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

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EU-ADR consortium**





The EU-ADR Project (formerly known as ALERT)

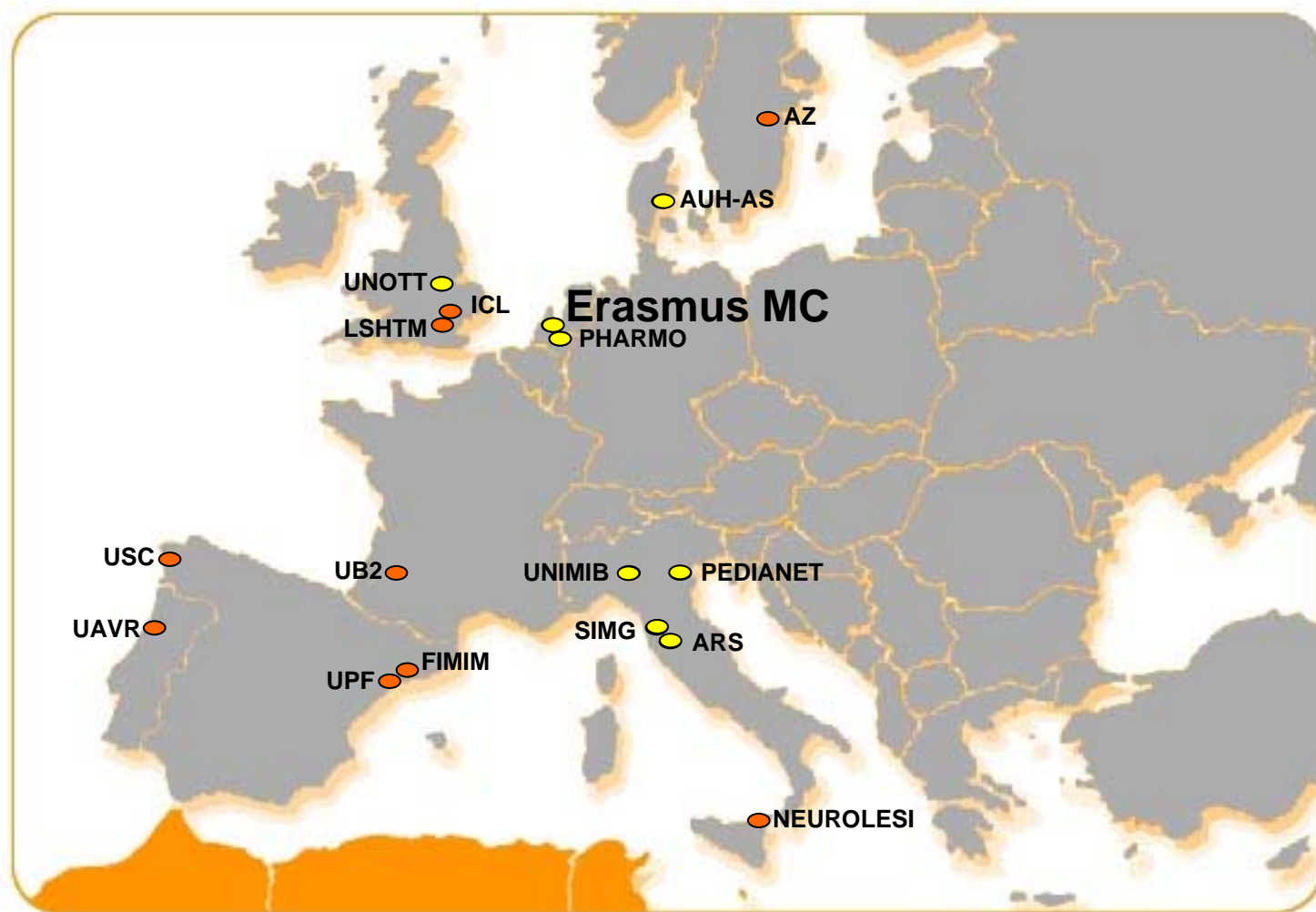
Exploring and **U**nderstanding **A**dverse **D**rug
Reactions by Integrative Mining of Clinical Records
and Biomedical Knowledge

<http://euadr-project.org/>

Started february 2008

EU-ADR IS A RESEARCH AND DEVELOPMENT PROJECT FUNDED BY THE INFORMATION AND COMMUNICATION TECHNOLOGIES (ICT) AREA OF THE EUROPEAN COMMISSION UNDER THE VII FRAMEWORK PROGRAMME

Consortium



● TAU (Tel-Aviv)

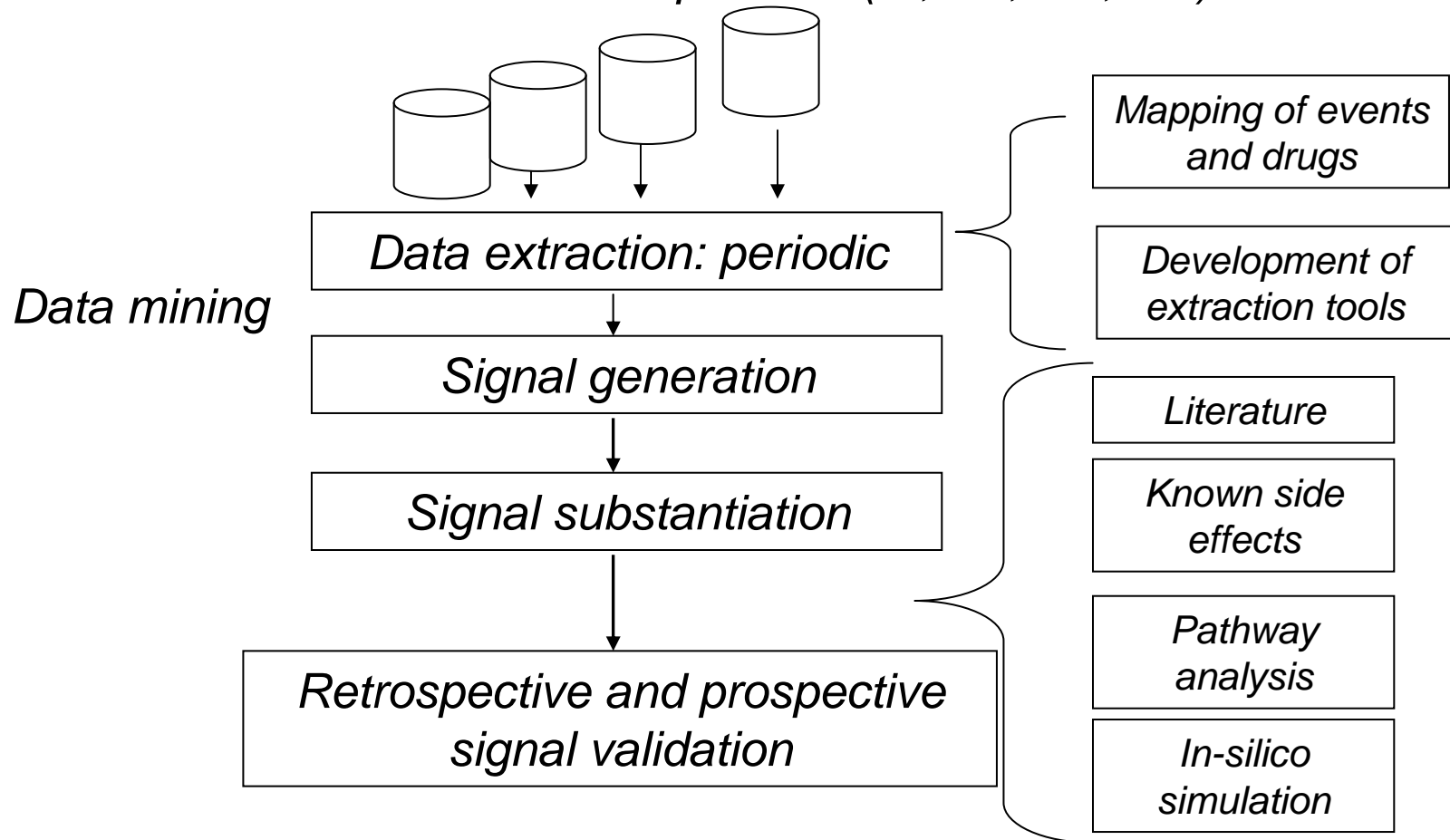
The overall objective of the **ALERT project** is the design, development and validation of a **computerized system** that **exploits data** from **electronic healthcare records** and **biomedical databases** for the ***early detection of adverse drug reactions.***

Supposed to be complementary to existing systems, have more power and detect signals earlier

EU-ADR concept



Medical databases: Now 30 Million persons (IT, NL, UK, DK)



Type of databases currently involved



Electronic medical

- IPCI (NL)
- QRESEARCH (UK)
- PEDIANET (IT)
- HSD (IT)

Administrative

- PHARMO (NL)
- Aarhus (DK)
- ARS: Tuscany (IT)
- UNIMIB: Lombardy (IT)

Open to other databases

Important choices

- Only selected number of events to be studied (events that are relevant in terms of drug safety)
- Data remain local (distributed network approach) and only query results will be shared

Event selection	Total score
Bullous eruptions	15
Acute renal failure	14
Acute myocardial infarction	13
Anaphylactic shock	13
Rhabdomyolysis	12
Aplastic anemia/pancytopenia	12
Neutropenia	12
Cardiac valve fibrosis	11
Acute liver injury	10
Extrapyramidal disorders	9
QT prolongation	9
Confusional state	9
Suicidal behavior/attempt	9
Thrombocypenia	8
Upper gastrointestinal bleeding	8
Convulsions	8
Peripheral neuropathy	7
Maculopapular erythematous eruptions	7
Venous thrombosis	7
Mood changes: depression and mania	7
Amnesias	7
Hemolytic anemia	6
Acute pancreatitis	6



Trifiro et al. Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? Pharmacoepidemiol Drug Saf. 2009 Sep 15

Linking databases and data extraction for signal generation in EU-ADR



Extraction of data

- Step 1: Mapping of codes (disease, drugs, language): UMLS
- Step 2: Application of Jerboa to elaborate and extract aggregated data locally (distributed network approach)

Quality control

- Step 3: Comparison of rates
- Step 4: Inspection of drug utilization
- Step 5: Assessment of drug-event associations (validation sets: true positive / true negative)

Avillach P. et al. A semantic approach for the homogeneous identification of events in eight patient databases: a contribution to the European eu-ADR project. Stud Health Technol Inform. 2009;150:190-4.

Step 1: Terminology mapping

How to deal with different codes between DBs?

Resource: **the UMLS**

- Unified Medical Language System
- Metathesaurus
 - include more than 150 source vocabularies
 - ~ 1,6 million concepts (sets of synonyms)
- Semantic Network
- Lexical Resources

www.euadr-project.org

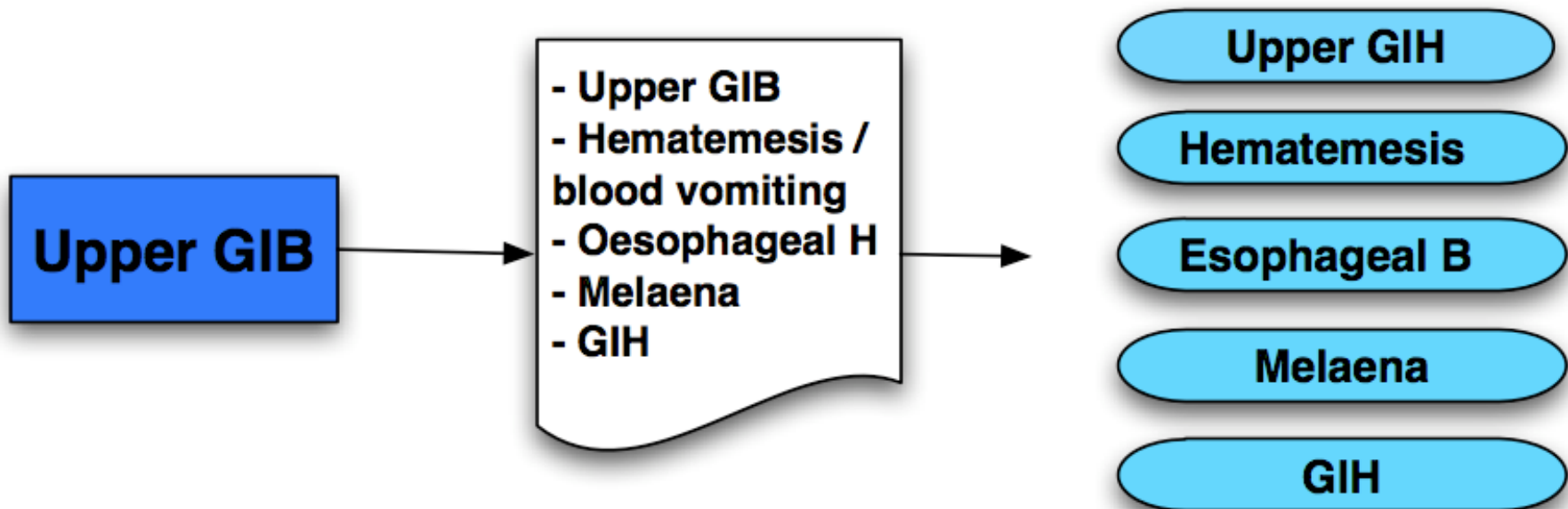
*From: Paul Avillach, Frantz
Thiessard, Bordeaux*

Workflow of Terminology mapping

1. Event

2. Event
Description Form

3. Search
for UMLS
concepts



3. Search for UMLS concepts

Upper GIH

Hematemesis

Esophageal B

Melaena

GIH

5. Conference call to discuss harmonisation issues

4. First Draft of Terminology mapping

C0041909		Upper gastrointestinal hemorrhage	
RCD	X30Be	Upper gastrointest haemorrhage	ENG
RCD	X30Be	Upper gastrointestinal haemorrhage	ENG
RCD	X30Be	Upper GI - gastrointestinal haemorrhage	ENG
RCD	X30Be	Upper GI-gastrointes haemorrh	ENG
C0018926		Hematemesis	
ICD10	K92.0	Haematemesis	ENG
ICD9CM	578.0	Hematemesis	ENG
ICPC	D14	Hematemesis/vomiting blood	ENG
ICPC2P	D14001	vomiting out blood	ENG
ICPC2P	D14001	Vomiting;blood	ENG
ICPC2P	D14003	Haematemesis	ENG
ICPC2P	D14003	Hematemesis	ENG
ICPCDUT	D14	Haematemesis/bloed braken	DUT
ICPCITA	D14	Ematemesi/vomito sanguinolento	ITA
RCD	J680.	Haematemesis	ENG
RCD	J680.	Vomiting blood	ENG
C0239293		Esophageal bleeding	
ICD9CM	530.82	Esophageal hemorrhage	ENG
ICPC2ICD10DUT	MTHU011694	bloeding; oesofagus	DUT
ICPC2ICD10DUT	MTHU054119	oesofagus; bleeding	DUT
RCD	J10y0	Haemorrhage of oesophagus	ENG
RCD	J10y0	Oesophageal haemorrhage	ENG
RCD	Xa7TU	Oesophageal bleeding	ENG

[...]

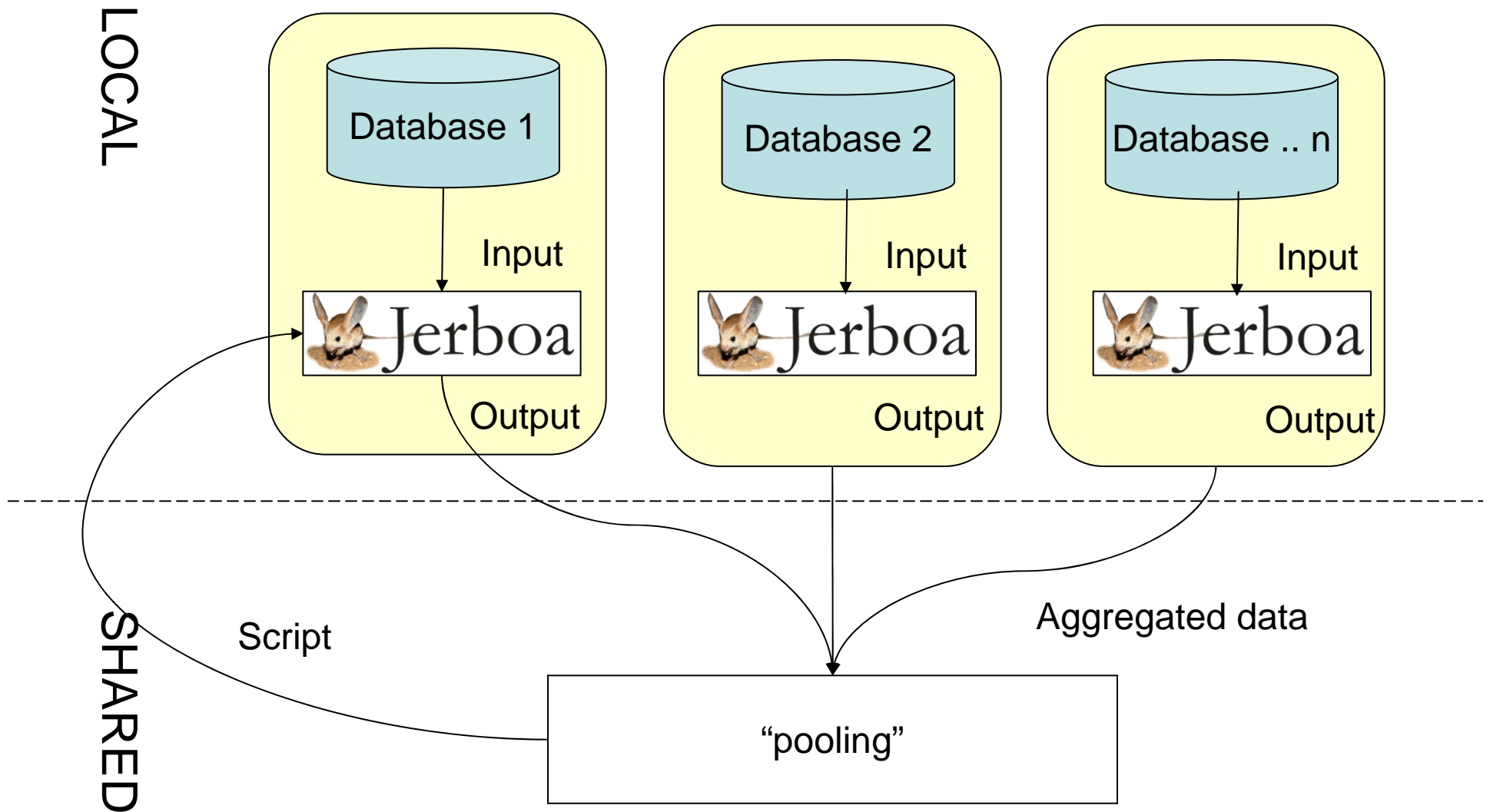
From: Paul Avillach, Frantz Thiessard, Bordeaux

Step 2: Data extraction

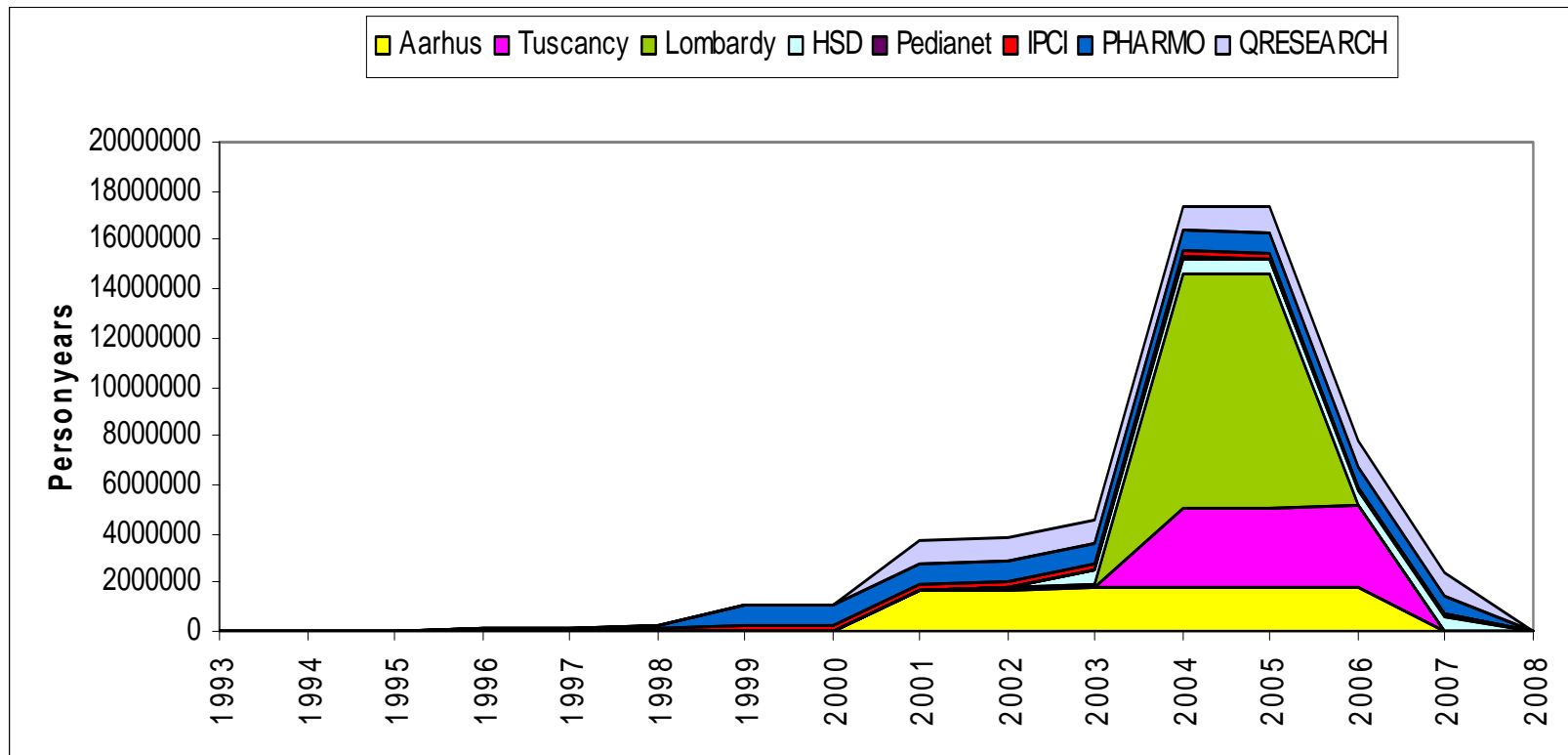
- Distributed network approach for obtaining the data
- No analytical capabilities or common software in all sites
- Software developed in JAVA on purpose:



Step 2: Software for extraction of data



Current status data availability

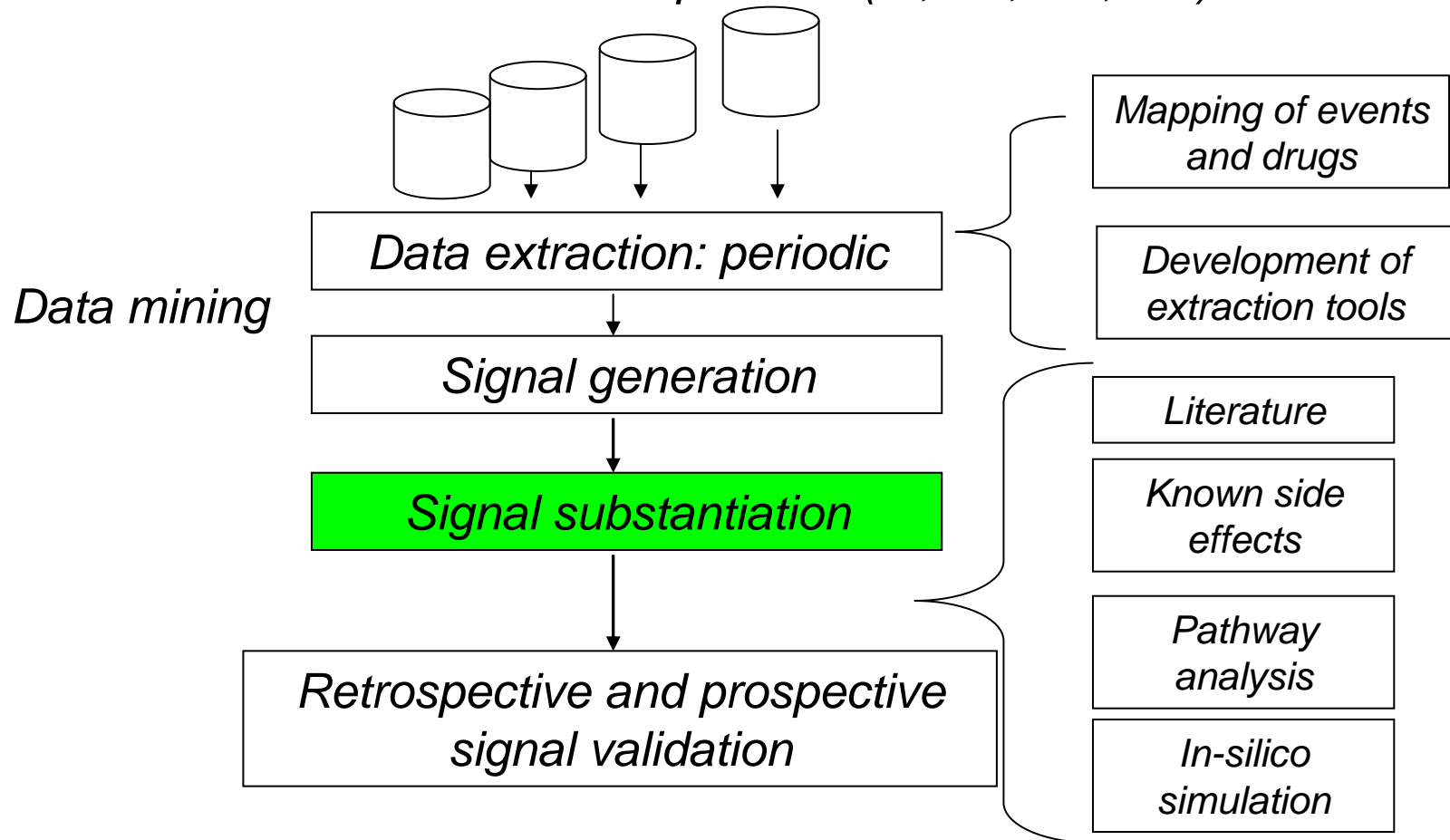


Aggregated data available on 20 million subjects, all databases, extensions and updates ongoing

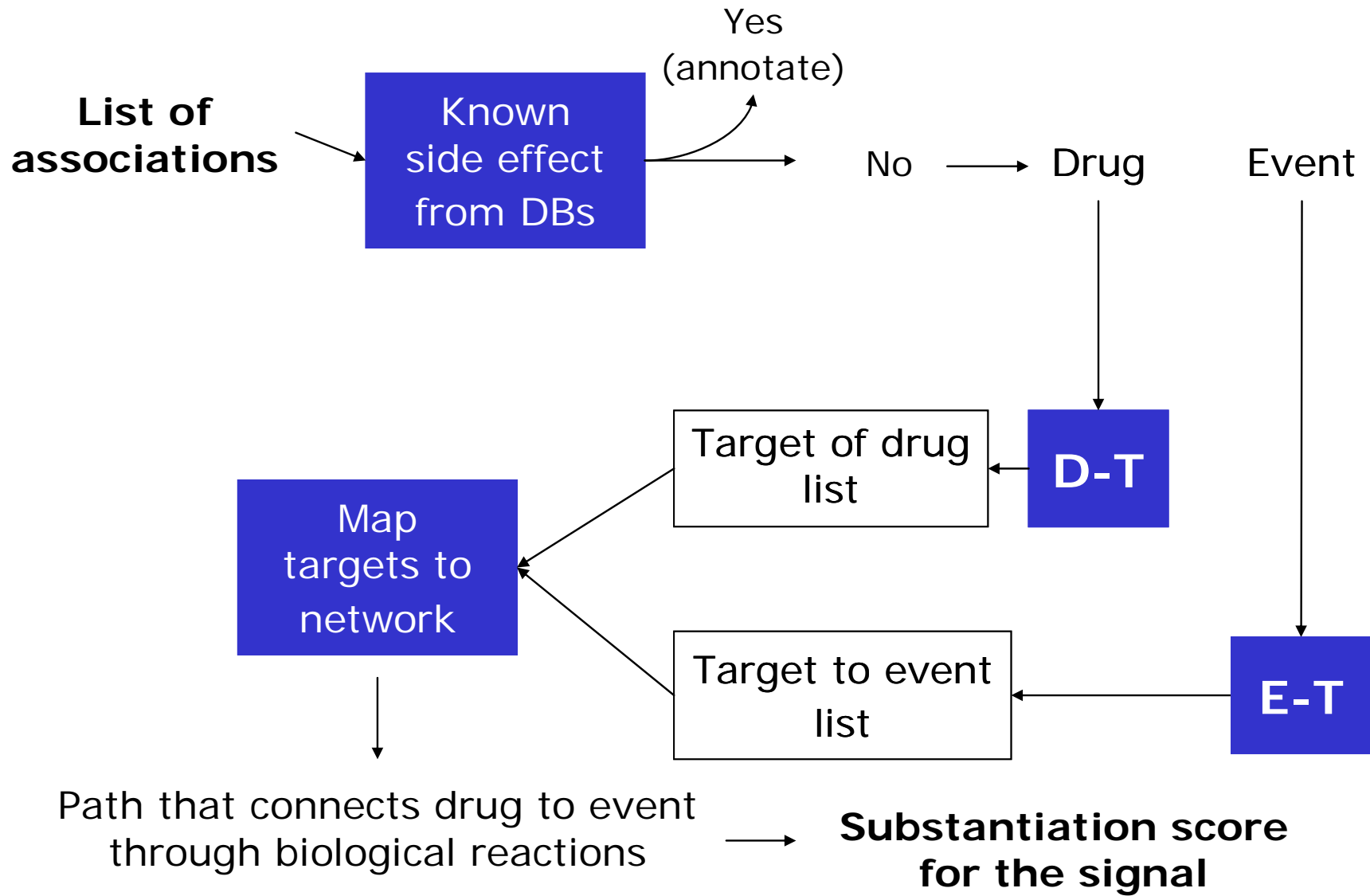
EU-ADR concept



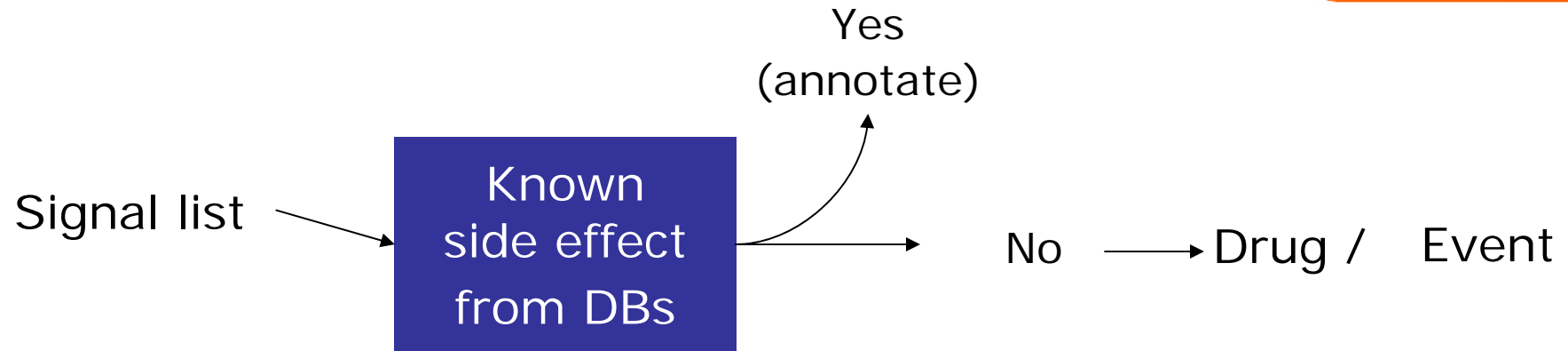
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Signal substantiation (automated)



Signal substantiation (automated)



Mining of already described drug-event relationships from:

Regulatory databases:

- SPC

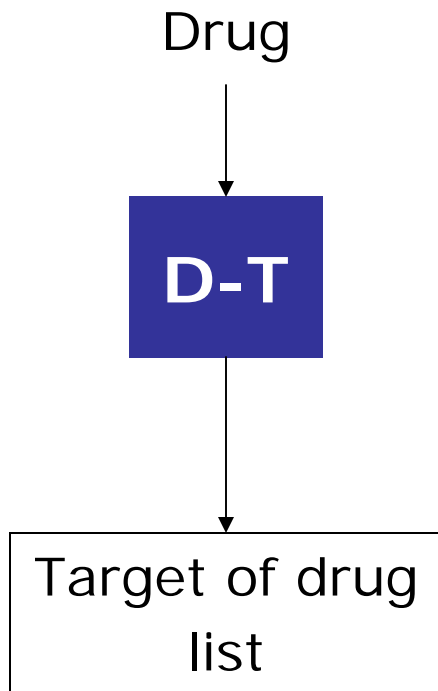
literature:

- Text mining on Medline records

Pharmacological databases:

- Expert curated databases
- Requires text mining as most information is in plain text

Signal substantiation (automated)



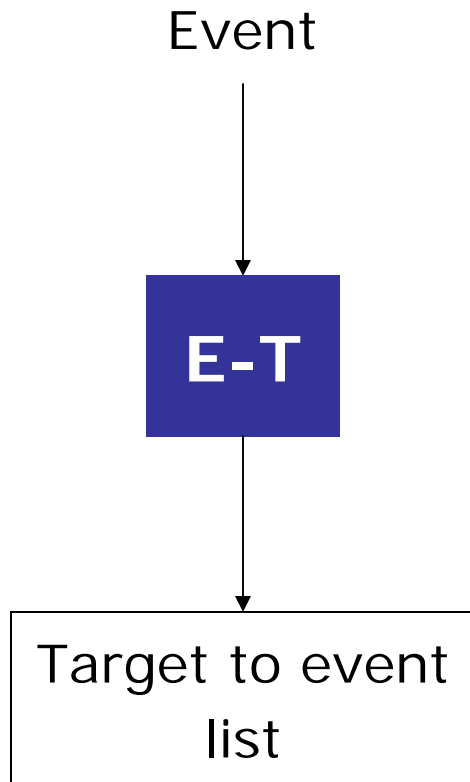
The following information is obtained for a drug:

- List of metabolites
- List of targets

Is a combination of the following

- List of targets for the drug and its metabolites obtained by *in silico* profiling
- List of targets for the drug and its metabolites obtained by text mining of literature and specialized databases

Signal substantiation (automated)

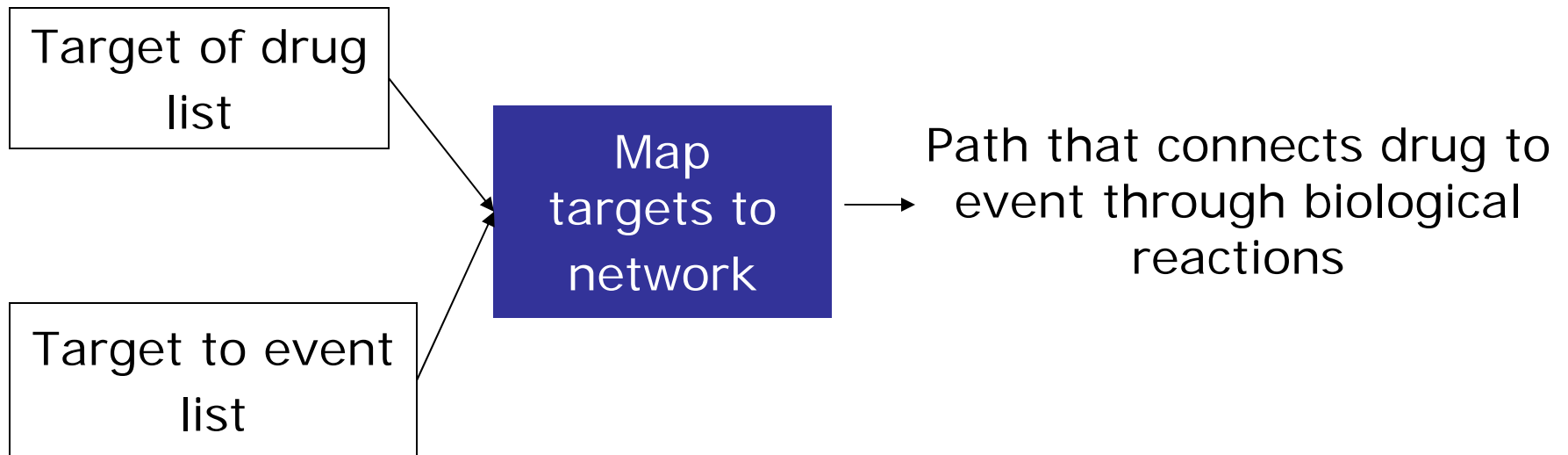


The following information is obtained for a event:

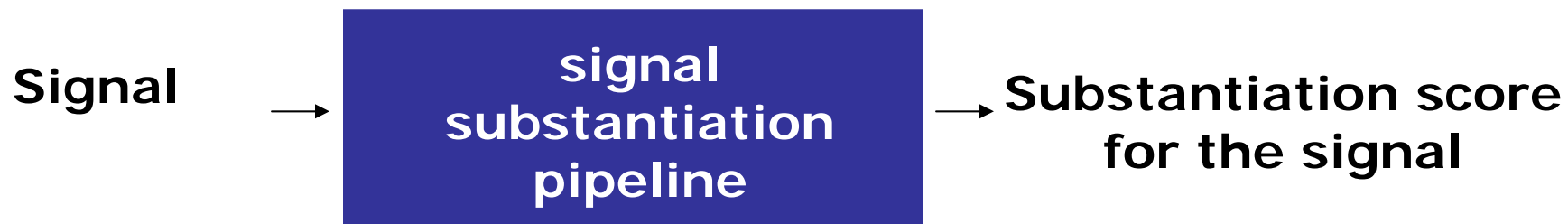
- target-event relationships by text mining of the literature and/or specialized databases

- Sequence variants of the targets that might be associated with the phenotype (event) are considered

Signal substantiation (automated)



Signal substantiation (automated)



Conclusion

- EU-ADR is aiming to develop a system to complement existing pharmacovigilance tools.
- EU-ADR is methodologically oriented
- Jerboa already used by many other projects (vaccine safety, NSAID safety)
- EU-ADR is open: other databases are welcome to join