PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by an European ConsorTium

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What are the needs ?

At the time of authorisation of medicines, information is most often lacking on adverse reactions that occur:

- with a low frequency
- after a long delay
- in specific population groups such as pregnant women or patients with chronic diseases.

This is because clinical trials carried-out during drug development have a selected population, often include limited number of patients and have a limited duration.

What are the needs ?

Additional information on the safety of medicines need to be collected and analysed quickly as soon as the product is launched on the market.

This is called “Pharmacovigilance”. It includes:

- collection and compilation of data on adverse drug reactions through spontaneous reporting systems
- prompt detection of new safety issues (« signals »)
- evaluation of signals in observational (« pharmaco-epidemiological ») studies or clinical trials
- based on this information, constant re-evaluation of the benefit-risk of medicines

What are the needs ?

- **Data collection**
  - efficient and simple methods for early data collection directly from patients
  - non-prescribed medicines
  - linkage to health event databases
- **Signal detection**
  - spontaneous reports: in-depth analysis of methods and good practice recommendations
  - better use of electronic health records and clinical trials
- **Signal evaluation**
  - understanding the variability in results of studies of a same safety issue in different data sources
  - detailed guidance and standards regarding design, conduct and analysis of pharmacoepidemiological studies
- **Benefit-risk assessment**
  - Need for widely accepted method for integrating data on benefits and risks from clinical trials, observational studies and drug reaction reports
  - benefit-risk assessment for patients, prescribers, regulators...

PROTECT Goal

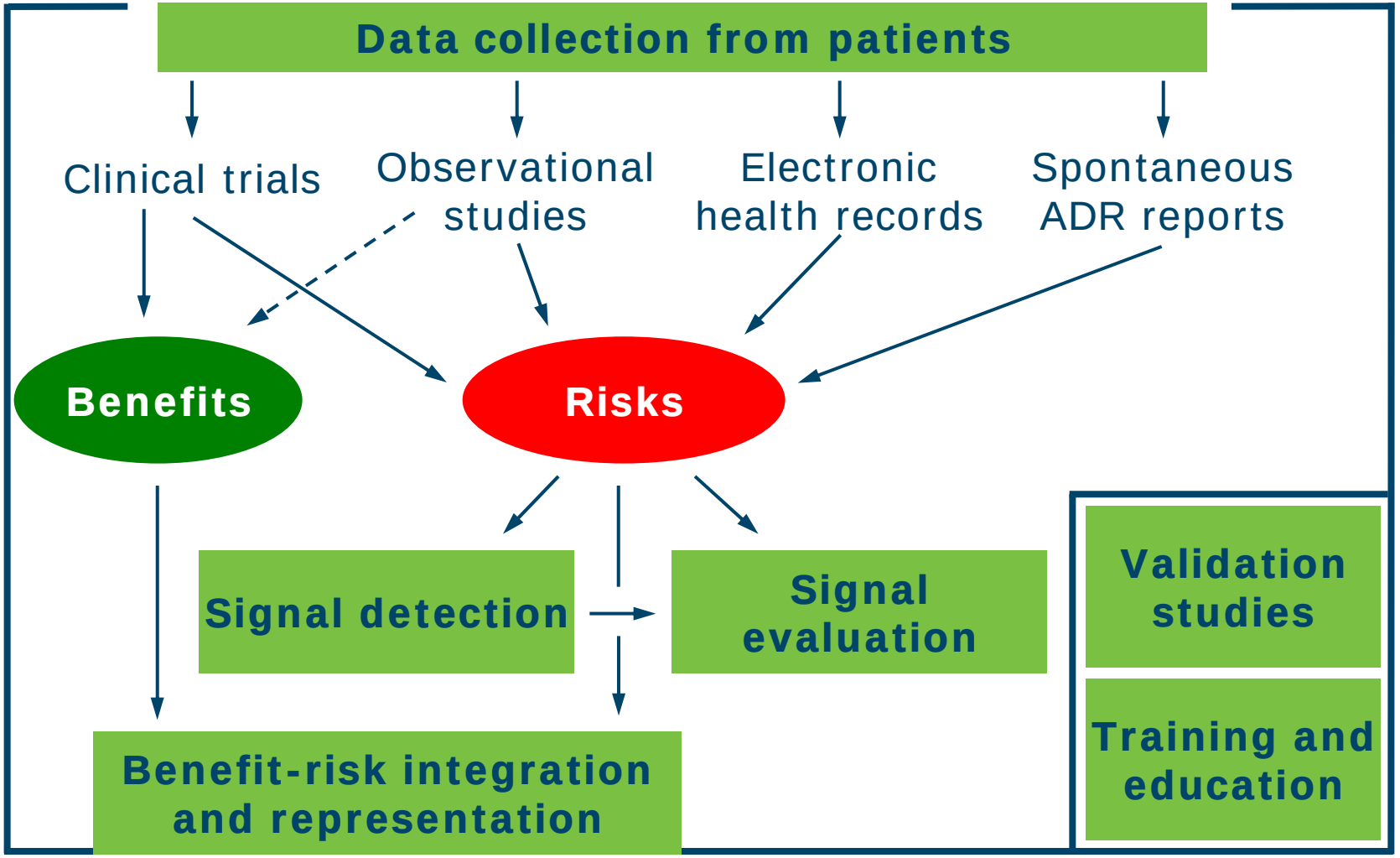
To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods:

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 are tested in real-life situations.

PROTECT includes six modules



Data collection from patients

Objectives:

- 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 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 
- The Netherlands 
- Poland 
- United-Kingdom 

Data collection from patients

Design of research

Study subject picks up a leaflet in a pharmacy 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.

Data collection from patients

Why is it important?

- These new methods will be increasingly important for medicines where numbers of patients in pre-authorisation studies are limited and **close surveillance of treated patients** is needed (e.g. orphan drugs, advance therapy products)
- Direct patient data collection will **help monitor the effects of drug use in pregnancy** as pregnant women are usually excluded from clinical trials
- Use of modern technology also has the potential to be used **to collect drug utilisation, outcome and other pharmacovigilance** data on other target populations
- By recruiting and collecting data directly from the patients, data on **long term follow up of safety, efficacy and outcomes** can be collected.

Signal detection

Objective:

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

Signal detection

Why is it important?

Optimisation of methods of signal detection will:

- **Facilitate the use of the available drug safety data** in an efficient and appropriate manner
- Facilitate the **early detection of new emerging safety issues** which may impact on patients' safety
- Facilitate the (re-)assessment of the **benefit-risk profile of medicines** at the earliest possible stage and during their life-cycle.

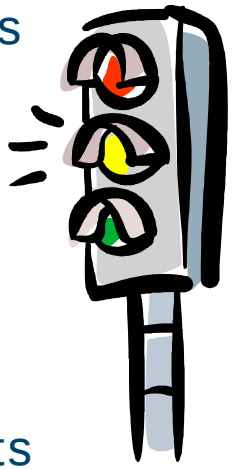
Signal detection: sub-projects

1. Merits of disproportionality analysis
2. Structured database of known adverse drug reactions (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

Signal detection: progress status (example 1)

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

Signal detection: progress status (example 2)

4. Signal detection recommendations

- Aim:
  - to synthetise findings and outcome from other 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 (dosage,
  - Supporting systems (analytical methods, medical triages)

Signal evaluation

Objectives

To:

- develop
- test
- disseminate

methodological standards for the:

- design
- conduct
- analysis

of pharmacoepidemiological studies applicable to:

- different safety issues
- using different data sources

Signal evaluation

Why is it important?

- To promote **standard recommendations for essential methodological parameters** for the conduct of PE studies.
- To build an **appropriate infrastructure and research tools** to rapidly address any urgent safety issues arising in the EU.
- To disseminate guidelines on how to identify and use **national drug utilisation data** for quicker assessment of the public health impact of safety signals
- As these methods will be tested in a wide range of data sources, PROTECT will facilitate the **evaluation of safety issues in different population groups**

Signal evaluation

Three Working Groups

1. Databases
2. Confounding
3. Drug Utilisation

Signal evaluation (example 1)

- Conduct of 5 Adverse Event-Drug pair studies in different EU databases
  - Selection of 5 key issues already known for some drugs, based on defined criteria, e.g. public health impact
  - Development of study protocols
  - Comparison of results of studies
- Initial list of 55 safety issues and 55 drugs
- Result of selection:

Hip Fracture and antidepressants
Acute liver injury and antibiotics
Myocardial infarction and beta2 agonists
Suicide and antiepileptics
Cancer and calcium channel blockers

Signal evaluation (example 2)

Use of national drug utilisation data

- Inventory of data sources on drug utilisation data for several European countries.
- Evaluation and dissemination of methodologies for drug utilisation studies in order to estimate the potential public health impact of adverse drug reactions

Benefit-risk integration and representation

Objectives:

- 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

Benefit-risk integration and representation

Why is it important?

- PROTECT will provide a clearer understanding of **how to weigh benefits and risk of a medicine** and highlight the data and value judgments needed in these process
- The development of a shared framework also has the **potential to shorten delays in decision-making** about the licensing of medicines.
- To take into account **perspectives of patients, healthcare prescribers, regulatory agencies, and drug manufacturers** in decision-making
- **Continuous benefit-risk evaluation** from post-approval though lifecycle of products
- **Visual representation** and better understanding

Benefit-risk integration and representation

- Review of methodologies, technologies and representation
  - 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

Validation studies

Objective:

To validate and test the feasibility of methods developed in PROTECT to other data sources and population groups not used in case studies.

Validation studies

Why is it important?

- **Large number of data sources in Europe with information on adverse drug reactions**, e.g. disease registries established by specialists, pregnancy registries, drug registries.
- **Many data sources are under-used** for the evaluation of drug safety or are even not known.
- It is important to evaluate the **applicability and feasibility of the tools developed in PROTECT** to these other data sources.
- This will also require **identification and characterisation of other data sources**.
- This project will contribute to **broaden the scope of drug safety monitoring** in Europe.

Training and Communication

Objective:

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

Training and Communication

1. Identify PROTECT results 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)

Good start - works well!

EAB/SC Kick-off meeting:
1+2 Oct 2009

Release of Partners' forum:
13 Oct 2009

Publication Policy & Process to handle safety concerns adopted by SC:
16 March 2010

Start date:
1 Sep 2010

WP 2-7 Kick-off meetings:
Sept - Oct 2009

Month 7:
1 March 2010

Signature of the Grant Agreement:
11 Feb 2010

1st half-year report adopted by SC:
4 May 2010

31 partners

Different views and needs!

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

Thank you!

The PROTECT community

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More information?

Website: www.imi-protect.eu

Email: Protect_Support [AT] ema.europa.eu