



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



PROTECT



Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

The Innovative Medicines Initiative's PROTECT project

INTERNATIONAL POSTMARKETING SURVEILLANCE
DISCUSSION

FDA, JUNE 18, 2010

Presented by: Xavier Kurz, European Medicines Agency

An agency of the European Union



Content

- The Innovative Medicines Initiative
- The PROTECT project
- Progress of scientific work as of 14 April 2010

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



The Innovative Medicines Initiative (IMI)

IMI's overall goal is to reinvigorate the biopharmaceutical sector in Europe

To address these challenges, “IMI will harness the know-how and expertise available across Europe's biopharmaceutical sector, by pooling competencies and resources from the public and the private domain”.

Four domains of research:

- Predictive safety
- Predictive efficacy
- Knowledge management
- Education & training

IMI funding programme



IMI Strategic Research Agenda



Identifies pre-competitive bottlenecks in the R&D process

Proposes recommendations to address these bottlenecks

Proposes a new model of Public-Private collaborations to implement these recommendations

For each topic: currently three-step process

- Competition between public consortia based on Expression of interest
- Merge between winning consortium and EFPIA consortium to develop the Full Proposal
- Full proposal is re-assessed by external experts

IMI: Ongoing projects

1st Call

- 15 projects, 395 teams, total budget of 281 M€
- Drug Safety (4), NeuroSciences (3), Training (4), Diabetes & Lung Diseases (4)
- EMA involvement:
 - Consortium leader (1)
 - Consortium member (1)
 - Advisory Board member (4)

IMI: Ongoing projects

2nd Call

- Knowledge management, Cancer Biomarkers, Rapid diagnosis of infections, Inflammatory disorders
- 124 Expressions of interest, 1,118 Applicants
- 25 EU Member States (all MS except Malta and Latvia)
- 7 FP7 Associated countries (Albania, Bosnia, Israel, Norway, Serbia, Switzerland, Turkey)
- 7 FP7 Third countries (Canada, China, Russia, Senegal, Ukraine, United-States)

IMI: Indicative call topics for 3rd call (2010)

- New in vitro assays and in vivo models for improved prediction of Drug Induced Liver Injury (DILI) in man.
- Novel biomarkers and models for cardiovascular safety.
- Immunogenicity: clinical relevance and risk minimisation of antibodies to biopharmaceuticals.
- Immunosafety of vaccines: new biomarkers associated with adverse events (early inflammation and autoimmune disease) + epidemiology
- Improving the scientific and preclinical models and tools for tuberculosis medicines research.
- Functional MRI application in CNS drug development for better patient characterisation in neurogenerative diseases like AD, MS, PD.
- Translational endpoints in autism, incl. establishment of a network of clinical centres of excellence.
- Personalised medicine in diabetes treatment.
- Training programs for the informed patient, incl. establishment of a pan-European industry-patient organisation network.

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.

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

SMEs:

Outcome Europe
PGRx

Others:

WHO UMC
GPRD
IAPO
CEIFE

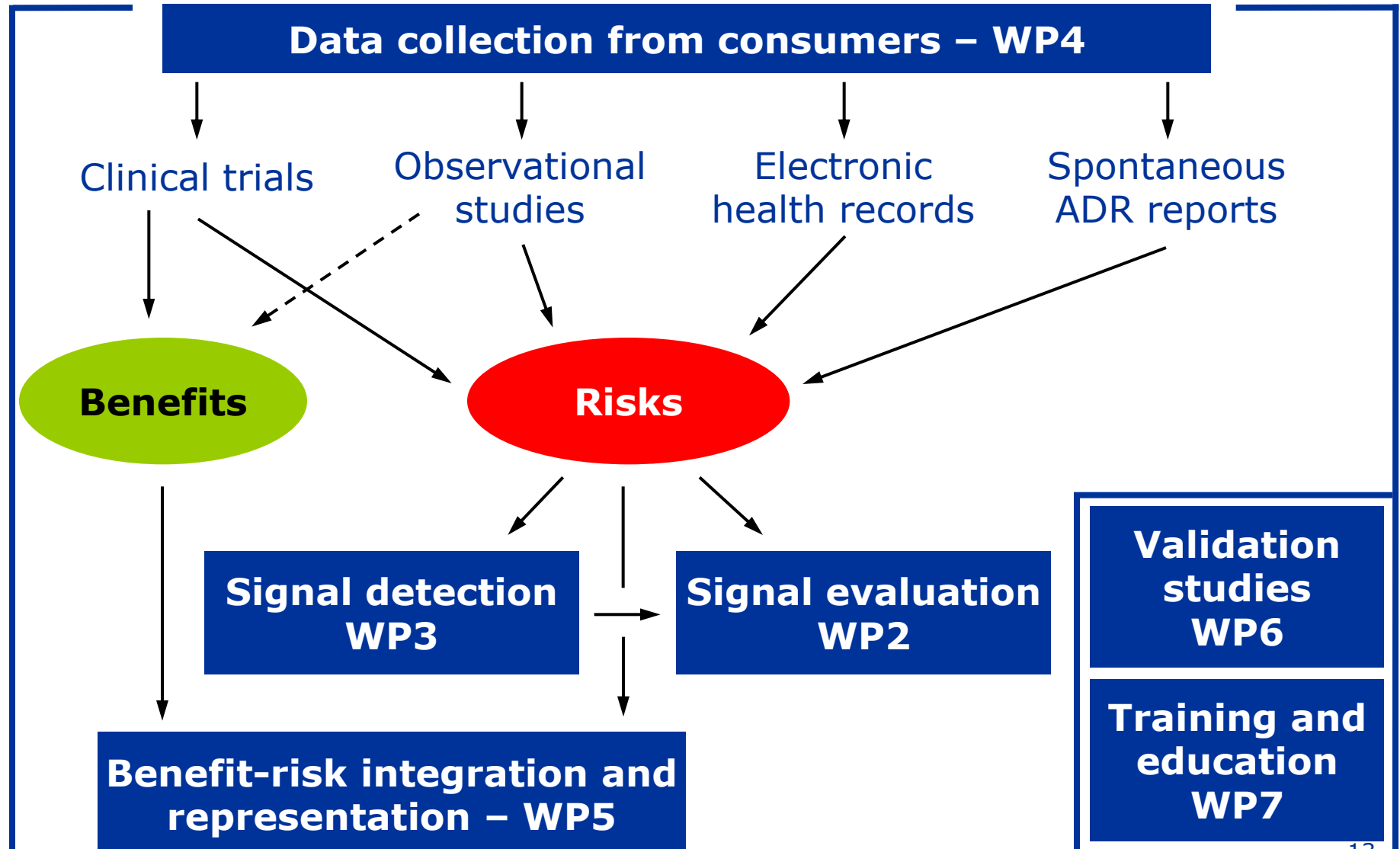


Private

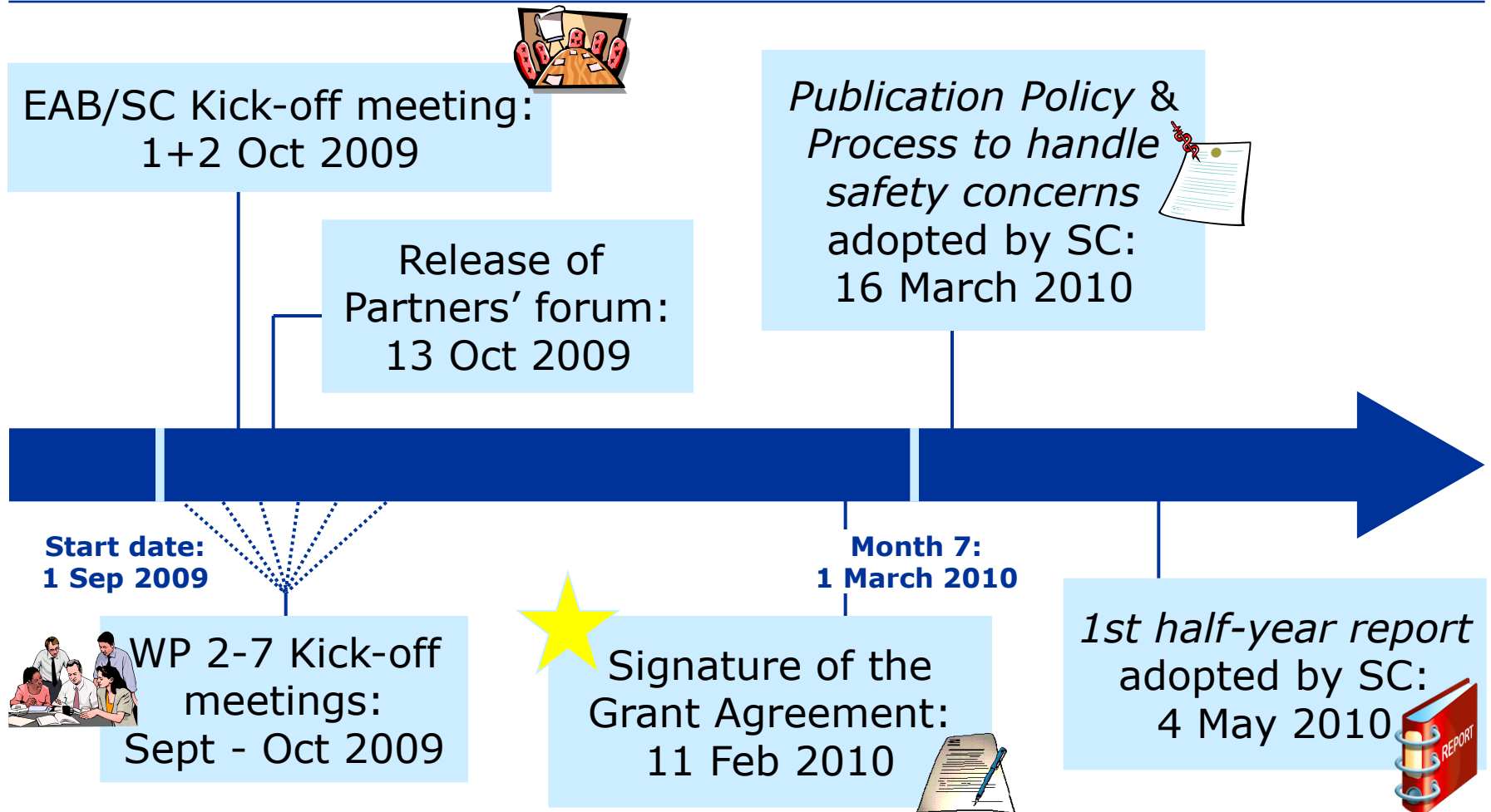
GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer Schering
Astra Zeneca
Lundbeck
NovoNordisk

Members of the External Advisory Board

Name	Affiliation	Expertise
Corinne De Vries, PhD	Department of Pharmacy and Pharmacology, University of Bath, UK	Pharmacoepidemiology
Trevor Gibbs, MD	Former Head of Global Pharmacovigilance and Product Safety, GSK, UK; Chief Medical Officer at ii4sm	Pharmacovigilance, Health Outcomes, Public Health
David Haerry	European AIDS Treatment Group (EATG), Brussels, Belgium	Public Health Patients' preference
Vicky Hogan, PhD	Director, Office of Risk Management and Science, Marketed Health Products Directorate (MHPD), Health Canada	Benefit-risk assessment
Michael Lewis, MD	EPES Epidemiology, Pharmacoepidemiology and Systems Research GmbH, Berlin, Germany	Pharmacoepidemiology
Allen Mitchell, MD	Slone Epidemiology Center, Boston, USA	Perinatal epidemiology Pharmacoepidemiology
Marcus Müllner, MD	Head of AGES PharmMed (Austrian Medicines and Medical Devices Agency), Austria	Benefit-risk assessment Clinical epidemiology Pharmacovigilance
Gerald Dal Pan, MD, M.H.S.	Director, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA	Pharmacovigilance, Drug development, Public Health & Risk management
Munir Pirmohamed, MD	Department of Pharmacology and Therapeutics, University of Liverpool, UK	Pharmacology Pharmacovigilance
Samy Suissa, PhD	Department of Epidemiology/Biostatistics, McGill University, Montreal, Canada	Biostatistics Pharmacoepidemiology



Milestones



Work Package 2

Objectives:

To:

- Develop
- Test
- Disseminate

methodological standards for the:

- Design
- Conduct
- Analysis

of pharmacoepidemiological studies applicable to:

- different safety issues
- using different data sources



Work Package 2: Work plan

Three Working Groups

- WG 1: Databases
- WG 2: Confounding
- WG 3: Drug Utilisation



Work Package 2: WG 1 plan - Databases

WG 1 plan

- Conduct of 5 Adverse Event-Drug pair studies in different EU databases
 - Selection of 5 key AE-drug pairs
 - Identification of key characteristics of databases
 - Development of study protocols for all 5 AE-drug pairs
 - Compare results of studies

Work Package 2: WG 1 progress status

Selection of 5 Key AEs and drugs

- Selection criteria:
 - AEs that caused regulatory decisions
 - Public health impact (seriousness of the event, prevalence of drug exposure, etiologic fraction)
 - Feasibility
 - Range of relevant methodological issues

Work Package 2: WG 1 progress status

Selection of 5 Key AEs and drugs

- Initial list of 55 events and >55 drugs
- Finalisation based on literature review and consensus meeting

Hip Fracture and antidepressants

Acute liver injury and antibiotics

Myocardial infarction and beta2 agonists

Suicide and antiepileptics

Cancer and calcium channel blockers

Work Package 2: WG 2 plan - Confounding

Objective

- To evaluate and improve innovative methods to control confounding

Method

- Creation of simulated cohorts
- Use of methods to adjust for observed and unobserved confounding
 - e.g. time-dependent exposure, propensity scores, instrumental variables, PERR adjustment

Work Package 2: WG 3 plan - Drug Utilisation

WG 3 plan

- Use of national drug utilisation data
- Inventory of data sources on drug utilization data for several European countries.
 - To describe and update the main characteristics of multinational European working groups on drug utilisation monitoring and research
 - Explore use of IMS data by companies
- Evaluation and dissemination of methodologies for drug utilisation studies in order to estimate the potential public health impact of ADRs

Work Package 3

Objective:

A yellow rectangular sticky note with a purple pushpin at the top left corner. The text "To Do:" is written on it in a black, cursive script, with the word "Do" underlined.

To assess existing methods, and develop new ones, for signal detection from spontaneous reports, electronic health records and clinical trials.

Scope

- To develop new methods for signal detection
- To implement and examine the value of screening methods in electronic health records
- To provide advice on good signal detection

Work Package 3: Sub-projects

1. Merits of disproportionality analysis
2. Structured database of known ADRs
3. Risk estimates from trials
4. Signal detection recommendations
5. Better use of existing ADR terminologies
6. Novel tools for grouping ADRs
7. Other information to enhance signal detection
8. Signal detection based on SUSARs
9. Subgroups and risk factors
10. Signal detection in Electronic Health Records
11. Drug-drug interaction detection
12. Duplicate detection



Work Package 3: Progress status

1. Merits of disproportionality analysis

- Development of protocols to demonstrate the value of existing or new methods for signal detection in prospective and retrospective testing

2. Structure database of known ADRs

Aim:

- to establish a **structured** format of already known ADRs to:
 - triage out known ADRs
 - reduce masking effects

Achievement (14/04/10):

- **212** (out of 355 centrally-authorised products) products completed
- List of 850 groups of closely related MedDRA terms shared by GSK
- Free text extraction currently under investigation

Work Package 3: Progress status

4. Signal detection recommendations

Aim:

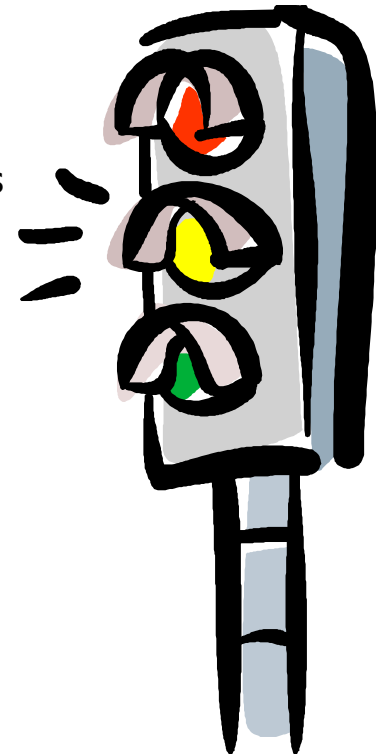
- to synthesise findings and outcome from other WP3 sub-projects
- Starting point is database survey

Scope:

- EudraVigilance, VigiBase
- National data sets: AEMPS, BFARM, DKMA, MHRA
- Company data sets: AZ, Bayer, Genzyme, GSK

Focus:

- Size (# reports) and breadth (# drugs and ADR terms)
- Types of reports (AEs or ADRs, Vaccines, Seriousness, ...)
- Additional information (presence of data elements available for stratification and sub-setting, e.g. demographics)
- Supporting systems (analytical methods, medical triages)



Work Package 4

Objectives:

To Do:

- To assess the feasibility, efficiency and usefulness of modern methods of data collection including using web-based data collection and computerised, interactive voice responsive systems (IVRS) by telephone
- To pilot approaches between data sources
- To measure the acceptability of these methods and assess the transferability of data collection methods in different countries and for other conditions

Prospective study in pregnant women in four countries is under development:

• Denmark 

• United-Kingdom 

• The Netherlands 

• Poland (tbc) 

Work Package 4: Patient workflow overview

Study subject picks up a leaflet in a pharmacy or browses specific web sites to find out about the study in one of 4 countries.

Study subject enrolls for the web or phone (IVRS) method of data collection.



Web

n = 1200 per country

Study subject completes the surveys online.



IVRS

n = 200 per country

Study subject completes the surveys via an outbound reminder or by inbound call she initiates.

Final outcome survey is completed at the end of pregnancy.

Work Package 5

Objectives:

A yellow sticky note with a purple pushpin at the top left corner. The text 'To Do:' is written in black, handwritten-style ink.

- To assess and test methodologies for the benefit-risk assessment of medicines
 - To develop tools for the visualisation of benefits and risks of medicinal products
-
- ➔ Individual and population-based decision making
 - ➔ Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers
 - ➔ From post-approval through lifecycle of products

Work Package 5

Review of methodologies and representations

- analysis and integration of different sources of evidence
- elicitation of preference values and uncertainties
- visual methods of benefit-risk representation

Selection of candidate methodologies

- criteria will include ability to assist decision-making by patients and prescribers

Choice and implementation of case studies

Visualisation technologies will be tested and developed if needed

Set of recommendations

Work Package 6

Objective:



To validate and test the feasibility of methods developed in PROTECT to other data sources and population groups.

Work Package 6

1. To apply tools and methods developed in WP2

- Feasibility in other types of data sources, e.g. disease registries
- Elements to be considered for the choice of methods and data sources:
 - usefulness
 - potentiality for high quality studies
 - impact of results
- Description of data source characteristics
- Recommendations regarding specific data elements and methods to be included

2. To evaluate signals detected by WP3 in other types of data sources

3. Testing of tools developed by WP4 and WP5, as defined at a later stage.

Work Package 7

Objective:



To identify training opportunities and support training programmes to disseminate the results achieved in PROTECT.



Work Package 7

1. Identify PROTECT deliverables that could be introduced in undergraduate and continuous education, and liaise with IMI pharmacovigilance and pharmacoepidemiology training consortium (EU2P)
2. Identify best tools for disseminating the project results and increasing expertise outside the consortium
3. Identify training opportunities from within the consortium that may be offered to consortium partners and possibly to PhD students (eg. EU2P)

More information?

Website: www.imi-protect.eu

Email: Protect_Support@ema.europa.eu