represent a new source of evidence, but instead intends to bring these disparate sources together such that users can review evidence from across the sources such that the individual pieces of evidence can be evaluated in context.

5. The authors have to discuss or implement automate data curation protocol to update LAERTES frequently based on big healthcare data in the future.

6. Some related studies for drug safety risk assessment were lost in Introduction of the current version, such as doi: 10.1021/ci300367a; doi: 10.1021/ci400010x; and doi: 10.1136/amiajnl-2013-002512

Reviewer 2:



- Motivating User Stories: Given Table 2 already outlines the user stories in a precise manner, the verbose version presented in subsections 1) 2) and 3) appears redundant.

- Open Annotation Data (OA) model: As mentioned in the paper, Open Annotation Data (OA) model is used as an integrated representation language in the data architecture of LAERTES, and some of the source data models are being described using OA (see Figure 3-6). However, the Open Annotation Data (OA) model is not described in the paper. It is important to describe the OA model (main concepts and properties of this model) and also discuss the rationale for using this model as a representation language in the data architecture of LAERTES.

- Running Example: The paper presents a schema level overview of the source models (see Figure 3-6) and described different use-cases for querying integrated evidence sources using SPARQL constructs. However, the paper lacks in terms of presenting a running example (at an instance-level) and demonstrating how LAERTES integration modules utilize semantic enrichments to link evidence sources relevant for HOIs, e.g. by selecting one of the concrete scenario (i.e. a particular adverse event vs combination of drugs) driven from the already described user stories.

- *ETL evidence sources into LAERTES: It is mentioned that five evidence sources are now loaded and integrated into LAERTES. The paper does not discuss the challenges faced in bridging this interoperability, and also does not describe **the methodologies and modules used** in loading these sources.*

- *Results: The authors have tried to demonstrate the use of LAERTES in solving the addressed user stories. However, The paper does not present experimental results in terms of precision, recall and accuracy of the proposed integration modules of LAERTES (i.e Evidence sources found and integrated in LAERTES for an adverse event signal detection vs correct/relevant evidence sources?)*

Reviewer 3:



I did not see any mention in the paper of how the weighting of evidence can be represented. An outcome may be reported, or might have been backed up through objective tests. An adverse event might be identified on a single patient, or on multiple patients. It would seem helpful that an evidence discovery tool (and, potentially, an evidence generation tool) should enable items of evidence to be annotated with some weighting information. I hope the authors might be willing to add a few sentences to the discussion section to either indicate if this is not a relevant characteristic for this tool, or to indicate how weighting information might be provided for within the architecture.