Federation of databases to evaluate the arrhythmogenic potential of drugs: the ARITMO project

Fabrizio De Ponti
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Consortium partners

ARITMO - Arrhythmogenic potential of drugs

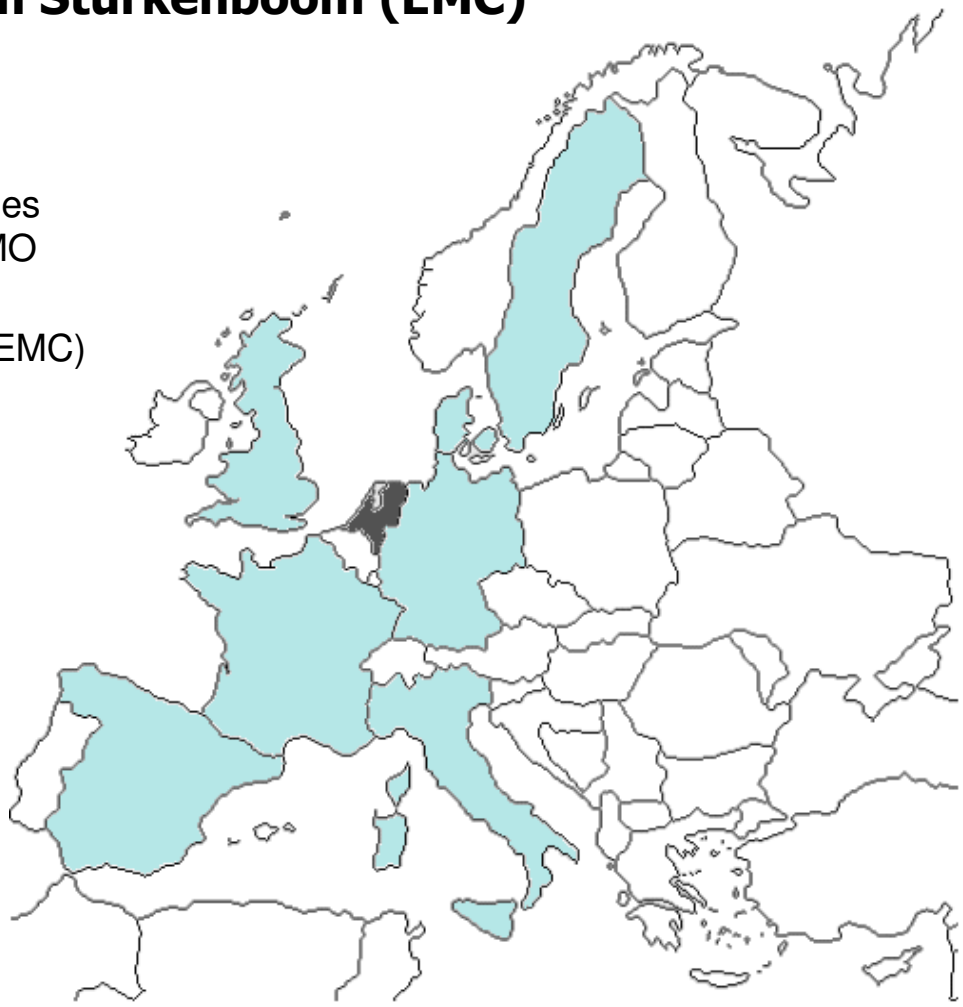
Grant agreement n. 241679

Project coordinator: Miriam Sturkenboom (EMC)

TIMELINE: 2010-2012

European Countries enrolled in ARITMO

ARITMO leader (EMC)



SEVENTH FRAMEWORK PROGRAMME

Consortium partners

Participant no.	Participant organisation name	Country
1 (Coordinator)	Erasmus Universitair Medisch Centrum Rotterdam (**EMC**)	Netherlands
2	Fundació IMIM (**FIMIM**)	Spain
3	London School of Hygiene and Tropical Medicine (**LSHTM**)	United Kingdom
4	Alma Mater Studiorum-Università di Bologna (**UNIBO**)	Italy
5	Universitaet Bremen (**UNI-HB**)	Germany
6	University of Newcastle (**UoNEW**)	United Kingdom
7	Université Victor Segalen Bordeaux2 (**UB2**)	France
8	Fondazione Salvatore Maugeri Clinica del Lavoro e Della Riabilitazione (**FSM-MCL**)	Italy
9	Charite - Universitaetsmedizin Berlin (**CHARITE**)	Germany
10	Universita Degli Studi di Verona (**UNIVR**)	Italy
11	St. George's Hospital Medical School (**SGUL**)	United Kingdom
12	AstraZeneca AB (**AZ**)	Sweden
13	PHARMO Coöperatie U.A (**PHARMO**)	Netherlands
14	Fondazione Scientifica SIMG-ONLUS (**F-SIMG**)	Italy
15	Aarhus Universitetshospital, Aarhus Sygehus (**AUH-AS**)	Denmark
16	Academisch Medisch Centrum bij de Universiteit van Amsterdam (**AMC**)	Netherlands
17	Drug Safety Research Trust (**DSRU**)	United Kingdom

The ARITMO website

http://www.aritmo-project.org

ARITMO – KEY POINTS

THEORETICAL ASPECTS

QT interval prolongation as surrogate marker of cardiotoxicity→ risk of torsade de pointes → ventricular fibrillation

class *vs* molecule effect

CLINICAL ASPECTS

INDIVIDUAL LEVEL

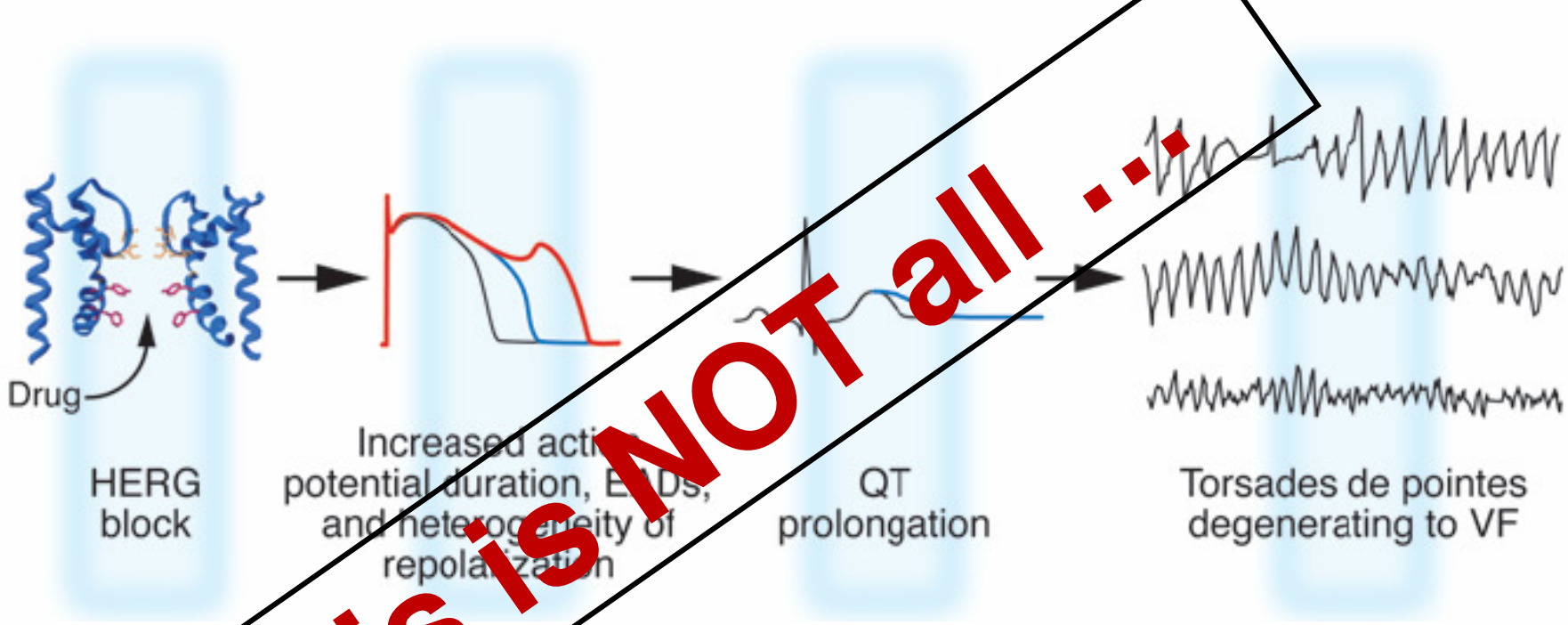
- practical issues out of the hospital setting
- issues in drug prescription

POPULATION LEVEL

REGULATORY ASPECTS

Regulatory measures and implications for drug development

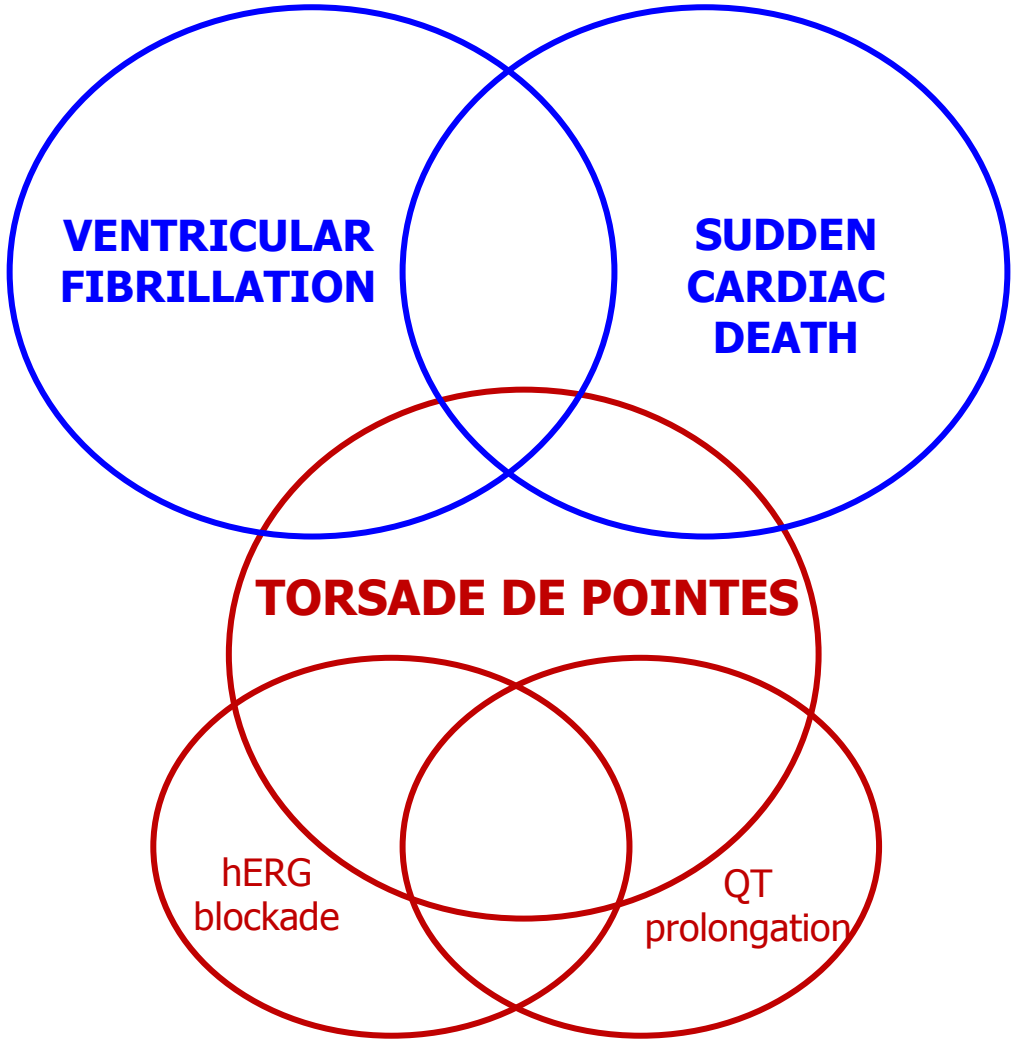
From hERG to TdP



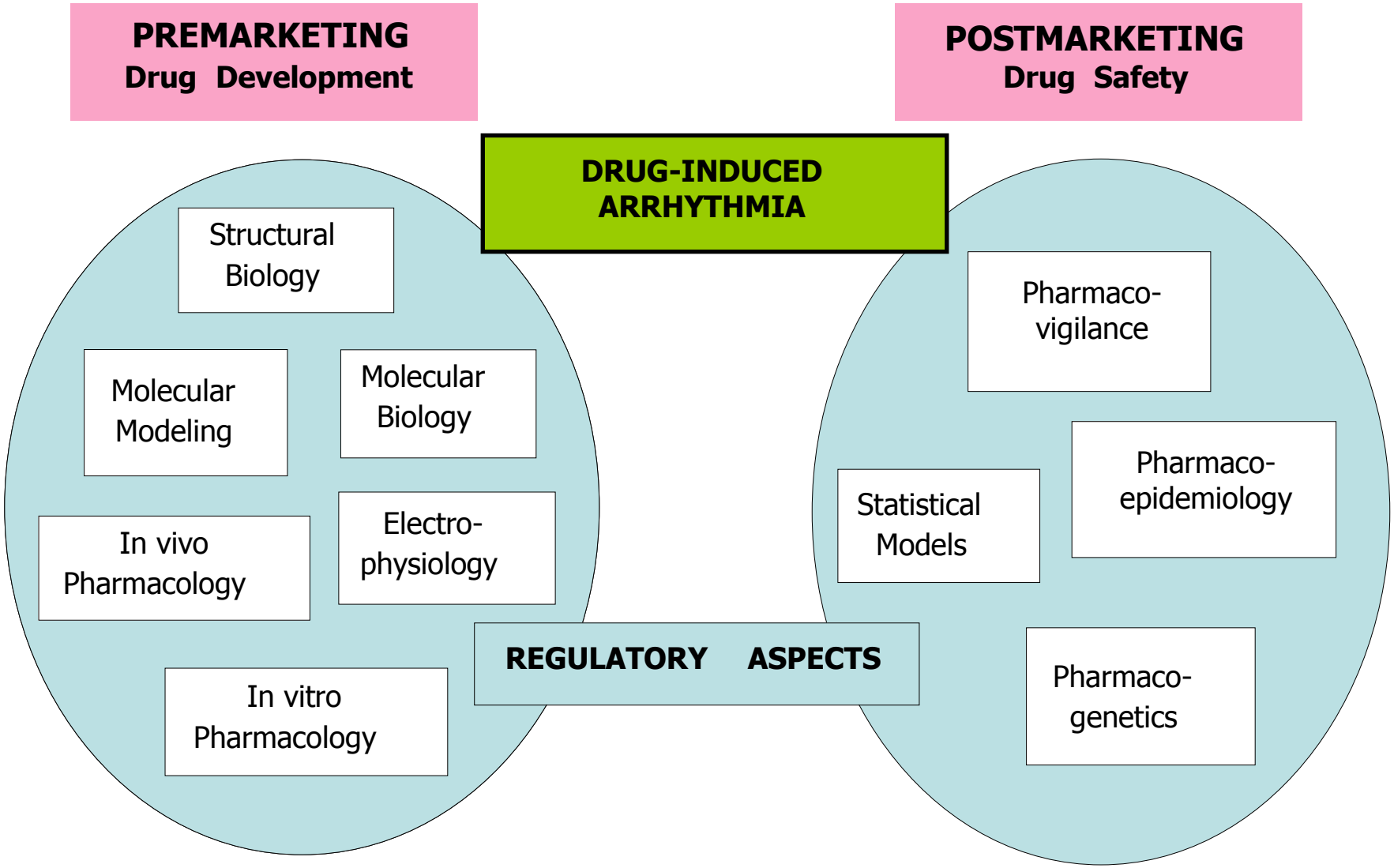
This is NOT all ...

Roden & Viswanathan. J Clin Invest 2005; 115: 2025-32.

SPECTRUM OF DRUG-INDUCED ARRHYTHMIA



MULTIDISCIPLINARY NETWORK



ARITMO will analyse the arrhythmogenic potential of drugs in the following classes **(> 450 compounds**):

1) Antipsychotics (ATC N05A)

2) Anti-infectives [antibacterials (J01) antimycotics (J02) and antivirals (J05)]

3) H1-antihistamines (ATC R06)

THE ARITMO DRUG LIST

(approx. 590 different V level ATC codes)

ARITMO OUTCOMES

- TORSADE DE POINTES
- QT PROLONGATION/ABNORMALITIES
- VENTRICULAR TACHYCARDIA/FIBRILLATION
- SUDDEN CARDIAC DEATH/SUDDEN UNEXPECTED DEATH

SPECIFICITY

SENSITIVITY

The contribution of databases in ARITMO

In ARITMO, data originated from several databases and heterogeneous sources will be integrated.

WP3: SPONTANEOUS REPORTING SYSTEM DATABASES

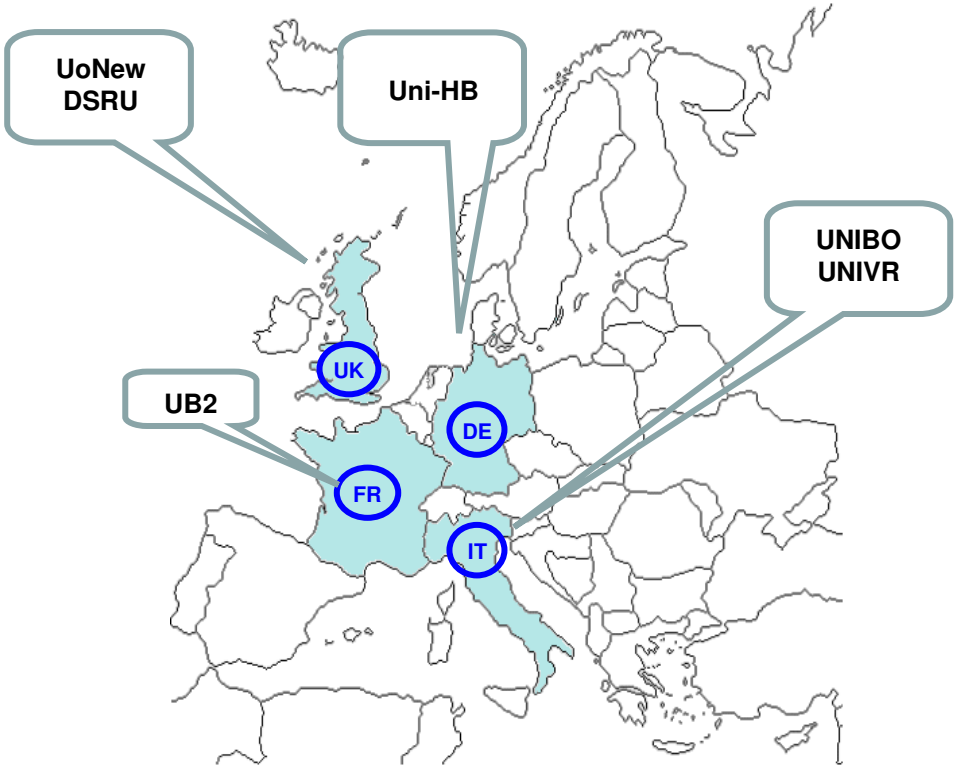
WP4: ANALYTICAL FIELD STUDIES

WP5: ANALYTICAL DATABASE STUDIES

WP6: LITERATURE DATABASES

WP7: In Silico/hERG DATABASES

WP8: **CREATION OF A DATABASE** with integrated information from all WPs (list of drugs with assigned scores)



WP3: Pharmacovigilance

Fabrizio De Ponti,
Elisabetta Poluzzi, Emanuel Raschi
University of Bologna, Italy

Signal Detection!

Signal detection in spontaneous reporting systems

- Case by case approach

  → **Case Listing** and **Event Reporting Rate**

- Statistical signal detection

  → **Disproportionality analysis**

ISSUES IN DATA COLLECTION

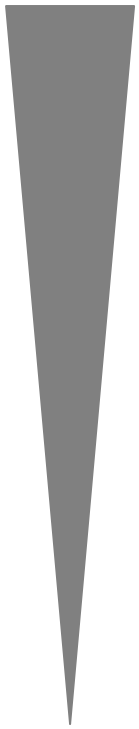
- **Outcome definition** (TdP, QT interval abnormalities, Ventricular tachycardia/fibrillation, Sudden Cardiac Death)
- **Outcome codification** (different terminologies, MedDRA and WHO-ART)
- **Level and type of accessibility** (raw or aggregate data) of the database
- **Policy** related to data use in relation to each national Authority
- Data population **coverage**
- **Quality** of data
- **Ethical issues**

OVERVIEW OF DATABASES

	International Databases			National Databases			
Characteristics	AERS	WHO	Eudravigilance	FR	DE	IT	UK
Type of access	Full access of raw data (mainly US, European and Japanese data) from 2004	Full access (web based interface)	Full access (web based interface)	Full access (data since 2000)	Access, restricted, defined set of variables can be extracted	Full access (data since 1989)	Type II (complete dataset including narratives) and Ib (no narratives) applications
Total Source Population	US + EU	Worldwide	US + EU	Approximately 60 Millions	Approx. 82 Millions	Approx. 60 Millions	Approx. 60 million
Coding system for drug	ATC classification (*ad hoc* drug name archive)	ATC	Product Dictionary (ATC available)	Internal (ATC available)	ATC	Internal (ATC available)	Internal (no ATC available)
Coding system for event	MedDRA	WHO-ART and MedDRA	MedDRA	WHO-ART and MedDRA (bridge)	MedDRA	MedDRA and WHO-ART	MedDRA
Presence of free text	No	No		Yes	Free text information is available in paper form, but not electronically accessible.	Yes	Yes (in Type II data)

DATA AVAILABILITY

	before 2000	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
FDA_AERS												
WHO												
Eudravigilance												
FR (national)												
DE (national)												
IT (national)												
UK (national)												

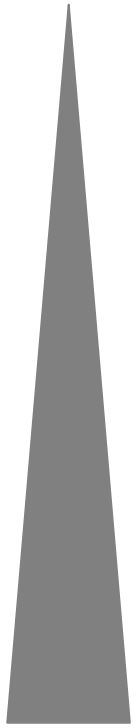


accuracy
(narratives)

NATIONAL
DATABASES

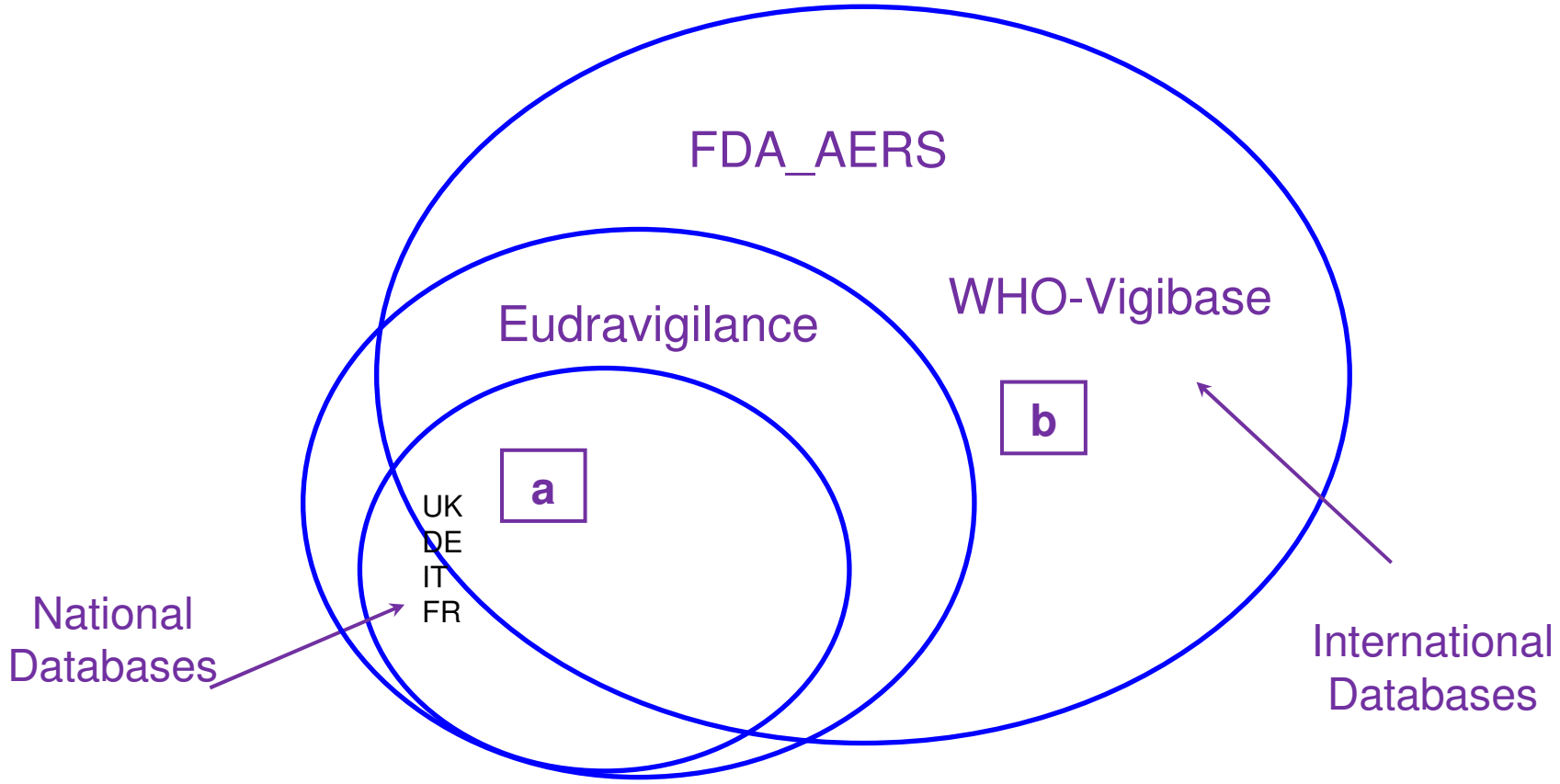
?

INTERNATIONAL
DATABASES



population
coverage

OVERLAP ANALYSIS ON TdP



a. **Cases of TdP retrieved both in National and International Databases, according to pre-specified key fields (i.e. suspect drug, event date, age, sex, reporter country).**
b. **Cases of TdP retrieved only in International Databases (e.g. extra-EU data from the FDA_AERS).**

AREAS OF INTERACTION WITH EMA

	CHMP QT subgroup	ARITMO
PLANNED TIMELINES	**2010-2012**	**2010-2012**
FUNDING	-	European Commission
DRUGS OF INTEREST	virtually all medicinal products undergoing centralized procedure	ARITMO drug list (antiinfectives, antihistamines and antipsychotics)
EXPECTED OUTCOMES	Influence scientific and regulatory discussion at the ICH level, identifying situations where there would not be mandatory requirement for TQT studies	• Integrated evaluation of TdP liability • Support regulatory decision • Information for prescribers and patient groups

WP5: Analytical Database Studies

Miriam Sturkenboom,
Gianluca Trifirò, Alessandro Oteri
Erasmus Medical Center, The Netherlands

Pooling of Healthcare Databases

Objectives

- To describe the **utilization of antipsychotics, antihistamines and anti-infectives** in Germany, Denmark, Italy, Netherlands and UK
- To assess the **rate and relative risk** of the study outcomes during use of the various drugs
- To **define, map and validate** the outcome and exposure of interest in the various DB and the protocol
- To **develop the software** for local standardized elaboration of data in various databases allowing for pooling and centralized analysis

OVERVIEW OF DATABASES

Characteristics	IPCI (NL)	PHARMO (NL)	THIN (UK)	HSD (ITA)	Emilia Romagna Regional DB (ITA)	Aarhus DB (DK)	GePaRD (Germany)
Type of database	GP	Record linkage	GP	GP	Claims	Claims	Claims
Total Population	1 million	2.4 million	2.6 million	1.2 million	4 millions	1.6 million	17 million
Coding system for drug	ATC	ATC	BNF	ATC	ATC	ATC	ATC
Coding system for event	ICPC	ICD9-CM	READ	ICD9-CM	ICD9-CM	ICD10	ICD10-GM
Presence of free text	Yes	No	Yes	Yes	No	No	No

Data Availability

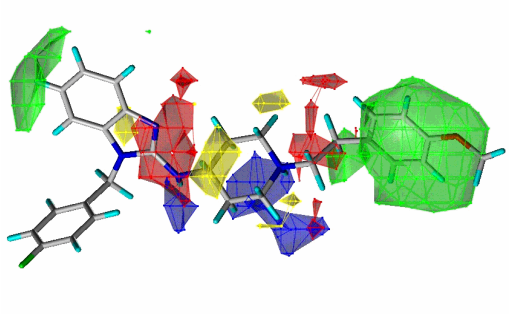
	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
IPCI	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
PHARMO			■	■	■	■	■	■	■	■	■	■	■	■	
THIN	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
HSD					■	■	■	■	■	■	■	■	■	■	■
ERD								■	■	■	■	■	■	■	■
AARHUS							■	■	■	■	■	■	■	■	■
GePaRD									■	■	■	■	■		

ISSUES IN TERMINOLOGY MAPPING

- **4 Outcomes and 56 Covariates**
- **4 terminologies**:
  - ICD9-CM (GePard, HSD, Emilia Romagna Regional DB, PHARMO)
  - ICD10 (Aarhus University Hospital DB)
  - ICPC2 (IPCI)
  - READ v.2 (THIN)

- **Free text in 3 languages**:
  - Italian
  - Dutch
  - English

In Silico Databases



ChEMBL database: https://www.ebi.ac.uk/chembldb
PDSP database: http://pdsp.med.unc.edu/pdsp.php
IUPHAR database: http://www.iuphar-db.org

All pharmacodynamic (FIMIM) and pharmacokinetic (AZ) data on the drugs of interest will be made available through a navigation tool that is currently being customised for ARITMO drugs and data.

iPHACE
Integrative Navigation in Pharmacological Space
http://cgl.imim.es/iphace/

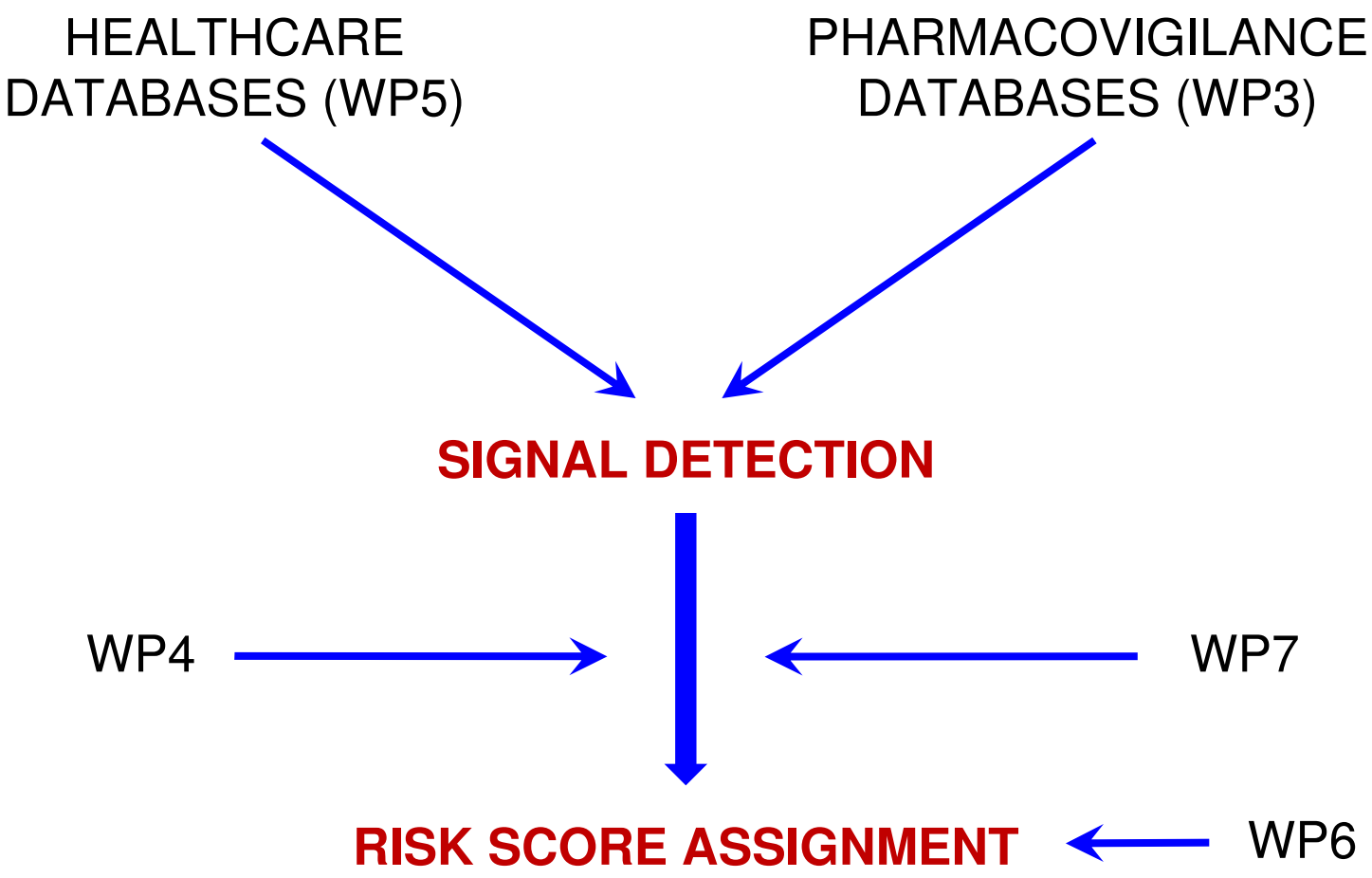
WP8: Evidence Integration

Database with integrated information from all WPs

Algorithm for risk stratification (within each drug class)

SUPPORT REGULATORY AGENCIES AND PHYSICIANS IN DECISION-MAKING PROCESS

FRAMEWORK


HEALTHCARE DATABASES (WP5)
PHARMACOVIGILANCE DATABASES (WP3)
SIGNAL DETECTION
WP4
WP7
RISK SCORE ASSIGNMENT
WP6

THE POPULATION PERSPECTIVE

POPULATION ⟷ **DRUG**

PHARMACOEPIDEMIOLOGY

↑

European exposure to ARITMO drugs with relevant risk level

(in collaboration with EURODURG and ISPE-SIG-DUR)