Perspectives on Medication Safety through ICT:
From Post-marketing Drug Surveillance to Clinical Decision Support Systems for Adverse Drug Event Prevention

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Basic Vita Information

- Origin: **Thessaloniki, Grèce**
- Background:
  - **PhD** in Medical Informatics, 2005
    Topic: Information Management and Processing in Distributed Biomedical Information Systems via Autonomous Software Agents
  - **MSc** in Medical Informatics, 2001
  - **DEng** in Electrical & Computer Engineering, 1998
- Engaged to research from **1998**:
  - Aristotle University of Thessaloniki (**AUTH**) & Center for Research & Technology Hellas (**CERTH**)
- Fields of research:
  - Pervasive healthcare, personal health systems, patient safety systems, accessibility, medical imaging

Presentation Layout

- Introduction: The Importance of Medication Safety & What Information Technologies can offer?
- Part A – Detection of Potential Adverse Drug Reactions: The SAFER Marie-Curie fellowship
- Part B - Identification & Prevention of Adverse Drug Events: The PSIP project
- Concluding Remarks

The Necessity of Post-Marketing Drug Surveillance

- Before approval for entering the market: **Randomized Clinical Trials (RCT)**

- But **RCT not capable of detecting all possible problems** (time constraints, limited sample population size and potential bias)

⇨ **Post-marketing surveillance constantly required** to identify any previously undiscovered drug risks throughout the time a drug is actively prescribed

Increasing Interest in Patient Safety: *To Err is Human…*

KOHN LT, CORRIGAN J, DONALDSON MS. To err is human building a safer health system. Washington, D.C.: National Academy Press; 2000.

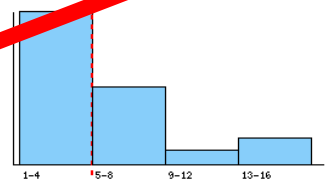
Hyperkalemia (K+>5.3)

Characteristics of identified stays, all the rules together

Data from the coded diagnostics

Effective	21
Average age	73
Men - Women	33% - 67%
Death	2

Cancers	29%
Cardiomyopathies	67%
Renal insufficiency	19%
Hepatic insufficiency	14%
Respiratory insufficiency	33%
Alcoholism	4%



Conditions leading to Hyperkalemia (K+>5.3)	Number of cases confidence ; median delay
(1) **HMWH can induce hyperkaliemia, specially with renal insufficiency.**	1
Renal failure & High weight heparin	25% ; 3j
(2) **HMWH can induce hyperkaliemia, specially with diabetic patients and renal insufficiency.**	1
Renal failure & High weight heparin & Diabetes	50% ; 3j
(3) **LMWH can induce hyperkaliemia, specially with diabetic patients**	1

Learning from mistakes & weaknesses

To Err is Human… in numbers!

- **More Americans die from medical errors than from car accidents, breast cancer, or AIDS annually**, 44,000-98,000 deaths/year
- Medication errors result in at least **1 death per day and 1.5 million people injured per year**
- Estimated US annual cost of **drug-related morbidity and mortality is nearly $17 billion**
- **Preventable adverse drug events** cost the healthcare system **$2.5 billion annually**

Institute of Medicine, Preventing Medication Errors, 2006

How to Leverage Post-marketing Medication Safety? *Information Technologies to the Rescue*

- Identify drug safety risks and prevent ADEs through:
  - Enriching **electronic data capture**
  - **Connectivity** in the healthcare enterprise => Reinforce Collaboration
  - Broaden the information space: **new landscapes of data are emerging** (cf. social media) => What can they offer?
  - **Large-scale data analysis** => understand the phenomena and plan prevention strategies
  - Comprehensive, Contextualized and Sustainable **Knowledge Bases**
  - Clinical **Decision Support** Systems:
    - be partners of healthcare professionals => "**right information to the right place at the right time**"
  - Provide a collaborative framework for "active" and "proactive" drug surveillance

What Do Healthcare Professionals Think about IT for Medication Safety?

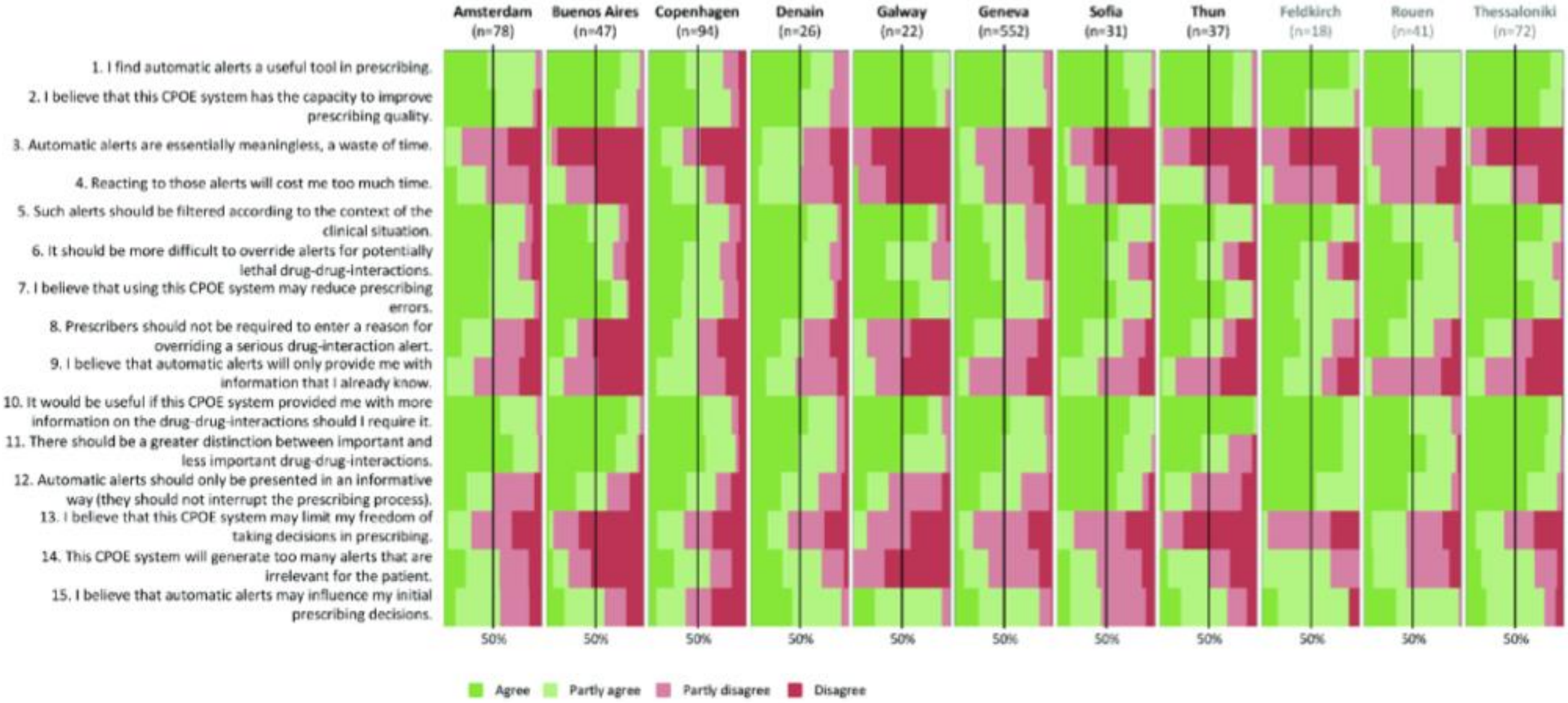
Attitude of Physicians Towards Automatic Alerting in Computerized Physician Order Entry Systems*

A Comparative International Survey

Methods Inf Med 2013; 52: 99–108
doi: 10.3414/ME12-02-0007

- 1,018 physicians from 11 hospitals in 9 different countries
- 8 (3) hospitals equipped (not equipped) with CPOE system

A Comparative International Survey: Content



A Comparative International Survey
Main Results

- The large majority of the physicians replied that:
  - **automatic alerts are useful in prescribing**
  - CPOE systems have the **capacity to improve prescribing quality** and may **help to reduce prescribing errors**
  - automatic alerts will **not provide only known information**
  - automatic alerts are **not a waste of time**
  - automatic alerting would trigger **too many irrelevant alerts**
  - there should be a **greater distinction between important and less important alerts**
  - **alerts should be filtered according to the clinical context**
  - automatic alerts should be **presented in an informative and non-interruptive way**

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Scope of the Presentation

- Part A – Detection of Potential Adverse Drug Reactions (ADRs)
- Part B – Identification & Prevention of Adverse Drug Events (ADEs)

What is a Drug Safety / Pharmacovigilance Signal?

- According to **WHO**: "*any information on a possible causal relationship between a drug and an adverse effect*".
- According to **FDA** : "*a concern about an apparent excess of an adverse event compared to what would be expected.*"

→ A verified signal constitutes an **Adverse Drug Reaction (ADR)**

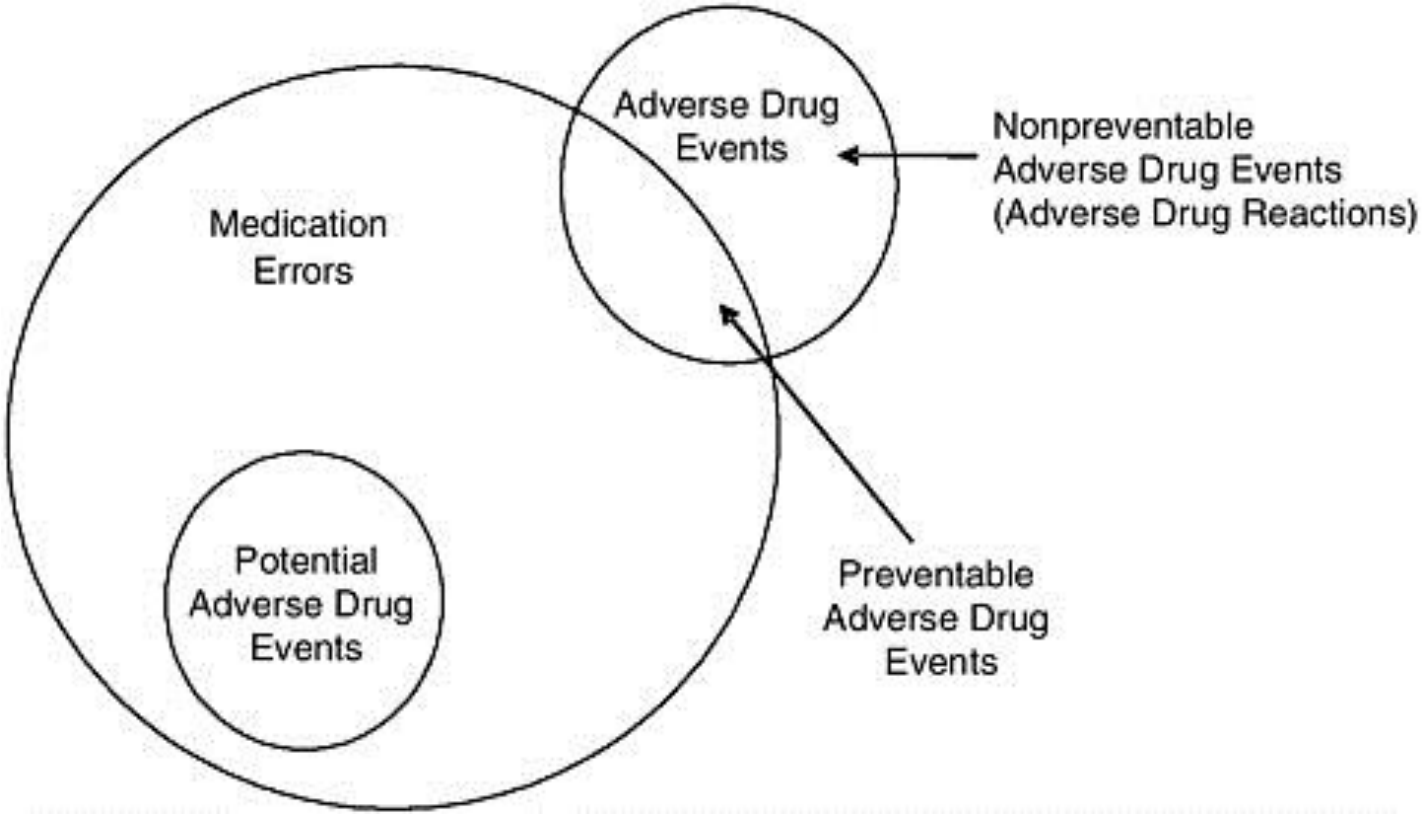
ADEs vs. ADRs

- "Adverse Drug Events:
  - "Any **injury** occurring during the **patient's drug therapy** and resulting either from appropriate care, or from unsuitable or suboptimal care"
- ADEs include **Adverse Drug Reactions** (ADR) during normal (proper) use of the medicine and any harm secondary to a **Medication Error**, both errors of omission or commission."*
- "If an Adverse Drug Event is caused by an **error** it is, by definition, **preventable**. Non preventable adverse drug events (injury, but no error) are called adverse drug reactions (ADRs) "**

*Committee of Experts on Management of Safety and Quality in Health Care (SP-SQS) / Expert Group on Safe Medication Practices: Glossary of terms related to patient and medication safety. (http://www.who.int/patientsafety/highlights/COE_patient_and_medication_safety_gl.pdf)

** Leape LL, Kabcenell A, Berwick DM and Roessner J. Reducing adverse drug events. Breakthrough series Guide Institute for Healthcare Improvement, Boston, 1998, p.84-91.

ADE = Non Preventable (i.e. ADRs) + Preventable



T.K. Gandhi, D.L. Seger, D.W. Bates, Identifying drug safety issues: from research to practice, Int J Qual Health Care. 2000 Feb;12(1):69-76.

Definitions

Table 1 Definitions

Incident	Definition	Example
Adverse drug event (ADE)	Injury due to a drug	Drug rash
Preventable	Due to an error	Coma due to overdose of sedative
Non-preventable (adverse drug reaction)	Injury, but no error involved	Allergic reaction in patient not known to be allergic
Medication error	Any error in any stage of the medication process, including ordering, transcribing, dispensing, administering or monitoring	A dose of non-critical medication is not given
Potential ADE	An incident with potential for injury; all potential ADEs are medication errors	An order was written for an overdose of medication but the mistake was intercepted by the pharmacy

T.K. Gandhi, D.L. Seger, D.W. Bates, Identifying drug safety issues: from research to practice, Int J Qual Health Care. 2000 Feb;12(1):69-76.

SAFER: Semantic integrAtion and reasoning Framework for pharmacovigilancE signals Research: *An Individual Marie-Curie Fellowship*

http://www.safer-project.eu/

MARIE CURIE ACTIONS

The Scope of the M-C Fellowships Program

- Career development of experienced researchers through:
  - Engagement in novel research activities and training
  - Development of soft skills
  - Networking
  - Industrial exploitation
  - Appropriate dissemination

The Scope of SAFER

- Host Institution: **LIMICS, INSERM, UMR_S 1142, Paris, France**
- The overall idea: **exploiting and complementing evidence** obtained from **diverse drug safety signal detectors**
- Why:
  - Signal generation is characterized by **incomplete knowledge and uncertainty** in the results obtained from all types of signal detection methods
- Which detectors:
  - Analysis of spontaneous reports (SRS-based)
  - Analysis of longitudinal observational data: e.g. EHRs and claim databases
  - Analysis of unstructured/free-text data: e.g. scientific papers and patient self-reports in social media):
- Position statement:
  - Each method may contribute (at a different level, with its strengths and weaknesses) in **complementing our knowledge on drug safety risks**

→ **An integrative perspective may add value!**

What is a Signal Detector?

- An software **implementation of an analysis method** (typically statistical method) for **identifying causal relationships between drugs and clinical conditions / health outcomes**
- Designed to **operate on a specific type of data** (i.e. contingency tables of drug-condition pairs or more complex data model)
- Offers a **set of parameters / analysis options**, e.g. thresholds for decision making, ranking criteria, etc.
- Provides as **output a ranked list of drug-condition pairs along with features denoting their statistical significance**

Example: GPS[1] Implementation (PhViD[2])
Input Data & Parameters (1/2)

Usage

```
GPS(DATABASE,  RR0 = 1, MIN.n11 = 1, DECISION = 1, DECISION.THRES = 0.05,
RANKSTAT = 1, TRONC = FALSE, TRONC.THRES = 1,
PRIOR.INIT = c(alpha1 = 0.2, beta1 = 0.06, alpha2 = 1.4,
beta2 = 1.8, w = 0.1), PRIOR.PARAM = NULL)
```

Arguments

`DATABASE`	Object returned by the function `as.PhViD`.
`RR0`	Value of the tested risk. By default, `RR0=1`.
`MIN.n11`	Minimum number of notifications for a couple to be potentially considered as a signal. This option does not affect the calculation of the hyper parameters. By default, `MIN.n11 = 1`.

[1] ***Gamma Poisson Shrinker, used by FDA to screen reports gathered in FAERS.*** Details: W. DuMouchel, "Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system", The American Statistician, vol.53, pp. 190–196, 1999.
[2] http://cran.r-project.org/web/packages/PhViD/

Example: GPS Implementation (PhViD)
Input Data & Parameters (2/2)

DECISION	Decision rule for the signal generation based on 1 = FDR (Default value) 2 = Number of signals 3 = Ranking statistic. See RANKSTAT
DECISION.THRES	Threshold for DECISION. Ex 0.05 for FDR (DECISION=1).
RANKSTAT	Statistic used for ranking the couples: 1 = Posterior probability of the null hypothesis 2 = 5% quantile of the posterior distribution of λ 3 = Posterior Expectation of $\log_2(\lambda)$
TRONC	If TRUE, only the data with at least TRONC.THRES notifications are considered in the calculation of the hyper parameters and the likelihood is a product of mixture of two negative binomial truncated by TRONC.THRES-1. By default, TRONC=F
TRONC.THRES	See TRONC
PRIOR.INIT	Vector of initialization of the prior parameters $(\alpha_1, \beta_1, \alpha_2, \beta_2, w)$. By default, PRIOR.INIT $= c(\alpha_1 = 0.2, \beta_1 = 0.06, \alpha_2 = 1.4, \beta_2 = 1.8, w = 0.1)$, ie the prior parameters found in DuMouchel (1999).
PRIOR.PARAM	Chosen hyper parameters. By default, PRIOR.PARAM = NULL which means that the hyperparameters are calculated by maximising the marginal likelihood.

Example: GPS Implementation (PhViD) *Output*

Value

ALLSIGNALS	Data.frame summarizing the results of all couples with at least MIN.n11 notifications ordered by RANKSTAT. It contains notably the labels, the cell counts, the expected counts, RANKSTAT, the ratios(count/expected count), the marginal counts and the estimations of FDR, FNR, Se et Sp. If RANKSTAT!=1, the last column is the posterior probability of the null hypothesis.
SIGNALS	Same Data.frame as ALLSIGNALS but restricted to the list of generated signals.
NB.SIGNALS	Number of generated signals.
INPUT.PARAM	Parameters entered in the function.
PARAM	A list that contains the prior hyper parameters (PRIOR.PARAM). Additionally if PRIOR.PARAM=NULL, it also contains the prior hyper parameters initialization (PRIOR.INIT) and the convergence code (see nlm()).

How Many Detection Methods Are There? List of Detection Methods in OMOP (only)

- Disproportionality Analysis (DP) - OMOP Research Team
- Univariate Self-Controlled Case Series (USCCS) - OMOP Research Team
- Observational Screening (OS) - ProSanos Corporation
- Multi-Set Case Control Estimation (MSCCE) - OMOP Research Team
- Bayesian Logistic Regression (BLR) - OMOP Research Team
- Case Control Surveillance (CCS) - Lilly
- IC Temporal Pattern Discovery (ICTPD) - Uppsala Monitoring Centre
- Case-Crossover (CCO) - University of Utah
- HSIU Population-Based Method - Indiana University
- Maximized Sequential Probability Ratio Test (MSPRT) - Harvard Pilgrim
- Conditional Sequential Sampling Procedure (CSSP) - Harvard Pilgrim
- High-Dimensional Propensity Score (HDPS) - OMOP Research Team
- Incident User Design (IUD-HOI) - M. Alan Brookhart

A Lot!

What is the Foreseen Value of Combining Detectors?

- Support the **detection of true associations** and **minimize false positive findings**
- Support **timely decisions on signal definition**: 1 source – 1 method is a limitation
- **Methods are developed to analyze single sources**: Each source has pros and cons, so the results are effected!
- **Not all events are equally detectable**, suggesting that specific events might be monitored more effectively using other data sources:
  - General belief: SRSs may be better suited for the surveillance of rare events and less suited for outcomes with high background rates such as acute myocardial infarction
- Interesting to apply **comparisons** different datasets to explore **replication of outcomes**
- Indications originated from statistical methods, should be **carefully evaluated and confirmed by other means**
- In quantitative signal detection **no true gold standard** is available
- No individual approach to detect signals is adequate and **the concurrent use of other methods is therefore essential**

Overall Rationale

- ☞ Explore a quite novel# signal detection strategy which is based on **comparison/synthesis in the framework of replicated signaling**
- Aim: to exploit different signal detection methods applied on different data/information sources

Belief that potential signals replicated in multiple data sources or in independent studies represent increased confidence, and thus are more likely to be true.

Source: *R. Harpaz et al., "Combing signals from spontaneous reports and electronic health records for detection of adverse drug reactions", JAMIA 20(3): 413-9, 2013.*

Others in Favor of the "Integrative" Viewpoint

- **Literature**:
  - I. Ahmed et al., "Bayesian pharmacovigilance signal detection methods revisited in a multiple comparison setting", Statist Med, 28, 2009, 1774-92.
  - M. Hauben and G.N. Norén, "A decade of data mining and still counting", Drug Saf, 33(7), 2010, 527-34.
  - C.W. Kelman et al., "Evaluating medicines: let's use all the evidence", MJA, 186(5), 2007, 249-52.

- Wide-scale **research initiatives**:
  - **Mini-Sentinel**: http://www.mini-sentinel.org/
  - **OMOP** (Observational Medical Outcomes Partnership) project: http://omop.fnih.org/
  - **EU-ADR** (Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge) project: http://www.euadr-project.org/

How Drug Safety Data / Signals Vary?

MedWatcher: Professionals' Reports vs. Patient Self-Reports

Reports

Sort by: Date: Descending

For Coumadin

90 — Report

Coumadin AUG 19, 2012

On Aug 19, 2012, a 90-year-old male experienced cerebral hemorrhage, resulting in disability. Coumadin was considered to be a primary suspect medicine in this adverse event reported by a pharmacist in the US.

84 — Report

Coumadin AUG 10, 2012

On Aug 10, 2012, an 84-year-old male experienced hypocoagulable state, resulting in hospitalization. Coumadin was considered to be a primary suspect medicine in this adverse event reported by a consumer in Italy.

82 — Report

Coumadin AUG 02, 2012

On Aug 2, 2012, an 82-year-old female experienced injury, resulting in a serious adverse event. Coumadin was considered to be a primary suspect medicine in this adverse event reported by a consumer in Italy.

Tweet

coumadin JAN 04, 2013

bleeding, bleeding bleeding, bleeding bleeding bleeding. heparin, coumadin. bleeding, bleeding bleeding. yeah. bleeding.

Tweet

Pradaxa OCT 31, 2012

I have started itching since taking Pradaxa. Should I guts it out or go back to coumadin? http://t.co/lreLPtfr

Tweet

Coumadin OCT 25, 2012

Coumadin makes me feel sick

How Drug Safety Info / Signals Vary?

EU-ADR Workflow: Searching Medline for Drug-Event Pairs

Substantiation Results

- Substantiation Score: Evidence Found
- Extra Scores (7)
  - Numeric: 0.72248566
  - Intersect: UniProt ID P07550
  - Intersect: UniProt ID P11712
  - Intersect: UniProt ID P05177
  - Intersect: UniProt ID P08588
  - Intersect: UniProt ID P18089
  - Intersect: UniProt ID P03372
- Evidence
  - Protein P05177 (2 relationships)
    - Relation 1
      - SourceId
        - Source: UMLS
        - Name: Acute myocardial infarction
        - Code: C0155626
      - TargetId
        - Source: UP
        - Name: CYP1A2
        - Code: P05177
      - Observation Date: Fri Jul 12 13:39:35 GMT+200 2013
      - Information Sources (1)
        - Information Source 1
    - Relation 2
      - SourceId
      - TargetId
      - Observation Date: Fri Jul 12 13:37:57 GMT+200 2013
      - Information Sources (1)
  - Protein P07550 (2 relationships)
  - Protein P03372 (4 relationships)
  - Protein P08588 (2 relationships)

Substantiation Results

Workflow Output XML


```
<euadr:relationships xmlns:euadr="http://euadr.biosemantic.erasmusmc.org/" xmlns:common="http://com
<euadr:globalScore>
        <euadr:value>1</euadr:value>
        <euadr:extraScores>
                <euadr:extraScore>
                        <euadr:name>Numeric</euadr:name>
                        <euadr:value>0.72248566</euadr:value>
                </euadr:extraScore>
      <euadr:extraScore>
                <euadr:name>Intersect</euadr:name>
                <euadr:value>P07550</euadr:value>
      </euadr:extraScore>
      <euadr:extraScore>
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      </euadr:extraScore>
        </euadr:extraScores>
</euadr:globalScore>
<euadr:creator xmlns:ns1="http://euadr.biosemantic.erasmusmc.org/">
    <euadr:service>http://ibi.imim.es/axis2/services/AdrPathService?wsdl</euadr:service>
```
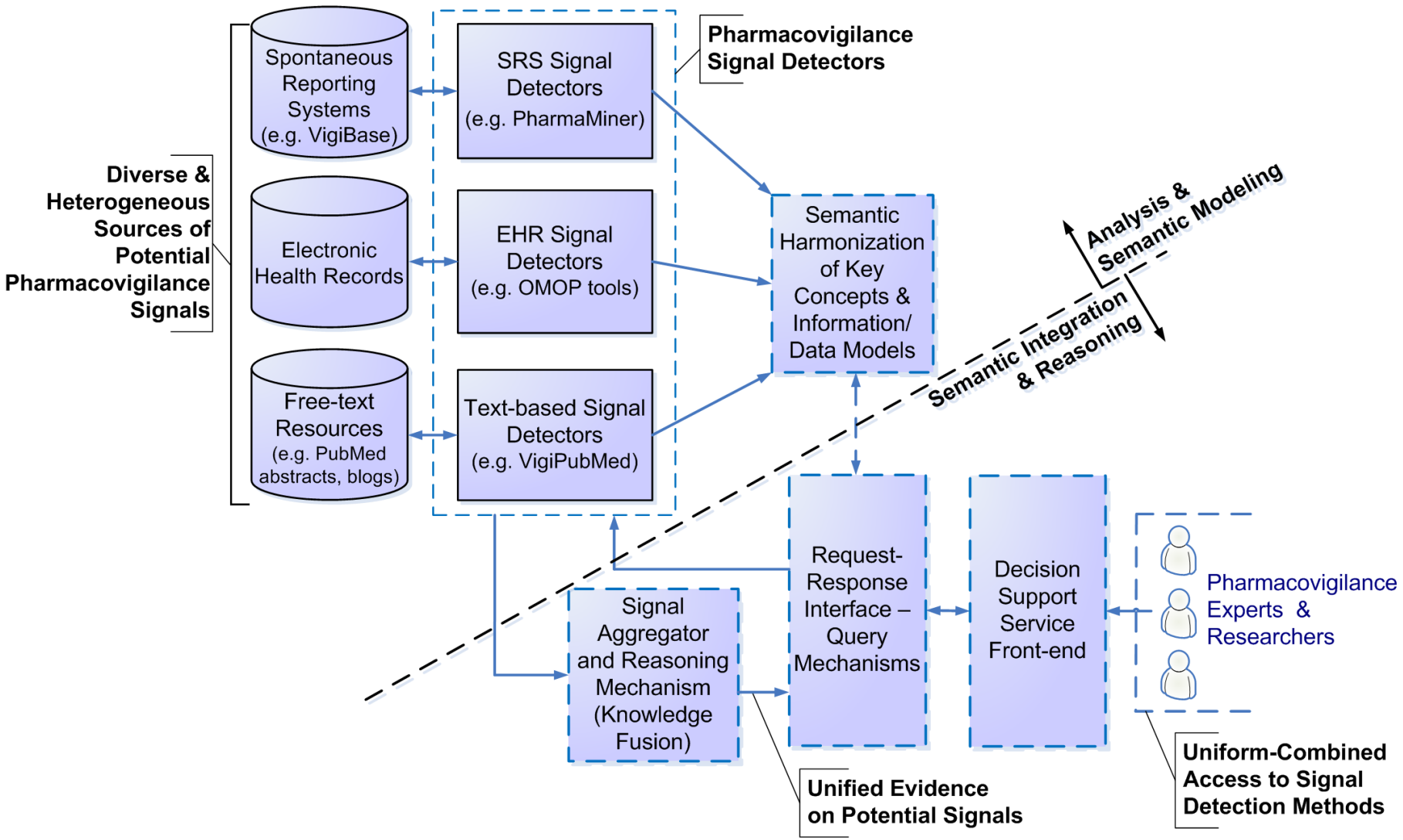

How Drug Safety Info / Signals Vary?
PSIP ADE Detection Rule Base

Effect	ID	Conditions	denain_all	frederiksberg_all	rouen_all
appearance of hepatic cholestasis	b075-0	NO every traumatism & high weight heparin	3/65=**4.6**% delay=2j p=0.2275	0/2=**0**% delay= p=1	1/21=**4.8**% delay=2j p=0.7205
appearance of hepatic cholestasis	b076-0	NO every traumatism & low weight heparin	9/894=**1**% delay=3j p=0.0007	14/2031=**0.7**% delay=4j p=0.2532	5/54=**9.3**% delay=2j p=0.825
appearance of hepatic cytolysis (enz.>110)	b073-0	high weight heparin	0/72=**0**% delay= p=1	0/2=**0**% delay= p=1	2/24=**8.3**% delay=3.5j p=0.2588
appearance of hepatic cytolysis (enz.>110)	b074-0	low weight heparin & age < 70	3/554=**0.5**% delay=2j p=0.2736	4/943=**0.4**% delay=5j p=1	0/26=**0**% delay= p=0.6213
appearance of hepatic cytolysis (enz.>110)	b074-1	low weight heparin & age ≥ 70	1/507=**0.2**% delay=4j p=0.0398	3/1122=**0.3**% delay=2j p=0.4799	0/33=**0**% delay= p=0.3948
appearance of high INR (INR≥5)	b001-0	vitamin K antagonist & 5-HT agonist & NO respiratory obstruction	1/16=**6.3**% delay=4j p=0.2131	4/46=**8.7**% delay=7.5j p=0	0/1=**0**% delay= p=1
appearance of high INR (INR≥5)	b001-1	vitamin K antagonist & 5-HT agonist & respiratory obstruction	6/15=**40**% delay=7j p=0	0/5=**0**% delay= p=1	*No stay matches the conditions*
appearance of high INR (INR≥5)	b002-0	vitamin K antagonist & thymoanaleptic	9/54=**16.7**% delay=6j p=0	4/58=**6.9**% delay=7.5j p=0	0/2=**0**% delay= p=1
appearance of high INR (INR≥5)	b003-0	vitamin K antagonist & selective serotonine recapture inhibitor & NO respiratory obstruction	1/14=**7.1**% delay=4j p=0.1891	4/39=**10.3**% delay=7.5j p=0	0/1=**0**% delay= p=1

SAFER: An Integrative Approach for Drug Safety Signal Detection/Exploitation



SAFER: Research Objectives

1) **Semantic representation of signal detectors**:
   - **systematic analysis** of various types of signal detection methods/tools corresponding to the abovementioned pharmacovigilance signal sources
   - Aim: **formal description** in terms of their input, preconditions of use, capabilities and supported output
2) **Semantic mediation framework**:
   - Design and development of an **integrated framework** enabling queries to various (available) pharmacovigilance signal detectors
   - Aim: **Transparent and uniform access** to diverse signal detectors
3) **Signal aggregation and reasoning**:
   - Introduction of an advanced **reasoning scheme** capable of exploiting and processing the **aggregated evidence** acquired from the diverse signal detection methods/tools
   - Aim: Harmonize, compare, rank and synthesize the acquired information
4) **Framework evaluation**:
   - In both technical and pharmacovigilance terms via a representative set of detection methods that will be integrated, along with existing signal and medication safety data, concerning **serious adverse drug effects**
   - Aim: assess the contribution in drug risk identification and decision support, in terms of **more reliable and timely signal definition**

SAFER Application Scenarios

- **Scenario #1**: "Combinatorial signal detection without specific target" or "**Strong Signals Identification**"
- **Scenario #2**: "Exploring evidence from multiple signal detectors for a specific target" or "**Targeted Signal Identification**"
- For both scenarios:
  - Focus on new signals, i.e. exclude/manage what is already known
  - Hide from the end-user the various technical details underlying each detector (too many and complex parameters in some models)
  - Provide comprehensive, supportive information on the findings (NOT just a couple of numbers!), consisting of relevant data, provenance of data (where does the evidence come from? what is the context of the findings?), etc.

Scenario #1 - Combined Signal Detection without Specific Target: *Rationale*

- **Users**:
  - Pharmacovigilance researchers
  - Pharmacovigilance / Patient Safety Authorities
- **Goal**: Produce a highly selective, ranked set of candidate ADRs
- **Type of use**: Routine screening for new, interesting[#] drug safety risks
- **Input**: Basic detectors parameterization (and optional selection of the detectors and the ranking strategy to be employed in the analysis)
- **Output**: Prioritized list of potential signals + supporting info per case

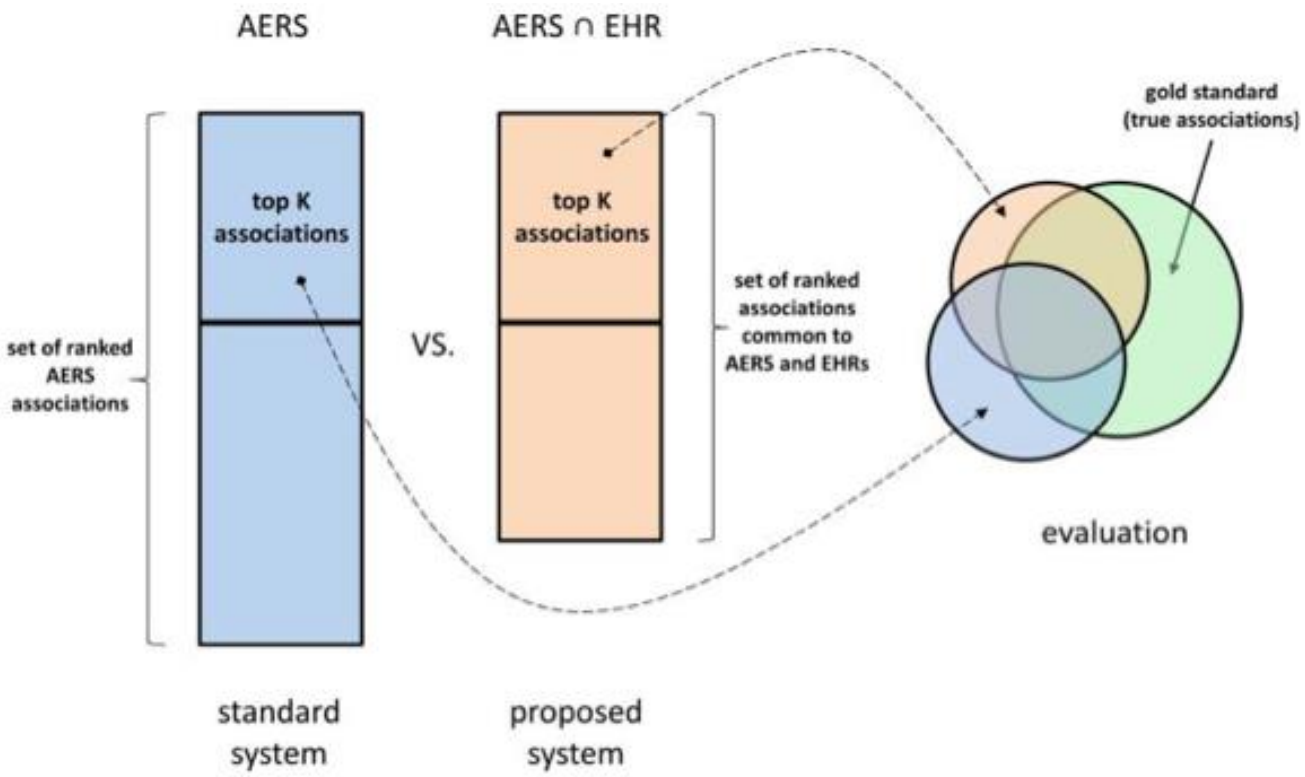
[#] *Either the most probable or those requiring more attention (cf. Approach-1 and Approach-2 on prioritization)*

Scenario #1 - Combined Signal Detection without Specific Target: *Prioritization (1/2)*

Establish a scheme to perform **signal prioritization** (i.e. part of "*knowledge fusion*" or "*signal aggregation and reasoning*" in SAFER)

<u>Approach #1</u>

Computational (IR) perspective, e.g. "*Precision@K*" as a ranking method



*<u>Figure source</u>: R. Harpaz et al., Combing signals from spontaneous reports and electronic health records for detection of adverse drug reactions, JAMIA, **Sept. 2012**, http://dx.doi.org/10.1136/amiajnl-2012-000930*

Scenario #1 - Combined Signal Detection without Specific Target: *Prioritization* (2/2)

Approach #2

Follow the domain experts' perspective, e.g. the ***triage logic*** proposed by WHO-UMC[#]

- Criteria: (i) ADR unexpectedness; (ii) ADR seriousness[#]; (iii) disproportionality; (iv) rapidly increasing disproportionality (the change of the IC value over time was considered more relevant than a high value of IC in isolation); (v) newer drugs; (vi) reports from multiple countries; (vii) special interest reactions (a limited list of events likely to be associated with drugs)

[#] *Lindquist M., Use of triage strategies in the WHO signal-detection process, Drug Saf. 2007;30(7):635-7.*

[#] *Seem straight-forward to be computed, if data are available*

Technical Challenges

- **Computational issues** in using the detectors:
  - Need a powerful infrastructure: e.g. a computing cluster
  - Work-around: Employ archived, signal-detection outcomes, if available.
- Develop the required **data transformations** in case of applying detectors on new data
- **Mappings** between terminology systems or vocabularies necessary since detectors explore different data
  (e.g. RxNorm vs. ATC, drug commercial name vs. substance, etc.)
- Define a **semantic model for uniformly invoking detectors and exploring their outcomes** (statistics, context data, provenance)
- **Interfacing with analysis platforms**, e.g. R, SAS, etc.
- Enable **risk follow-up**, e.g. "*an initial indication has been retrieved, so I would like to make a more targeted search now…*"

Just One of Many Challenges: The Issue of Common Definitions

AERS and EHR—event and outcome definitions

Event	AERS MedDRA PT event definitions	EHR Outcome definitions
Pancreatitis	Pancreatitis acute	Lab tests: amylase >300 U/l or lipase >120 U/l
Rhabdomyolysis	Rhabdomyolysis, blood creatine phosphokinase MM increased	Lab test: 5× normal levels of creatine kinase
QT	Long QT syndrome, ECG QT prolonged, Torsade de pointes, ECG QT interval abnormal, ventricular tachycardia	UMLS codes: C0023976, C0151878, C0743431, C0855333, C1560305

AERS, adverse event reporting system; EHR, electronic health record; PT, preferred term.

Computational Aspects - OMOP *Minimal* Technology Requirements: *Hardware*

1. Space requirements are dependent on the size of the raw databases being used.
2. To create CDM, you will need 3 times as much freespace as the size of the database.
3. Data can be stored in either SAS or RDBMS; the OMOP Research Lab stores data in both SAS and Oracle.
4. You will need an additional 3 times the size of database for tempspace (TEMP, UTILLOC) to run the methods.
5. For running methods: minimal recommendations include 20 processors, 64-bit OS (Windows or Unix), 32-gigabytes of RAM.

SAFER: Ultimate – High Level – Goals

- Contribute in the **interpretation of potential pharmacovigilance signals** by introducing an intermediate-qualitative step between signal detection and verification

- Leverage **reliable and timely decisions** on signal definition

- Support the **detection of true associations and minimize false positive findings** (the major limitation of most signal detectors currently available)

⇨ Provide an **integrated platform for pharmacovigilance signal research**

Identification & Prevention of Adverse Drug Events in PSIP (Patient Safety with Intelligent Procedures in Medication): *An Integrated Project*

http://www.psip-project.eu/

The PSIP (Patient Safety through Intelligent Procedures in medication) Project

- **FP7 EU-funded** large scale integrated project (Jan 08 – July 11) related to **patient safety and medication**

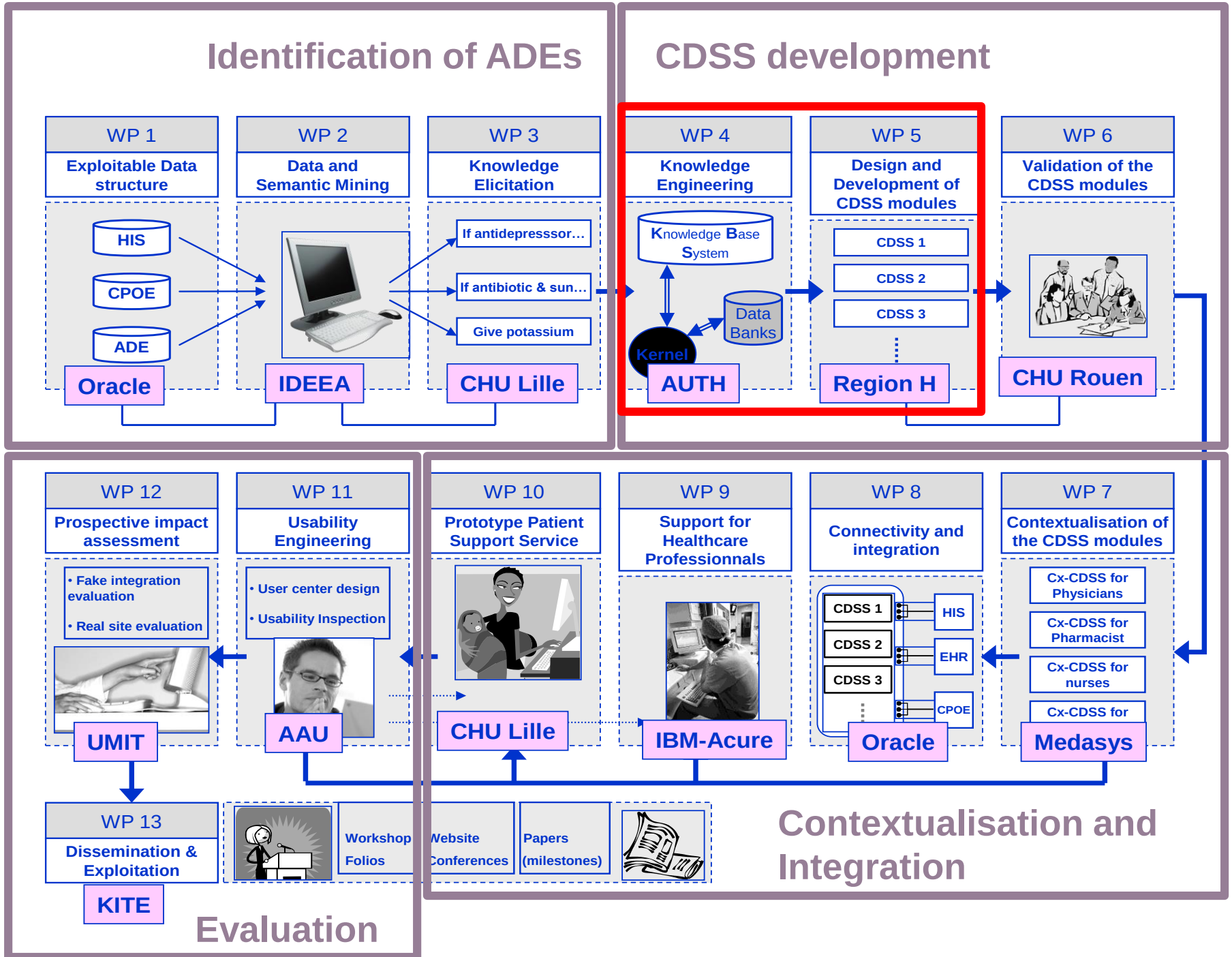
- **Primary Objectives:**
  - Facilitate the **systematic production of epidemiological knowledge** on Adverse Drug Events (ADEs)
  - Ameliorate the entire medication cycle in a hospital environment by ADEs prevention

- **Scientific Goals:**
  - **Identification of ADEs**, via data and semantic mining applied on large volumes of patient data, so as to obtain a better knowledge of the **prevalence of ADEs** and of their **characteristics** per Medical Department, Hospital, Region, and Country
  - Development of concepts, methods and knowledge-based modules to provide **contextualized CDSS** (alerting) functions for **ADEs prevention**

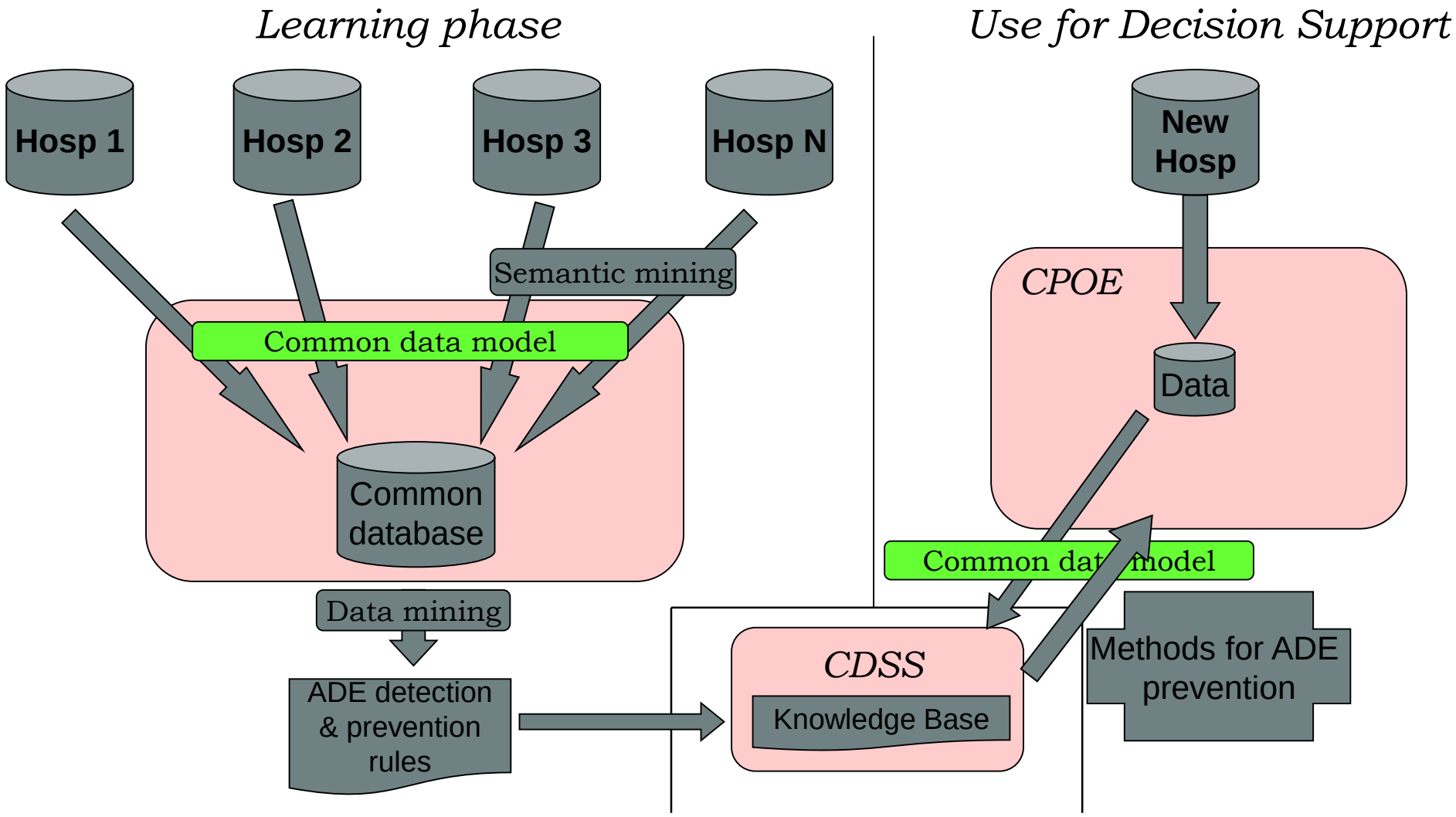
PSIP

The PSIP Consortium

1. University Hospital of Lille and University of Lille2 (F)
2. University Hospital of Rouen (F)
3. Denain General Hospital (F)
4. 10 hospitals from the «Capital Region of Copenhagen» (DK)
5. Oracle (Europe)
6. IBM Denmark – division ACURE (DK)
7. Medasys (F)
8. Vidal SA (F)
9. KITE solutions (I)
10. Ideea Advertising (RO)
11. Aristotle University of Thessaloniki (GR)
12. Aalborg University (DK)
13. UMIT – Innsbruck University (A)


Identification of ADEs
CDSS development
WP 1
Exploitable Data structure
HIS
CPOE
ADE
Oracle
WP 2
Data and Semantic Mining
IDEEA
WP 3
Knowledge Elicitation
If antidepresssor…
If antibiotic & sun…
Give potassium
CHU Lille
WP 4
Knowledge Engineering
Knowledge Base System
Data Banks
Kernel
AUTH
WP 5
Design and Development of CDSS modules
CDSS 1
CDSS 2
CDSS 3
Region H
WP 6
Validation of the CDSS modules
CHU Rouen
WP 12
Prospective impact assessment
• Fake integration evaluation
• Real site evaluation
UMIT
WP 11
Usability Engineering
• User center design
• Usability Inspection
AAU
WP 10
Prototype Patient Support Service
CHU Lille
WP 9
Support for Healthcare Professionnals
IBM-Acure
WP 8
Connectivity and integration
CDSS 1
CDSS 2
CDSS 3
HIS
EHR
CPOE
Oracle
WP 7
Contextualisation of the CDSS modules
Cx-CDSS for Physicians
Cx-CDSS for Pharmacist
Cx-CDSS for nurses
Cx-CDSS for
Medasys
WP 13
Dissemination & Exploitation
KITE
Workshop
Folios
Website
Conferences
Papers
(milestones)
Contextualisation and Integration
Evaluation

Common Data Model for ADE Detection & Prevention



ADE Detection Rules

- A rule is a set of conditions that may lead to an outcome:
  - Condition_1 & … & Condition_k → Outcome
  - C_1 & … & C_k → O

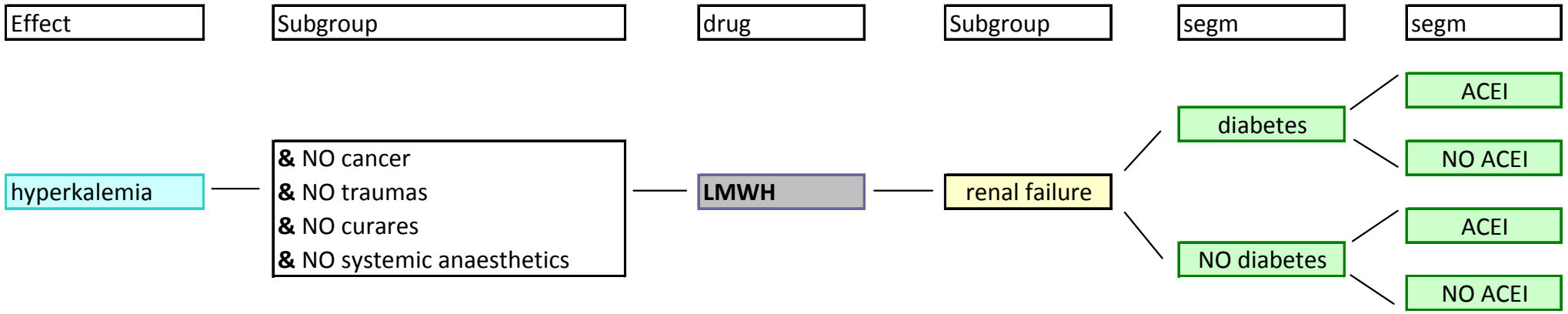
- **Retrospective** use:
  - IF C_1 & … & C_k & O THEN potential ADE
  - Computation of contextualized statistics

- **Prospective** use:
  - IF C_1 & … & C_k THEN probability of outcome
  - Use of the contextualized statistics for alert filtering

Organization of the Rules

- *Primary Causes* = Drugs
- *Subgroup* = Choosing a more specific population
- *Segmentation* = Within the studied population, presence or absence of one or several additional factors (statistical impact)
- *Conclusion* = Adverse Event

Example Rule



LMWH : Low Molecular Weight Heparin
ACEI: Angiotensin Converting Enzyme Inhibitors

Summary physician	**LMWH can induce hyperkalemia, especially in patients with diabetes and renal insufficiency.**
Detail physician	Some cases of hypoaldosteronism and/or metabolic acidosis have been described with heparins. This risk increases with diabetes and renal insufficiency. Ref. : Martindale -The complete drug reference- 34ème ed, The Pharmaceutical Press, London 2005 : 927-31. Moreover lack of insulin prevents potassium from entering in the cells, and hyperglycemia makes potassium get out of the cells more easily, by increasing osmolarity.
Advice physician:	Clinical and biological monitoring should be enhanced in case of treatment by a low molecular weight heparin, particularly in patients with diabetes and renal insufficiency.
Comment patient:	Low molecular weight heparins can increase blood potassium levels, especially in patients with diabetes and renal

Rules and Contextualized Statistics per Medical Department

Rule: vitamin K antagonist & amoxicilline&clav.ac. & age ≥ 70 → appearance of high INR (INR≥5)

Department	Confidence (PPV)	Support (frequency)	Median delay	Relative risk	Fisher's test P value
X all departments	10/57=**17.5%**	10/5322=**1.9‰**	6.5j	13.38	0
X medicine B	3/17=**17.7%**	3/966=**3.1‰**	3j	9.31	0.005
X pneumology	5/28=**17.9%**	5/818=**6.1‰**	11j	6.41	0.0016
Y all departments	1/10=**10%**	1/11923=**0.1‰**	6j	33.09	0.0306
Y apoplexy	*No stay matches the conditions*				
Y cardio & endocrinology	1/2=**50%**	1/1967=**0.5‰**	6j	51.71	0.0202
Y geriatrics	0/2=**0%**	0/493=**0‰**		0	1
Y gynecology	*No stay matches the conditions*				
Y intensive care unit	*No stay matches the conditions*				
Y internal medicine	0/5=**0%**	0/1514=**0‰**		0	1
Y obstetrics	*No stay matches the conditions*				
Y orthopedics	*No stay matches the conditions*				
Y rheumatology	*No stay matches the conditions*				
Y urology	*No stay matches the conditions*				
Z all departments	0/1=**0%**	0/1022=**0‰**		0	1
W all departments	0/8=**0%**	0/7685=**0‰**		0	1

Department	Confidence (PPV)	Support (frequency)	Median delay	Relative risk	Fisher's test P value
X all dpts	10/57=**17.5%**	10/5322=**1.9‰**	6.5j	13.38	0

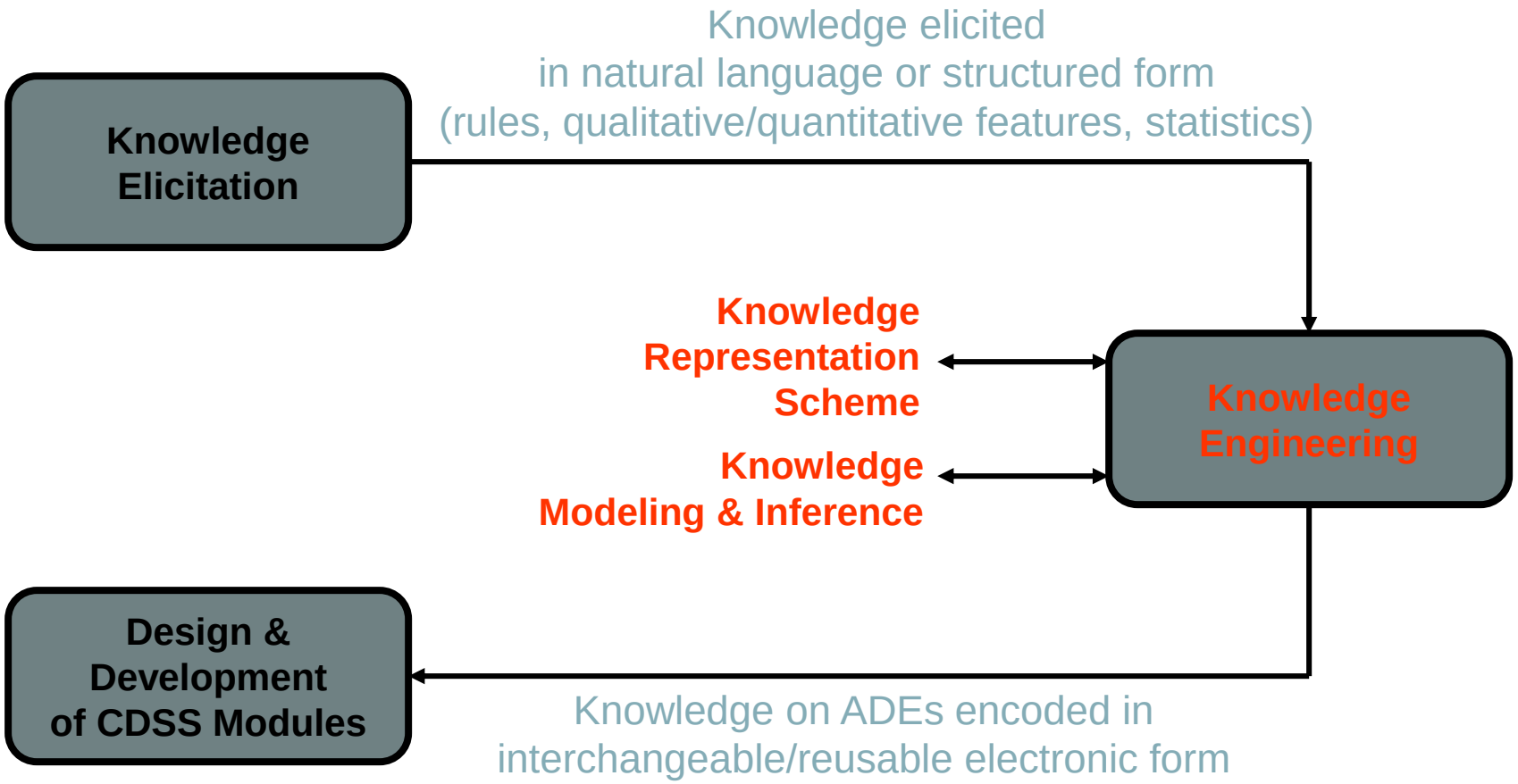
Comment:

- *Les pénicillines augmentent le risque hémorragique sous AVK.*
- *Une augmentation de l'activité des anti-vitamine K peut être observée chez les patients traités par pénicillines. Le risque hémorragique est accru.*
  Ref : thésaurus IAM-AFSSAPS juin 2009.
- *En cas de prise de pénicillines, la posologie des AVK sera adaptée et la surveillance clinique et biologique accrue.*

The Resulting Ruleset

Kind of Outcome	# Rules
Coagulation disorders	
Hemorrhage (detected by the administration of haemostatic)	7
Heparin overdose (activated partial thromboplastin time>1.23)	5
VKA overdose (INR>4.9 or administration of vitamin K)	59
Thrombopenia (count<75,000)	24
Other coagulation disorders	23
Ionic and renal disorders	
Hyperkalemia (K^+>5.3 mmol/l)	63
Renal failure (creatinine>135 µmol/l or urea>8 mmol/l)	8
Other ionic disorders	4
Miscellaneous	
Anemia (Hb<10g/dl)	2
Bacterial infection (detected by the administration of antibiotic)	4
Diarrhea (detected by the administration of an anti-diarrheal)	2
Fungal infection (detected by the administration of an antifungal)	10
Hepatic cholestasis (alk. Phos.>240 UI/l or bilirubins>22 µmol/l)	3
Hepatic cytolysis (ala. trans.>110 UI/l or asp. trans.>110 UI/l)	4
Hypereosinophilia (eosinophilocytes>10^9/l)	4
High level of pancreatic enzymes (amylase>90 UI/l or lipase>90 UI/l)	7
Neutropenia (count<1,500/mm^3)	2
Others	5
Total	***236***

Knowledge Engineering Rationale in PSIP



PSIP Primary Knowledge Sources for ADE Prevention

1. **ADE rules from data mining**: Outcome from unified patient records of hospitals participating in the project, according to a **common data model** - provided in the form of rules associating the parameters/variables related to ADEs

```
<?xml version="1.0" encoding="ISO-8859-1"?>
<rules>
  <rule validated="1" number="1" effect="bi.kidney_i" from="3"
      type="bikidneydr1antibioticquinolone1dr1diureticspotassiumLowering1">
    <condition>
        <field>dr1.diuretics_potassiumLowering</field>
        <operator><![CDATA[>=]]></operator>
```

2. **Drug interactions**: e.g. **drug to drug**, **drug to allergy class**, **drug to contraindications**, and so forth, that are already known and registered in existing databases - we employ the **VIDAL Database**

appearance of thrombopenia[Lab]	83	dt1	& CDiag(hepatic insufficiency)=0
appearance of thrombopenia[Lab]	155	dt4	Lab(cytolytic hepatitis)=1

Key Issue: Representing "source" knowledge in structured form to avoid potential ambiguities and facilitate the

3. **Li**
ex

appearance of low inr[Lab]	vidal_1	vidal	Drug(vitamin K antagonist (antithrombotic))=1 & Drug(resin[antilipemic])=1
appearance of low inr[Lab]	vidal_2	vidal	Drug(vitamin K antagonist (antithrombotic))=1 & Drug(antiacids)=1
appearance of low inr[Lab]	vidal_3	vidal	Drug(vitamin K antagonist (antithrombotic))=1 & Drug(antituberculosis[antibiotic])=1
appearance of low inr[Lab]	vidal_4		Drug(vitamin K antagonist (antithrombotic))=1
appearance of low inr[Lab]	vidal_5		
appearance of low inr[Lab]	vidal_6		
appearance of low inr[Lab]	vidal_7		
appearance of kidney insufficiency[Lab]	59		

4. **H**
re
c
g

```
<variable name="dr1.antisecretAgt_protonPumpInhib">
  <code value="A02BC01"><![CDATA[Oméprazole]]></code>
  <code value="A02BC02"><![CDATA[Pantoprazole]]></code>
  <code value="A02BC03"><![CDATA[Lansoprazole]]></code>
  <code value="A02BC04"><![CDATA[Rabéprazole]]></code>
  <code value="A07XA04"><![CDATA[Racécadotril]]></code>
</variable>
```

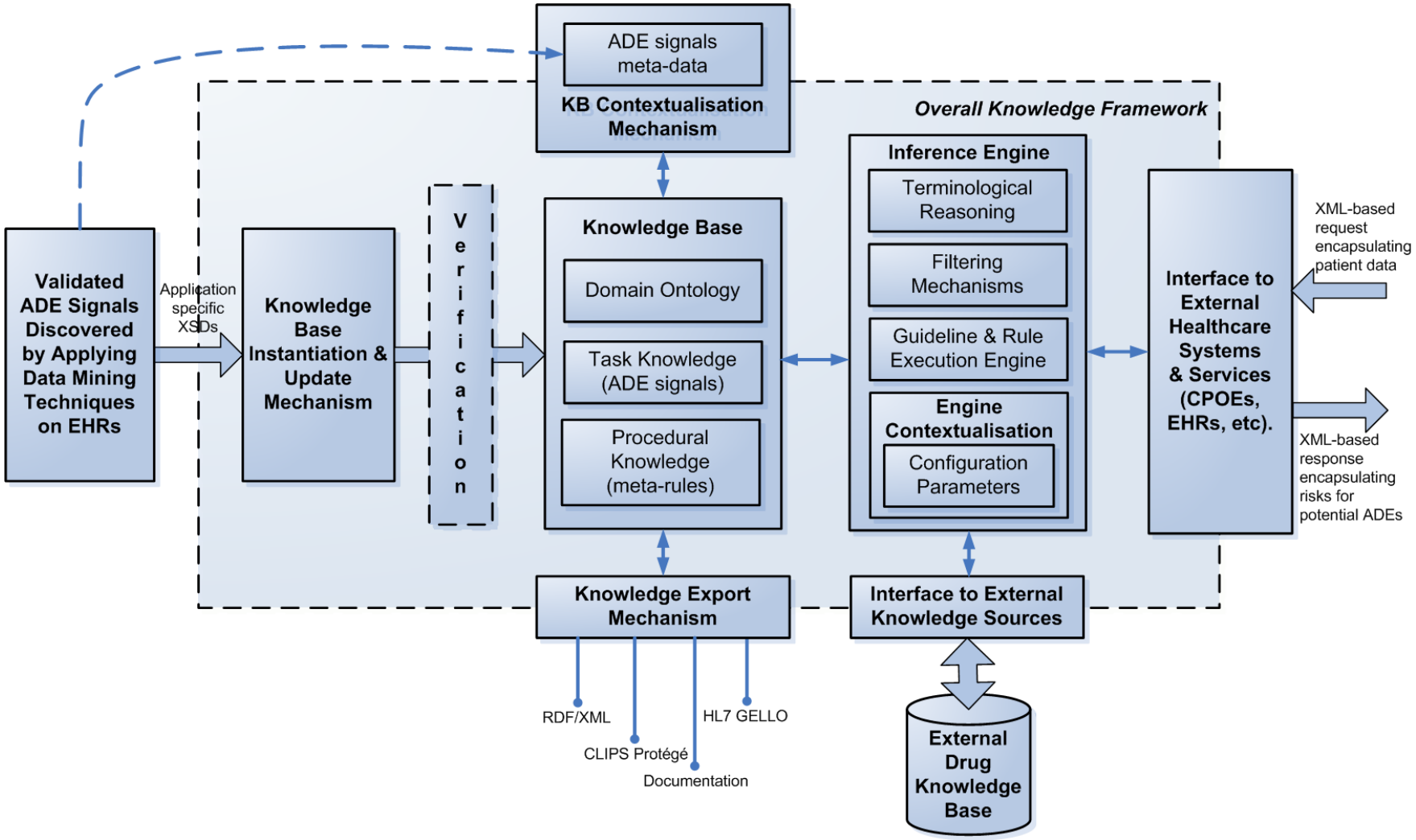
Methods Employed for Knowledge Modeling

1. **Ontologies**:
   - To construct the **vocabulary/terminology** of **concepts/variables** related to ADEs that take part in the rules
   - **Standard terminologies** (such as ICD-10, ATC, etc.), according to which the concepts are expressed, have to be represented

2. **Rule modeling**: Rules have to be effectively represented in the KB and executed by the KBS engine

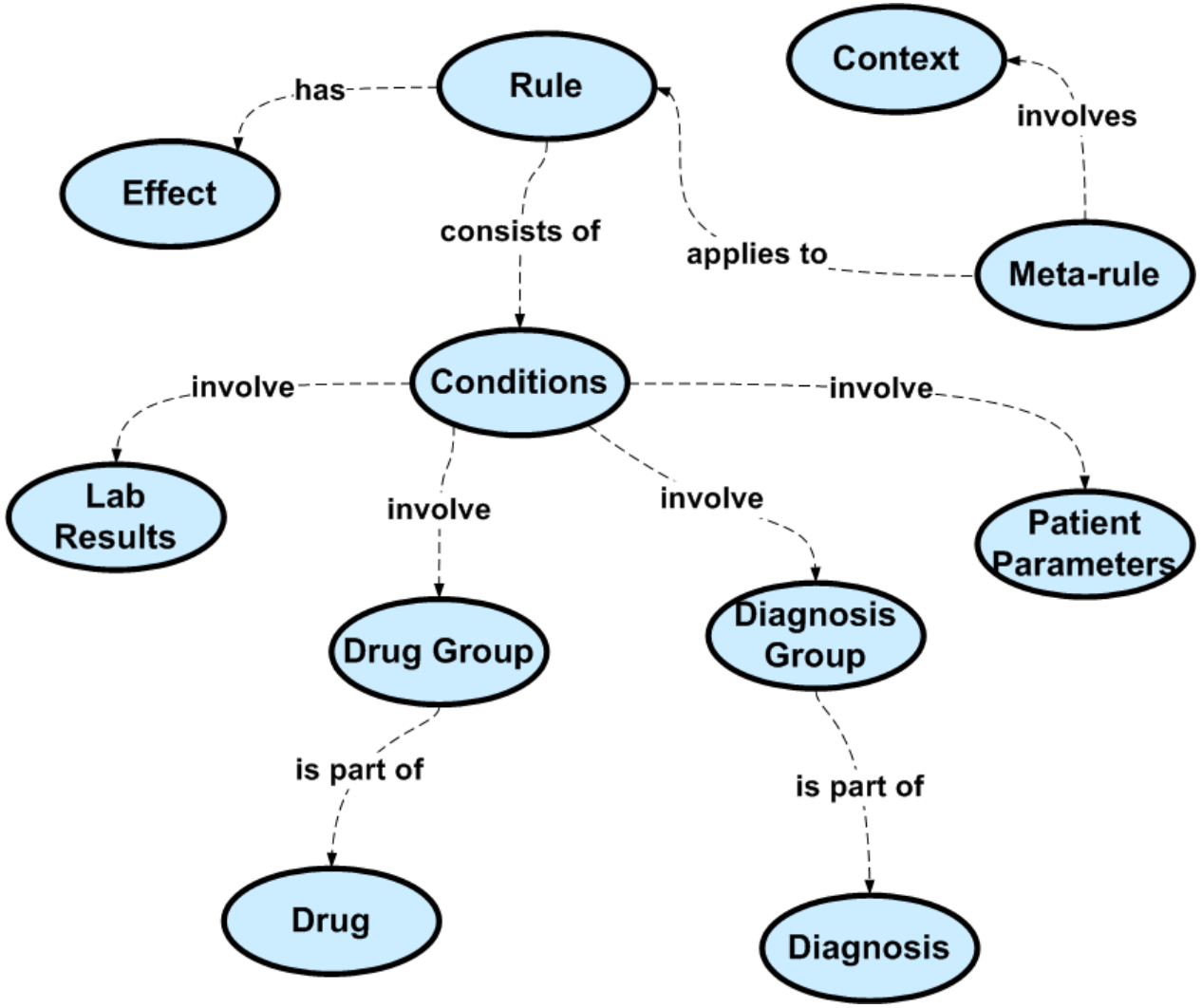
3. **Guideline/protocol modeling**:
   - Rules originated from data mining are rather **complex**, i.e. each rule typically comprises of several **intermediate rules –** encoding via **conditional workflows/pipelines**
   - Favorable for **representing procedures** within hospitals
   - Enables **unification of domain knowledge** and **task/procedural knowledge** into an efficient problem-solving model - particularly suited to develop a CDSS

Overall Knowledge Framework Architecture: *The Thessaloniki Team*



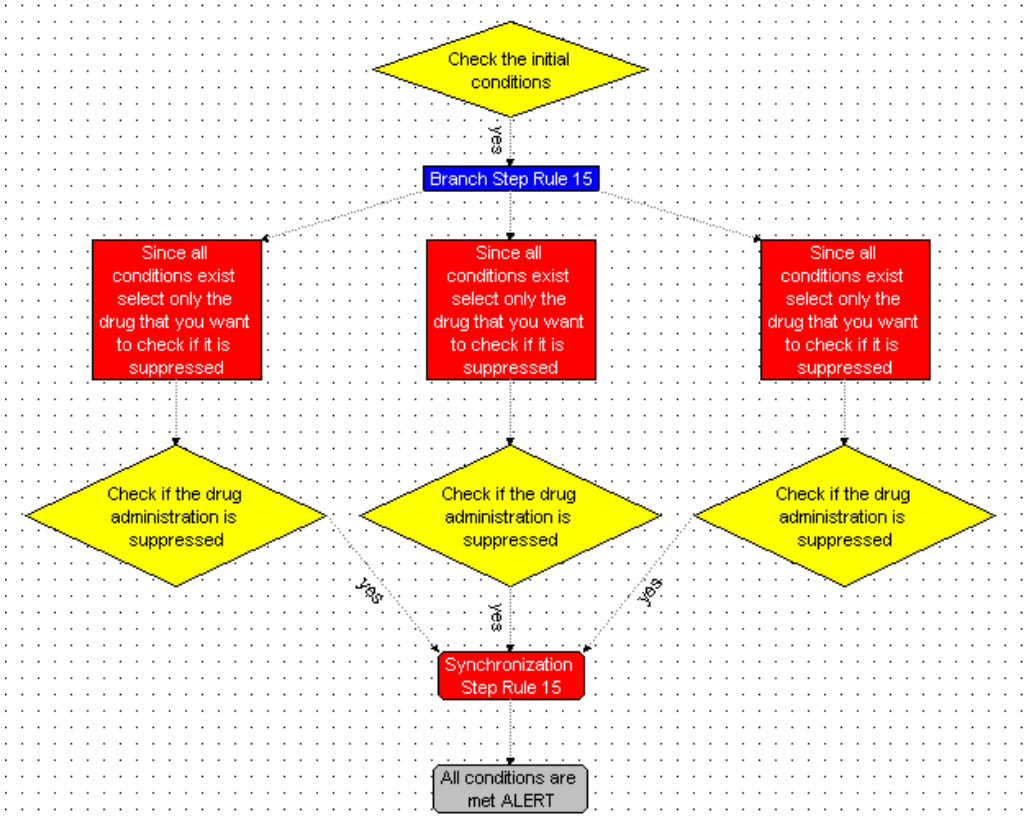
V. Koutkias et al., "Knowledge Engineering for Adverse Drug Event Prevention: On the Design and Development of a Uniform, Contextualized and Sustainable Knowledge-based Framework", Journal of Biomedical Informatics, vol. 45, no. 3, 2012, pp. 495-506.

Knowledge Model: Conceptual Schema



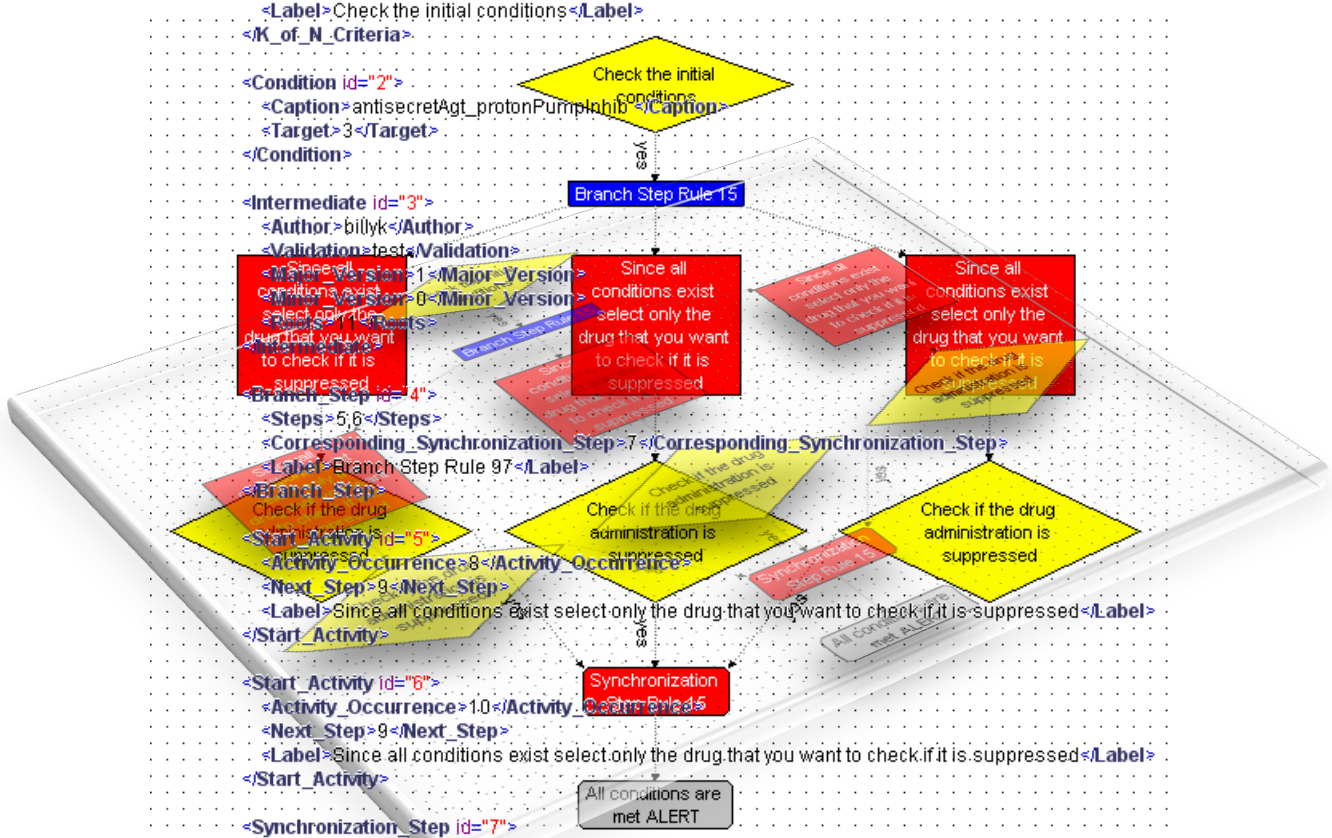
Computer Interpretable Guidelines as the Knowledge Representation Formalism

appearance of hyperkaliemia	15	dt1	renal failure=1 & Suspension of antithrombotic=0 & high weight heparin=1 & Suspension of proton pump inhibitor=0 & sympathomimetic=0 & Suspension of high weight heparin=0

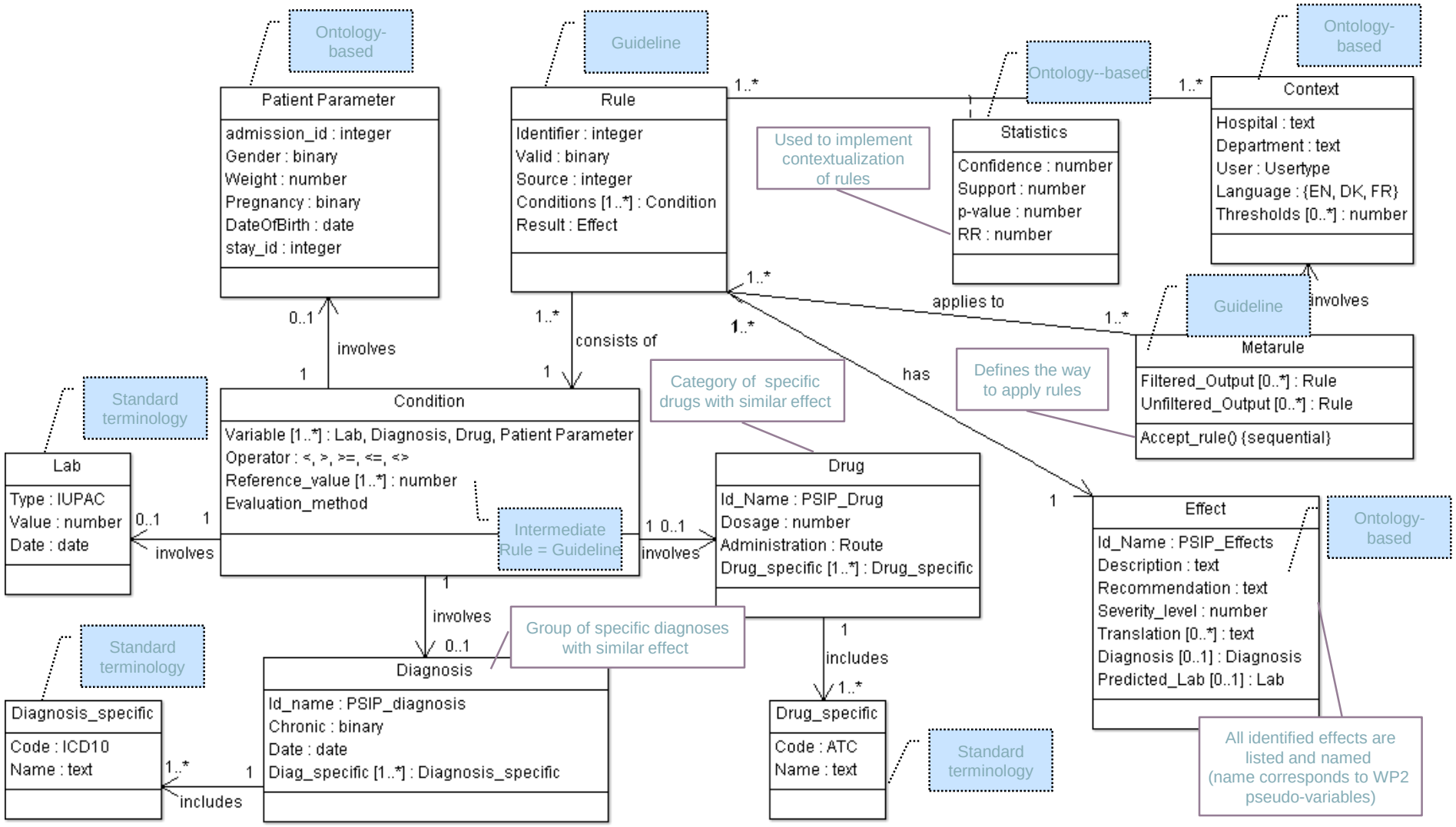


CIG Underlying Formalism

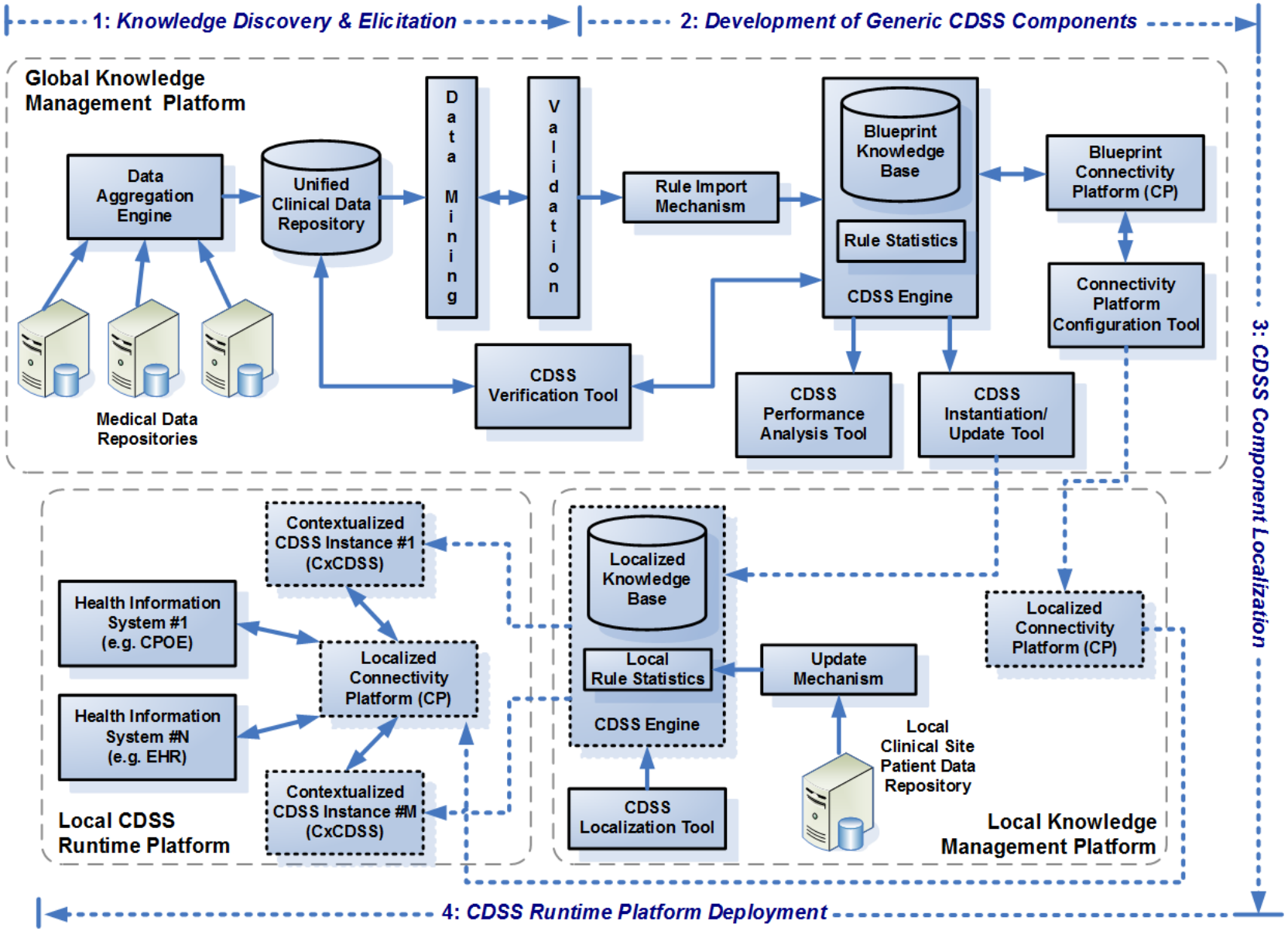
```
<Library>
  <K_of_N_Criteria id="1">
    <Positive_Criteria>2</Positive_Criteria>
    <Satisfied_Step>4</Satisfied_Step>
    <Label>Check the initial conditions</Label>
  </K_of_N_Criteria>

  <Condition id="2">
    <Caption>antisecretAgt_protonPumpInhib</Caption>
    <Target>3</Target>
  </Condition>

  <Intermediate id="3">
    <Author>billyk</Author>
    <Validation>test</Validation>
    <Major_Version>1</Major_Version>
    <Minor_Version>0</Minor_Version>
    <Assets>11</Assets>
  </Intermediate>

  <Branch_Step id="4">
    <Steps>5,6</Steps>
    <Corresponding_Synchronization_Step>7</Corresponding_Synchronization_Step>
    <Label>Branch Step Rule 97</Label>
  </Branch_Step>

  <Start_Activity id="5">
    <Activity_Occurrence>8</Activity_Occurrence>
    <Next_Step>9</Next_Step>
    <Label>Since all conditions exist select only the drug that you want to check if it is suppressed</Label>
  </Start_Activity>

  <Start_Activity id="6">
    <Activity_Occurrence>10</Activity_Occurrence>
    <Next_Step>9</Next_Step>
    <Label>Since all conditions exist select only the drug that you want to check if it is suppressed</Label>
  </Start_Activity>

  <Synchronization_Step id="7">
    <Next_Step>10</Next_Step>
    <Continuation>wait_for_all</Continuation>
    <Label>Synchronization Step Rule 97</Label>
  </Synchronization_Step>
</Library>
```



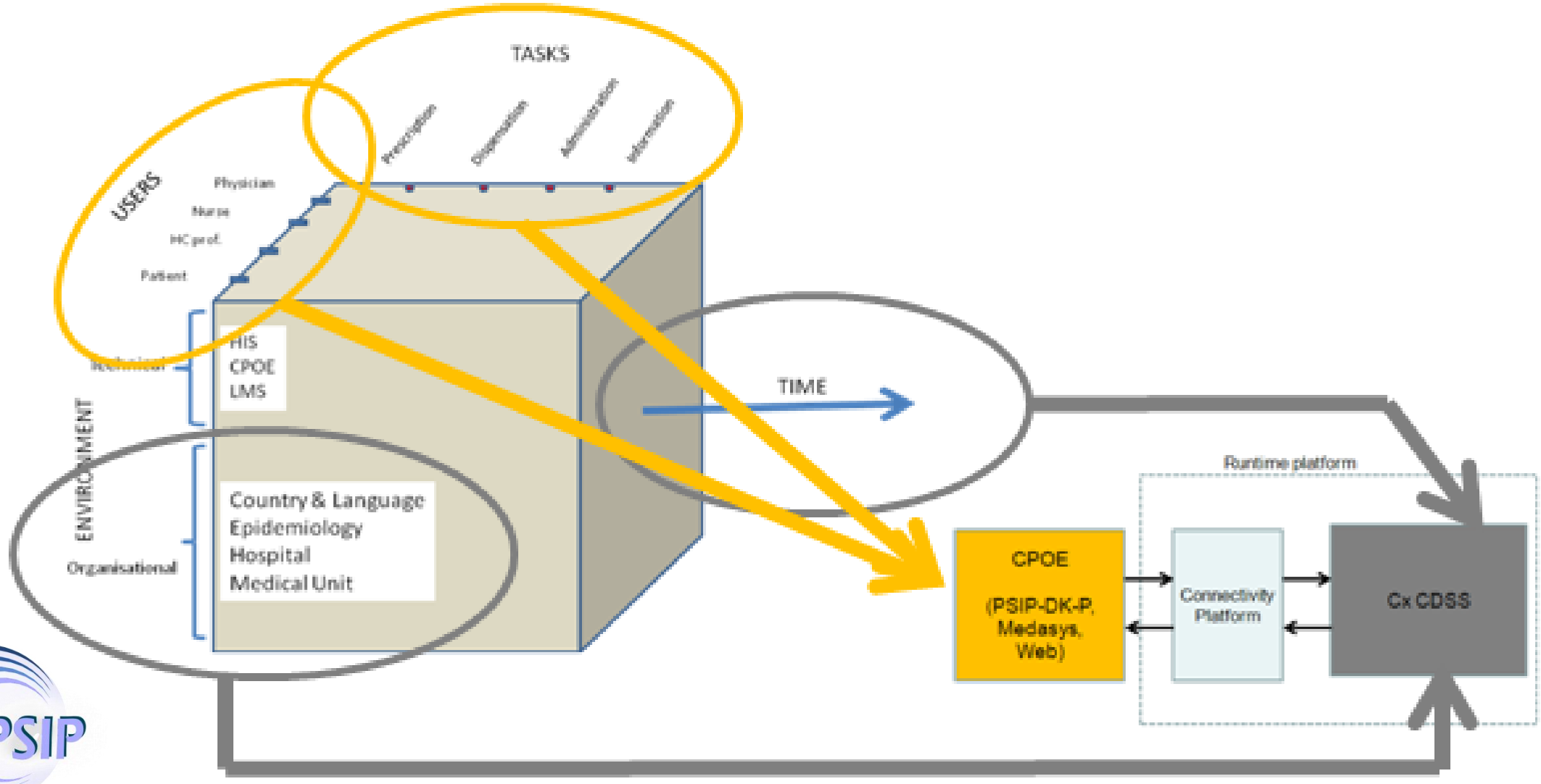
Knowledge Model: Class Diagram



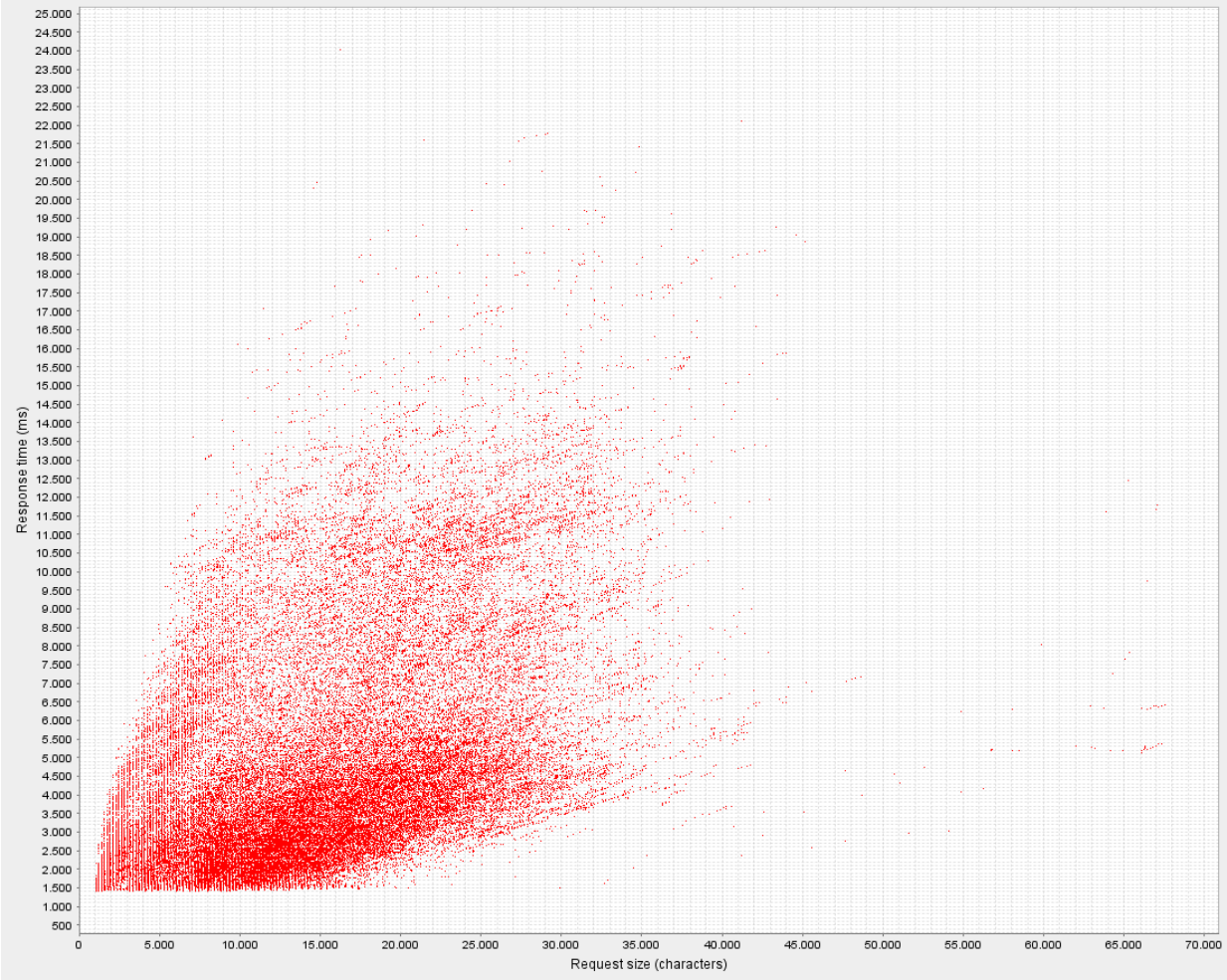
From Knowledge Discovery to Decision Support at the Point-of-Care through Contextualization



A Model for CDSS Contextualization

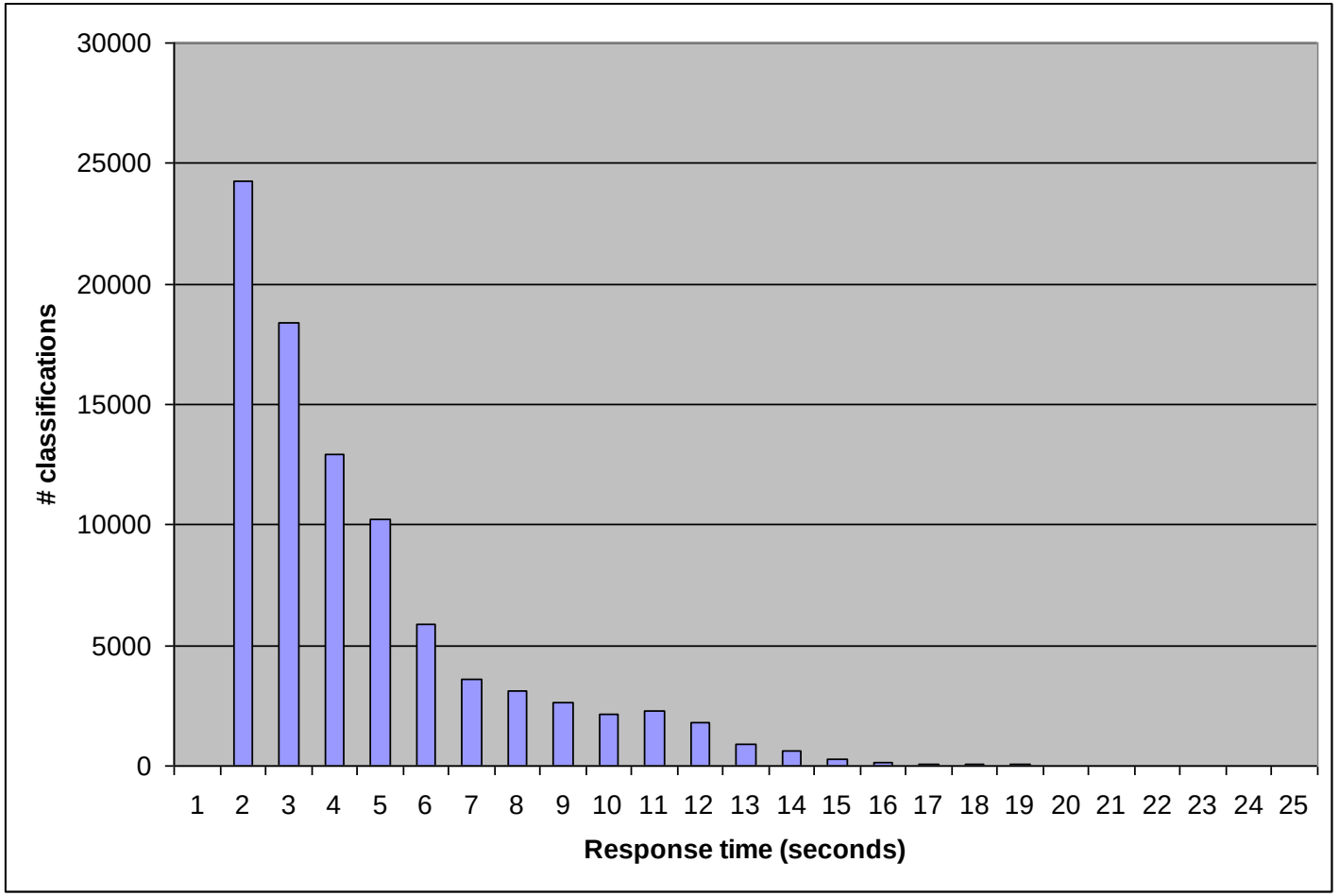


Technical Validation: CDSS Response Performance Analysis



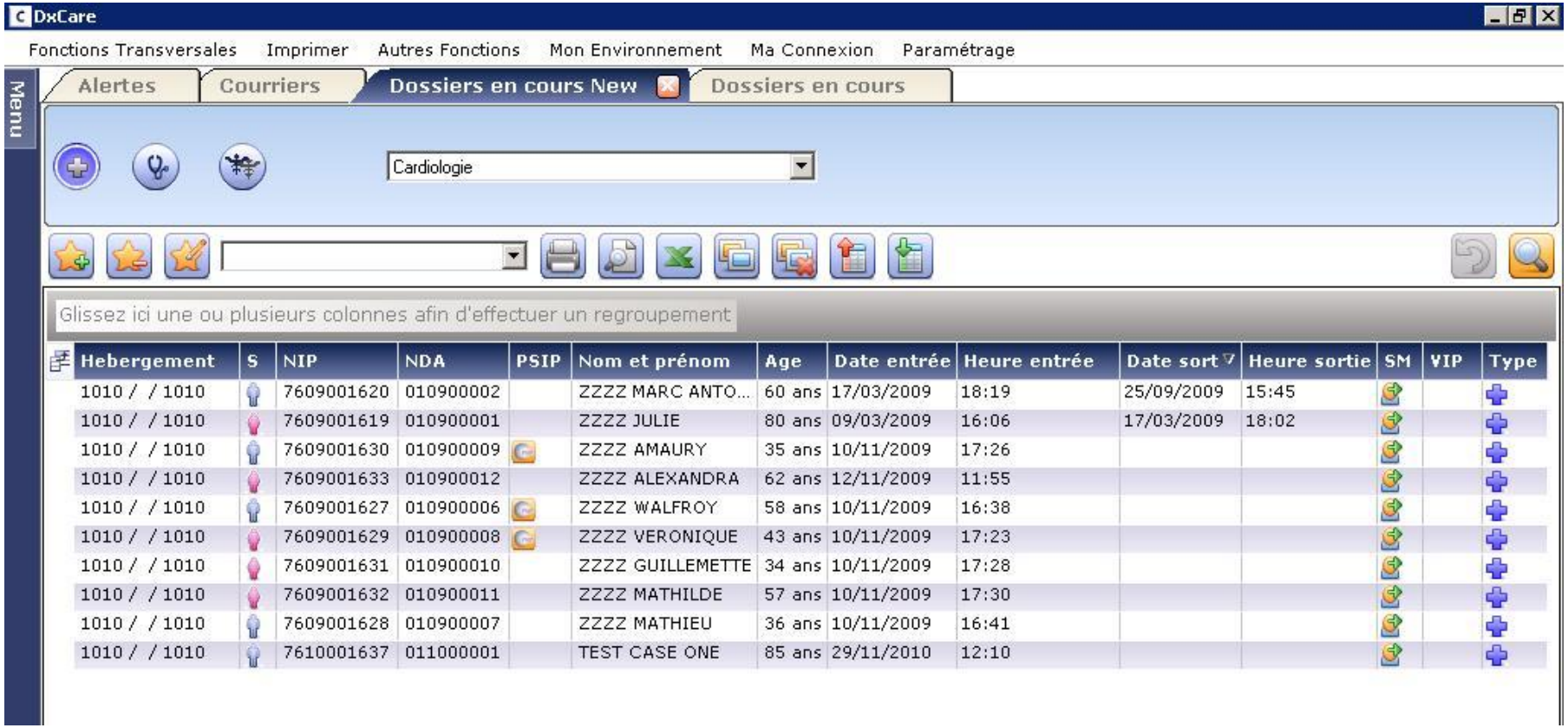
Scatter plot of the response time (ms) and request size (89.340 classifications)

Technical Validation: CDSS Response Performance Analysis



Histogram of the CDSS performance (89.340 classifications)

Incorporating the CDSS Services in Commercial Systems



Hebergement	S	NIP	NDA	PSIP	Nom et prénom	Age	Date entrée	Heure entrée	Date sort	Heure sortie	SM	VIP	Type
1010 / / 1010		7609001620	010900002		ZZZZ MARC ANTO...	60 ans	17/03/2009	18:19	25/09/2009	15:45			
1010 / / 1010		7609001619	010900001		ZZZZ JULIE	80 ans	09/03/2009	16:06	17/03/2009	18:02			
1010 / / 1010		7609001630	010900009		ZZZZ AMAURY	35 ans	10/11/2009	17:26					
1010 / / 1010		7609001633	010900012		ZZZZ ALEXANDRA	62 ans	12/11/2009	11:55					
1010 / / 1010		7609001627	010900006		ZZZZ WALFROY	58 ans	10/11/2009	16:38					
1010 / / 1010		7609001629	010900008		ZZZZ VERONIQUE	43 ans	10/11/2009	17:23					
1010 / / 1010		7609001631	010900010		ZZZZ GUILLEMETTE	34 ans	10/11/2009	17:28					
1010 / / 1010		7609001632	010900011		ZZZZ MATHILDE	57 ans	10/11/2009	17:30					
1010 / / 1010		7609001628	010900007		ZZZZ MATHIEU	36 ans	10/11/2009	16:41					
1010 / / 1010		7610001637	011000001		TEST CASE ONE	85 ans	29/11/2010	12:10					

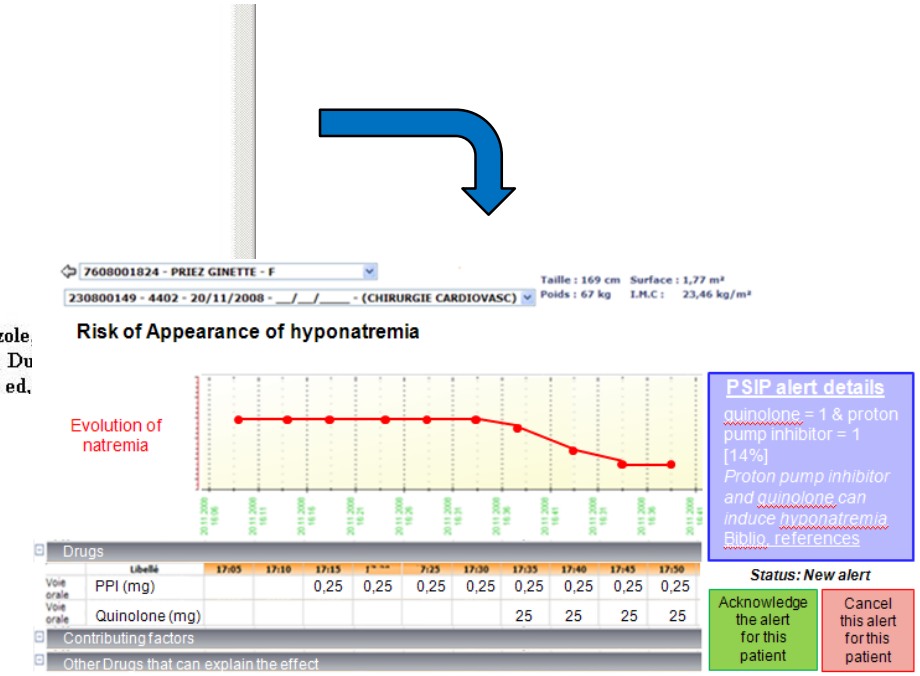
Incorporating the CDSS Services in Commercial Systems

Graphical presentation of alerts

Hypocalcemie (calcemie<2.2 mmol/l) [5.722 %]
Les IPP peuvent entrainer une hypocalcemie.
Informations complémentaires
Les inhibiteurs de la pompe a protons peuvent entrainer une hypocalcemie.

Cause(s):
hypoalbuminemie is False; PANTOPRAZOLE is True
Source: PSIP

Hyponatremie (Na+<130) [4.878 %]
Les IPP peuvent entrainer une hyponatremie.
Informations complémentaires
**Des cas d'hyponatremie ont ete observes chez des patients traites par omeprazole, lansoprazole et pantoprazole.
Ref. : Mignot G. Gastrointestinal drugs. In: Du Aronson JK, Eds. Meyler's side effects of drugs. Amsterdam: Elsevier, 14eme ed,**



Prototypes for Healthcare Professionals & Patients

The Scorecards: Retrospective Use of ADE Detection Rules

You are logged as: *expert* | Review cases | Synthesis | English | Print | Contact | Disconnect

VKA overdose (INR≥4.9)

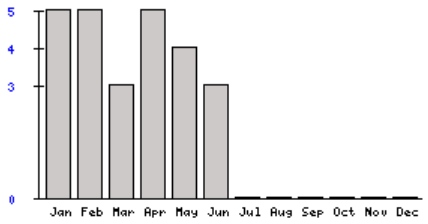
Characteristics of identified stays, all the rules together

Data from the coded diagnostics

Effective	25
Average age	75
Men - Women	32% - 68%
Deaths	0%

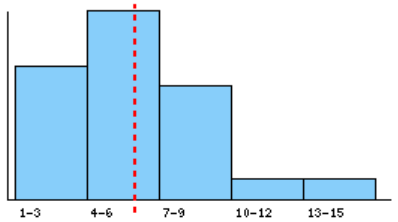
[illegible]	16%
Cardiomyopathies	76%
Renal insufficiency	20%
Hepatic insufficiency	12%
Respiratory insufficiency	36%
Alcoholism	4%

Histogram of the appearence's delay of the event:



Adverse events occurred under the above conditions.

Characteristics of identified stays, all rules together: VKA overdose (INR≥4.9)



Conditions leading to VKA overdose (INR≥4.9)	Number of cases confidence ; median delay
(1) Increased effect of the oral anticoagulant and hemorrhagic risk by thymoanaleptic.	5
VKA & Thymoanaleptic & NO Selective serotonine recapture inhibitor	16% ; 5j
(2) Increased effect of the oral anticoagulant and hemorrhagic risk by SSRI.	2

6 MONTHS
7,800
hosp.

25 cases of High INR

The Scorecards: Retrospective Use of ADE Detection Rules

Hospital CH Denain, Stay 603[redacted]

Back to the stay | More information | Rule info

PSIP

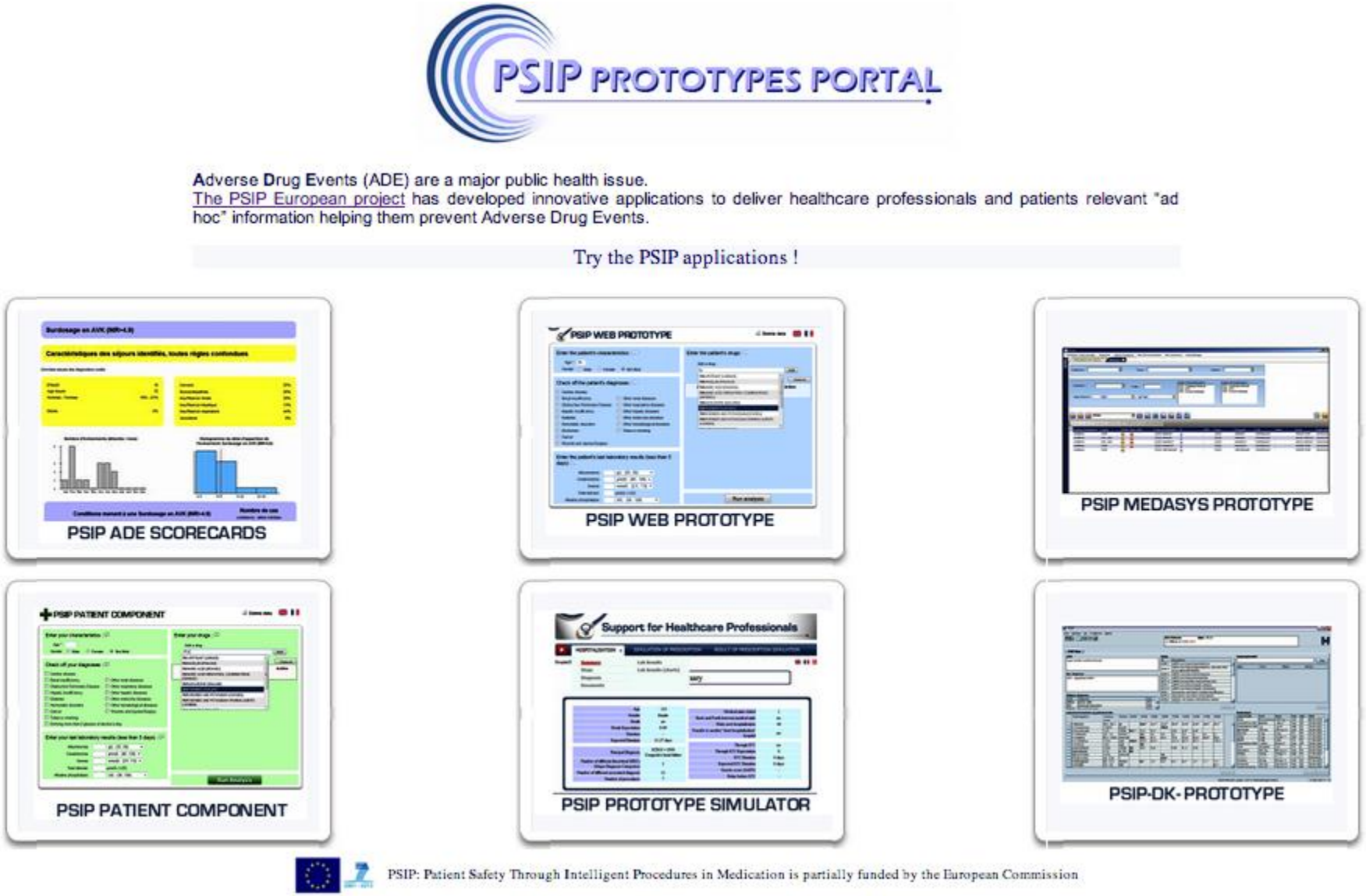
ATC	Drug name	0 … 10
	500 ml GLUCOSE MACOPH + POTASSIUM CHL A	
J01CR02	AMOXICILLINE-AC CLAVU 1G/125MG SACHETS MERCK=AUGMENTIN	
L02BG03	ARIMIDEX 1MG CPR ENR	
R03BB01	ATROVENT 0,5MG/2ML SOL PR INHALATION PAR NEBULISEUR EN RECIPIENT UNIDOSE	
J01CR02	AUGMENTIN 1G/200MG PDR INJ INJ FLACON	
R03AC03	BRICANYL 5MG/2ML SOL PR INHALATION BUCCALE EN RECIPIENT UNIDOSE	
C07AB07	CARDENSIEL 1.25 MG, CPR	
A12BA01	DIFFU-K 600MG GELULE MICROENCAPSULE JAUNE/BLANC	
C01AA05	DIGOXINE NATIVELLE 0,25MG CPR BLANC SECABLE	
A06AD15	FORLAX 10G PDR ORALE SACHET PR SOL BUV	
B05BA03	GLUCOSE MACOPH 5% SOL INJ POCHE 1000ML ISOTONIQUE	
	HEPARINE CHOAY 25000UI/5ML IV SOL INJ FLACON	
A12BA01	KALEORID 1000MG LP CPR ENR	
C03CA01	LASILIX 20MG/2ML SOL INJ AMPOULE= FUROSEMIDE 1 % RENAUDIN 2ML	
C03CA01	LASILIX 40MG CPR BLANC	
C03CA01	LASILIX FAIBLE 20MG CPR BLANC	
R07A	OXYGENE	
R07A	OXYGENE	
B01AA	PREVISCAN 20MG CPR DANS BOITE INCLUANT UN CARNET DE SUIVI	
R03BA02	PULMICORT 1MG/2ML SUSP PR INHAL UNIDOSE PR INHALATION BUCCALE	
	SAP RISORDAN	
C09AA05	TRIATEC 2.5 MG, CPR	

Show all | Hide all

100 % FORMULE	HB	PB%	TP.
BNP	HT	PE%	TRNT
CCMH	IGA (g/l)	PLAQ.	UREE SG
CL1	IGG (g/l)	PN%	VGM
CREAT.	IGM (g/l)	PROTIDES TOTAU	Ly
CRP	☑ INR	RA.	Mo
DIGOXINE	K1	TCA	Pb
GB	L%	TCA patient	Pe
GLYJ.	MONOCYTES%	TCAr	Pn
GR(Millions/ml	NA1	TCMH	

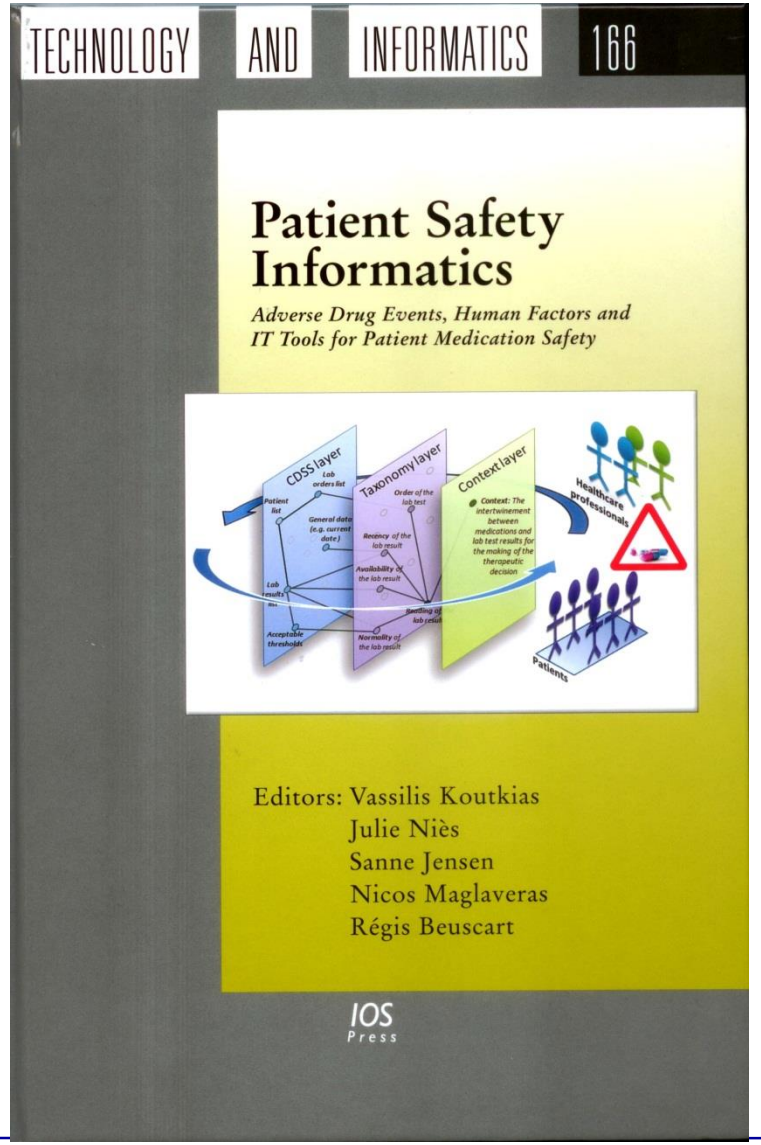
INR

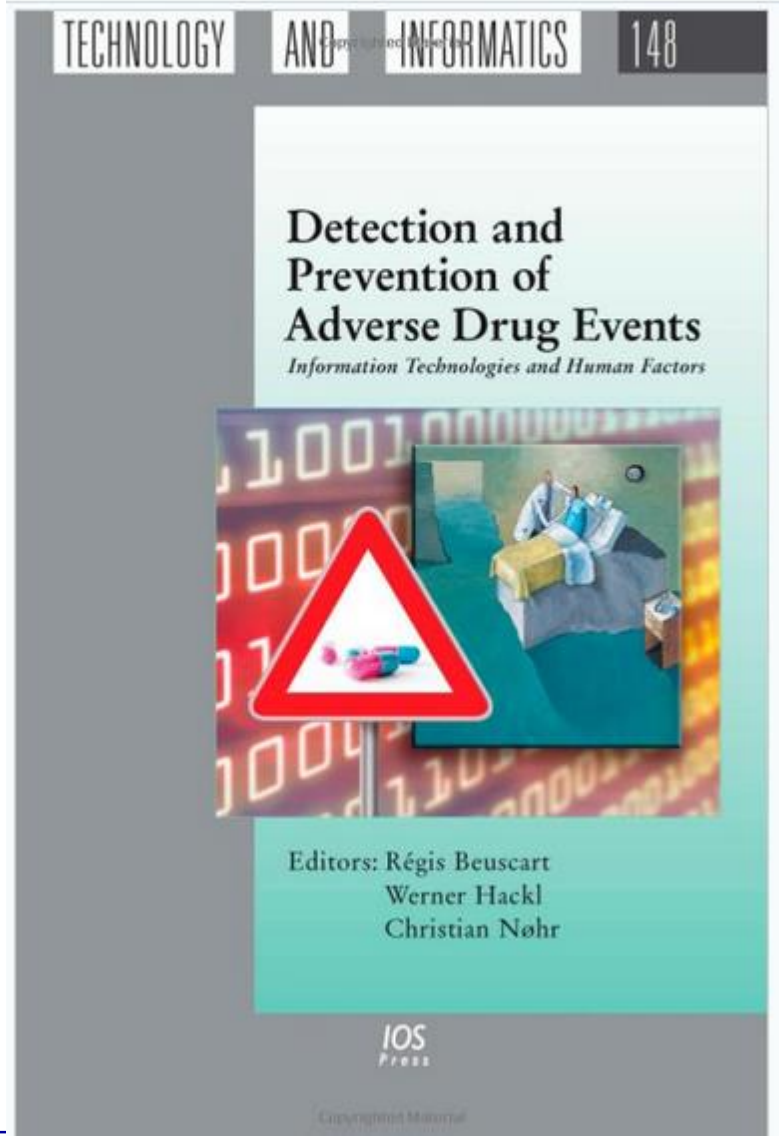
Prototypes: http://psip.univ-lille2.fr/prototypes/public/



Prospective Use of CDSS: Simulation Study in RegionH/DK

Bibliography





Concluding Remarks

- Medication safety is a major public health issue
- Information Technologies provide means to contribute in identification and prevention of safety risks
- Very active research area currently (we presented just two approaches out of various taking place)
- Significant steps forward recently, but many challenges are still there
- Important synergies established to leverage medication safety via an active drug surveillance system
- The human factors perspective is important in introducing medication safety systems at the point of care

Discussion

Thank you!

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