EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory Science: Are regulators leaders or followers?
Health data to support medicines regulation:
- identifying the opportunities
- improving the methods
- building the capacity

Presented by: Dr Peter Arlett
Head, Pharmacovigilance and Risk Management,
European Medicines Agency

Health data to support medicines regulation

In this talk:

- Introduction
- Case histories
- Health data and pharmacoepidemiology through the product lifecycle
- Resources and capacity building
- Improving methods
- New law: an opportunity for the pharmacoepidemiologist, statistician and programmer
- Conclusions

Introduction

Are medicines regulators leaders or followers?

Both:

- Followers - as science and scientific evidence should underpin medicines regulation
- Leaders – as sometimes science needs a guide

But you decide.....

Introduction

Old model vs. new vision

Old model – regulator places obligations on industry and then assesses the results of industry studies

New vision – regulatory decision-making is based on assessment of all available data including:

- industry studies
- academic studies
- public authority studies (including by regulators)
- use of data from real-life health outcomes

Introduction

Enabling the vision requires:

Science

Law

Resource

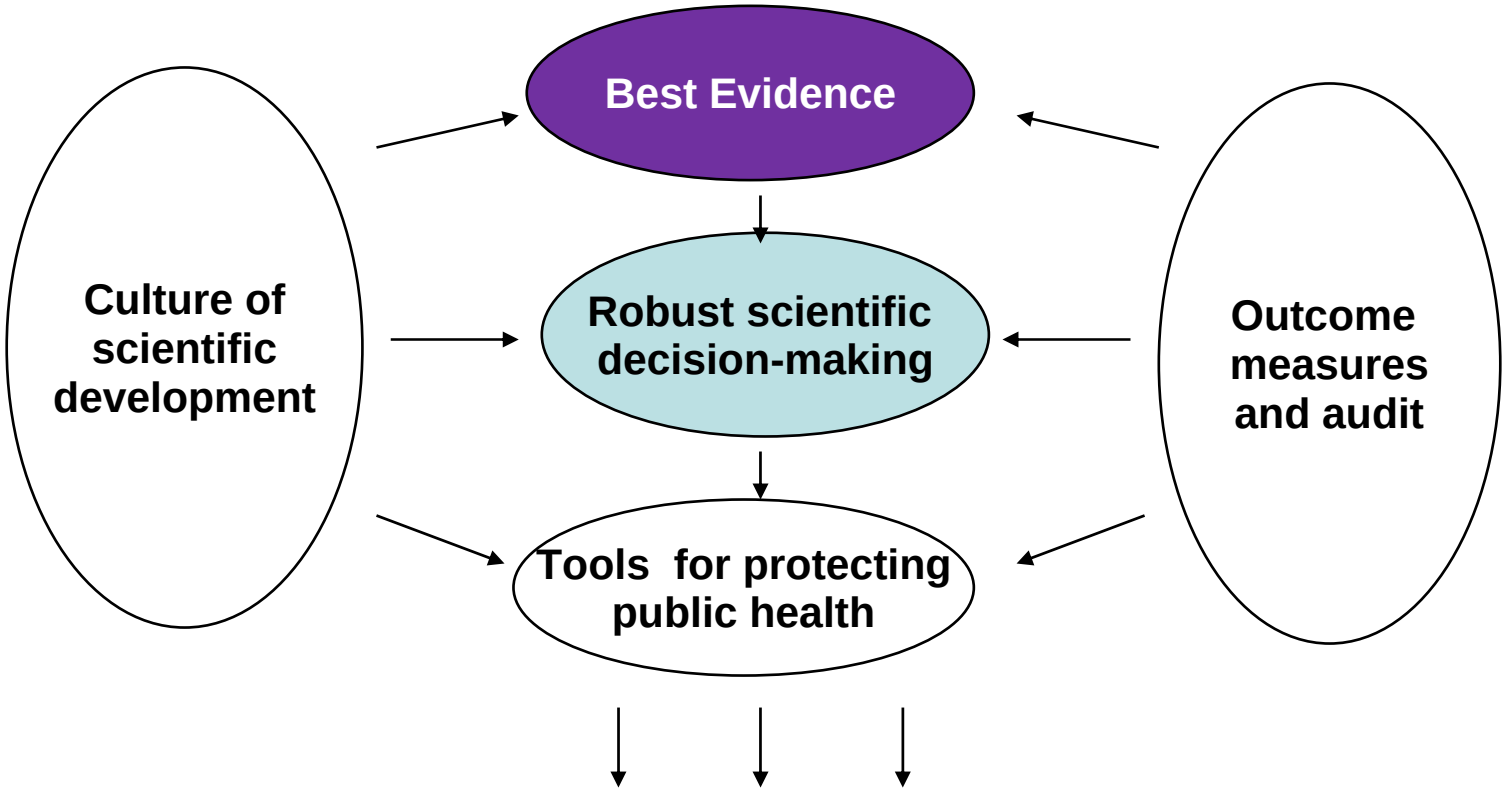
Introduction

Health data and epidemiology:

Resources that should support decision-making throughout the lifecycle of a medicine....

.... More later

Working Model for Excellence in Pharmacovigilance **and** Medicines Regulation



Measurable excellence in terms of public health benefit

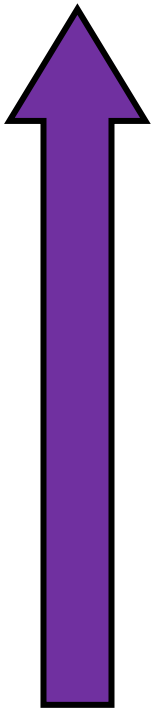
Waller & Evans. Pharmacoepidemiology & Drug Safety 2003;12:17-

7

Introduction

If we accept the evidence hierarchy we should embracing the entire spectrum of evidence.....

Lower degree of uncertainty (e.g. causality, incidence)

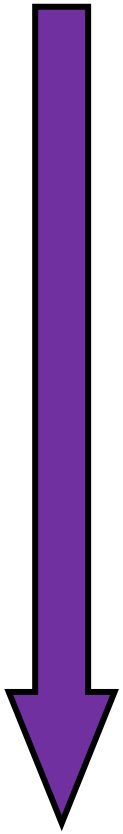


- **Meta-analysis**
- **Clinical trial**
- **Prospective cohort (with controls)**
- **Case control study**
- **Observational cohort (no controls)**
- **Individual case report / case series**

Introduction

'high' evidence may be of limited relevance to real world use.

Lower degree of uncertainty (e.g. causality, incidence)



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Introduction

Brave new world – a call to arms for medicines regulators!

Ensuring that health protection and promotion are effective, through study of effects of medicines in real life situations:

- New pharmacovigilance legislation 'EMA / MSs shall monitor the outcome of risk minimisation measures contained in risk management plans…'

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European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim

Anti-diabetes medication to be taken off the market

September 2010 EMA recommended the suspension of the marketing authorisations for the rosiglitazone-containing anti-diabetes medicines Avandia, Avandamet and Avaglim. These medicines will stop being available in Europe within the next few months.

Patients who are currently taking these medicines should make an appointment with their doctor to discuss suitable alternative treatments. Patients are advised not to stop their treatment without speaking to their doctor.

Doctors should stop prescribing rosiglitazone-containing medicines. Patients taking rosiglitazone-containing medicines should be reviewed in a timely manner to amend their treatment.

Case histories: Avandia

Avandia - PhV data to support decision making

Aug 2010 THIN database drug utilisation study conducted to investigate off-label use

Aim: Measure the proportion of patients treated with rosiglitazone with concomitant cardiac disorder listed as contraindicated conditions in the SPC. Ref: ENCePP Studies databases

23 Sep 2010 EMA Launch call for tender

Aim: Evaluate the impact of regulatory decisions taken by the EMA regarding rosiglitazone on drug utilisation data (e.g., switch to other therapies, compliance with therapeutic indications) and new potential and identified risks (possible new acute ADRs in diabetic patients, and modifications on objective chemical parameters of disease). Contract signed.

Post-authorisation activities for A/H1N1 vaccines during the influenza pandemic

European Medicines Agency

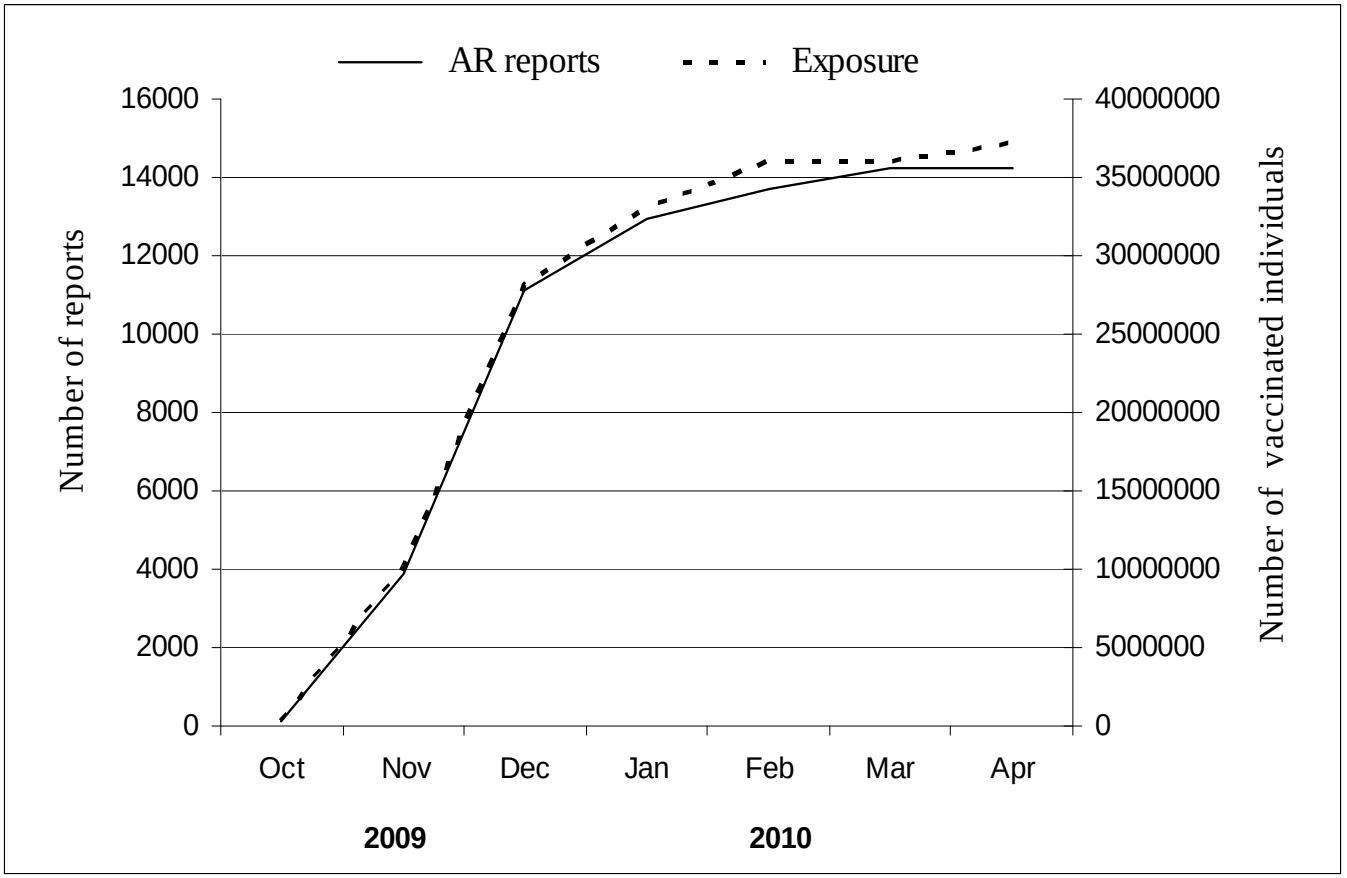
ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

HMA Heads of Medicines Agencies

European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring

- Strengthening of the spontaneous reporting system at national and European levels (EudraVigilance)
- Monthly simplified Periodic Safety Update Reports
  - List of Adverse events of special interests to be closely monitored
- Weekly collection of vaccine exposure data through survey of Member States
- Pandemic Pharmacovigilance Rapid Response Expert Group (PREG)
  - Rapid response to concerns raised by Member States
- Identification of research projects relevant for A/H1N1 vaccine B/R monitoring
  - 43 projects, 8 multicountry, 35 national (14 countries)
- Communication: weekly pandemic pharmacovigilance updates published on EMA website from December 5, 2010

Spontaneous reports were the main source of data on vaccine safety during the vaccination campaign…



As compared to other vaccines in pre-pandemic period:

- less missing values in AR reports
- faster reporting of AR by health care professionals
- faster reporting to EudraVigilance, thereby facilitating signal detection

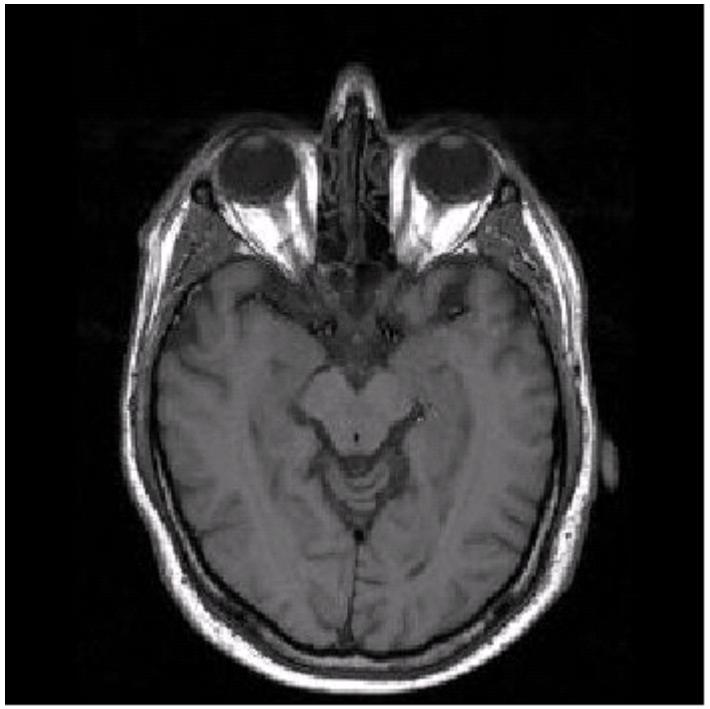
...but the pandemic highlighted avenues to improve benefit-risk monitoring for all vaccines and drugs.

- Capacity building for post-authorisation studies
- Pregnancy outcomes: network for sharing information, pooling of data or combining results – EMA funded study
- Infrastructure for observed-to-expected analysis
  - Vaccination coverage/exposure data – age and sex stratified
  - System for collection of EU-wide background incidence rates of events
- European vaccine health outcome resource
  - Prompt evaluation of signals detected in EudraVigilance
  - Benefit-risk studies

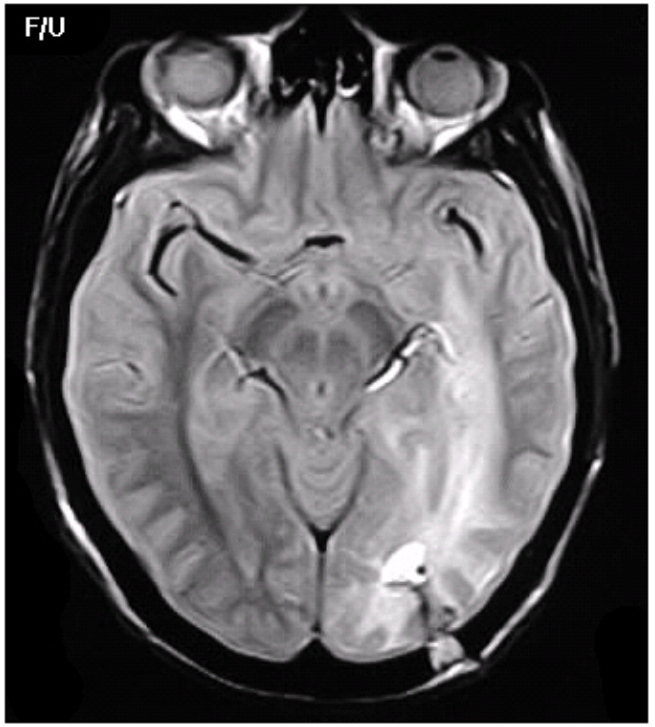
The EMA is working on it....with our partners !

Case histories: Progressive multifocal leucoencephalopathy (PML)

Normal brain



PML



Drug-related PML Research Agenda

Background:

- PML is a severe disease.
- Reported as an ADR of some immunosuppressive drugs (few Mabs).
- There is no effective treatment.
- Regulatory actions were taken regarding this ADR (*Tysabri, Raptiva and Mabthera).
- *PML Research Agenda* developed since December 2009.
- Initiative led by EMA, in collaboration with FDA.
- *PML Research Agenda* was adopted by the PhVWP and CHMP.

Aims of the Project:

- Define researchable questions that will help regulatory agencies to protect public health
- Communicate to stakeholders about the initiative. Tools for this: a **paper** in a medical/scientific journal and an **international workshop**.
- Stimulate partnerships and funding to fill knowledge and research gaps in the area.
- Ensure regular stocktaking of the project in the knowledge and knowledge gaps in this field.

Use of epidemiological models to investigate efficacy of Bluetongue vaccination

- ✓ **2 epidemiological models investigated the reduction of bluetongue (BT) transmission in cattle**
- ✓ **Basic reproduction number *R*0 premise: For vaccination to be effective it must reduce *R*0 below one**
- ✓ ***R*0 in vaccinated population was found below 1**
- ✓ **CVMP concluded that the demonstrated reduction in BT viraemia, although not complete, was sufficient for the vaccine to be effective at a population level**

Animal safety issue: BVD vaccine and bovine neonatal pancytopenia

- ‘Bleeding calf syndrome’
- Observational analyses and case-control studies for identification of potential risk factors for bovine neonatal pancytopenia
- Potential association between vaccination of dams using a particular BVD vaccine and the occurrence of bovine neonatal pancytopenia in calves
- Multi-factorial syndrome for which aetiology is unknown
- Studies on epidemiology and aetiology ongoing

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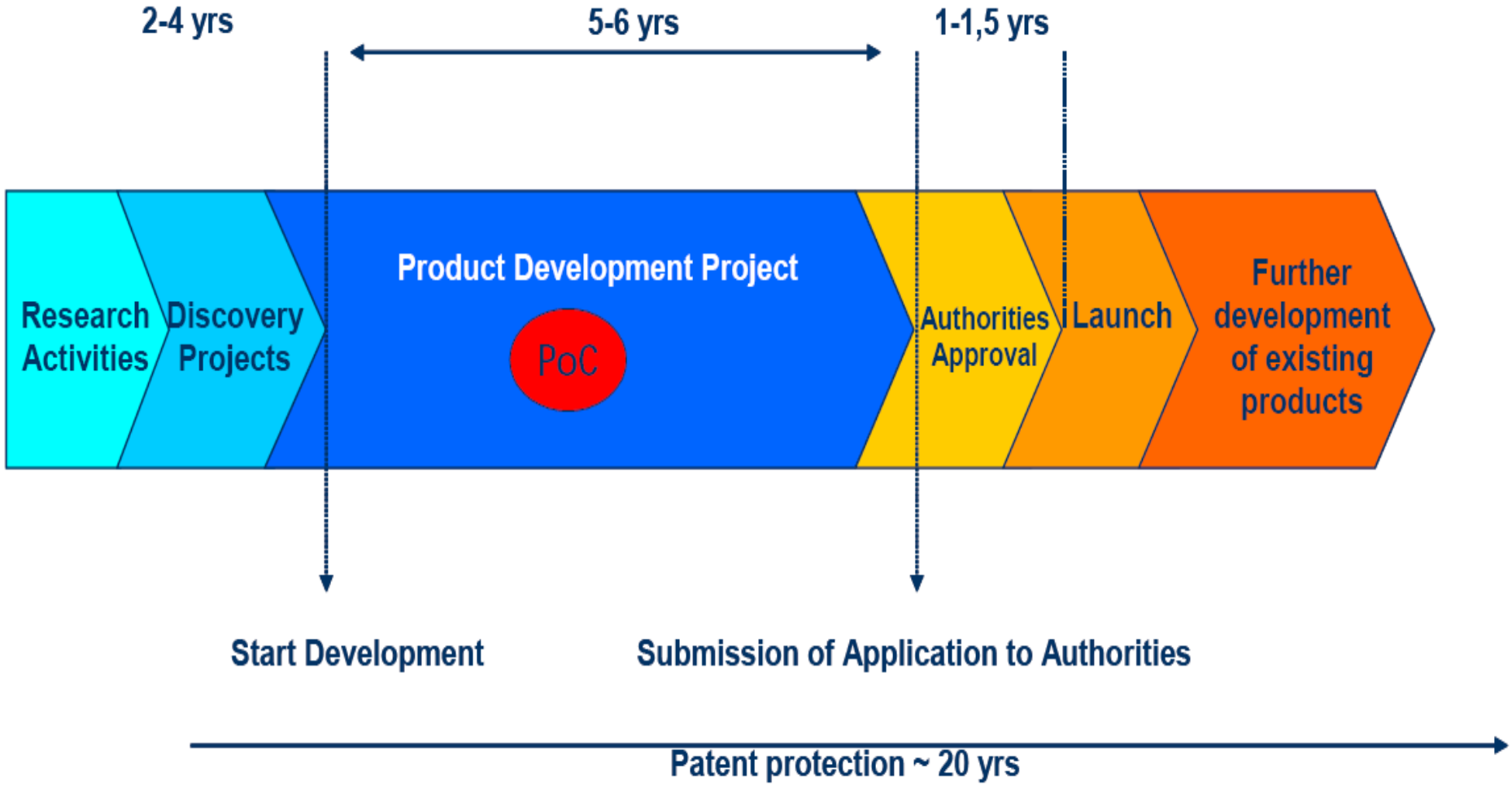
Health data and pharmacoepidemiology through the product lifecycle



Health data and pharmacoepidemiology through the product lifecycle

Assessing the need for medicines:

- Population-based databases to characterize frequency and distribution of disease
- Identify the population to be treated
- Identify whether the disease effects children
- Identify unmet medical need

Health data and pharmacoepidemiology through the product lifecycle

Identify orphan medicines:

- prevalence of five per 10,000 persons in the EU, from
  - administrative healthcare databases,
  - electronic medical records,
  - registries
  - surveys

Health data and pharmacoepidemiology through the product lifecycle

Clinical trials in development:

- Clinical trials can recruit from longitudinal patient data bases
- Clinical trial follow can up be through longitudinal patient data bases
- Population-based databases for background incidence rates to interpret adverse events in clinical trials
- Epidemiological techniques to study the safety and efficacy of medicines in rare diseases / niche populations

Health data and pharmacoepidemiology through the product lifecycle

At authorisation:

- The EU Risk Management Plan is key to proactivity and better health protection and promotion
- Based on pharmacoepidemiology:
  - Safety Specification – important known and potential risks + missing information
  - Pharmacovigilance Plan – routine PhV + additional studies
  - +/- Risk Minimisation Plan – including effectiveness measures
  - Future – Benefit risk management plans

Health data and pharmacoepidemiology through the product lifecycle

Post-authorisation safety:

- The entire evidence hierarchy
- Detecting signals (new or changing safety issues)
- Confirming signals e.g: observed vs. expected; impact / burden
- Formal association studies in case control, cohort, etc
- Assessing rare, delayed or chronic exposure adverse reactions

Health data and pharmacoepidemiology through the product lifecycle

Post-authorisation effectiveness and benefit risk:

- Efficacy in real life = effectiveness
- Health outcome studies can be done, e.g cohorts in:
  - administrative healthcare databases,
  - electronic medical records.
- Potential to bridge to HTA

Health data and pharmacoepidemiology through the product lifecycle

Drug utilization studies:

- For medicines exposure
- Compliance with indications and contra-indications
- Overdose and abuse of medicines
- Simple but effective form of risk minimisation effectiveness measurement

Health data and pharmacoepidemiology through the product lifecycle

EMA Review of PASS

- Review undertaken of PASS requested by the CHMP arising from positive opinions on new Marketing Authorisation Applications and Extensions of Indications in 2007
- As of 31 January 2010, of total requested, 86% had been progressed to a position of commencing data collection
- Median time to start 12.5 months
- 90% of these ongoing (median duration 30 months), remainder complete

Initiative on Effectiveness Measurement of risk minimisation

EU-RMP

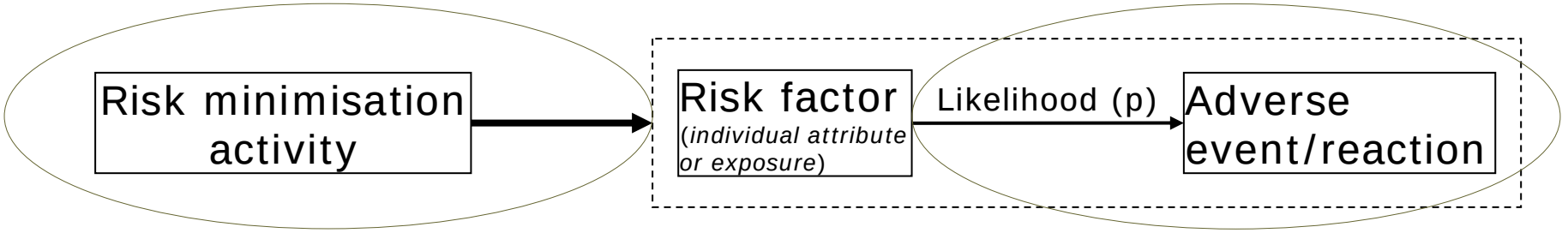
- **Part I**
  - Safety Specification
  - Pharmacovigilance Plan
- **Part II**
  - **Evaluation of need for risk minimisation *activities*** (i.e. routine & additional)
  - Risk minimisation plan

Background:

- Activities in Part II of RMP are *public health interventions* intended to prevent adverse events/reactions.
- Risk minimisation activities tend to be complex, and context dependent.
- "The evaluation of (effectiveness) evidence must distinguish between the fidelity of the evaluation process in **detecting the success or failure of an intervention**, and the relative success or failure of the intervention itself"

Rychetnik et al. **Criteria for evaluating evidence on public health interventions**.J Epidemiol Community Health 2002:56:119-127

When searching for evidence about the consequences of RMP interventions, we must distinguish between evidence on the **IMPLEMENTATION**, and evidence on the **OUTCOMES** of the intervention:



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Resources

Types of resource include:

Fees for pharmacovigilance (Fee Regulation and implementing rules)

Funding of studies (industry, FP7 – 18 Million Euros, EMA)

Capacity for studies and assessment

Knowledge and expertise

Databases, e.g:

- Eudravigilance – suspected ADRs and SUSARs
- EudraCT – clinical trials
- EPiTT – knowledge management and issues tracking
- ENCePP – centers, data sources, networks, studies

ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Strengthen further the post-authorisation monitoring of medicinal products in Europe, facilitate post authorisation studies: high quality; independent; multi-centre

- Network of excellence: public, fully searchable database of centres, networks and data sources
- Public searchable e-Register of studies
- Code of conduct to define relationship between funder and researcher and to ensure transparency
- Methodological checklist

How can that be achieved?

Standards	Stimulate consideration of important study principles in design of studies	**Methodological standards**
Transparency	Registry of studies Publication of protocol and results Understanding of who contributed what to study	**Database of studies**
Independence	Roles and responsibilities of stakeholders Freedom to publish	**Code of conduct**

CoRe requirements for ENCePP study

Lead Investigator from ENCePP Database of resources

ENCePP **C**ode of Conduct **– signed declaration and checklist**

Meth**o**dological standards for study protocols **– signed checklist**

Prior **Re**gistration in **e- Database of studies**

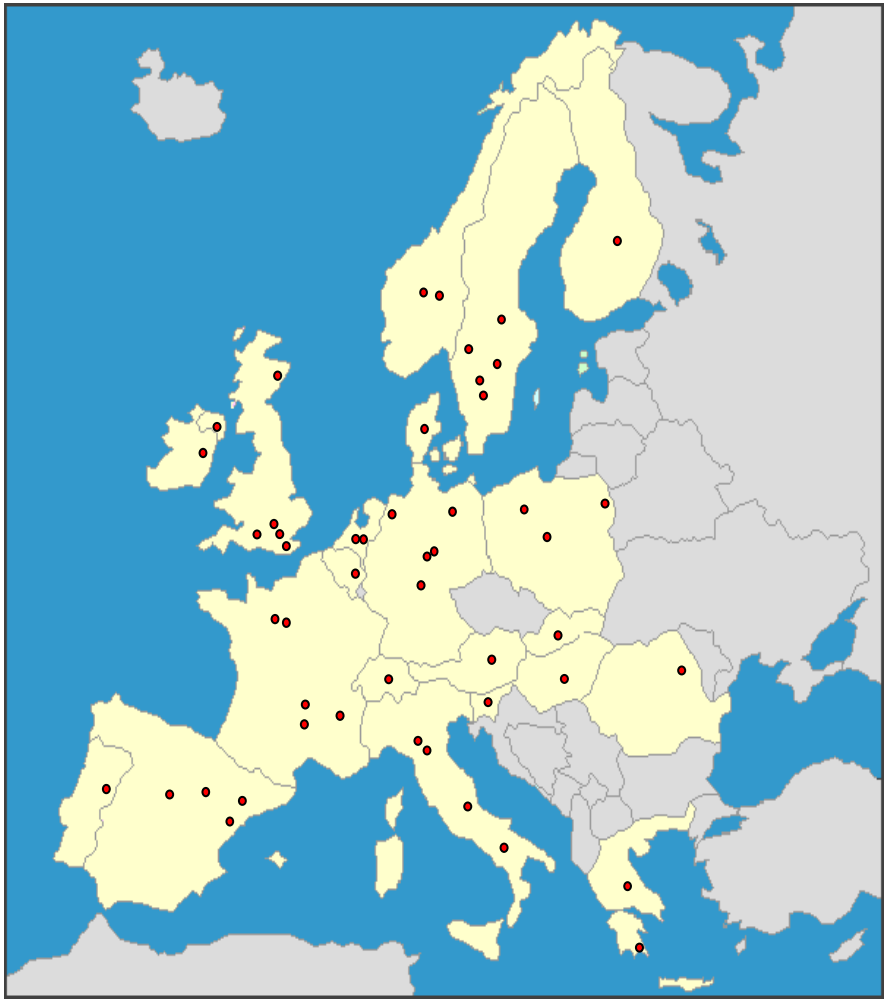

INDEPENDENCE
STANDARDS
TRANSPARENCY
enepp

ENCePP Expertise 2010

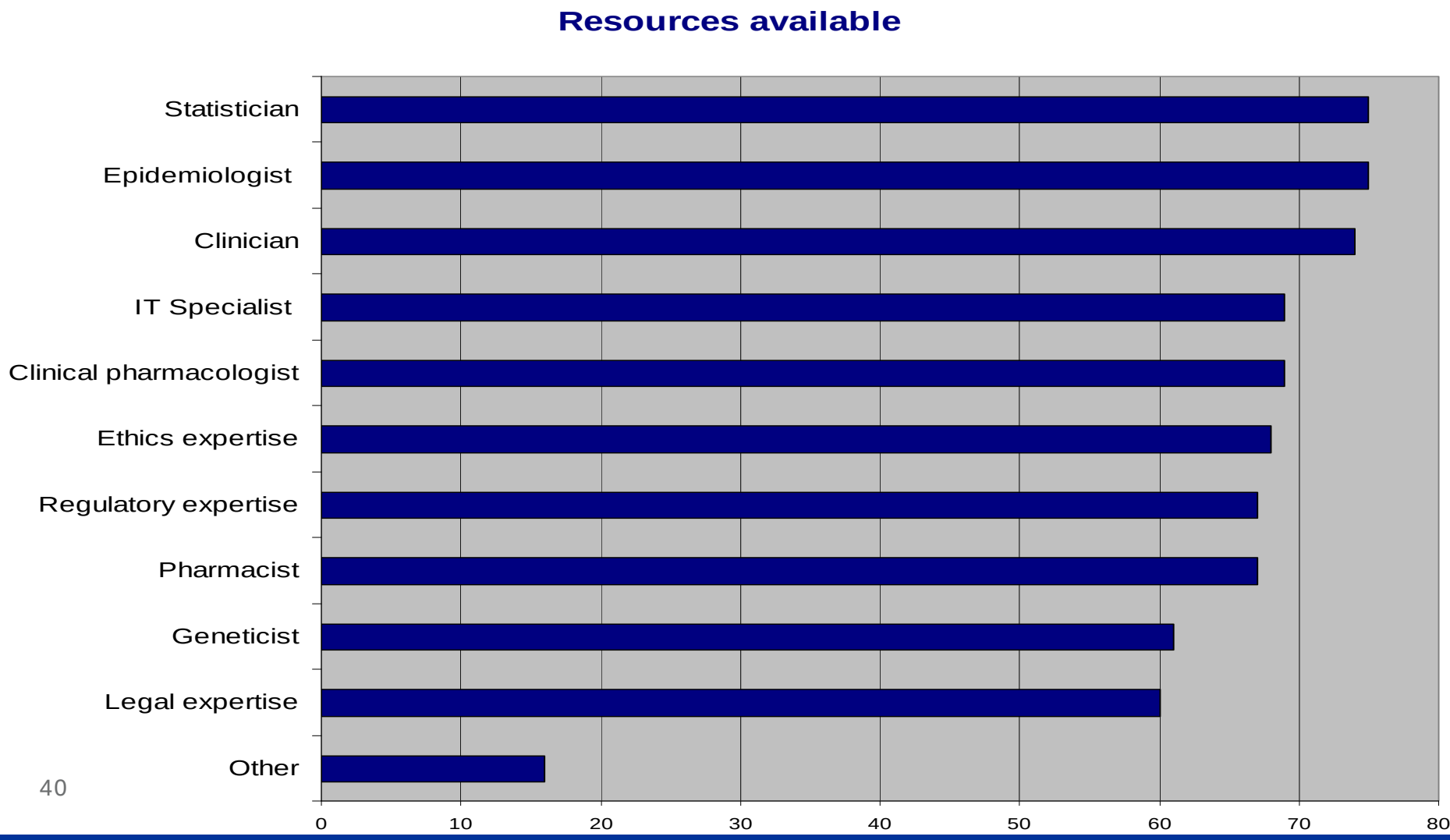
Some numbers from the ENCePP Resources Database:

- 75 research centres
- 11 networks
- 11 datasources

from 17 different EEA countries



ENCePP Centres expertise



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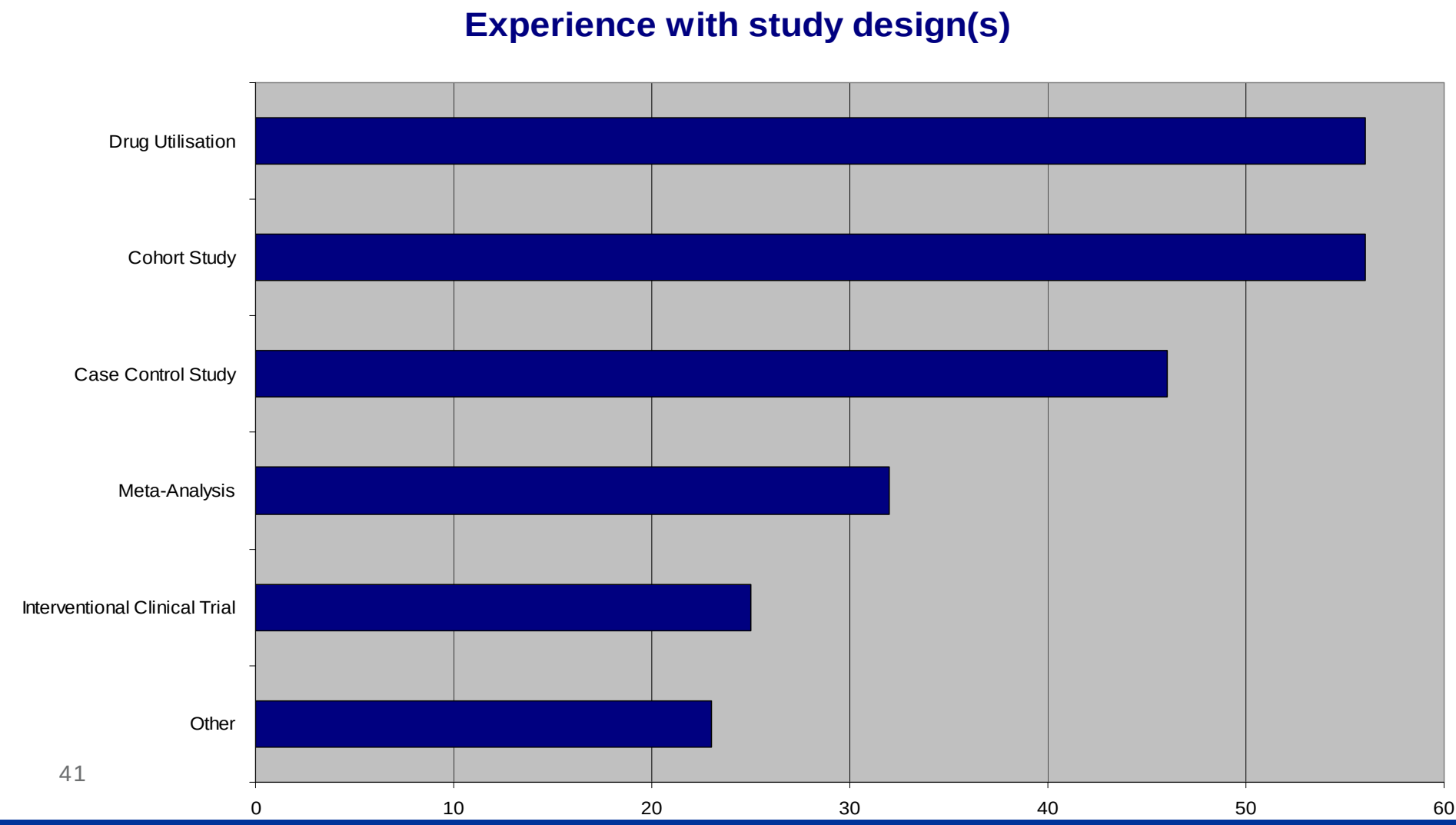

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PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

The PROTECT project

An Innovative Public-Private Partnership for New Methodologies in Pharmacovigilance and Pharmacoepidemiology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- PROTECT is receiving funding from the European Community's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu).

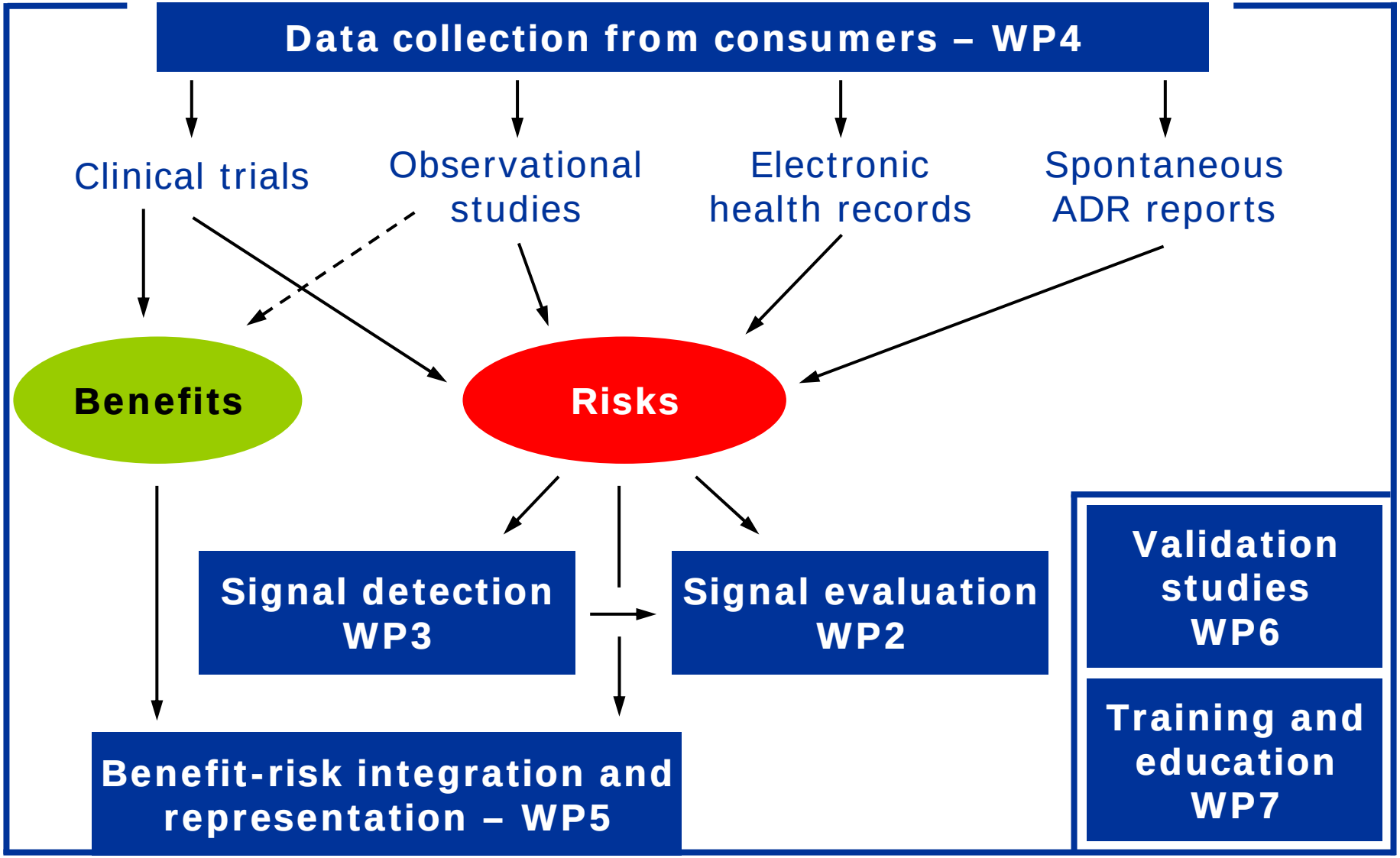
PROTECT Goal

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

- These methods will be tested in real-life situations.


Data collection from consumers – WP4
Clinical trials
Observational studies
Electronic health records
Spontaneous ADR reports
Benefits
Risks
Signal detection WP3
Signal evaluation WP2
Validation studies WP6
Training and education WP7
Benefit-risk integration and representation – WP5

Partners

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
University of Groningen
University of Utrecht
Imperial College London
University of Newcastle Upon Tyne

Others:
WHO UMC
GPRD
IAPO
CEIFE

SMEs:
Outcome Europe
PGRx

Private

GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer Schering
Astra Zeneca
Lundbeck
NovoNordisk

Example of one work package: Framework for pharmacoepidemiological studies

Objectives:

- **To:**
- develop
- test
- disseminate

methodological standards for the:

- design
- conduct
- analysis

of pharmacoepidemiological studies applicable to:

- different safety issues
- using different data sources

Two studies on the use of statins and the risk of fracture done in GPRD around the same period by two different groups.

	Meier et al., 2000		Van Staa et al., 2001	
Statins only	*Current use*	0.55 (0.44-0.69)	*Current use*	1.01 (0.88-1.16)
	N prescriptions		Time since use	
	- 1-4	0.51 (0.33-0.81)	- 0-3 months	0.71 (0.50-1.01)
	- 5-19	0.62 (0.45-0.85)	- 3-6 months	1.31 (0.87-1.95)
	- 20	0.52 (0.36-0.76)	- 6-12 months	1.14 (0.82-1.58)
			- > 12 months	1.17 (0.99-1.40)
	Recent use	0.67 (0.50-0.92)		
	Past use	0.87 (0.65-1.18)	*Past use*	1.01 (0.78-1.32)
Statins (current) and type of fractures	Femur	0.12 (0.04-0.41)	Hip	0.59 (0.31-1.13)
	Hand, wrist or arm	0.71 (0.52-0.96)	Radius/ulna	1.01 (0.80-1.27)
	Vertebral	0.14 (0.02-0.88)	Vertebral	1.15 (0.62-2.14)
	Other	0.43 (0.23-0.80)		

Why such a difference ?

		Meier et al., 2000		Van Staa et al., 2001
Source population		370 GPRD practices		683 GPRD practices
Study period		through Sept 1998		through July 1999
Design		Selected case control (3 cohorts)		Conventional case-control
N Cases		3,940		81,880
N Controls		23,379		81,880
Age	*50-69*	52.2%	*50-69*	47.9%
	70-79	28.9%	*70-84*	38.9%
	80-89	18.9%	*≥85*	13.2%
Sex	*Female*	75.0%	*Female*	75.6%
BMI	*≥25*	57.3%	*≥25*	52.3%

- Different patients (source population, study period, exclusion criteria)
- Study design (e.g. matching criteria for age)
- Definition of current statin use (last 6 months vs. last 30 days)
- Possibly different outcomes (mapping)
- Possibly uncontrolled/residual confounding

Work Package 2 - Databases

- WG 1 – Databases: Work Plan
- Conduct of 5 adverse event - drug pair studies in different EU databases
  - Selection of 5 key adverse event - drug pairs
  - Development of study protocols for all 5 pairs
  - Compare results of studies
  - Identify sources of discrepancies

Work Package 2 - Databases

- WG 1 – Databases: Progress status
- Selection of 5 key adverse events and drugs
- Initial list of 55 events and >55 drugs
- Finalisation based on literature review and consensus meeting
- Protocol under development

Antidepressants (incl. Benzodiazepines) **- Hip Fracture**
Antibiotics - **Acute liver injury**
Beta2 Agonists **- Myocardial infarction**
Antiepileptics - **Suicide**
Calcium Channel Blockers - **Cancer**

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New law: an opportunity for the epidemiologist statistician and programmer

A few highlights....

- Expert committee including pharmacoepidemiology
- Clear legal basis for post-authorisation safety studies
- Clear legal basis for post-authorisation efficacy studies
- Legal obligation for signal detection
- Benefit risk management planning
- Obligation to measure the effectiveness of risk minimisation

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Concluding remarks

New vision draws on all relevant data sources

Excellence is patient focused, proactive, proportionate, multi-disciplinary, B:R, transparent and science based

Health data and epidemiology support regulation throughout the medicines lifecycle

Embrace and challenge the evidence hierarchy

Call to arms: ensure protection and promotion of public health is effective in real life

We have the law: now we need the tools to implement it

for excellent protection and promotion of public health

Concluding remarks

Thomas:

- vision of science based excellence in medicines regulation
- ‘outside in’ view
- challenging the orthodox to improve the system

And finally……..

If the future Executive Director doesn't recognize the critical role of science and research in medicines regulation…….

……we will tell her that this is

'EVIDENCE BASED PROCESS IMPROVEMENT'

Mr Jim Slattery

And really really finally……..

Are regulators leaders or followers…….

……you decide

Acknowledgements

Member State network

ENCePP team and collaborators

IMI Protect team and consortium

Eudravigilance and signal detection teams

All the colleagues who protect and promote through risk management

European Commission, Council and Parliament

EMA's stakeholders