Experiences in big data for drug effects

Prof. dr. Miriam CJM Sturkenboom

Dep. Medical Informatics, Erasmus University Medical Center, The Netherlands

Content

Background

- Use of ‘big’ data in Pharmacoepidemiology and development of networks

Innovative Medicines Initiative

- EMIF
- ADVANCE

How is safety of drugs tested?

Too little known about safety and effects in special groups (children, pregnant women, elderly)

Fase 1 → Fase 2 → Fase 3 → ***Approved***

10-20

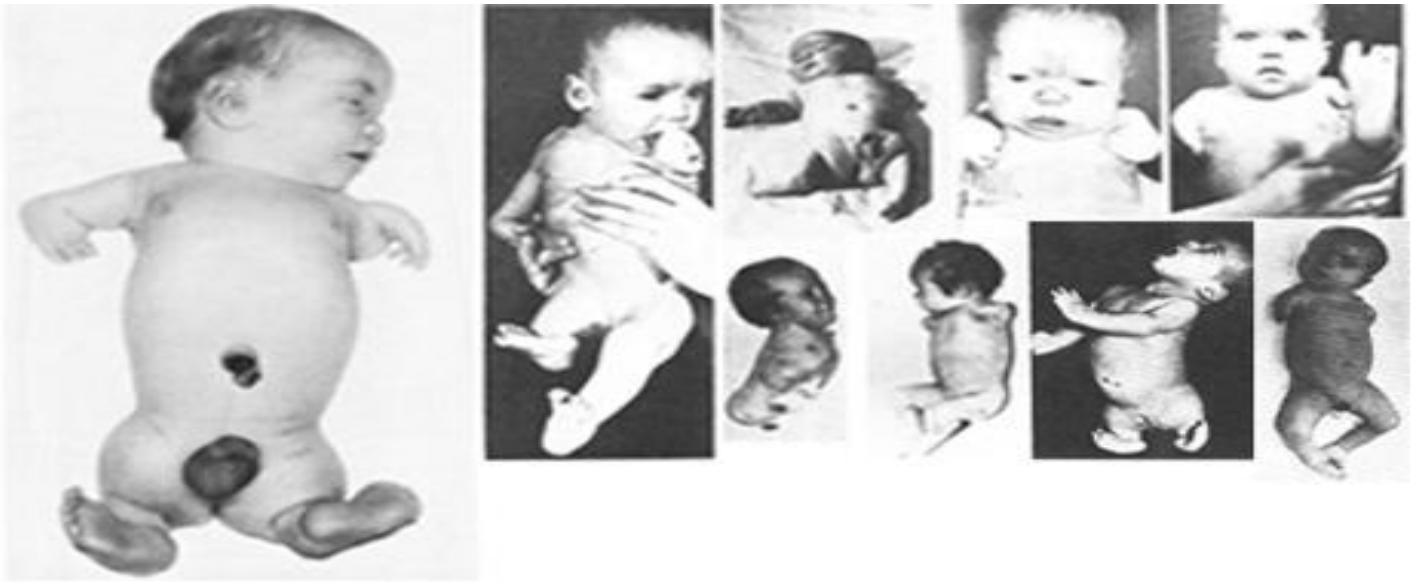
Till 100

100-3000

millions

Traditional post-marketing Pharmacovigilance method

Serious adverse effects resulting from the treatment with thalidomide prompted modern drug legislation more than 50 years ago.



ADRs reported by physicians, entered in database and then signal needs to be detected

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In period 2004-2007: safety scandals

- Post-marketing spontaneous reporting systems for suspected adverse drug reactions (ADRs) have been the main pillar to detect safety signals in Pharmacovigilance.
- It has become evident that adverse effects of drugs may be detected too late, when millions of persons have already been exposed. (examples: Vioxx, Lipobay, SSRIs, Rosiglitazone….)

- **Earlier detection is needed**

Characteristics of drug safety assessment

- Drug use is infrequent
- Highly variable use: cannot be remembered
  - Need for alternative data sources
- Serious idiosyncratic events are rare (1/10,000 – 1/100,000)

- Need for ‘big data’

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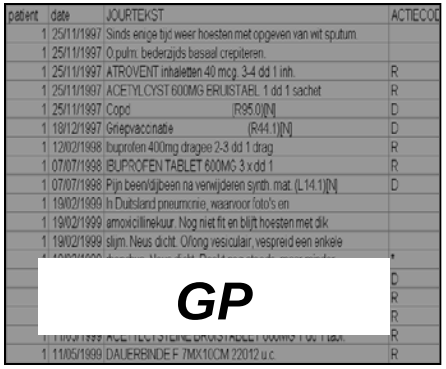
Routine health care data

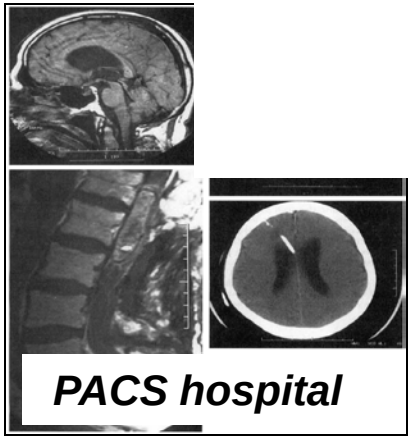
Wealth of data

prof. dr. MCJM Sturkenboom

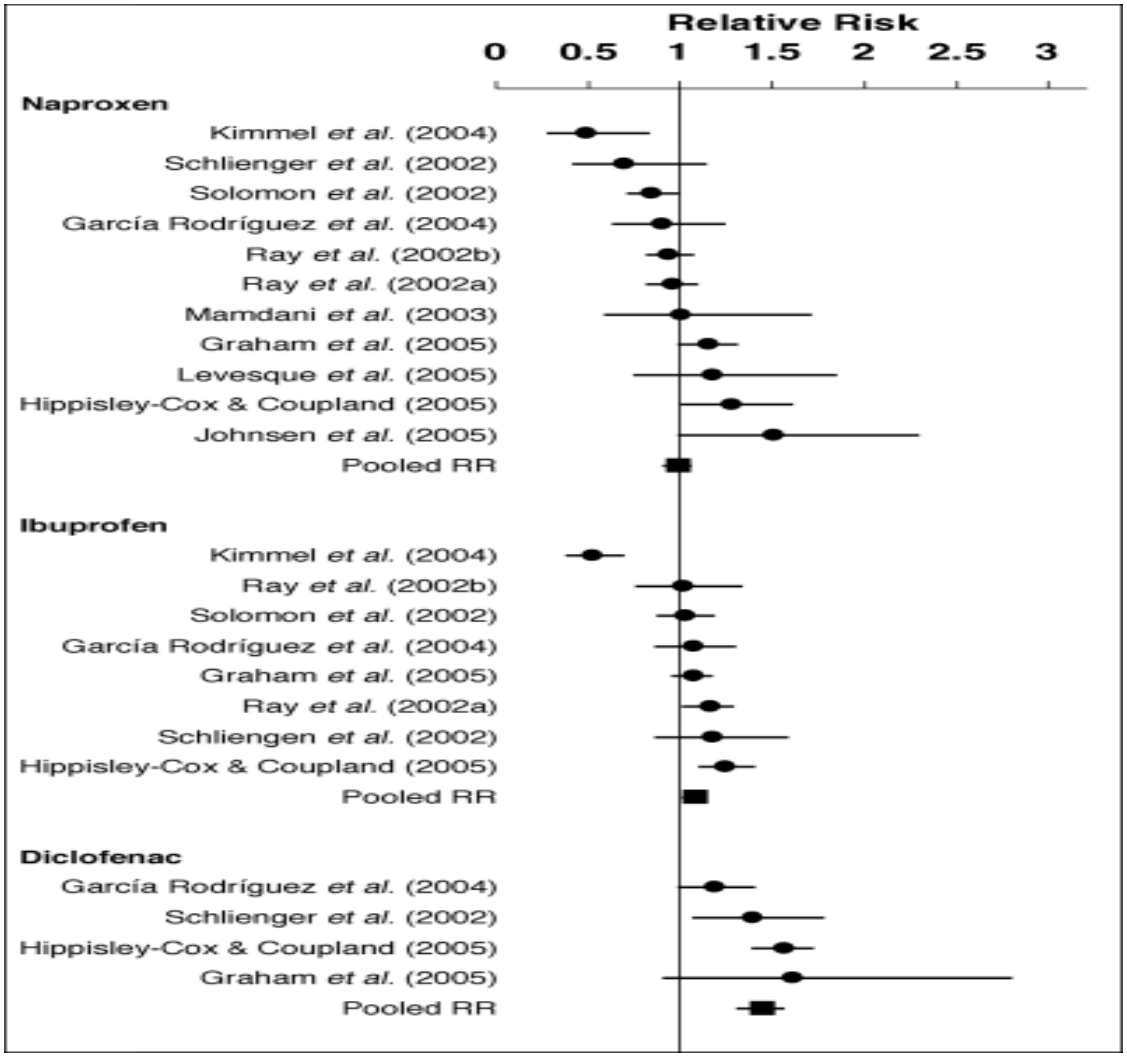


Routine health care data available in every country

Can be used for safety monitoring



Before 2007: Fragmented way of working: each center conducts its own study NSAIDs & AMI



From Hernandez-Diaz

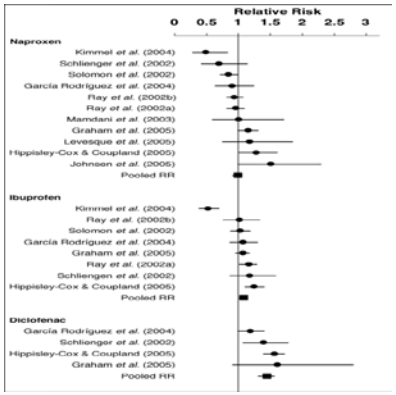
Can we do better than meta-analyses of disparate studies?

Combining of raw data in <u>central</u> datawarehouse: impossible

Central pooling of locally elaborated data

Common protocol studies

Meta-analysis of individual studies (traditional)



As a consequence of drug safety scandals:

Collaborative distributed system started across the world

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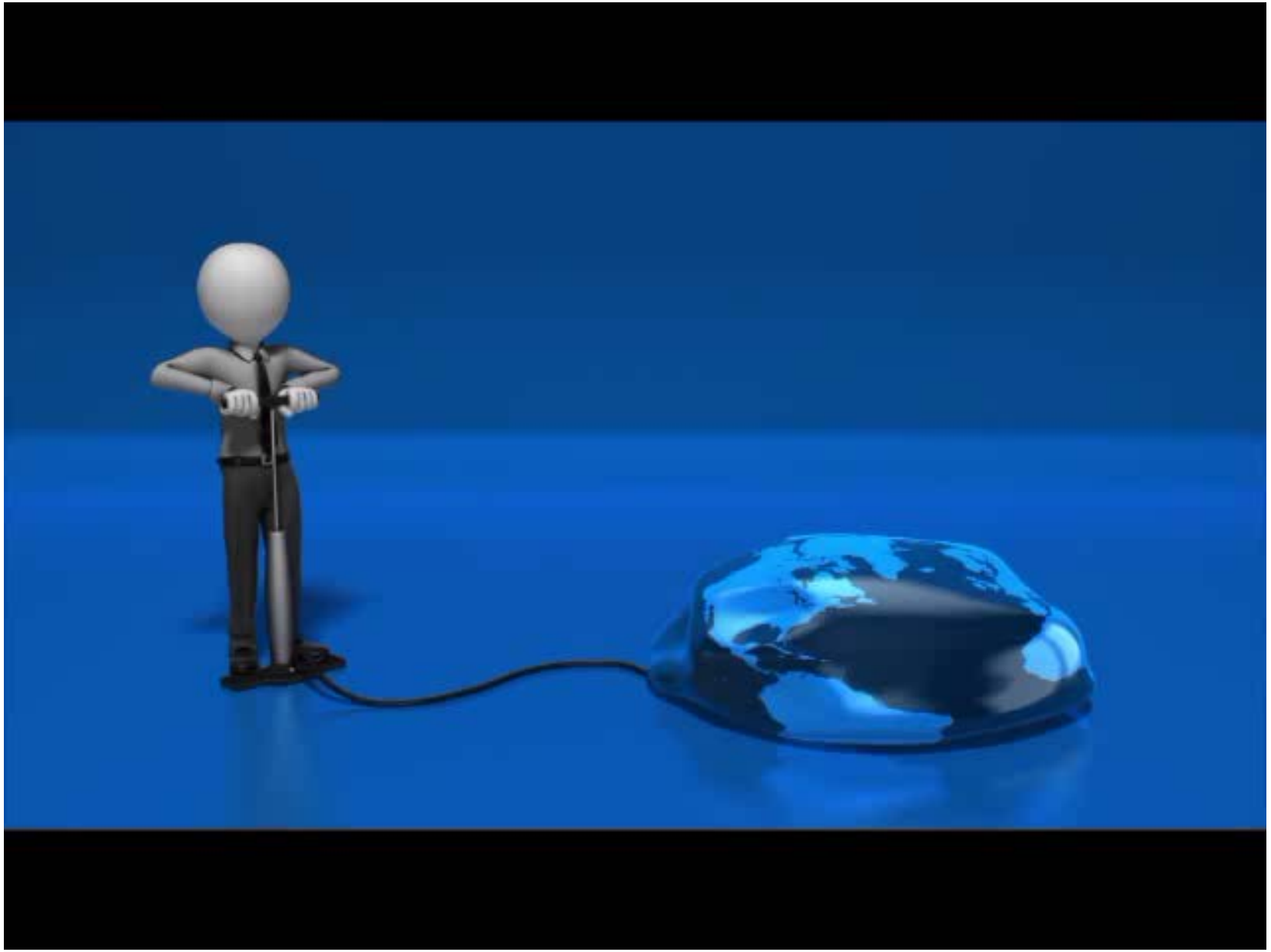

USA

Drug Safety Reform at the FDA — Pendulum Swing or Systematic Improvement?

Mark McClellan, M.D., Ph.D.

One reason drugs may be used for years before risks become evident is that we have no active drug-surveillance system.

With almost all prescriptions now processed electronically, and with the availability of increasingly detailed data on health care utilization and outcomes for insured Americans, we could implement a routine, systematic approach to active population-based drug surveillance that could identify potential safety problems much more effectively and relatively inexpensively.[4] For example, Richard Platt, a professor of ambulatory care and prevention at Harvard Medical School, has noted that with a (now feasible) data network incl
cardiovascu
an electroni
causality wh

Perspective

Protecting the Health of the Public — Institute of Medicine Recommendations on Drug Safety

Bruce M. Psaty, M.D., Ph.D., and Sheila P. Burke, M.P.A., R.N.

N Engl J Med 2006; 355:1753-1755 | October 26, 2006 | DOI: 10.1056/NEJMp068228

FDA-AA: aim to have 100 million lives monitored

http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm

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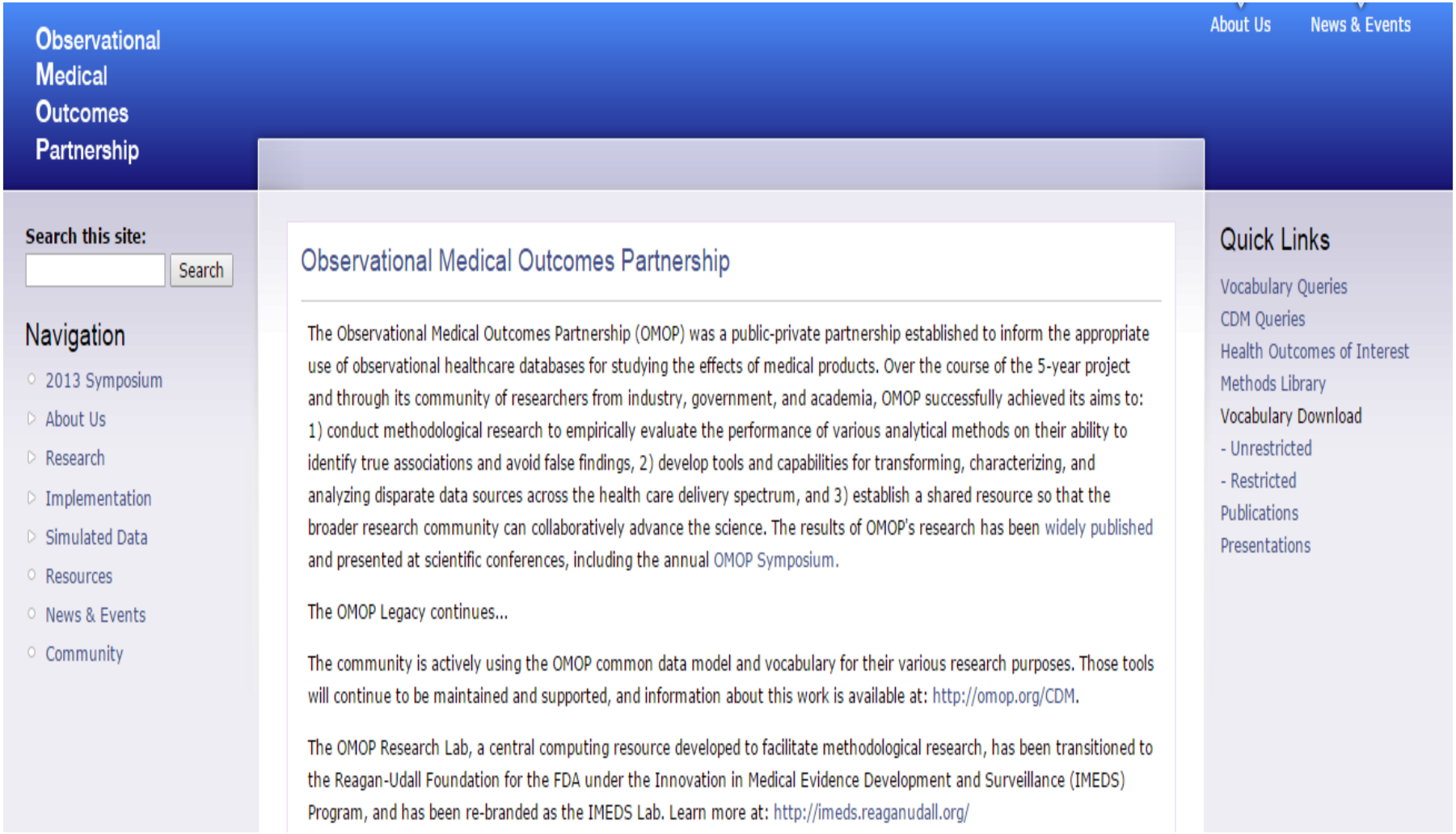
USA: OMOP public private partnership 2008-2013



2013: OMOP investigators established ODHSI community

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Who We Are | Who We Serve | Data Standardization | Software Tools | Resources | Join the Journey

Welcome to OHDSI!

The Observational Health Data Sciences and Informatics (or OHDSI, pronounced "Odyssey") program is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. All our solutions are open-source

http://www.ohdsi.org/who-we-are/mission-vision-values/

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2013: OMOP data in IMEDS

REAGAN - UDALL FOUNDATION FOR THE Food and Drug Administration

Reagan-Udall Foundation for the FDA
1025 Connecticut Ave., NW, Suite 1000 | Washington, DC. 20036
(202) 828-1205 | Comments@ReaganUdall.org

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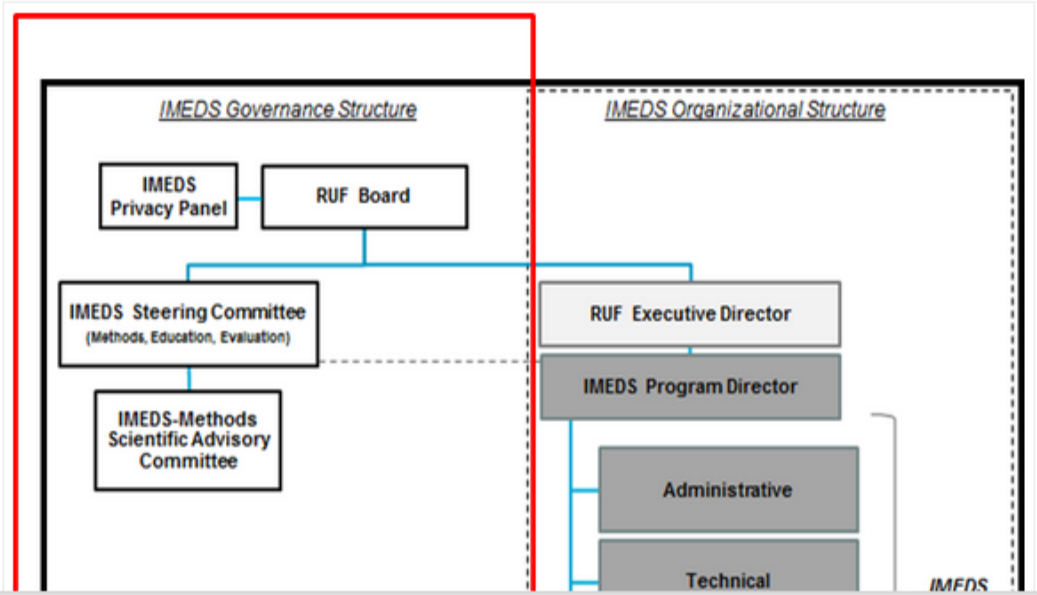
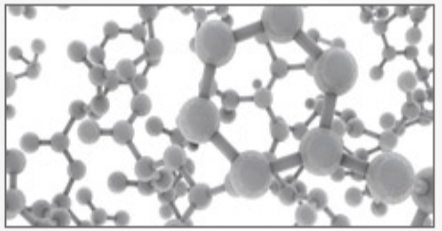
IMEDS Governance Structure

Governance Structure for the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program



IMEDS Charter

IMEDS Governance Structure



Learn More About Our Work

The Reagan-Udall Foundation leads and collaborates on programs, projects and other initiatives that advance its mission in support of the FDA. Find Out More »

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CNODES

CANADIAN NETWORK FOR OBSERVATIONAL DRUG EFFECT STUDIES

HOME ABOUT INVESTIGATORS PROJECTS LINKS CONTACT

Canadian Network for Observational Drug Effect Studies

Committed to rapid and sophisticated analysis

Welcome to CNODES

CNODES Organizational Structure

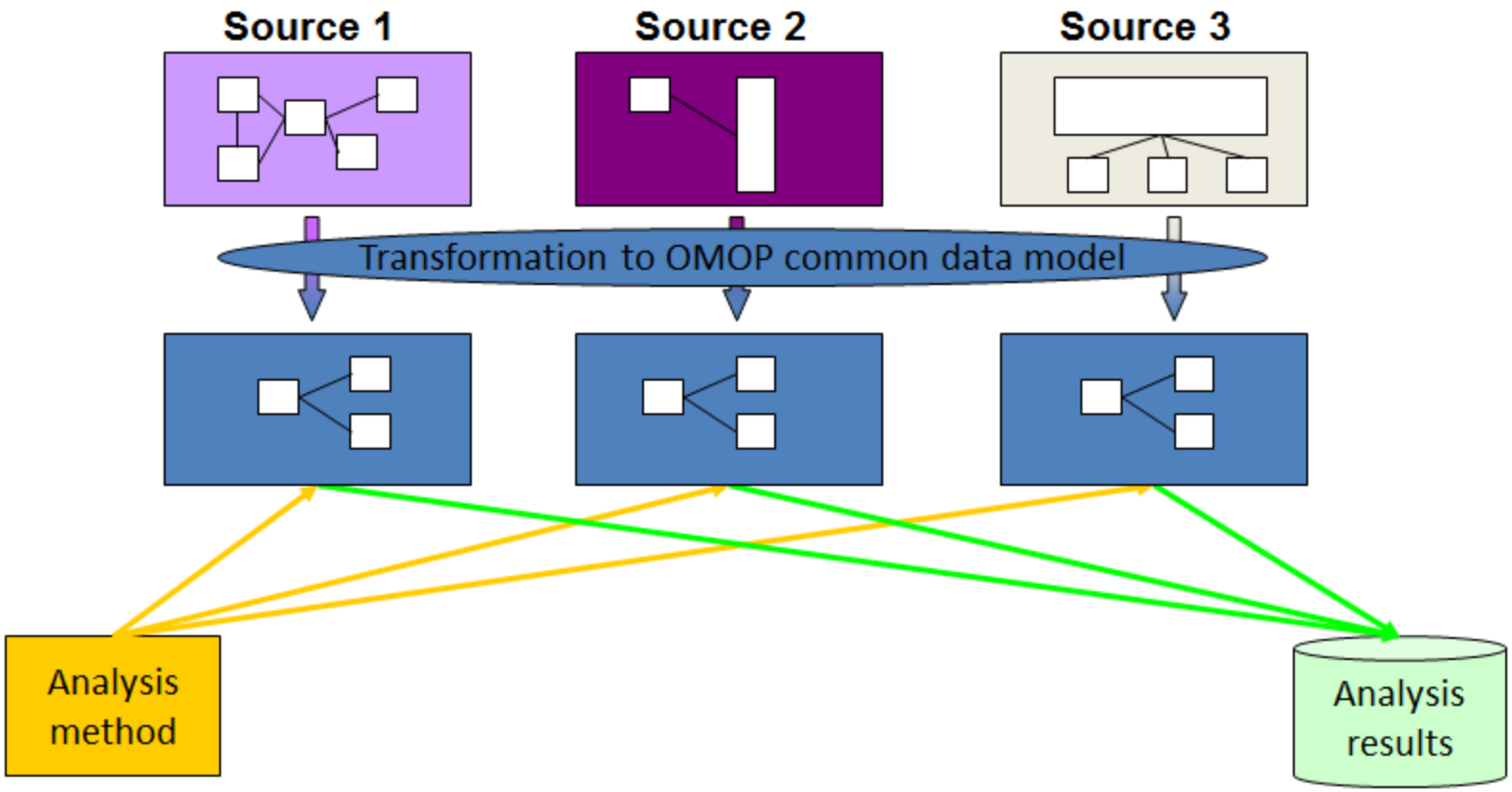
Completed Projects

- High-Dose Statins and the Risk of Acute Kidney Injury
- Proton Pump Inhibitors and the

http://aspennet.asia/aboutus.html

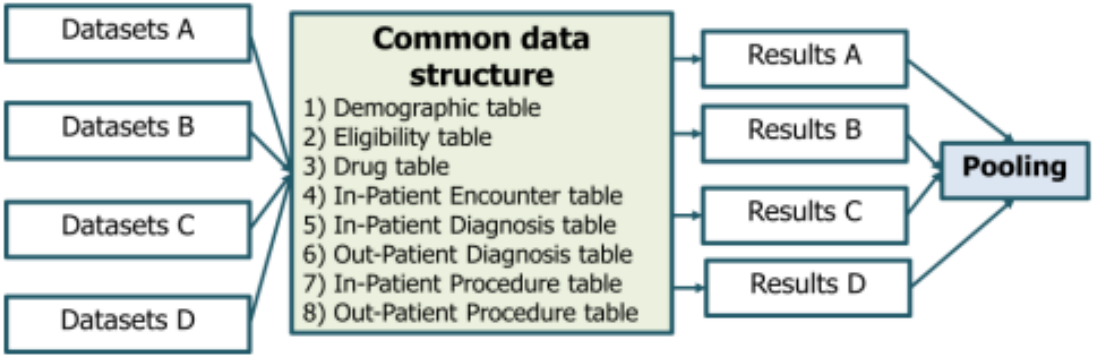
How are data pooled and do people work together?

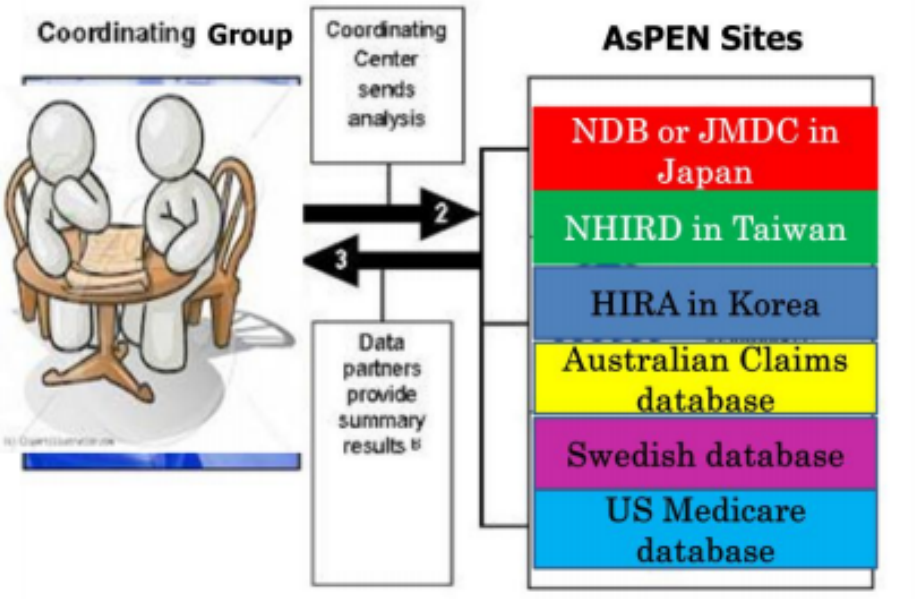
OMOP Common Data Model



What is a Common Data Model (CDM)?

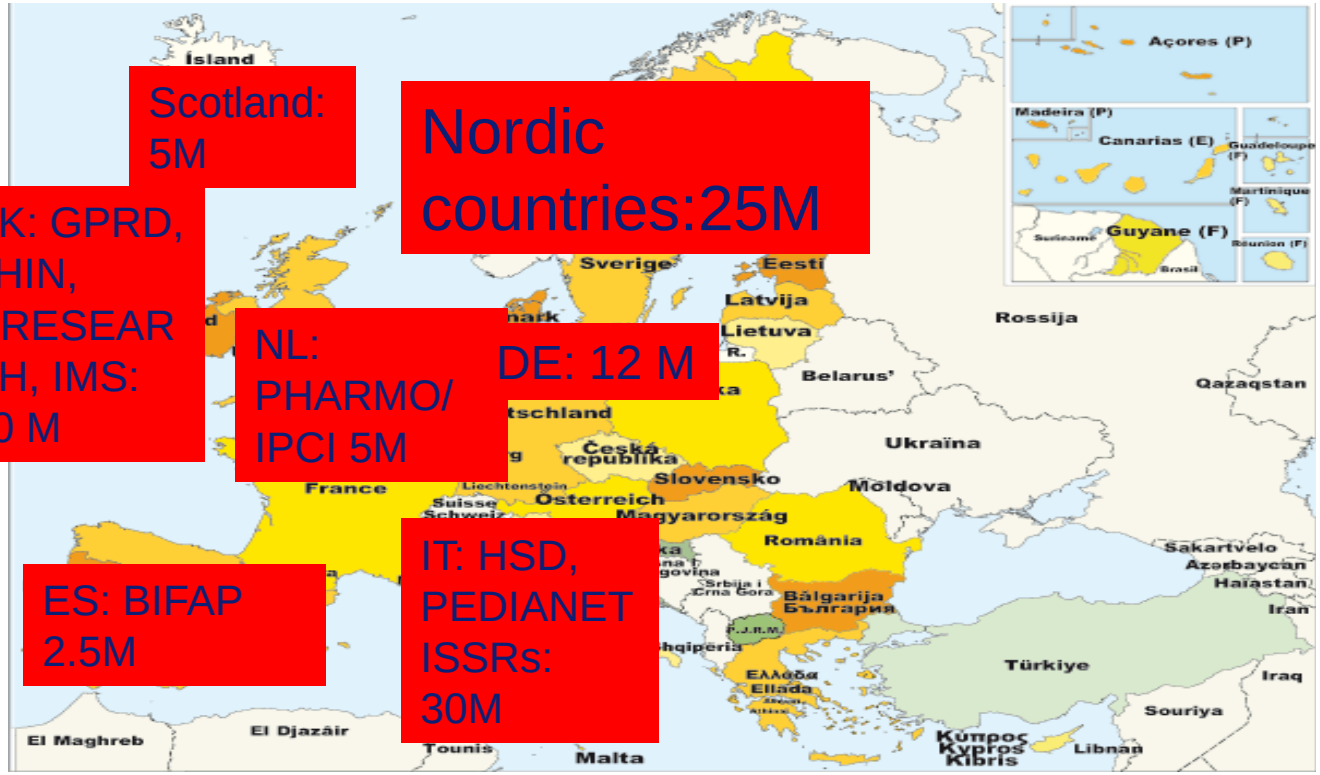
ASPEN: protocol specific common data files





What about Europe?

Do we have healthcare database in the EU?



Total EU population: 456 M
databases on more than 100 M available

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Use of DBs in EU

Most PASS done with DBs in North America!

- Very little EU
- Sometimes THIN/GPRD

Causes

- **Disparate databases**
- **Private / academic / governmental owners**
- **Not easily accessible**
  - **Heterogeneity between countries**
    - Coding /reimbursement of drugs
    - Coding of diseases
    - Language
    - Governance




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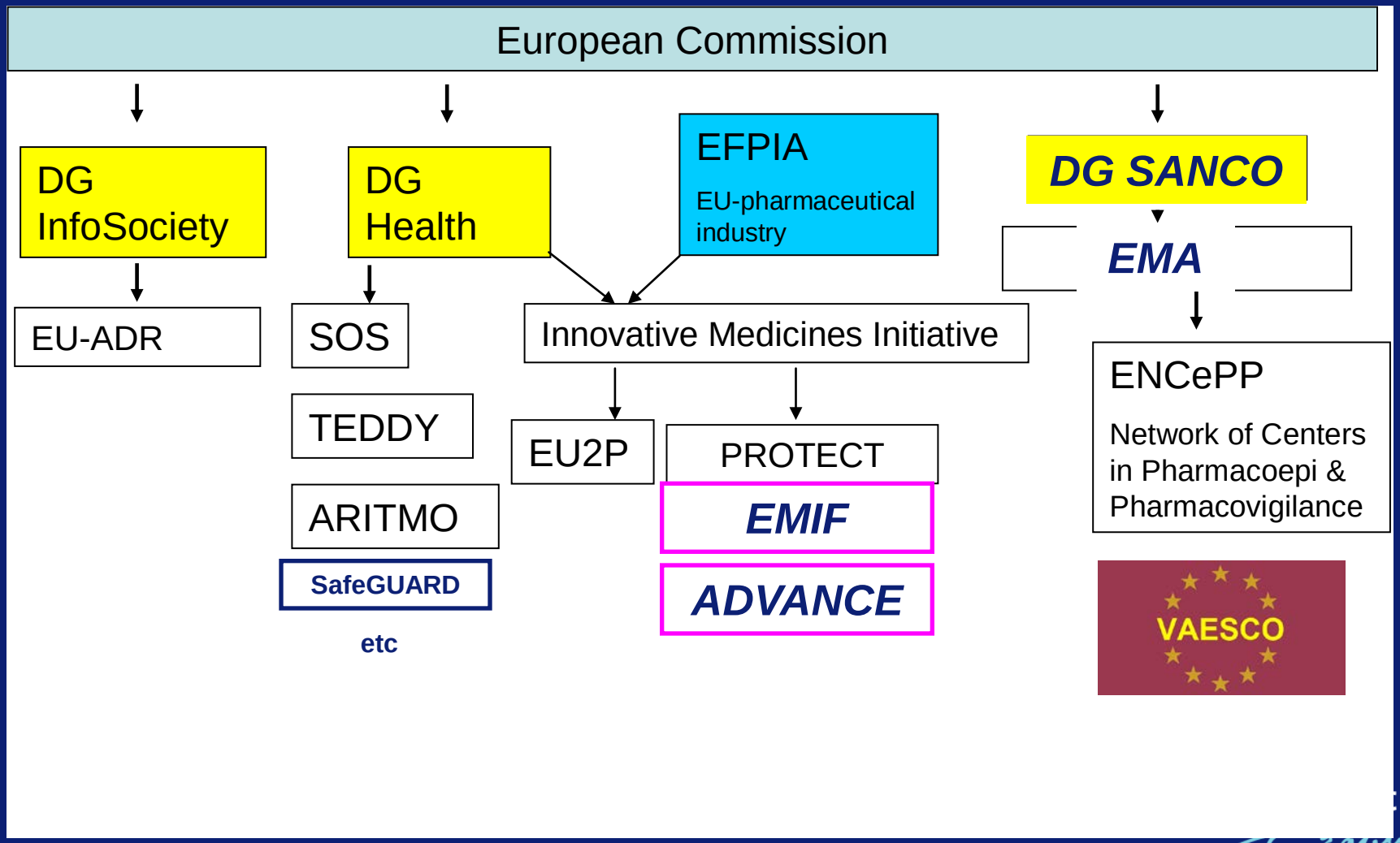
EC /EU Initiatives /projects to have Pan-European networks



2007: First project to link disparate database in EU

Home | Project | Activities | Partners | News | Private Zone | Forums

eu-adr

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

Contact | Links | Job Opportunities

Welcome to the EU-ADR website

The **EU-ADR** project aims to develop an innovative computerized system to detect adverse drug reactions (ADRs), supplementing spontaneous reporting systems. To achieve this objective, **EU-ADR** will exploit clinical data from electronic healthcare records (EHRs) of over 30 million patients from several European countries (The Netherlands, Denmark, United Kingdom, and Italy). In this project a variety of text mining, epidemiological and other computational techniques will be used to analyze the EHRs in order to detect 'signals' (combinations of drugs and suspected adverse events that warrant further investigation). **EU-ADR** is carried out by an interdisciplinary team of researchers who share the ultimate objective to demonstrate that an earlier detection of adverse side effects of drugs is possible by using modern biomedical

eu-adr Alliance

USER LOGIN

Username: *

Password: *

Log in

Request new password

http://euadr-project.org/

How to combine data in EU?
Dealing with EU heterogeneity

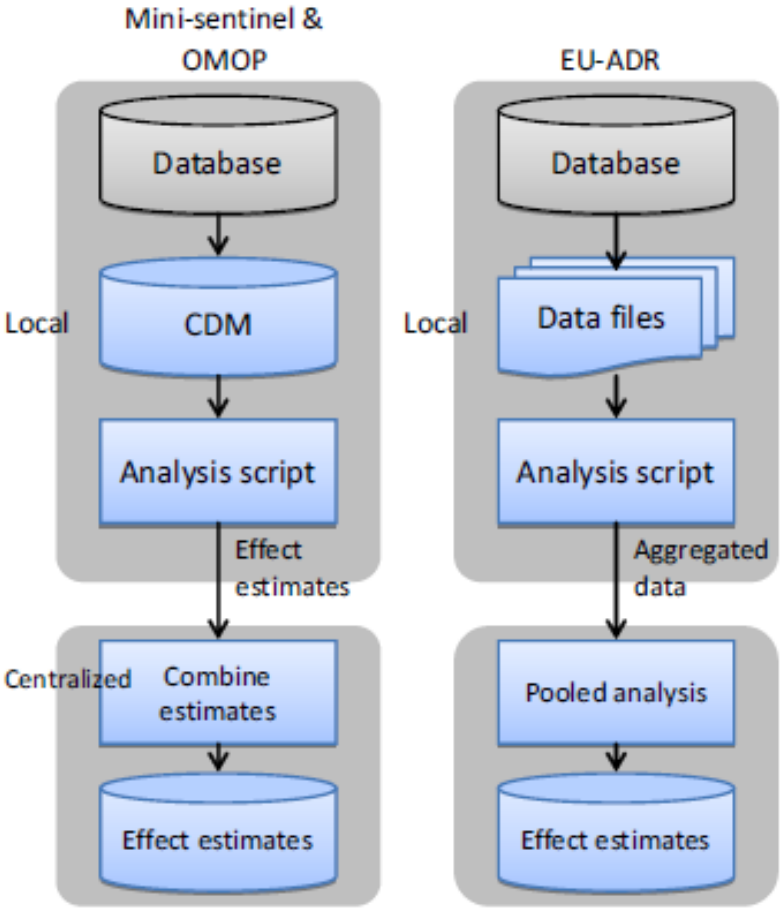
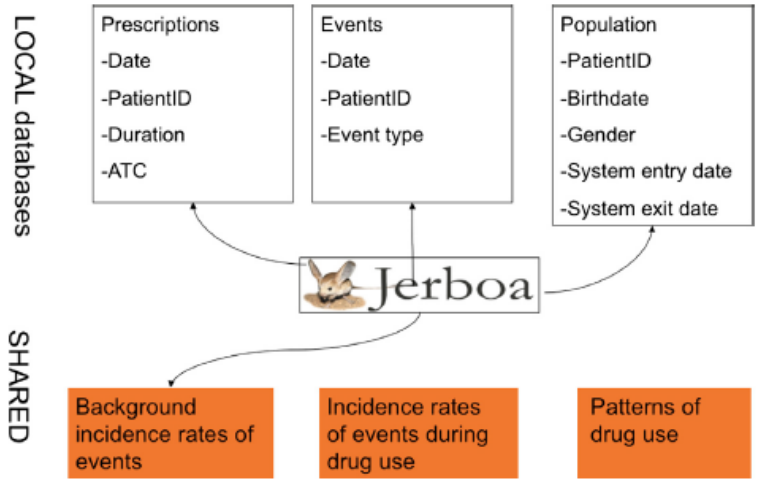


Fig. 1 *Distributed analysis architecture in Mini-Sentinel and Observational Medical Outcomes Partnership as compared with Exploring and Understanding Adverse Drug Reactions (EU-ADR).*

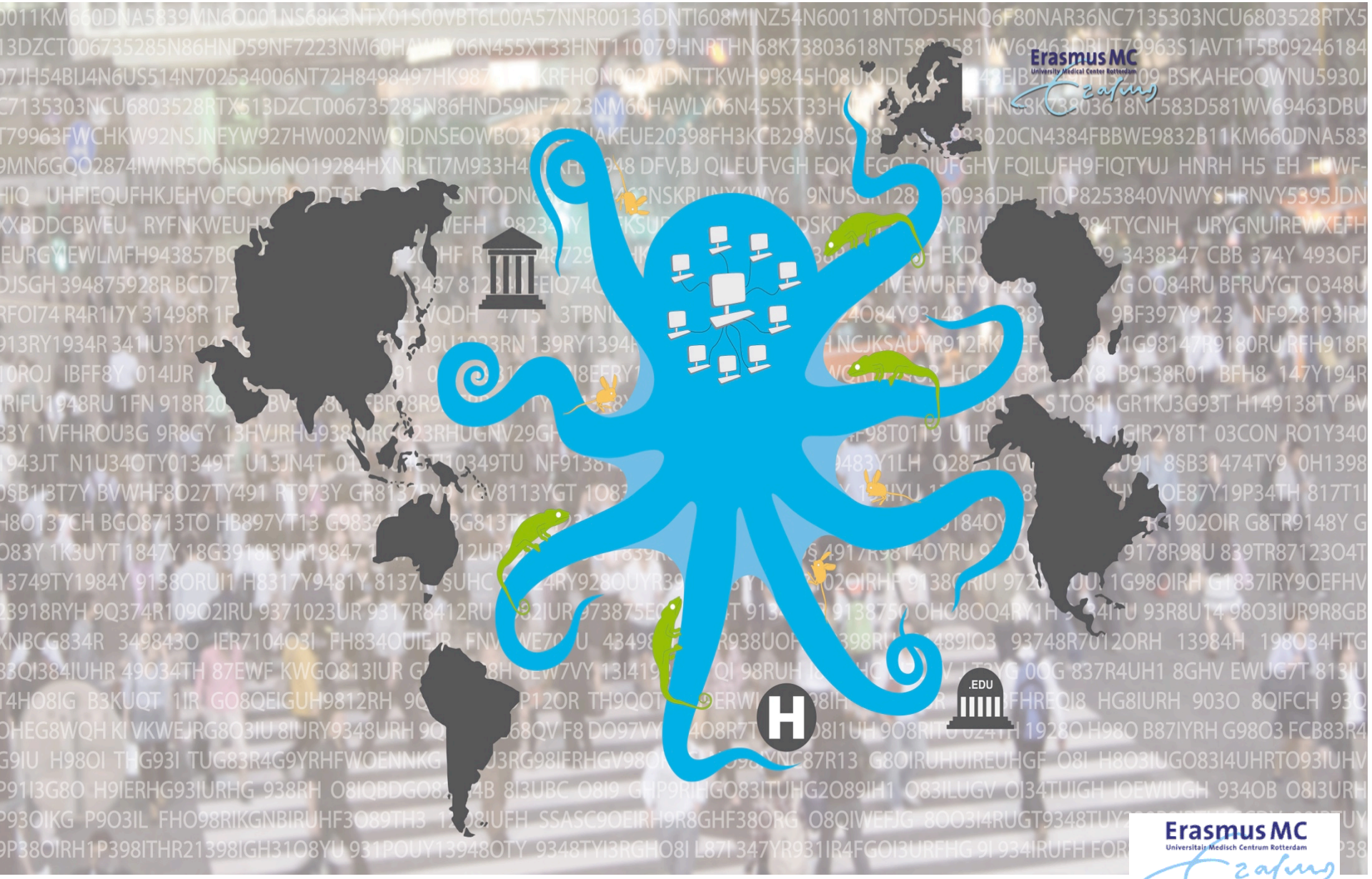


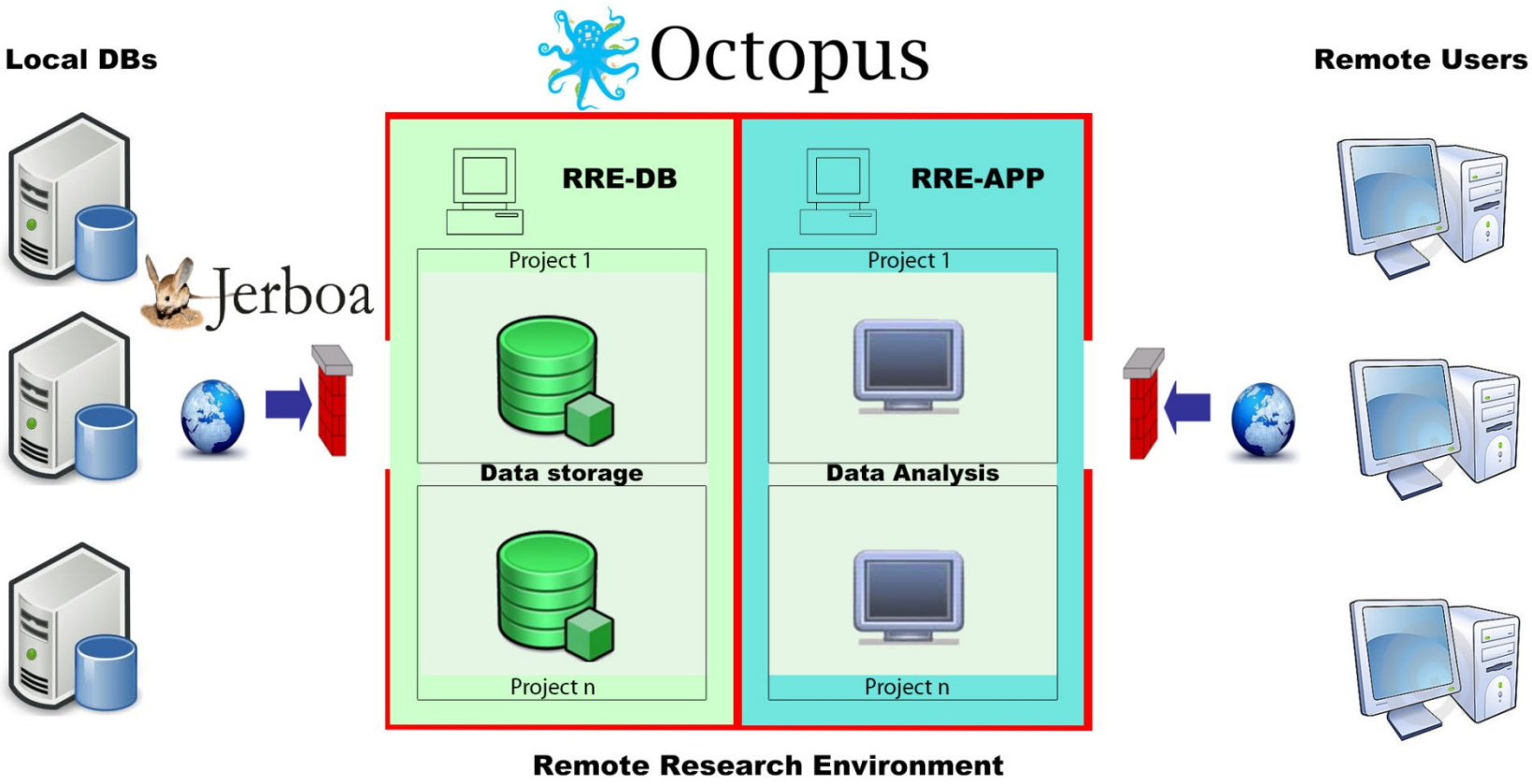
Review
Journal of INTERNAL MEDICINE
Click here for more articles from the symposium
doi: 10.1111/joim.12159

Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how?

G. Trifirò[1,2], P. M. Coloma[1], P. R. Rijnbeek[1], S. Romio[1,3], B. Mosseveld[1], D. Weibel[1], J. Bonhoeffer[4,5], M. Schuemie[1,6,7], J. van der Lei[1] & M. Sturkenboom[1]

Tools for collaborative studies





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Subsequent studies

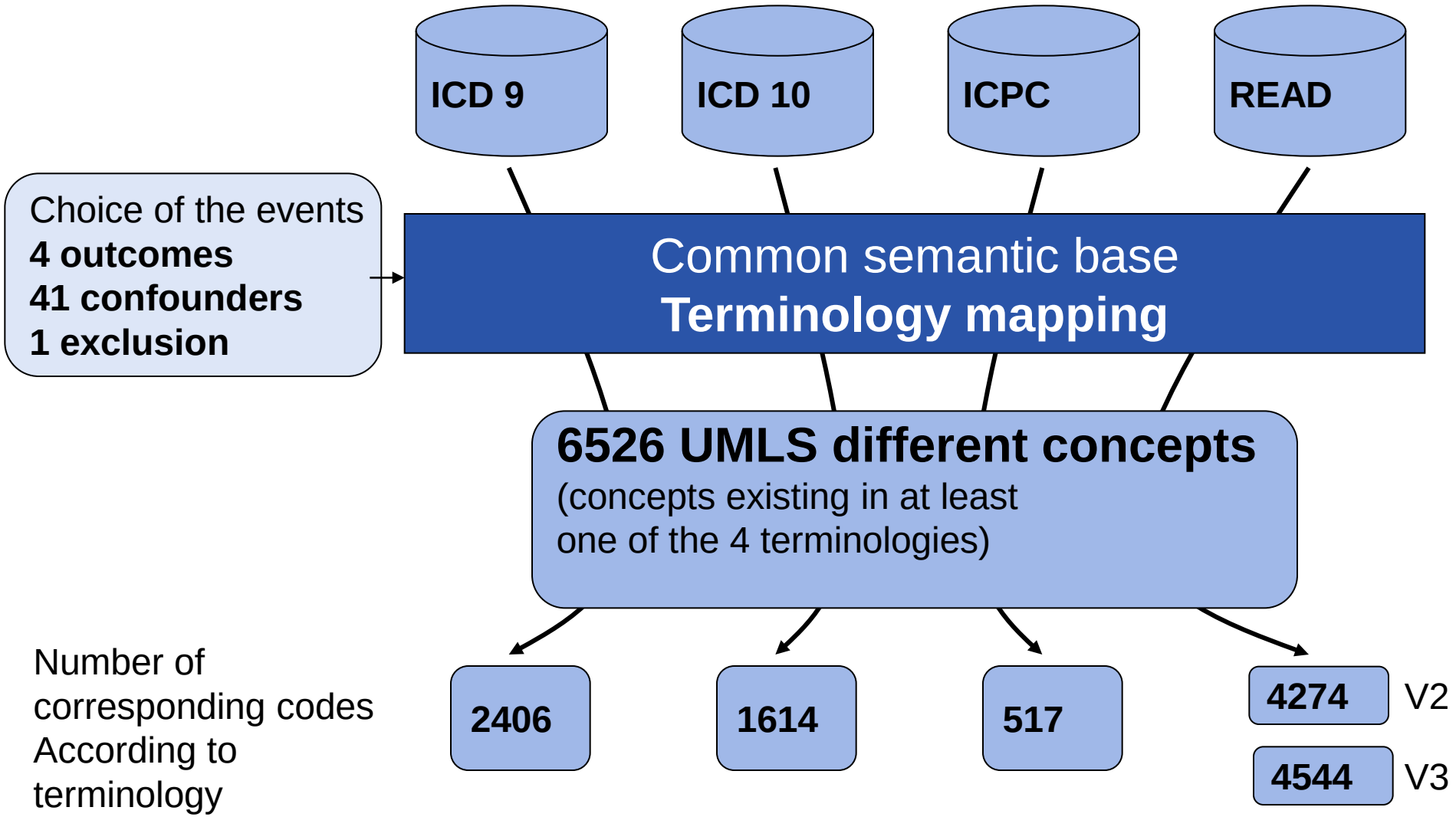
Drug Safety hypothesis testing

‘industrialization of processes’

EC funded study

- Safety of NSAIDs study requested by EMA
  - Collaborative study
  - 7 Health care databases: 4 countries
  - Common protocol
  - Same software

Terminology Mapping

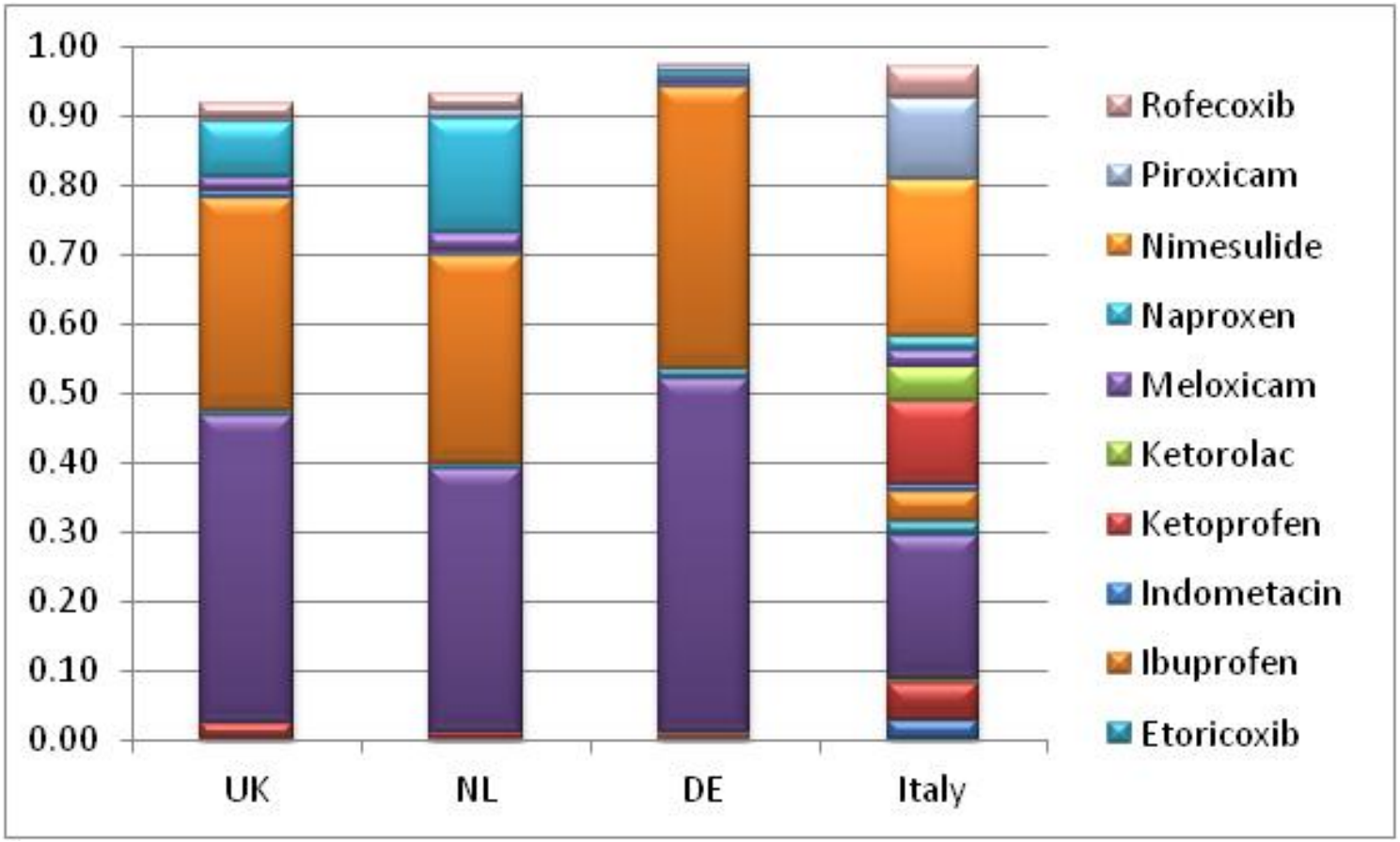


PARTICIPATING DATABASES IN SOS STUDY

Country	Database	Record System	Study Period	Number of Patients	Person-Years of Observation
Germany	GePaRD	Administrative	2005-2008	13,725,003	35,464,659
Italy	SISR-LOMBARDY	Administrative	2000-2008	7,612,788	57,847,589
	OSSIFF	Administrative	2000-2008	2,963,407	21,790,769
	PEDIANET	General Practice (Pediatricians)	2000-2010	221,115	1,064,867
Netherlands	PHARMO	Record Linkage	1999-2008	2,168,518	13,389,217
	IPCI	General Practice	1999-2011	1,009,275	2,655,991
UK	THIN	General Practice	1999-2008	4,816,668	23,166,431
Total:				**32.5 mio.**	**155 mio.**

ADVANTAGE OF COMBINED STUDIES: MORE HETEROGENEITY

Fraction of persontime of exposure to NSAIDs

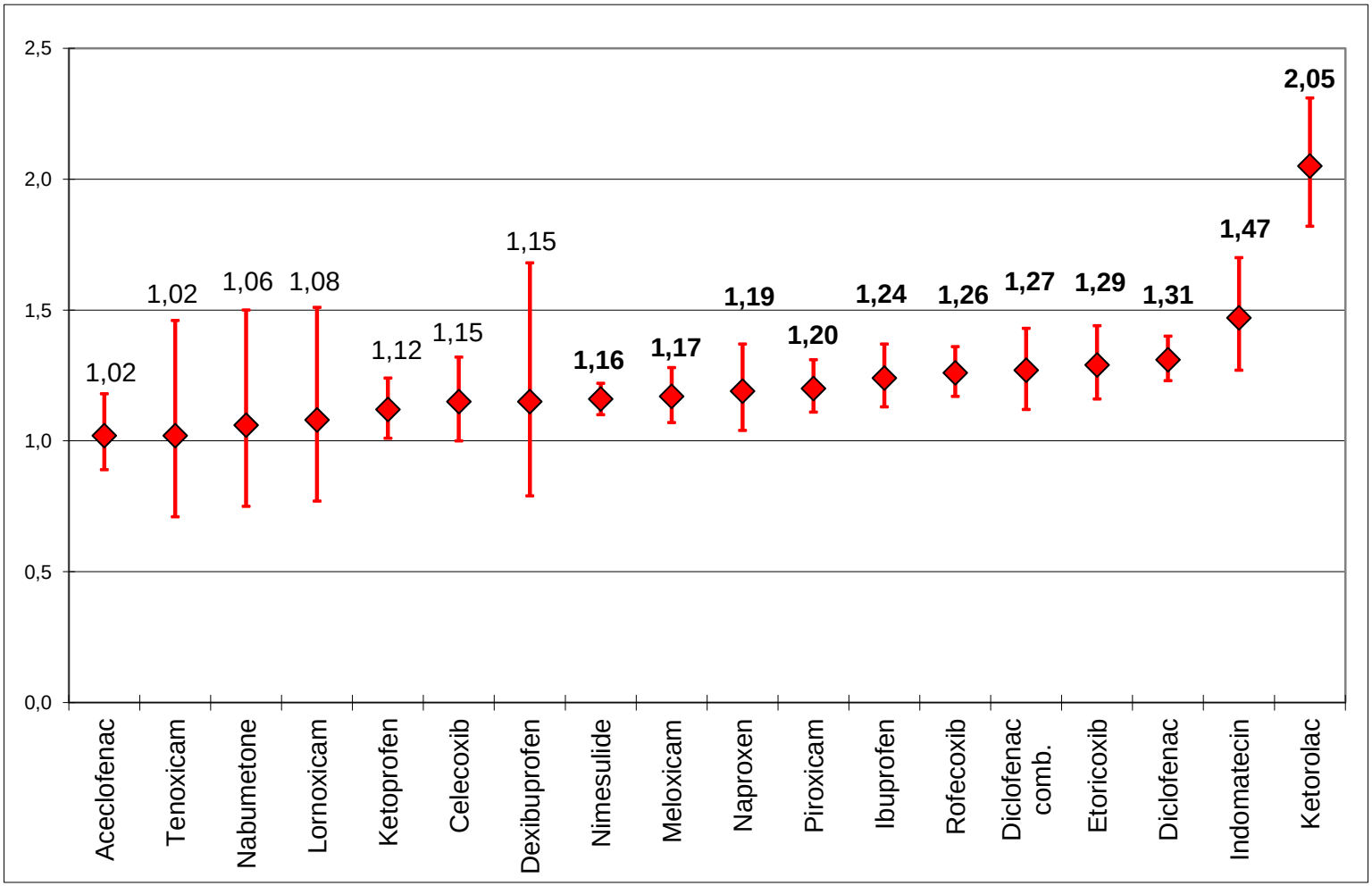


Acute Myocardial Infarction

N= 79,553 cases

18 individual NSAIDs could be studied

Random effect pooled estimates for AMI



Translation of approach to vaccine era

VAESCO

Safety of pandemic influenza vaccine

prof. dr. MCJM Sturkenboom

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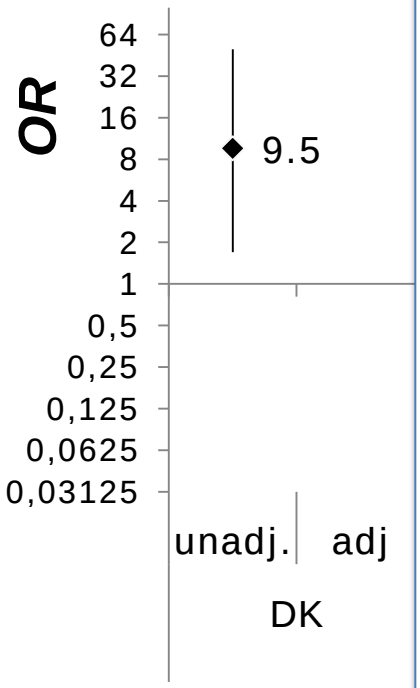
Relative risk of GBS (case control)



BMJ

BMJ 2011;343:d3908 doi: 10.1136/bmj.d3908 Page 1 of 13

RESEARCH

Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe

Jeanne Dieleman *senior pharmacoepidemiologist*[1], Silvana Romio *senior medical statistician*[1], Kari Johansen *senior infectious diseases scientist*[2], Daniel Weibel *senior epidemiologist*[3], Jan Bonhoeffer *consultant in infectious diseases and vaccines*[3], Miriam Sturkenboom *professor of pharmacoepidemiology and medical informatics*[1], and the VAESCO-GBS Case-Control Study Group

[1]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]European Centre for Disease Prevention and Control, ECDC, Stockholm, Sweden; [3]Brighton Collaboration, Basel, Switzerland

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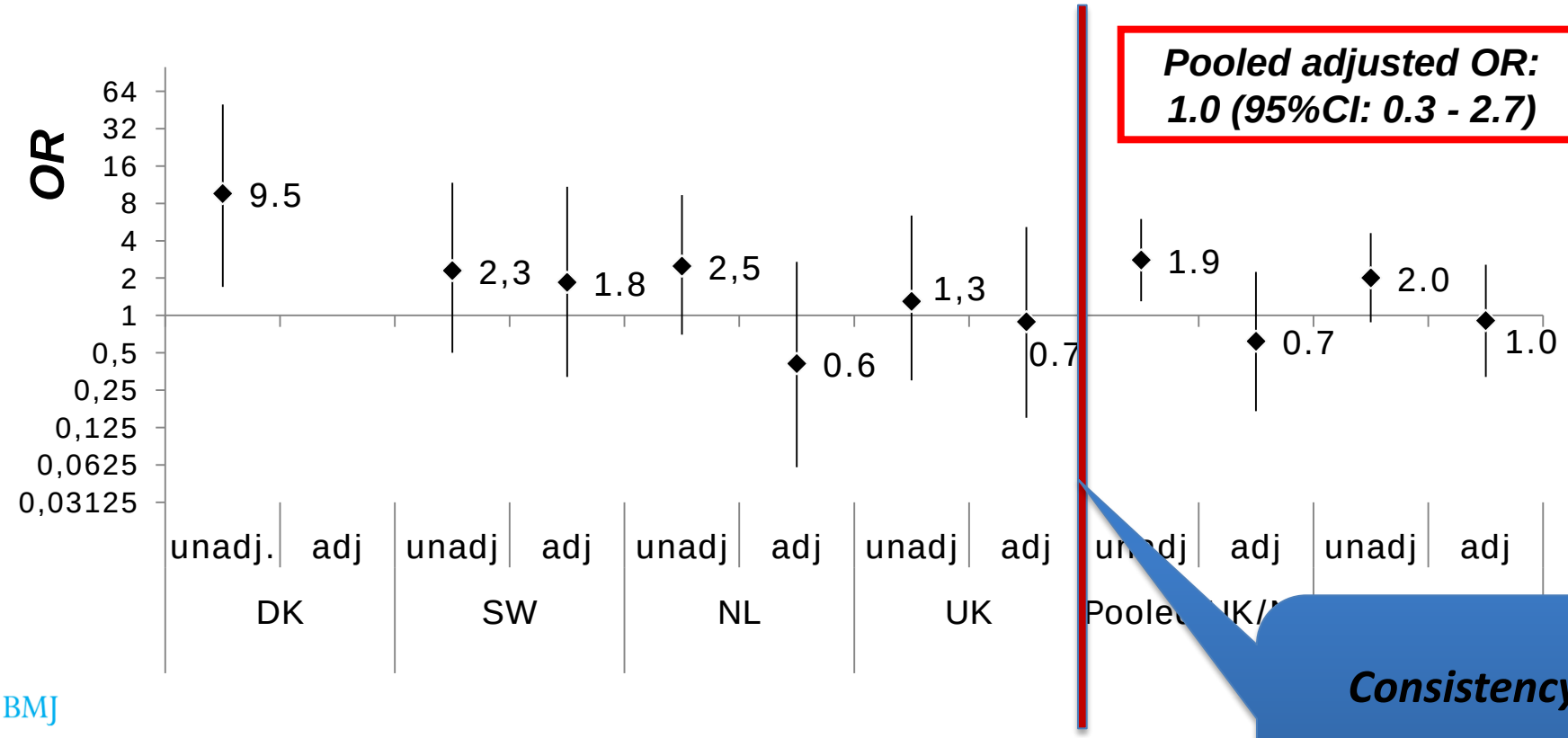
Relative risk of GBS (case control)



Pooled adjusted OR: 1.0 (95%CI: 0.3 - 2.7)

Consistency

Power

BMJ

BMJ 2011;343:d3908 doi: 10.1136/bmj.d3908 Page 1 of 13

RESEARCH

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Nice initiatives/projects but no sustainability

Innovative Medicines Initiative

Innovative Medicines Initiative

The IMI is a unique Public-Private Partnership (PPP) between the pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union represented by the European Commission.

European Medical Information Framework

Coordinator: Bart van Nieuwenhuyse

Our vision

To be the trusted European hub for health care data intelligence, enabling new insights into diseases and treatments

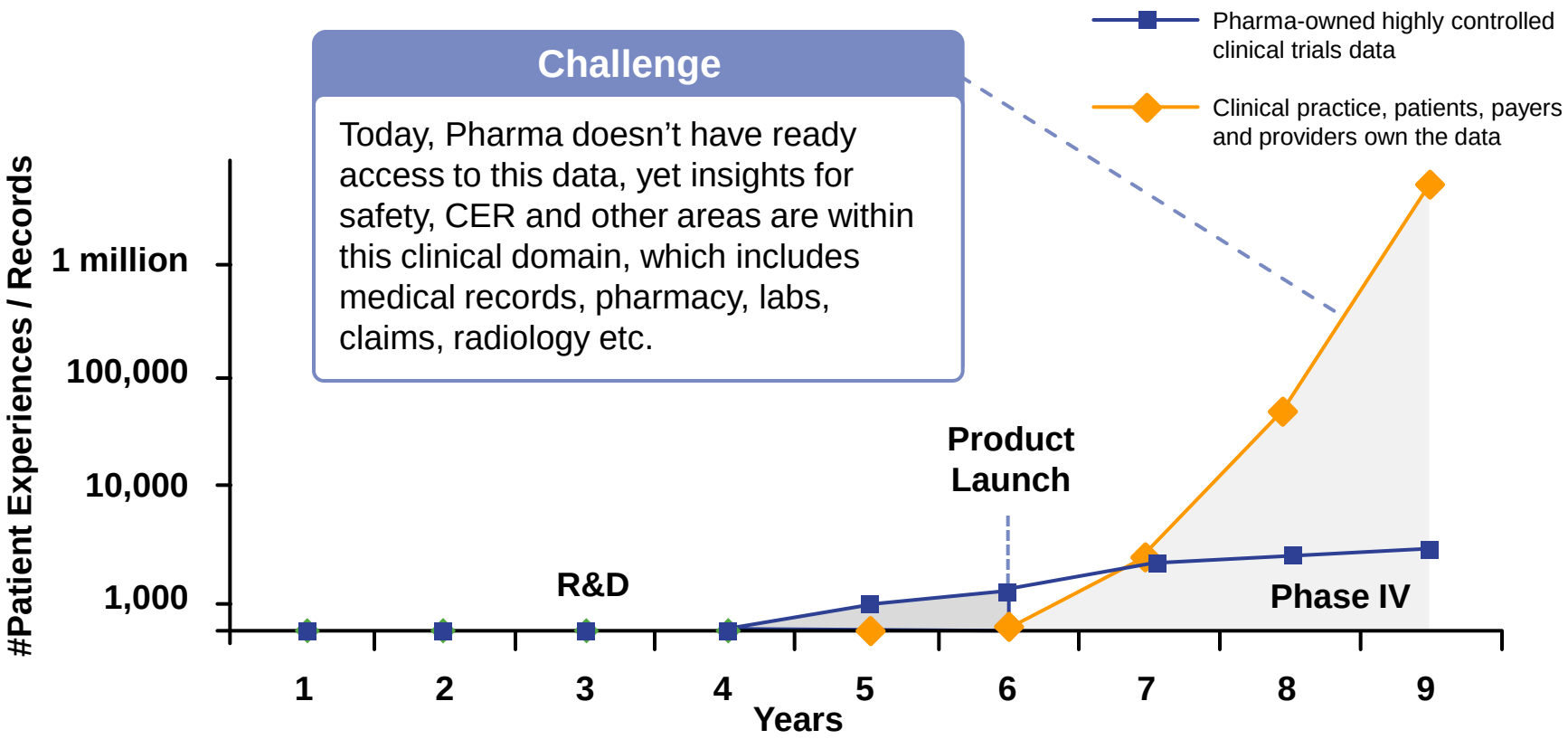
Why is EMIF needed?

Secondary use of health data to enrich research

The “burning platform” for life sciences

Challenge

Today, Pharma doesn’t have ready access to this data, yet insights for safety, CER and other areas are within this clinical domain, which includes medical records, pharmacy, labs, claims, radiology etc.



The value of healthcare data for secondary uses in clinical research and development - Gary K. Mallow, Merck, HIMSS 2012

Why is EMIF needed?

Potential applications of Real World Data

- Biomarker discovery
- Predictive modelling
- Disease insight generation (opportunity identification)

- Trial design and feasibility analysis
- Electronic health record (EHR)-facilitated recruitment
- Prospective cohort selection

- Analysis treatment pathways
- Collection of clinical and economic evidence
- Ongoing efficiency and safety monitoring

Our mission

The EMIF project aims to improve access to human health data for life sciences research. This will be achieved via a three-phase approach:

Knowing	Realise cohort integration and data source profiling to allow meta data browsing
Accessing	Allow searches on aggregated data across different sources and countries within a single point of access
Using	Allow advanced data analysis for specific research questions into the identification and validation of novel biomarkers

Project overview

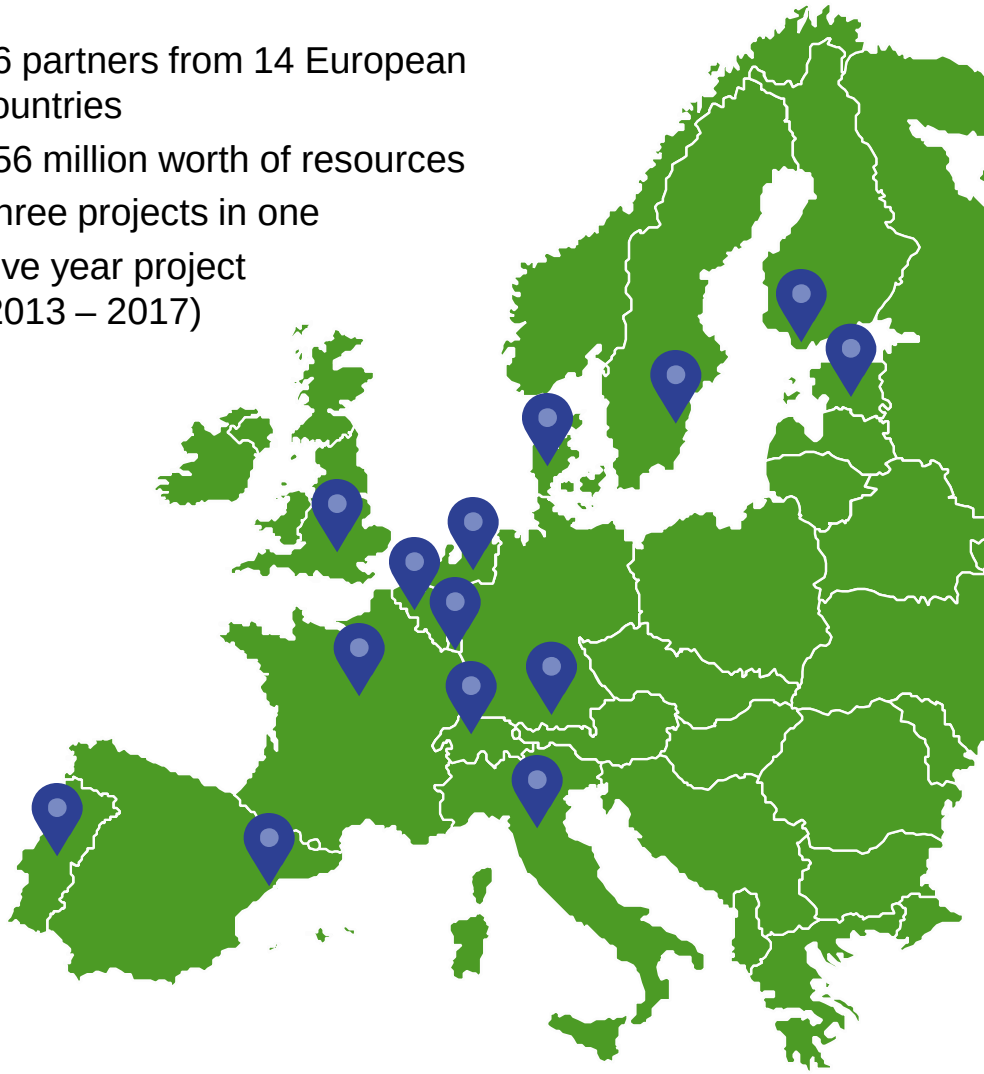
ACADEMIC PARTNERS

SME PARTNERS

EFPIA PARTNERS

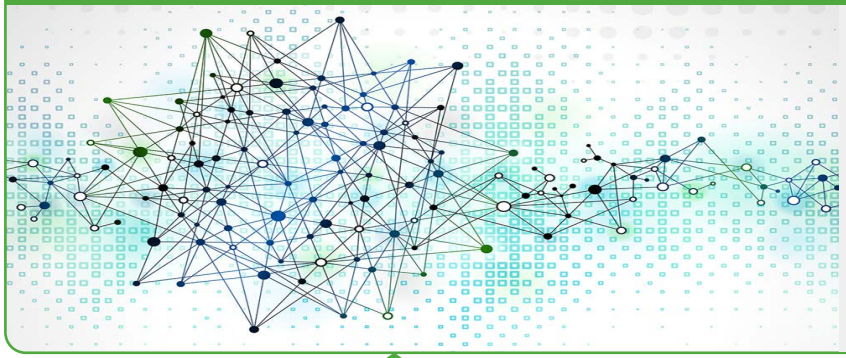
PATIENT ORGANISATION

- 56 partners from 14 European countries
- €56 million worth of resources
- Three projects in one
- Five year project (2013 – 2017)



Project objectives

EMIF-Platform

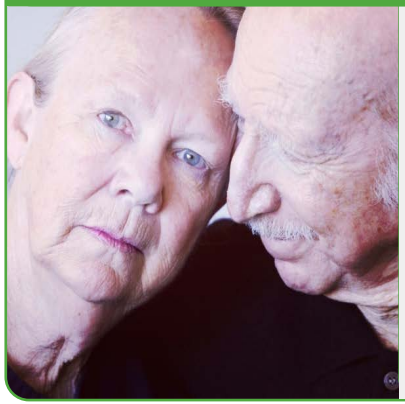


Develop a framework for evaluating, enhancing and providing access to human health data across Europe, support EMIF-Metabolic and EMIF-AD (the specific topics below) as well as support research using human health data in general

EMIF-Metabolic

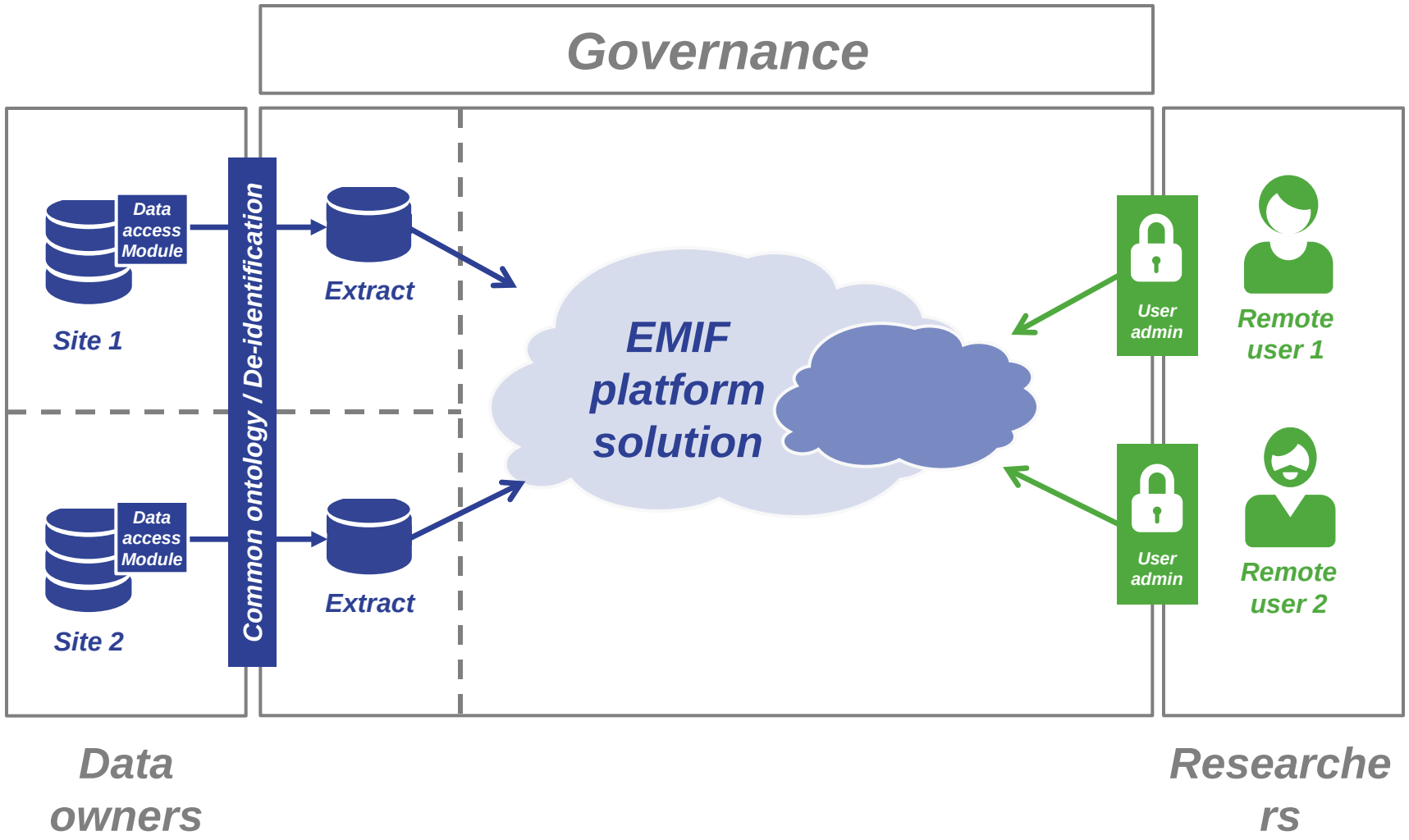
Identify predictors of metabolic complications in obesity, with the support of EMIF-Platform

EMIF-AD

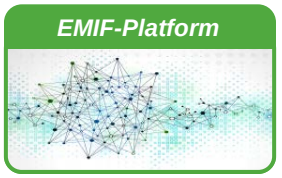


Identify predictors of Alzheimer's Disease (AD) in the pre-clinical and prodromal phase, with the support of EMIF-Platform

EMIF system overview



Data available through consortium

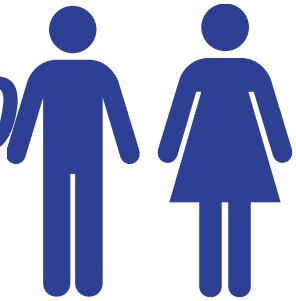


- Large variety in “types” of data

Primary care data sets | *Hospital data* | *Administrative data* | *Regional record-linkage systems* | *Registries and cohorts (broad and disease specific)* | *Biobanks*

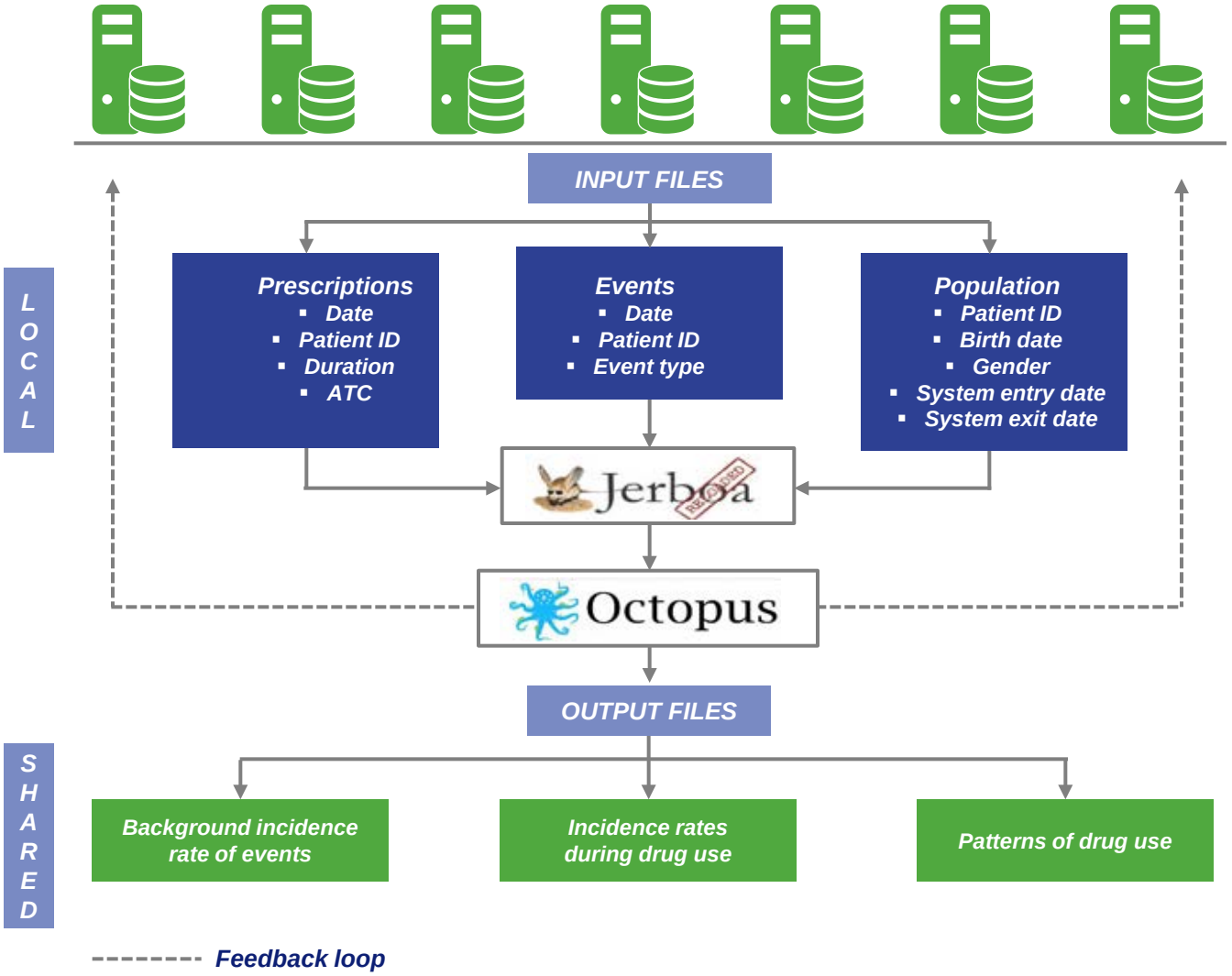
- Data is available from more than 53 million subjects from seven EU countries, including

25,000 ***subjects in AD cohorts***



more than ***94,000*** ***subjects in metabolic cohorts***

Primary data extraction



ADVANCE

Accelerated **D**evelopment of **VA**ccine be**N**efit-risk **C**ollaboration in **E**urope

Coordination team

Miriam Sturkenboom (EMC, coordinator)

Vincent Bauchau (GSK, EFPIA coordinator)

Jan Bonhoeffer (UNIBAS, Managing Entity)

Eva Molero (SYNAPSE, project management)

Innovative Medicines Initiative

efpia

After 2009 pandemic it was recognized that

- Rapid benefit & risk monitoring vaccines necessary component to maintain public confidence
- Many stakeholders work in isolation

Call for proposal 2012 by Innovative Medicines Initiative

- IMI funded project (5 million EC & 5 million in kind EFPIA)

- Unique collaboration (public private): 19 countries
  - European Centre for Disease Prevention and Control (ECDC)
  - European Medicines Agency (EMA)
  - National public health bodies:11
  - National regulators: 10
  - Vaccine manufacturers (GSK, Novartis, Sanofi Pasteur, SP MSD, J&J (Crucell), Pfizer, Takeda)
  - SMEs (P95, SYNAPSE)
  - Academic institutions: 9

- Start date: October 2013
- Duration: 5 years

VISION

- “Best evidence at the right time to support decision-making on vaccination in Europe.”

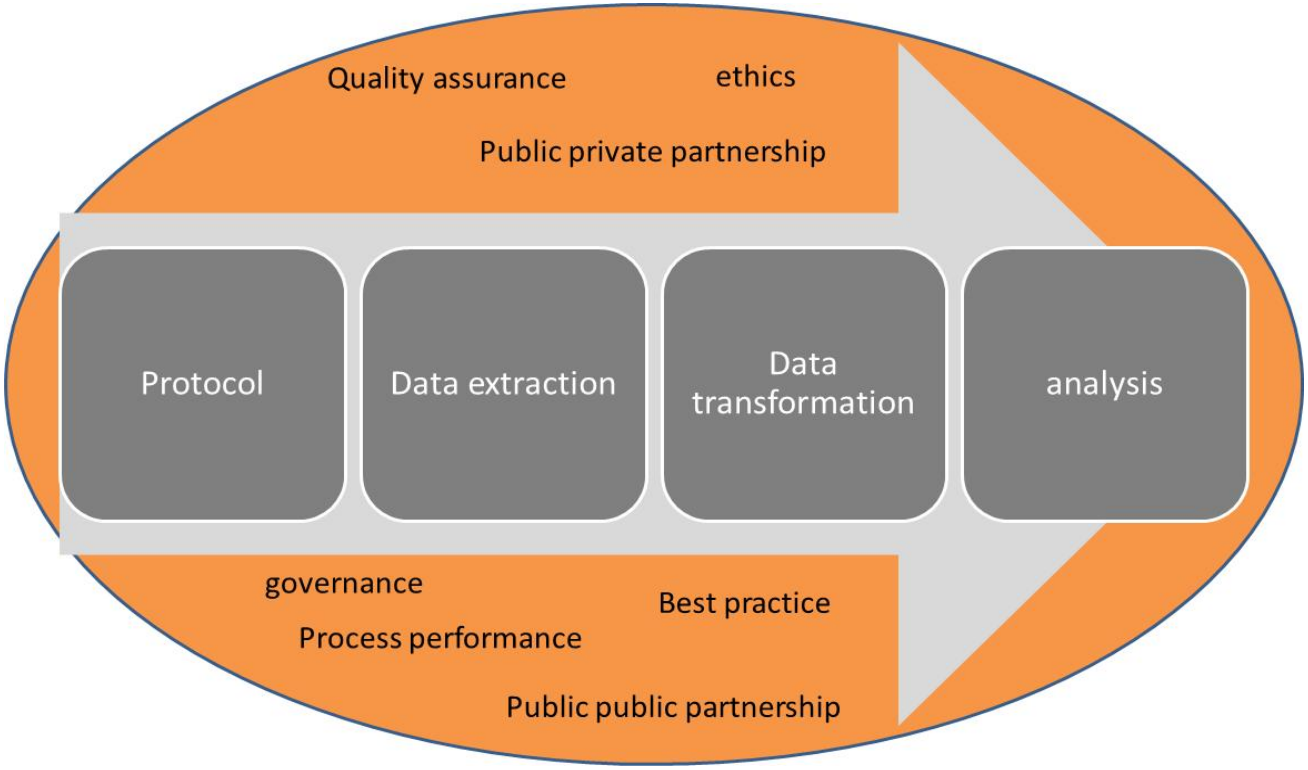
ADVANCE

MISSION

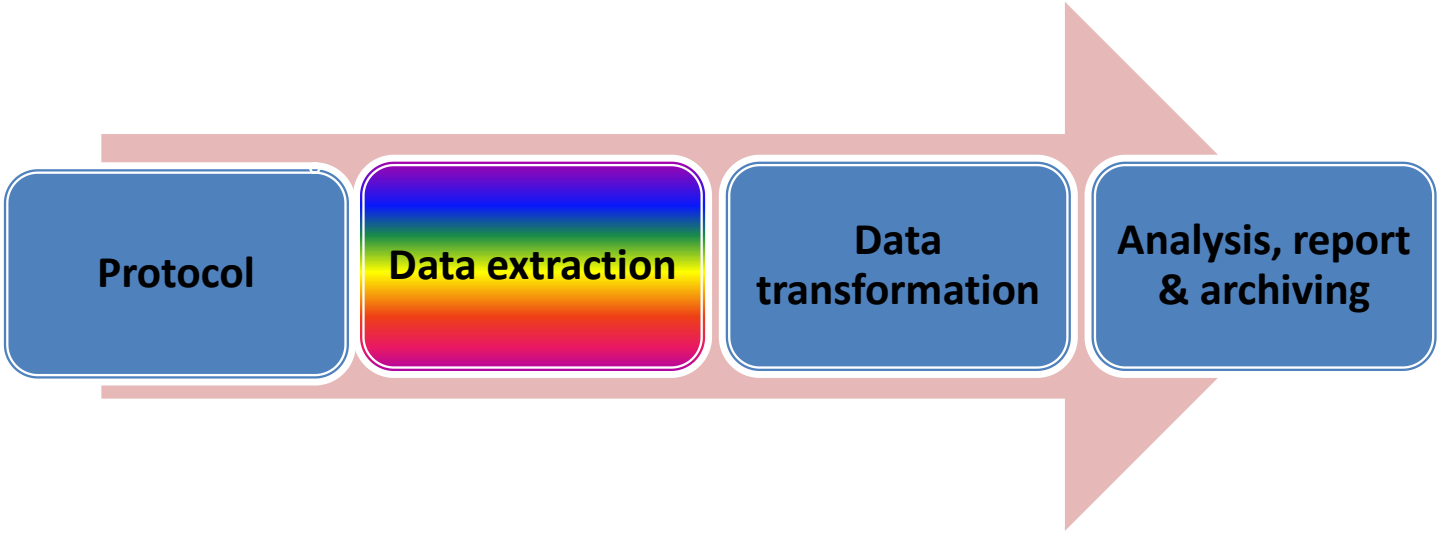
To establish a prototype of a sustainable and compelling system that rapidly provides best available scientific evidence on vaccination benefits and risks post-licensure for well informed decisions.

This will be achieved by developing and testing a code of conduct, rules of governance, technical infrastructures, data sources, methods, and workflows in a European network of stakeholders.

KEY ACHIEVEMENTS: AGREED WORKFLOW

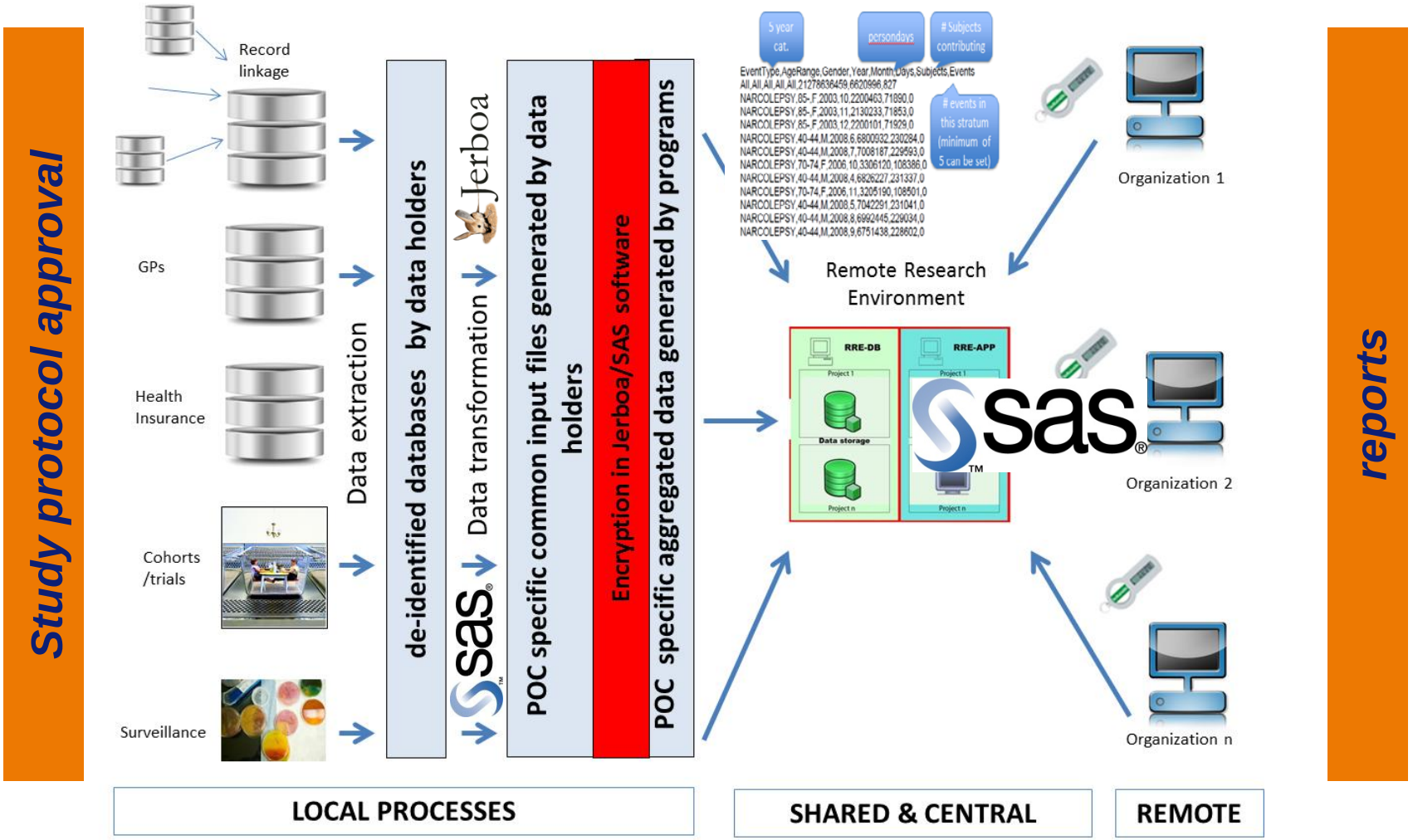


KEY ACHIEVEMENTS: AGREED WAY TO GENERATE EVIDENCE



PRISM, SENTINEL, VSD

ADVANCE Analysis



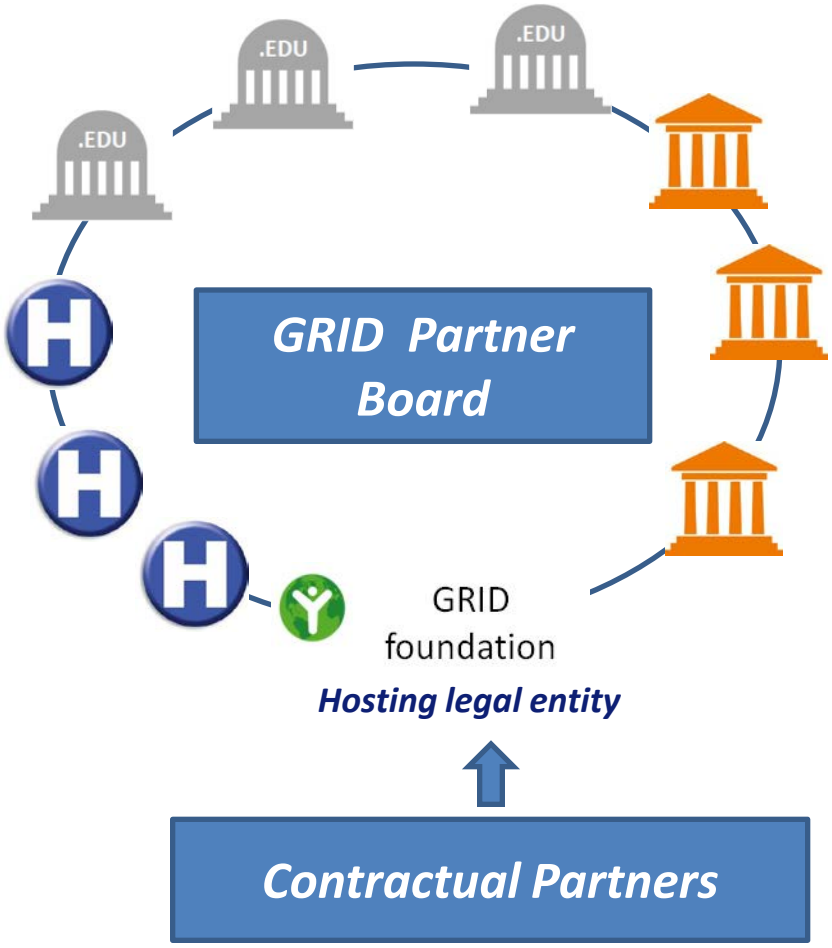
Legacies so far

The EU-ADR Alliance has the main goal of running studies and answering drug safety questions from members and external organisations in a collaborative and federated manner, in those cases where the participation of more than one database is required.

It is also devoted to maintenance and continuing improvement of the EU-ADR system.

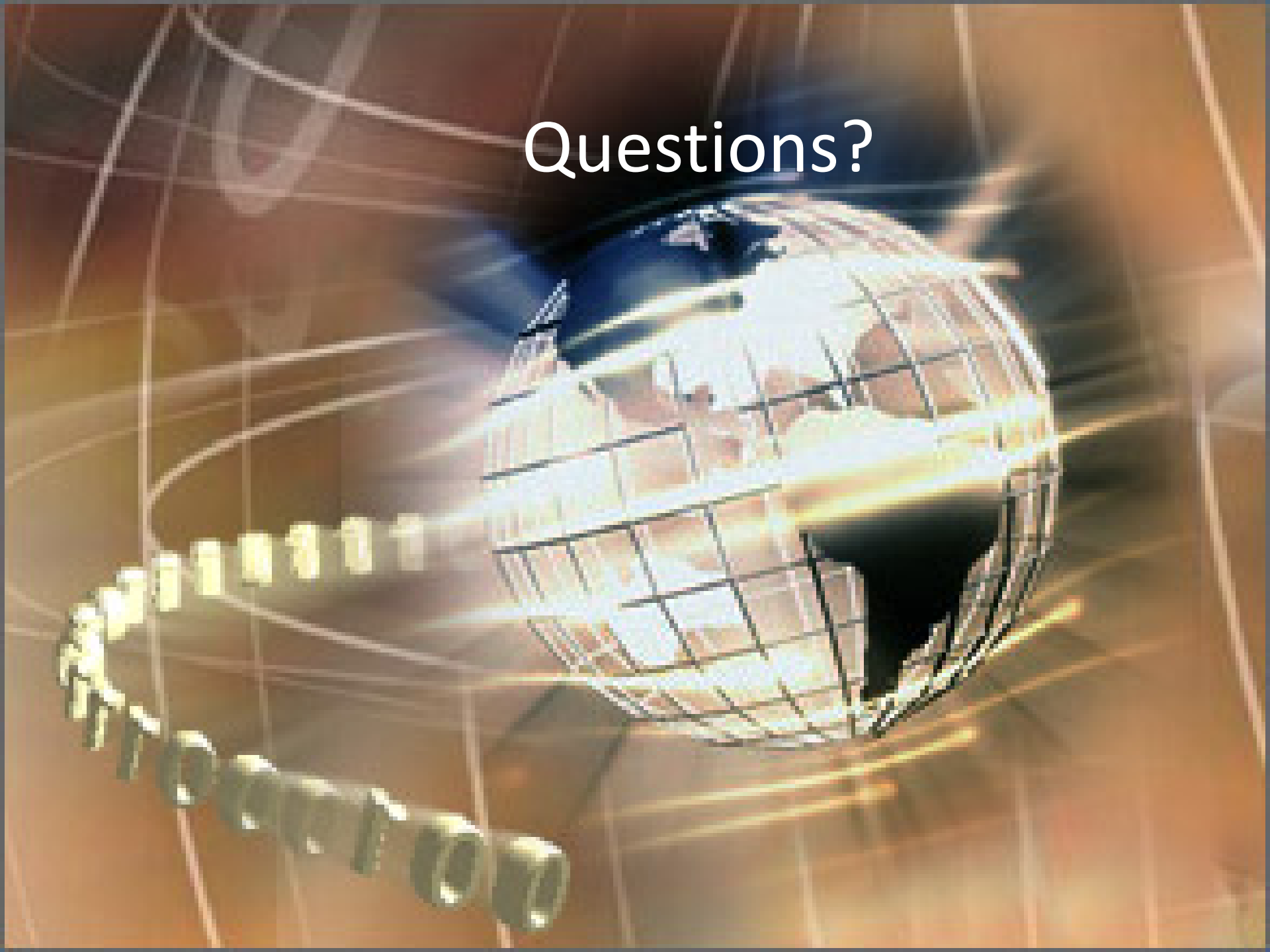
Information EU-ADR ALLIANCE management office: emolero@synapse-managers.com

VACCINE.GRID: Global Resource of Immunization Outcome Data



http://vaccinegrid.org/public.html

Erasmus MC
Universitair Medisch Centrum Rotterdam


Questions?