

Pharmacovigilance: Towards an Integrated Approach

Place : Auditório do INFARMED, I.P. - Edifício Tomé Pires

6 • June • 2024

REAL WORLD DATA IN PHARMACOVIGILANCE

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Scientific coordinator of the spin-off «INnovative Solutions for medical Predictions and big data Integration in REal world setting»- INSPIRE



Disclaimer and declaration of conflict of interest

- Full-time employee of University of Verona/AOUI Verona
- Declared conflicts of interest:
 - ✓ Participation to advisory boards and seminars on topics not related to this presentation and sponsored by the following pharmaceutical companies in the last two years: Eli Lilly; Sanofi; Amgen; Novo Nordisk; Sobi; Gilead; Celgene; Daikii Sankyo
 - ✓ Scientific coordinator of the UNIVR academic spin-off INSPIRE that carried out in the last two years observational studies/systematic reviews on topics not related to the content of this presentation and which were funded by PTC Pharmaceuticals, Kiowa Kirin, Shonogi, Shire Chiesi and Daiichi Sankyo

Agenda

- **Where do we stand in Pharmacovigilance?**
- What type of (and how much) real world data for signal management?
- Integration of information from SRS and longitudinal healthcare databases

Disaster-driven pharmacovigilance

N Engl J Med 363;9

Revisiting the Rosiglitazone Story —

Clifford J. Rosen, M.D.

In July 2007, 24 members of the Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) and the Drug Safety and Risk Management Advisory Committee of the Food and Administration (FDA) held meeting, which I chaired concluded that rosiglitazone insulin-sensitizing agent used in treating type 2 diabetes may be associated with an increased risk of myocardial infarction. This conclusion was based on concordant evidence from

of the joint advisory committee met for 20 hours to further advise the rosiglitazone. Ultimately, the committee agreed that the

Expert Opinion

JAMA®

Online article and related content current as of December 12, 2008.

BMJ 2007;334:120

WHAT HAVE WE LEARNT FROM

View?

General

Controversy surrounding the safety of cerivastatin

Michael H Davidson

Chicago Center for Clinical Research, 515 North State Street, Suite 2700, Chicago, IL 60610, USA & Rush-Presbyterian-St Luke's Medical Center, Chicago, IL, USA

The noted myotoxicity and subsequent withdrawal of cerivastatin from the worldwide market in August 2001 has demonstrated that the safety of statins is not a class effect. The total rhabdomyolysis rate for cerivastatin was 16 – 80 times more frequent than with other statins without providing additional efficacy. Cerivastatin has a pharmacokinetic profile (high potency, bioavailability, lipophilicity and renal excretion) that is different from other statins, which may explain the high myotoxicity rate. The cerivastatin experience has also provided insights into high-risk populations (i.e., the elderly, women, those with renal impairment, co-administration of interacting drugs) that are more prone to statin-induced myopathy. Ultimately, the lessons learned from this experience may significantly improve the safety of statin use in the future.

Keywords: myopathy, safety, statin

Expert Opin. Drug Saf. (2002) 1(3):207-212

Pharmacovigilance 1.0

- “Do we observe what we expect?”
- Key = disproportionality
- Ed Napke (1968)
 - Pigeon hole system
- Computerised
 - Data mining
 - First proposed in 70s
 - FDA started in 80s



Courtesy of Bruno Stricker

Pharmacovigilance 2.0

The screenshot shows the 'Segnalazione online' (Online Reporting) page of the Vigifarmaco system. The browser address bar shows 'maco.it/report/reports/new'. The page title is 'Segnalazione online di sospetta reazione avversa da farmaci'. The 'Paziente' (Patient) tab is selected and highlighted with a red circle. The form fields include: 'Iniziali' (text input), 'Data di nascita' (Day, Month, Year dropdowns), 'Età' (text input and 'Seleziona...' dropdown), 'Sesso' (Male/Female radio buttons), 'Altezza e peso' (Height in cm and Weight in Kg dropdowns), and 'Origine etnica' (dropdown). A 'Nuova' (New) button is located below the 'Condizioni predisponenti e/o concomitanti alla reazione avversa' field. A green sidebar on the right contains a 'Guida alla compilazione' (Filling Guide) with instructions on data entry and privacy. At the bottom, there are 'Prosegui' (Continue) and 'Annulla la segnalazione' (Cancel reporting) buttons.

maco.it/report/reports/new

Vigifarmaco Segnalazione online ▼ Aiuto Profilo di Jessica Pace Esci

Segnalazione online di sospetta reazione avversa da farmaci

Paziente Reazione avversa Farmaci Dettagli aggiuntivi Anteprima

Di seguito sono richiesti i dati anagrafici del paziente, con le iniziali al posto del nome per garantire l'anonimato. Si consiglia la compilazione completa dei campi, ma è comunque obbligatoria la compilazione di almeno uno dei dati tra "data di nascita", "età" o "sesso".

Iniziali

Le iniziali vanno indicate nell'ordine "nome e cognome"

Data di nascita / /

Età Seleziona... ▼

Sesso ☒ Maschio ☐ Femmina

Altezza e peso Altezza in cm Peso in Kg

Origine etnica

Condizioni predisponenti e/o concomitanti alla reazione avversa

Guida alla compilazione

I campi contrassegnati con l'asterisco (*) sono obbligatori.

I dati anagrafici del paziente consentono un'identificazione **parziale** del caso e aiutano ad evitare l'invio di segnalazioni "duplicate" (ovvero già presenti nel sistema).

Nel rispetto della privacy non vanno indicati per intero il nome o il cognome del paziente, ma solo le loro iniziali.

La data di nascita è particolarmente importante in caso di segnalazioni di reazioni avverse da vaccino: infatti le vaccinazioni dell'età evolutiva vengono somministrate, di norma, ad età prestabilita.

Le informazioni su sesso, peso, altezza possono essere utili per compiere degli approfondimenti e analisi specifiche.

Le informazioni sullo stato di gravidanza/allattamento consentono di acquisire dettagli importanti ai fini di individuare le potenziali conseguenze sul feto/neonato.

Pharmacovigilance 3.0?



Certainly! Here are some experts who are known for their expertise in the intersection of AI and pharmacovigilance:

1. Dr. Andrew Bate: Dr. Bate is a leading expert in pharmacovigilance and drug safety with a focus on AI and data mining techniques for adverse event detection and signal management. He has contributed significantly to the development of AI methodologies in pharmacovigilance.
2. Dr. Yvonne Lau: Dr. Lau specializes in pharmacovigilance and AI, particularly in the development and application of AI models and algorithms for drug safety monitoring, signal detection, and risk assessment.
3. Dr. Gianluca Trifirò: Dr. Trifirò is a renowned researcher in pharmacovigilance and

Drug Saf

DOI 10.1007/s40264-017-0592-4



CURRENT OPINION

From Big Data to Smart Data for Pharmacovigilance: The Role of Healthcare Databases and Other Emerging Sources

Gianluca Trifirò^{1,2} · Janet Sultana^{1,2} · Andrew Bate^{3,4}

pharmacovigilance. He has conducted research on the use of AI techniques and data analytics to improve drug safety. Regenerate response pharmacovigilance practices.

RESULTS BY YEA

> [Comput Biomed Res.](#) 1973 Dec;6(6):544-60. doi: 10.1016/0010-4809(73)90029-3.

of 1,551



An artificial intelligence program to advise physicians regarding antimicrobial therapy

E H Shortliffe, S G Axline, B G Buchanan, T C Merigan, S N Cohen



Overuse: Unnecessary adoption of AI or advanced ML techniques where alternative, reliable or superior methodologies already exists;

Misuse: Applications of ML that endeavor to **replace the role of physicians in situations which should still require a human input.**

Nat Med 2022 Oct;28(10):1996-1999

Real World Data vs Real World Evidence

- ❖ **RWD: data** relating to **patient health status** and/or the **delivery of health care routinely collected** from a **variety of sources**, such as electronic health records, claims and billing activities, drug and disease registries, patient-related activities in out-patient or in-home use settings, and health-monitoring devices.
- ❖ **RWE is the evidence generated using RWD.**

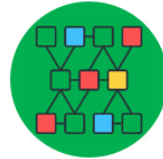
Food and Drug Administration definition

The landscape of healthcare data



90%

Of data worldwide has been generated in the last 2 years



80%

Of data is unstructured

Electronic health records
Primary care data, hospital records

Claims data

Registries

Existing disease
Registries / new
product registries

**Patient and
caregiver surveys**

The Future
Social
media data

“Big data will transform medicine. It’s essential to remember, however, that **data** by themselves are **useless**. To be useful, data must be **analyzed, interpreted, and acted on**». *N Engl J Med September 29, 2016; 375:13*

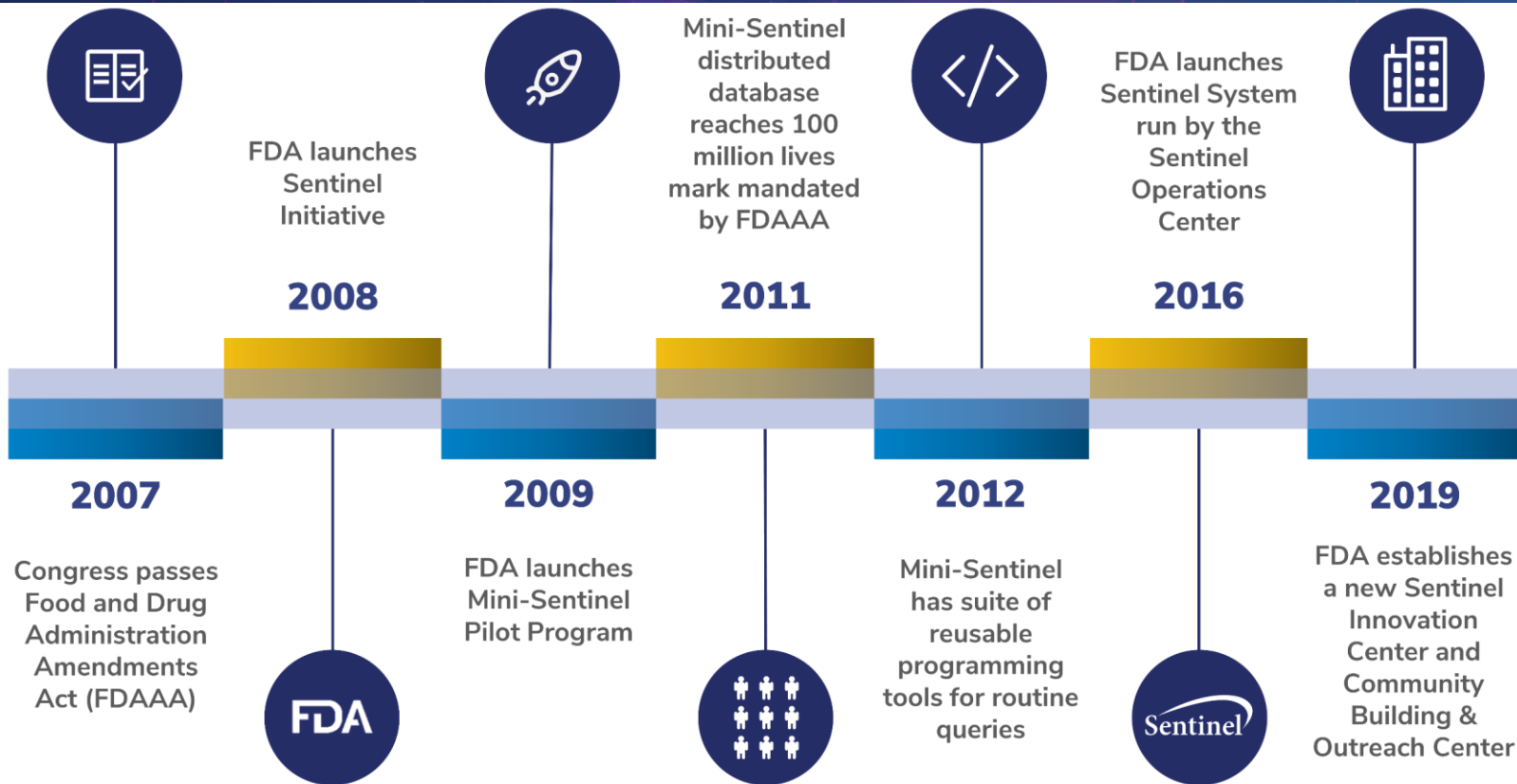
Drug utilisation

(via smart phone or web
based technologies)



“Water, water everywhere,
and not a drop to drink.”

DAVID CARNAHAN



Individual data partners



Site 1



Site 3



Site 2



Site 4



Data standardization

Site 1



Site 2

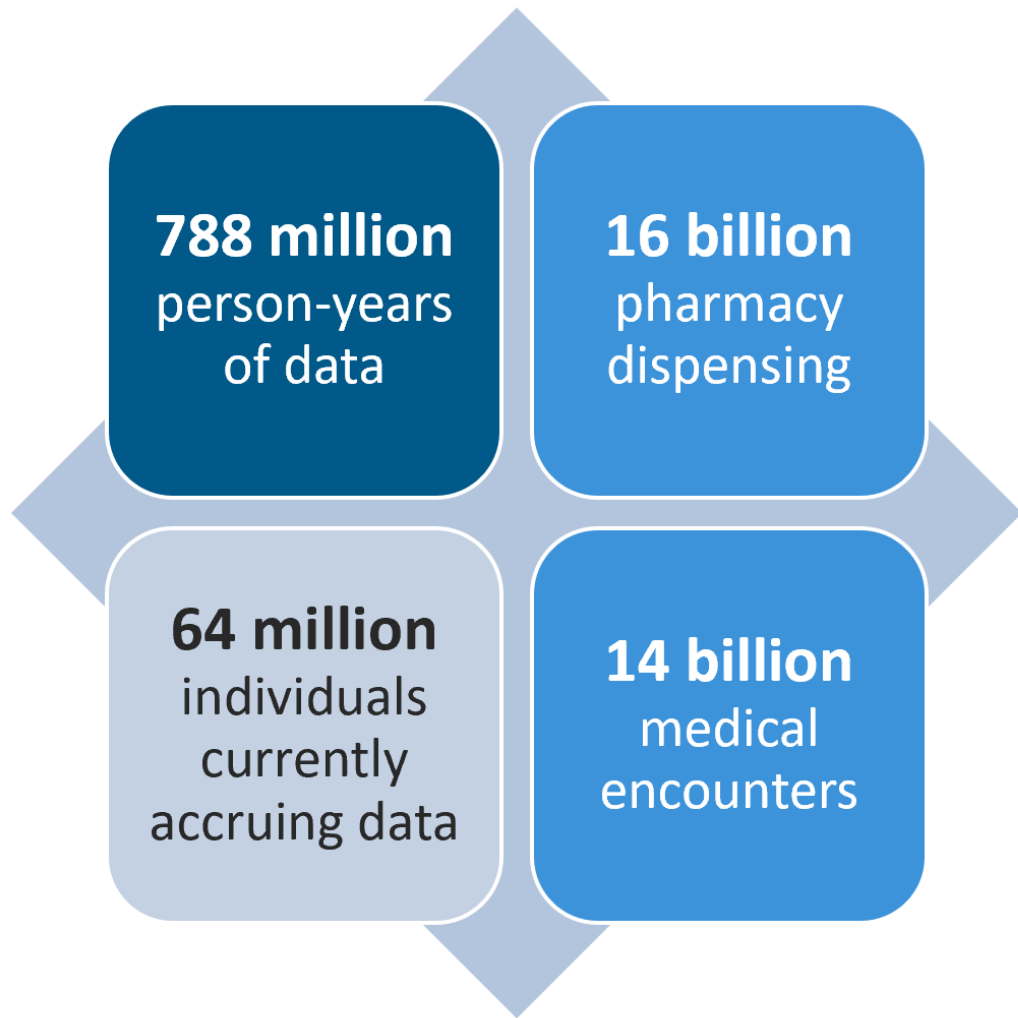


Site 3



Site 4





Inform label change



JNCI Cancer Spectrum (2021) 5(2): pkab009

doi: 10.1093/jncics/pkab009

First published online 4 February 2021

Article

Risk of Nonmelanoma Skin Cancer in Association With Use of Hydrochlorothiazide-Containing Products in the United States

Efe Eworuke , PhD,^{1,*} Nicole Haug, MPH,² Marie Bradley , PhD,¹ Austin Cosgrove, BS,² Tancy Zhang, MPH,² Elizabeth C. Dee, MPH,² Sruthi Adimadhyam , PhD² Andrew Petrone, MPH,² Hana Lee, PhD,³ Tiffany Woodworth , MPH,² Sengwee Toh, ScD²

Postmarketing Experience:

Non-melanoma Skin Cancer

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the **Sentinel System**, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of $\geq 50,000$ mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

Conduct signal identification studies

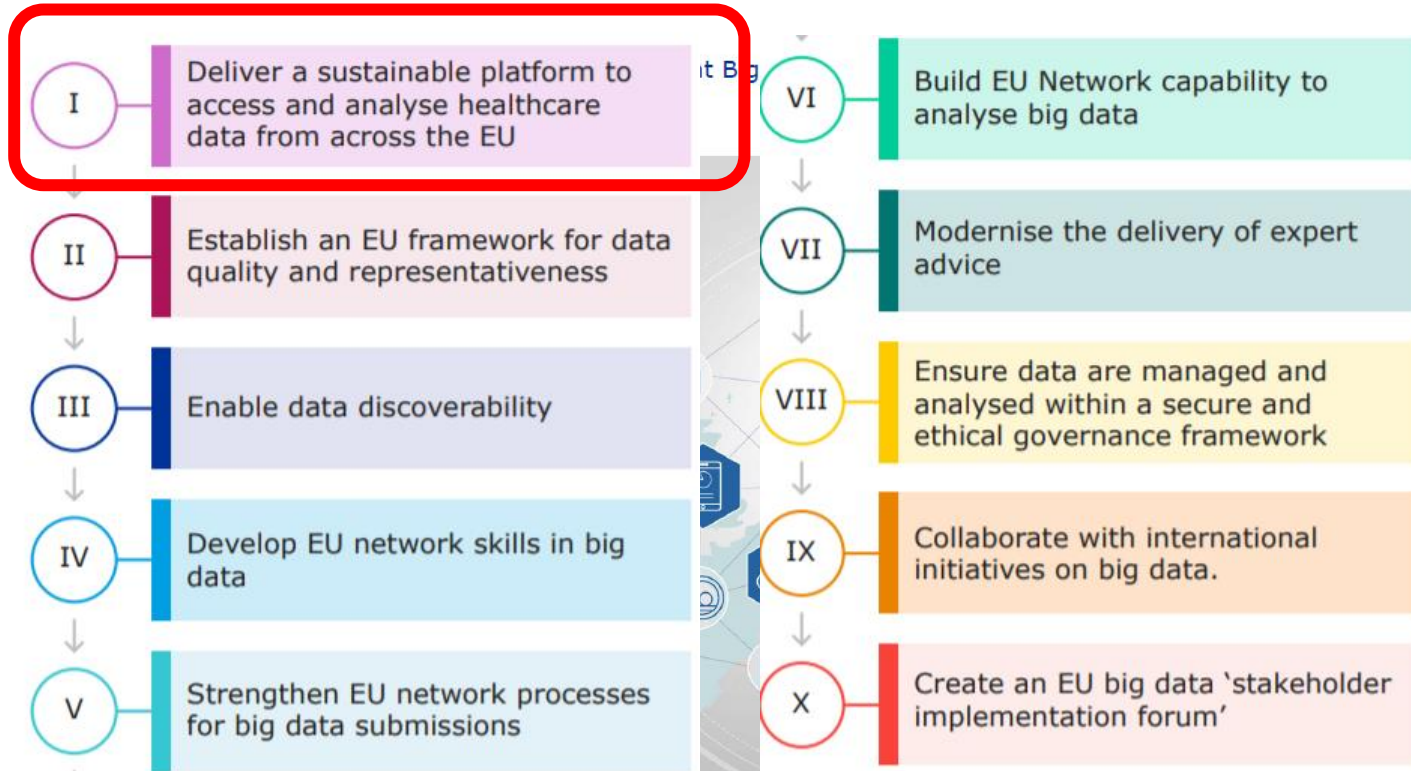
ORIGINAL ARTICLE

Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic

Shirley V. Wang,^a Judith C. Maro,^b Elande Baro,^c Rima Izem,^c Inna Dashevsky,^b James R. Rogers,^a Michael Nguyen,^d Joshua J. Gagne,^a Elisabetta Patorno,^a Krista F. Huybrechts,^a Jacqueline M. Major,^d Esther Zhou,^d Megan Reidy,^b Austin Cosgrove,^b Sebastian Schneeweiss,^a and Martin Kulldorff^a

Epidemiology 2018;29: 895–903

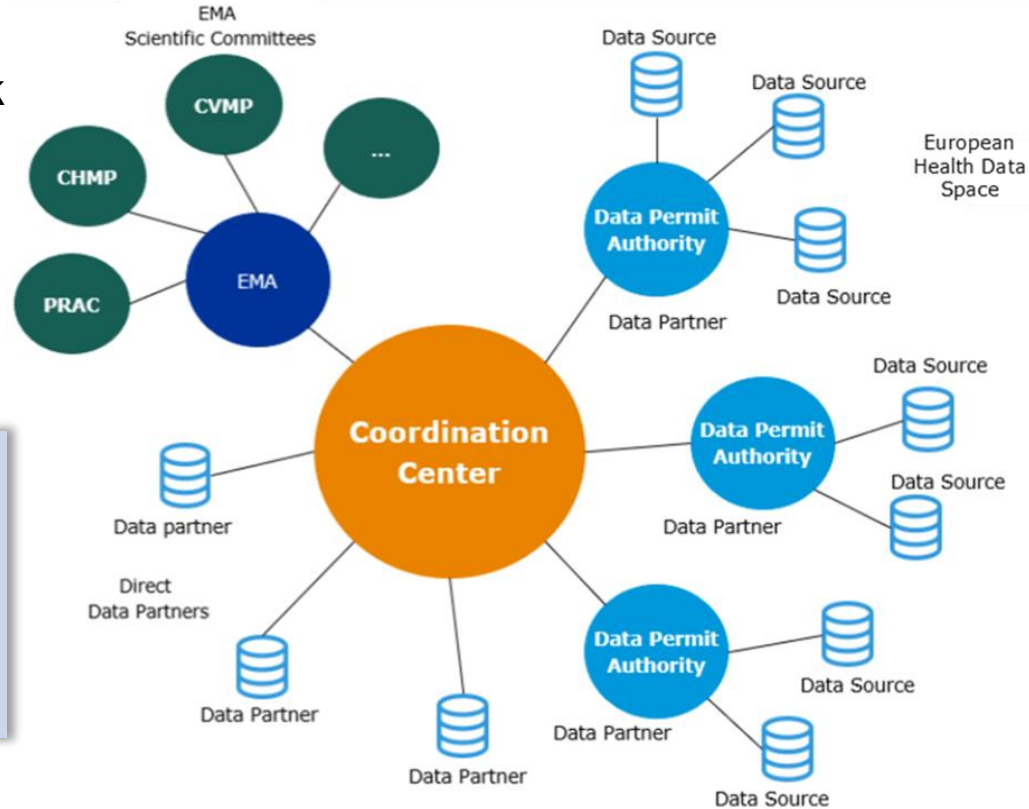
Priority recommendations of the HMA-EMA joint big data task force



DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence** from **real world healthcare data**

FEDERATED NETWORK PRINCIPLES

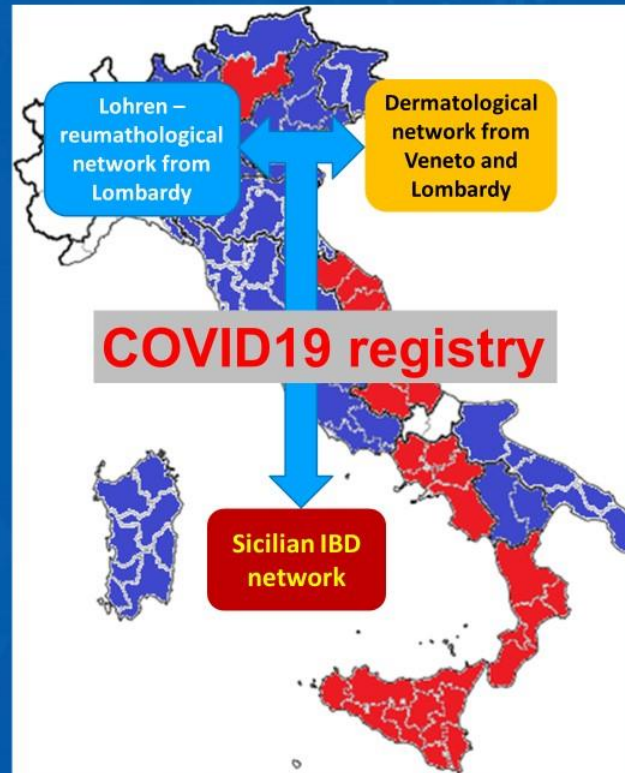
- Data stays **local**
- **Use of Common Data Model** (where applicable) to perform studies in a timely manner and increase consistency of results



The VALORE project: the Italian multi-database network for post-marketing surveillance of biologics including biosimilars

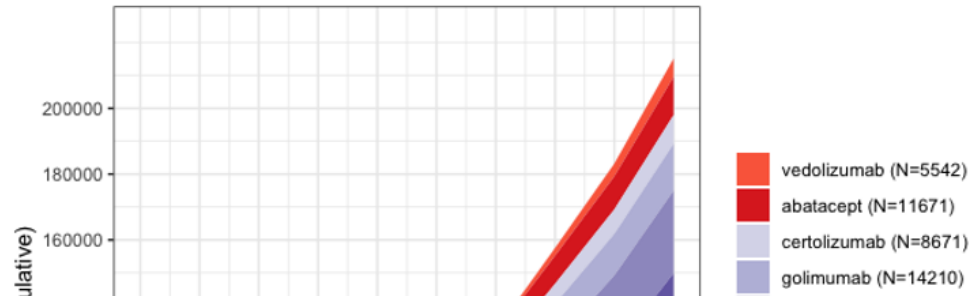


BioDrugs. 2021 Nov;35(6):749-764



On a total population of 54 million persons from 16 Regions, more than **240,000 users** of biological drugs can be identified from the network of claims databases, with at least **10%** being biosimilars.

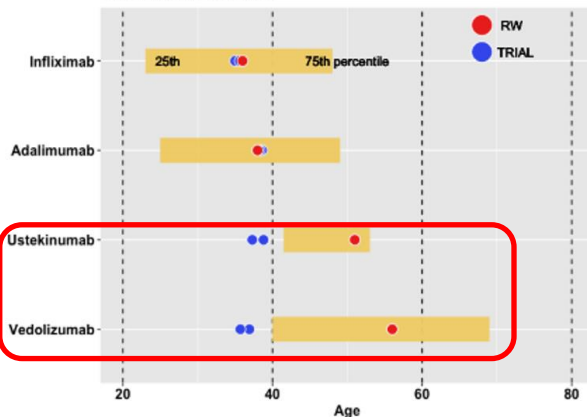
Cumulative number of biological drug users during the years 2010-2019, stratified by single molecule



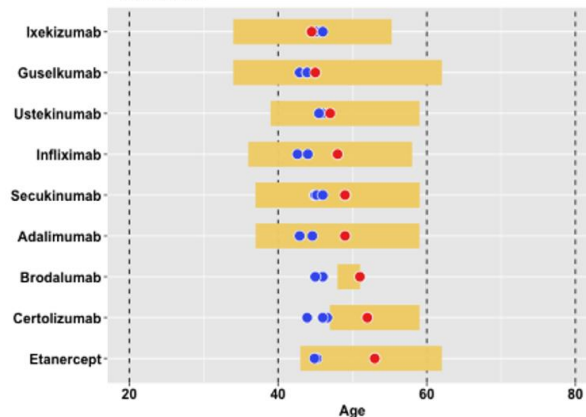
- **>520,000 PYs** of exposure to biologics for immune mediated inflammatory diseases and almost **35,000 users of biosimilars**
- Among biologic drug users: **>2,000 pregnant women, >10,000 very old patients and almost 10,000 children and adolescents**

Comparison of the baseline characteristics of pivotal RCTs population vs. RW population, stratified by individual drug and indication for use – *Mean age*

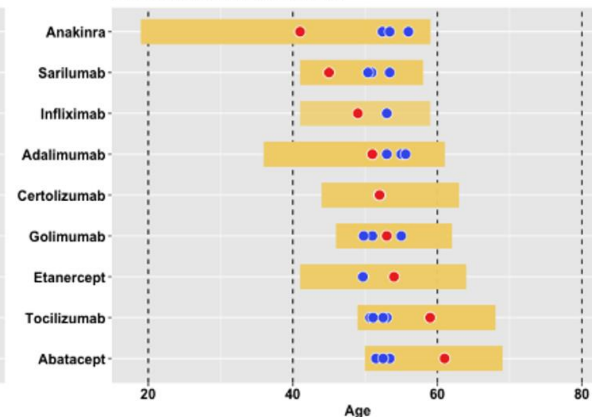
CROHN'S DISEASE



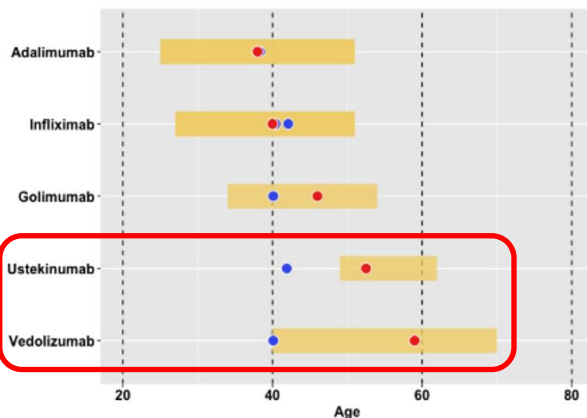
PSORIASIS



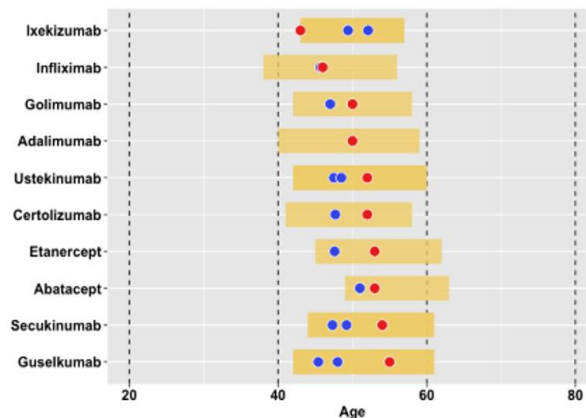
RHEUMATOID ARTHRITIS



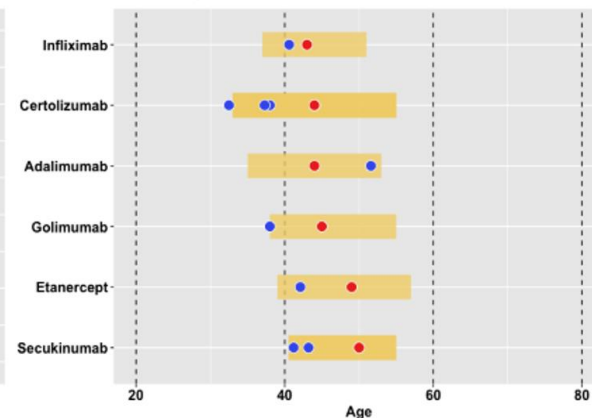
ULCERATIVE COLITIS



PSORIASIS ARTHRITIS



ANKYLOSING SPONDYLITIS



Agenda

- Where do we stand in Pharmacovigilance?
- **What type of (and how much) data for signal management?**
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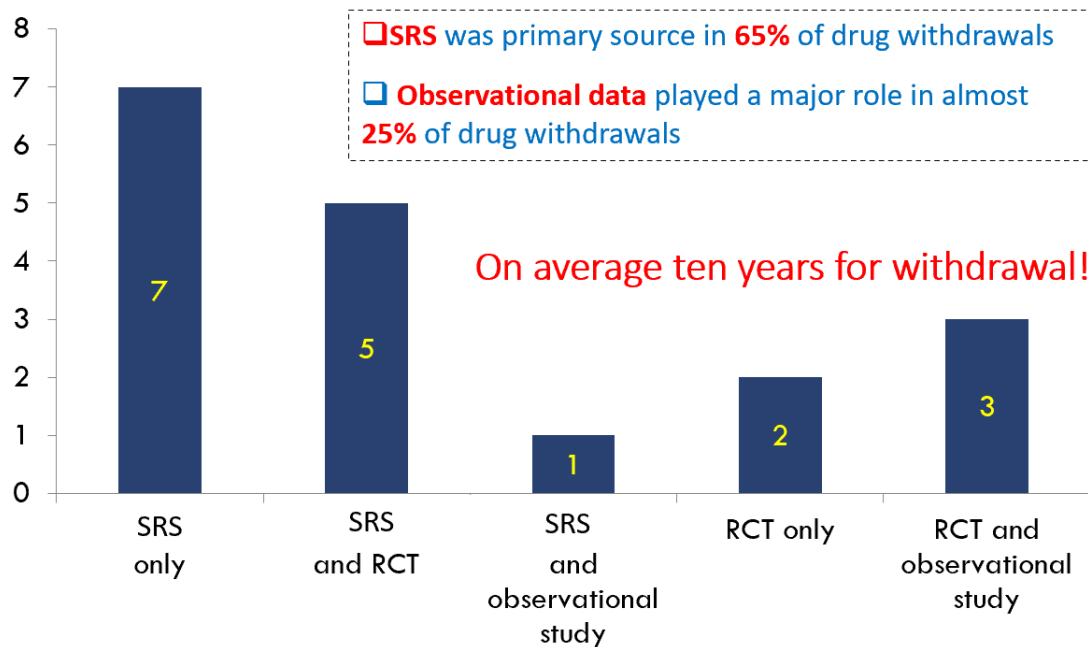
What is a signal in pharmacovigilance?



“Information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifactory action”.

Council for International Organizations of Medical Sciences (CIOMS)

Data sources triggering the drug withdrawals



Coloma P. et al. *Drug Saf.* 2013 Mar;36(3):183-97

Coloma P. et al. *Drug Saf.* 2013 Mar;36(3):183-97

Which «ingredients» for signal management?

**Spontaneous
reporting system**



**Active
Surveillance**



**Longitudinal
healthcare DBs**



Massive amounts of reports of COVID-19 vaccine related (suspected) adverse reactions

Vaccine	N. reports
Pfizer	1,242,962 (+16,332 for new variants)
AstraZeneca	550,875
Moderna	383,064 (+ \approx 8,000 for new variants)
Janssen	71,407
Novavax	1,645

Do we always need Big Data in PV? - 1



Family Matters

By Bonnie Rochman

OBESITY

Smaller Dishes Could Cut Childhood Obesity

By Bonnie Rochman @brochman | April 08, 2013 | 32 Comments

f Share

f Like 1.2k

t Tweet 618

g +1 32

in Share 20

Read Later

Smaller plates, fewer calories? The latest study shows one way to fight childhood obesity may be to shrink the size of the dinner plate.

According research published in the journal *Pediatrics*, first-graders served themselves more and downed more calories when they used a large plate instead of a smaller one.

Simply advising parents — and kids — to eat less and exercise more hasn't turned the childhood obesity



Do we always need Big Data in PV? - 2

Natalizumab and PML

- ❖ **Natalizumab** is a monoclonal antibody targeted against the integrin alpha-4, that was initially approved for the treatment of multiple sclerosis and Crohn disease;
- ❖ This drug was **withdrawn** from the market by manufacturer in **2005** after **3 patients developed PML**;
- ❖ After implementation of a **global risk management program**, natalizumab was reintroduced in 2006;
- ❖ In certain high-risk individuals, natalizumab has been associated with a **PML incidence** of up to **1 in 85 exposures**.

Ransohoff RM. Natalizumab for multiple sclerosis. N Engl J Med. 2007;356:2622-2629.

Fox RJ, Rudick RA. Risk stratification and patient counseling for natalizumab in multiple sclerosis. Neurology. 2012;78:436-437

Advanced tools and emerging data sources for drug safety signal detection cannot replace **thorough clinical observation!**

“Big data enables us to generate a lot of conclusions; we have to be able to discriminate whether they represent causal relationships or spurious coincidence.”

Professor Guido Rasi

Agenda

- Where do we stand in Pharmacovigilance?
- What type of (and how much) data for signal management?
- **Integration of information from SRS and longitudinal healthcare databases**

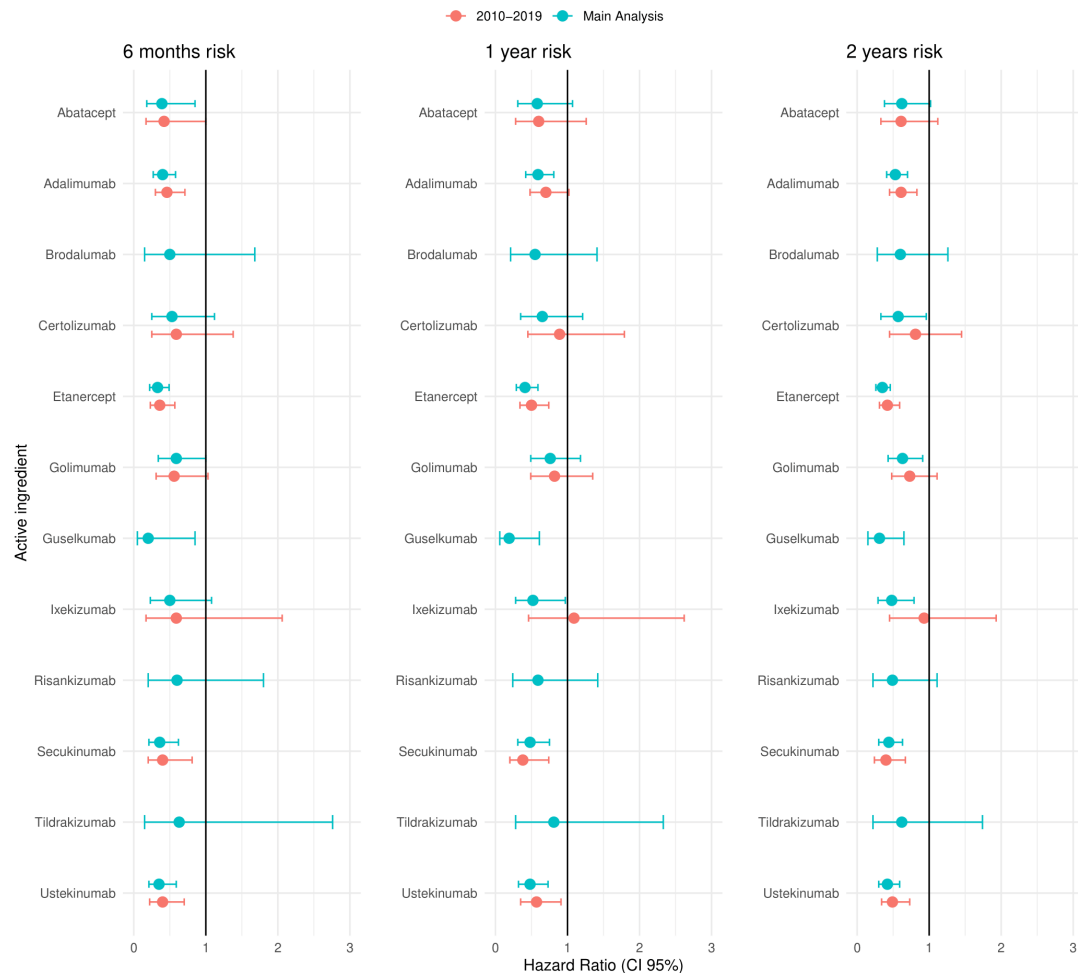
Integration of information obtained from SRS and longitudinal healthcare databases (HDB)

1. To derive key information from SRS (e.g., ADR risk factors, TTO, treatment changes) for analysis of specific outcomes that can be tracked in HDB
2. To generate safety signals in SRS that can eventually be strengthened/validated through the analysis of longitudinal health databases

To derive key information from SRS for analysis of specific outcomes that can be tracked in HDB

Outcome CESIT –	N. report RNF	% severe	Most frequent PTs	Most commonly implicated drugs	Median time to onset (min- max), days
Renal diseases	76	86%	Acute kidney disease (28), renal function impairment renale (17)	everolimus (14), tacrolimus (13)	288 (0-6,339)
Infections	65	82%	Pneumonia (13), Urinary infections (13)	tacrolimus (36), everolimus (21)	602 (0-12,033)
Cardiac diseases	33	73%	Tachycardia (9), heart failure (8)	Everolimus (8), tacrolimus (5)	241 (0-5,190)
Cancers	23	96%	Baso-cellular carcinoma (4), squamous cell carcinoma(4)	Tacrolimus (9), micofenolato mofetile (7)	616 (61-5,793)

Risk of severe infection per active ingredient in patients with Pso/PsA



*reference: infliximab;

Main analysis: censoring for switch/swap to different bDMARD, discontinuation, death or end of follow-up (31 December 2022);
2010-2019 analysis: main analysis censoring criteria + censoring at 31/12/2019;

COX analysis adjusted for all covariates (sex, age, comorbidities, previous and concomitant use of drugs)

To generate safety signals in SRS that can eventually be strengthened/validated through the analysis of longitudinal health databases






Received: 21 November 2022 | Revised: 15 February 2023 | Accepted: 8 March 2023

DOI: 10.1002/pds.5610

ORIGINAL ARTICLE

WILEY

Observed-over-Expected analysis as additional method for pharmacovigilance signal detection in large-scaled spontaneous adverse event reporting

Meiwen D. X. van der Boom  | Rike van Eekeren  | Florence P. A. M. van Hunsel 

WHAT HAVE WE LEARNT FROM Vioxx?

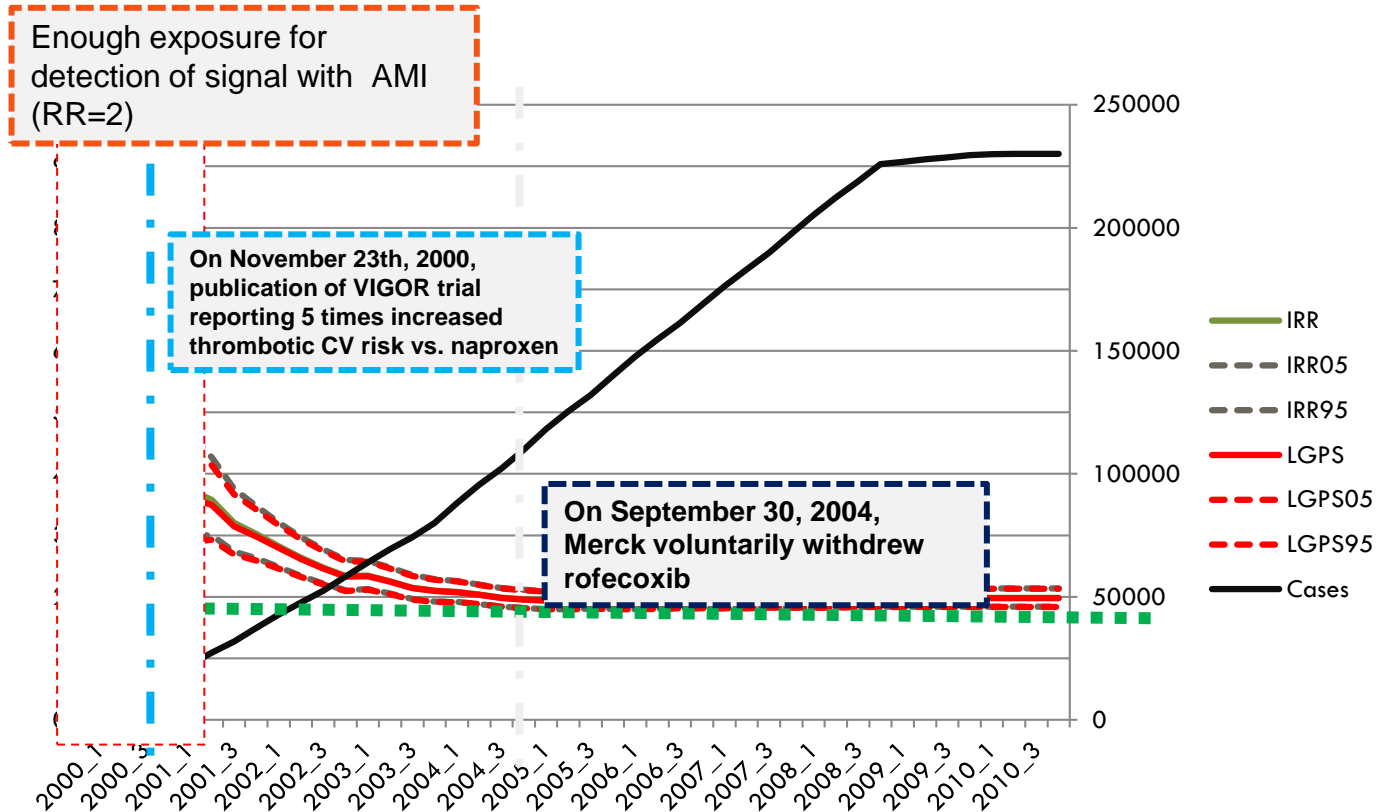
In October UK patients who had cardiovascular events while taking rofecoxib lost the right to fight Merck in the US for compensation. But researchers and journals can still benefit from this case if they learn from the mistakes, write **Harlan Krumholz and colleagues**



Rofecoxib (Vioxx) was introduced by Merck in 1999 as an effective, safer alternative to non-steroidal anti-inflammatory drugs for the treatment

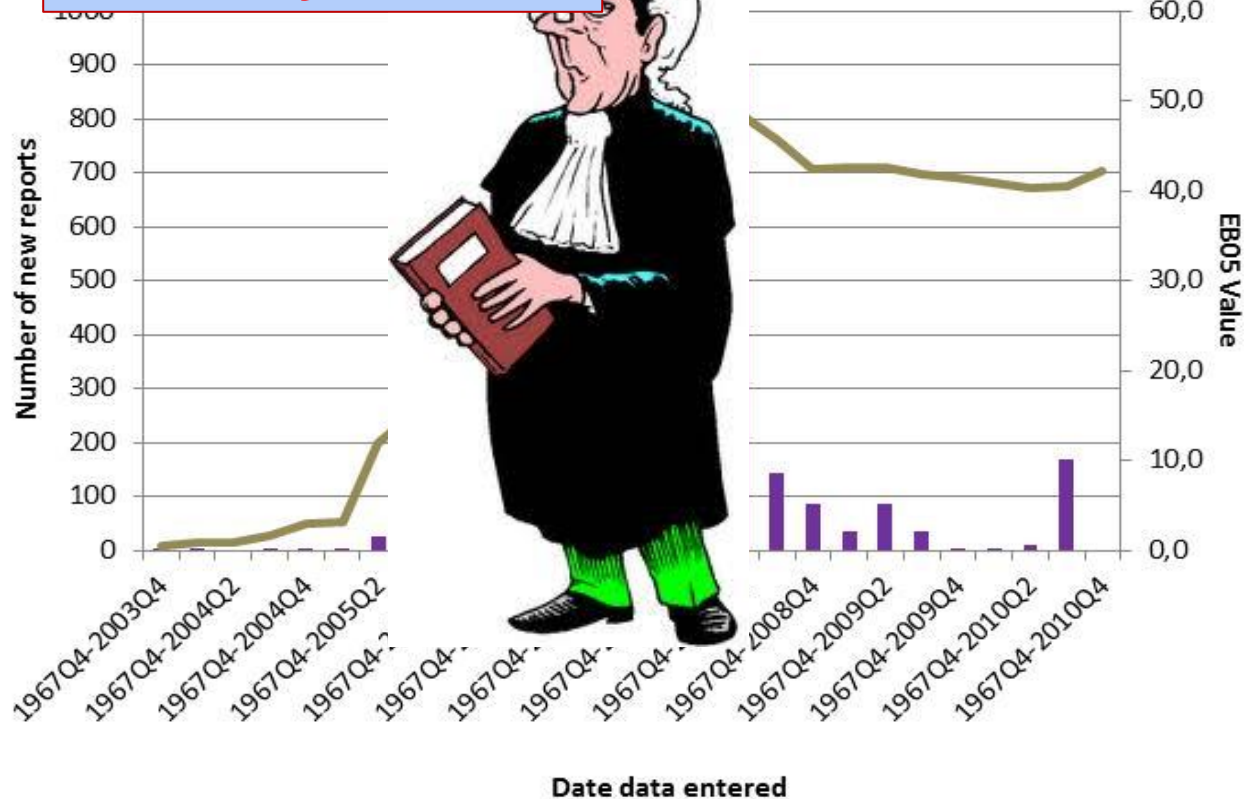
volunteers by about half.^{1,2} In internal emails made public through litigation,³ Merck officials sought to soften the academic authors' interpretation that cyclo-oxygenase-2 (COX 2) inhibition within the vascular endothe-

Rofecoxib and AMI in EU-ADR



Rofecoxib and AMI in WHO - Vigibase

The lawyer bias?



Data mining= earliest date of onset of the ADR

Data load= report entered date

Join us



Members Login

1. To organize introductory pre-conference course on pharmacoepidemiology as well as symposia on RWE/big data in pharmacovigilance at ISoP annual conferences, especially providing updates on the activities of the above-mentioned large scale regulatory-driven networks;
2. To develop methodological papers on how SRS and RWE should complement with each other and more in general on the role of RWE/big data in all the stages of signal management process, from signal validation to signal strengthening and detection. A mapping exercise of all the ongoing initiatives concerning signal management using Big Data could be a more immediate goal of this SIG.
3. To facilitate liaison and establish a more solid collaboration between ISOP and International Society for Pharmacoepidemiology (ISPE) as well as with EMA's European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), the Institute for Safe Medication Practices and other key international programs (e.g. ECAMET) in order to promote joint activities.

Conclusions

- ❖ Availability of **large amounts of healthcare data** from **several sources** and increasingly **powerful tools** to analyze such data are a great opportunity for postmarketing surveillance of drugs on **wider scales, beyond traditional SRS**;
- ❖ However, observational studies on drug/vaccine safety carried-out using longitudinal health databases **don't** usually **consider information derived from SRSs**;
- ❖ Findings generated using RWD require **robust clinical interpretation and critical judgment** and **in no way large-scale distributed network of longitudinal healthcare DB will replace SRS for signal management**;
- ❖ EHRs, health insurance claims, and drug/disease registries should **not be considered in isolation**, but as part of a wider data context along with other data sources, especially SRS for postmarketing surveillance!

A full-page background image showing a sunset over a coastal town. The sky is filled with vibrant orange and red clouds, with a bright sun low on the horizon. In the foreground, the dark silhouettes of buildings and a coastline are visible. In the background, there are mountains, including a prominent conical mountain on the left.

Thanks for the attention

"The human mind is like a parachute. It works better when it is open".

Gianluca Trifirò

gianluca.trifiro@univr.it