A European perspective to networking in drug safety, EU-ADR as example

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The EU-ADR Project
(formerly known as ALERT)

Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge

http://euadr-project.org/

Started February 2008

EC- Grant agreement no.: 215847

Infosociety
Partners

- TAU (Tel-Aviv)
- UPF FIMIM
- UAVR
- USC
- LSHTM
- UNOTT
- UB2
- ICL
- SIMG
- Erasmus MC
- PHARMO
- AUH-AS
- AZ
- UNIMIB
- PEDIANET
- ARS
- NEUROLESI
- TAU (Tel-Aviv)
The overall objective of EU-ADR is:
The design, development and validation of a computerized system that exploits data from electronic healthcare records and biomedical databases for the early detection of adverse drug reactions.

Supposed to be complementary to existing systems, have more power and detect signals earlier.
EU-ADR concept

8 Medical record and claims databases:
Now 30 Million persons (IT, NL, UK, DK)

Data mining

Data extraction: periodic

Signal detection

Signal substantiation

Hypothesis testing and system validation

Mapping of events and drugs
Development of extraction tools

Literature
Known side effects
Pathway analysis
In-silico simulation

www.euadr-project.org
Key objectives and achievements

- To define a list of important adverse events that should be monitored.
  - Delivered and published 23 events (Trifiro’ et al. PDS 2008)

- To compile validation sets of signals (true positive and true negative drug-event combinations), to be used throughout the project for learning and testing purposes.
  - Delivered (60 pairs, currently being extended)

- To provide a mapping between the different terminologies used in the EHR systems
  - Delivered and published: all based on UMLS (Avillach P et al. JAMIA)
  - Benchmarking ongoing and has been tested also with US/Asian data, presented at ICPE 2009
  - Harmonization and benchmarking done for 6 events/ ongoing for other 6
Key objectives and achievements

- To establish a common data framework that allows for extraction of the relevant data from each EHR system for subsequent text and data mining processing.
  - Distributed data network approach chosen
  - Jerboa software (JAVA based) developed which locally elaborates common input files to generate de-identified data (flexible script)
  - 100 million person-years currently combined (8 databases)
  - Jerboa program used in multiple other EC-funded projects, across US and ASIA and in the H1N1 safety studies
  - Data mining done for all drugs against 6 (harmonized) events

- To develop text mining techniques that detect the selected medical events in free-text and map these terms to corresponding standard codes.
  - Work ongoing to be delivered in the coming year
Key objectives and achievements

- To develop data mining algorithms that produce a prioritized set of adverse drug reaction signals.
  - Work in progress: EU-ADR has won the OMOP cup for signal detection methods
  - Comparison of methods is being conducted to be delivered next year

### Ranking

**Disproportionality methods (traditional)**
- BCPNN
- MGPS
- Fisher ET

**Cohort methods**
- Incidence rate ratio (MH)

**Case based methods (exposure odds)**
- Matched Case control
- Case crossover
- SCCS

**Other methods**
- Leopard
- Rule based

**False discovery rate**
- Bayesian EB, HB

**Methods developed by different partners**
Key objectives and achievements

To automatically detect scientifically and mechanistically sound explanations for the drug-event pairs by means of a combination of analyses of repositories of known side effects, biomedical literature, in silico predictions and pathway mapping.

Repositories of known side effects: webservice working
Biomedical literature: protein mapping: done and working webservice
In silico predictions of targets: running webservice
Pathway mapping: fine-tuning is ongoing
Next year we will deliver information on the validity

To develop a computerised system that integrates the different software components and adds a web interface for seamless access to the knowledge created by the project.
System designed and security being dealt with, will be delivered in coming year; currently being tested for different use scenarios
Key objectives and achievements

To perform retrospective and prospective validation of the system and the results.

*Event validation*: to be done in coming year, chart review for positive predictive values

*Comparison* between signals detection in EU-ADR and in FDA-AERS/WHO in terms of complementarity and velocity

*Hypothesis testing studies*
New signals will be tested according to properly designed studies using the UE-ADR platform
Signal substantiation (automated)

- List of associations
- Known side effect from DBs
  - Yes (annotate)
  - No
- Drug
- Event

- Map targets to network
  - Target of drug list
  - Target to event list
  - Path that connects drug to event through biological reactions

- D-T
- E-T

Substantiation score for the signal
Implications for Sentinel

- No direct implications rather opportunities
- Signal detection methods evaluation
- Comparison of system with existing spontaneous reporting systems
- Computerized system might be used by FDA (starts with a drug-event list)
- Signal substantiation pipeline could be useful for Sentinel system
- Common data input files might be exchanged between US and EU to allow for upscaling and collaboration
- Benchmarking is useful method of improving transparency for all databases