Making the most of existing evidence in the OHDSI evidence generation environment

An update from the Knowledge Base (Laertes) workgroup

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Outline for today’s update

1. Motivation for the work and the current status of the LAERTES evidence base
2. Use of the evidence base to generate “negative controls”
3. Demo of the negative control workflow within Atlas
4. Discussion
Some of you might remember…

OMOP's Vision of Risk Identification - 2013
http://omop.org/node/649
The 2013 OMOP symposium presented a vision...

• **Large-scale evidence generation**
  – Large patient-level datasets offer unprecedented opportunities for evidence generation
  – We no longer need to constrain ourselves to custom-selecting one piece of evidence at a time
  – What we do need is a standardized, systematic approach to interrogate, evaluate, and synthesize **all the diverse evidence** that is at your disposal to guide your decision-making
To go forward, we must go back

“What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?”

- Strength
- Consistency
- Temporality
- Plausibility
- Experiment
- Coherence
- Biological gradient
- Specificity
- Analogy

Coherence

Sir Bradford-Hill 1965:
“The cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease.”

OMOP 2013:
Observational data is only one piece of the puzzle. We need an interactive framework to explore observational analysis results alongside other evidence from published literature, product labeling, spontaneous adverse event reporting, and biomedical ontologies.
“Like a photo mosaic, a clear and understandable image of a potential drug safety issue can emerge when the relevant sources of evidence are brought together”

Knowledgebase (LAERTES) Workgroup

• Objective:
  – The objective of this workgroup (WG) is to establish an open-source standardized knowledge base for the effects of medical products and an efficient procedure for maintaining and expanding it.

• See:
  – Project homepage: http://goo.gl/Dz1zx9
  – Github project: https://github.com/OHDSI/KnowledgeBase
    • Known issues and bugs: https://goo.gl/grcka7
  – WebAPI documentation: http://goo.gl/2JCb92
The LAERTES evidence base

- Synthesizes adverse drug event evidence within a standard framework for clinical research
  - Standardizes drugs and HOIs
    - RxNorm and SNOMED
  - Summarized across evidence sources
  - Enables “drilling down” to examine specific evidence items
An integrated evidence base of information sources relevant to medication safety investigations

Newly selected information sources and integration methods

User feedback

Evaluation

Expert:
• Panel of medication safety experts

External:
• New drug-HOI associations from regulatory bodies
• Published case reports evaluated for causality

Predicted/inferred drug-HOI associations

A “silver standard” reference set – the drug-HOI “Knowledge Base”
Current status of the evidence base

- Spontaneous adverse event data (FAERS, VigiBase™, ClinicalTrials.gov)
- Literature (PubMed, SemMed, CTD)
- Product labeling (SPL, SPC)
- Indications / Contraindications / Targets (NDF-RT, DrugBank)
- Observational healthcare data (claims + EHR)


Evidence Sources

Spontaneous adverse event data (FAERS, VigiBase™, ClinicalTrials.gov)

Literature (PubMed, SemMed, CTD)

Product labeling (SPL, SPC)

Indications / Contraindications / Targets (NDF-RT, DrugBank)

Observational healthcare data (claims + EHR)

ClinicalTrials.gov:
- Test version – drugs w/ trials
- VigiBase™: In process

SemMed (Kilicoglu et al):
- Case reports: 11,933(+), 411(-)
- Clinical trials: 7,794(+), 682(-)
- Other: 56,297(+), 3,209(-)
- CTD: 432,850

FAERS:
- Reports and PRR: 2,753,078

PubMed (Avillach et al.):
- Case reports: 41,229
- Clinical trials: 682
- Other: 67,002

US SPLs (Duke et al.):
- Adverse Drug Reactions: 254,738

Indications/contraindications:
- From the standard vocabulary
- Drug Targets
- DrugBank 4.0 (OMOP mapping)

Can be done on local installations
- Public data pending
# Timeliness and number of evidence items

<table>
<thead>
<tr>
<th>title</th>
<th>coverage_end_date</th>
<th>record count</th>
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<tbody>
<tr>
<td>PubMed</td>
<td>2016-03-16</td>
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<tr>
<td>CTD Chemical-Disease</td>
<td>2016-03-01</td>
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<td>US Product Labeling</td>
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<td>SemMedDB</td>
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<td>EU Product labeling</td>
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Basic web-based exploration of the evidence base

• Video demo:
  – Exploring LAERTES demo video

• Live site:
  – http://goo.gl/swZ6jf
<table>
<thead>
<tr>
<th>Ways to access the LAERTES Evidence Base</th>
<th>Database (AWS or custom)</th>
<th>RDF store (AWS or custom)</th>
<th>Linked Data (custom)</th>
<th>Web API</th>
<th>Atlas</th>
<th>KB Web</th>
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<tbody>
<tr>
<td>HOIs by Drug (RxNorm ingredient, clinical drug, branded drug)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Drugs by specific HOI SNOMED concept</td>
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<td>Part</td>
<td>Part</td>
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<td>Drugs by HOI SNOMED concept similarity</td>
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<tr>
<td>‘Drill down’ to proxy for the source documents</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Negative Controls</td>
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<td>CT.gov</td>
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</table>
Roadmap

• Main goals this year

1. A fully tested release version of the LAERTES drug-HOI evidence base
   • similar to how the OHDSI vocabulary is released
   • known issues addressed

2. A more user friendly interface for exploring the evidence base
   • Better support for the safety investigator user scenario

3. Develop explicit criteria for going from the drug-HOI evidence base to drug-HOI knowledge
   • Progress on the comprehensive knowledge base

4. Funding to conduct further research and development
Acknowledgements

• Funding:
  – National Library of Medicine (1R01LM011838-01)
  – National Institute of Aging (K01AG044433-01)
How to get Involved

• Join our meetings:

• Test and create issues:
  – [https://github.com/OHDSI/KnowledgeBase](https://github.com/OHDSI/KnowledgeBase)