The PROTECT project

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

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• The views expressed are those of the authors only.

• PROTECT work in this presentation is work by WP2 colleagues.

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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

Academic Institutions:
- University of Munich
- FICF (Barcelona)
- INSERM (Paris)
- Mario Negri Institute (Milan)
- Poznan University of Medical Sciences
- University of Groningen
- University of Utrecht
- Imperial College London
- University of Newcastle

Others:
- GPRD
- IAPO
- CEIFE

EFPIA companies:
- GSK (Deputy Co-ordinator)
- Sanofi-Aventis
- Roche
- Novartis
- Pfizer
- Amgen
- Genzyme
- Merck Serono
- Bayer
- AstraZeneca
- Lundbeck

Private

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

SMEs:
- Outcome Europe
- PGRx

Others:
- WHO UMC

Training and education WP7

Benefit-risk integration and representation – WP5

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

Validation studies WP6
WP 2: Framework for pharmacoepidemiological studies

To:
• develop
• test
• disseminate

Objectives:
• design
• conduct
• analysis

methodological standards for the:
• different safety issues
• using different data sources

WP2 participants and their role

WP2 has 3 Working groups (WG)

WP2 participants and their role

WP2 participants and their role

Work Package 2 – WG1: Databases

Conduct of adverse event - drug pair studies in different EU databases

• Selection of 5 key adverse event - drug pairs
• Development of study protocols for all pairs
• Compare results of studies
• Identify sources of discrepancies

Databases
• Danish National registries (DKMA)
• Dutch Mondrian databases (MONDRIAN)
• British GPRD databases (GPRD)
• British THIN databases (THIN)
• German Bavarian claims database (BAVARIA)

Selection of key adverse events and drugs

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

Population nr’s 6 EU databases

Database | Country | Source | Cum Population nr | Active population nr
--- | --- | --- | --- | ---
GPRD | UK | GP | 11 M | 2.6 M
Mondrian | NL | Multisource | 1.4 M (GP) | 1.6 M (GP), 12.5 M (Claims)
Bifap | ES | GP | 2.2 M | 1.2 M
Danish registries | DK | Multisource | 5.2 M (All DBs) | 5.2 M (All DBs)
THIN | UK | GP | 7.8 M | 3.1 M
Bavarian-Claims | DE | Claims | 10.5 M | 9.5 M
**Characteristics of 6 EU DBs**

<table>
<thead>
<tr>
<th>Database</th>
<th>Coding diagnoses</th>
<th>Coding drugs</th>
<th>Start year</th>
<th>Nation wide</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPRD</td>
<td>Read BNF</td>
<td></td>
<td>2001</td>
<td>7% UK</td>
</tr>
<tr>
<td>Mondrian</td>
<td>ICPC ICD</td>
<td>ATC</td>
<td>1991</td>
<td>90% NL (pharmacy), 6.6% NL (GP)</td>
</tr>
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<td>铗</td>
<td>ATC</td>
<td>2001</td>
<td>7% ES</td>
<td></td>
</tr>
<tr>
<td>Bifap</td>
<td>ICPC ATC</td>
<td></td>
<td>2001</td>
<td>90% NL (pharmacy), 0.6% NL (GP)</td>
</tr>
<tr>
<td>Danish registries</td>
<td>ICD ATC</td>
<td>1994 (med prod), 1977 (pat register)</td>
<td>100% DK</td>
<td></td>
</tr>
<tr>
<td>THIN</td>
<td>READ BNF</td>
<td></td>
<td>2003</td>
<td>5.7% UK</td>
</tr>
<tr>
<td>Bavarian Claims</td>
<td>ICD ATC</td>
<td>2001</td>
<td>Bavaría</td>
<td>84%</td>
</tr>
</tbody>
</table>

**Approach**

- Common protocol for each drug-ae pair
  - Descriptive studies for drug-ae pairs in all databases
  - 5 different study designs in selected databases
  - Extensive sensitivity analyses on main methodological issues
- Common standards, templates, procedures
  - Detailed data specification including definitions of exposures, outcomes, and confounders for each database.
  - Blinding of results of individual DB analyses
- Submission of protocols to ENCePP registry of studies

**WG1 Preliminary results:**

**Antibiotic use by age in 6 EU databases**

**WG1 Preliminary results:**

**Antidepressant use by year in 6 EU databases**

**WG1 Preliminary results:**

**BZD use by age in 6 EU databases**

**WG1 Preliminary results:**

**Incidence of hip/femur fracture by age in 2009 in 4 EU databases**
**Work Package 2 – WG2: Confounding**

**Work Plan**

- **Objective**
  - To evaluate and improve innovative methods to control confounding
- **Method**
  - Simulation studies to test methods
  - Application of methods to real-life data sets

**Progress status**

- Guideline for conduct of simulation studies
  - Propensity score methods
  - Instrumental variable methods
- First results
  - Usefulness of measures for balance for reporting of the amount of balance reached in PS analysis and selecting the final PS model
  - Comparison of methods to control for time-dependent confounding
  - Evaluation of IV in case-control and cohort studies

**Simulation study propensity scores**

Measuring balance and model selection in propensity score methods

**Application of propensity scores**

Balance measures for propensity score methods: a clinical example on beta-agonist use and the risk of myocardial infarction

**Work Package 2 – WG3: Drug Utilisation**

**Work Plan**

- Use of national drug utilisation data (incl IMS)
- 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
- Collaboration with EuroDURG agreed
Work Package 2 – WG3: Drug Utilisation

Progress Status

- Inventory on Drug Use data “Drug consumption databases in Europe”
  (last version August 2011: [http://www.imi-protect.eu/results.html])
  - 11 research working groups across Europe identified
  - Databases heterogeneous, administrative focus and influenced by the national health system structure
- Collecting DU data (in/out hospital)
  - from public databases (for 6 selected drugs)
  - from IMS (Antibiotics, Antidepressants and Benzodiazepines. Explored for other drugs)

Next steps

- Literature Search on Randomized Controlled Trials (RCT)
  - Search for existing meta-analyses or syntheses available in the literature (avoid duplication of work already done).
  - Dec 2011: Development of specific protocols for literature search
  - Jan 2012: Start of literature search starts.
- Public health impact of selected Drug AE pairs
  - Evaluate validity of drug use data
  - Estimate the exposed population to drugs and calculate population attributable risk

Finally

- Reduce variation due to methodological choice of individual researchers
- Explain variation due to characteristics of country/database
- Disseminate methodological guidance for PE studies
- More consistency in drug-ae studies to improve B/R assessment of medicines

Members of PROTECT WP2

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