The PROTECT project

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

Latest update: June 2012
PROTECT is receiving support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu), resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.
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.
Clinical trials
Observational studies
Electronic health records
Spontaneous ADR reports

Data collection from consumers – WP4

Clinical trials → Benefits
Observational studies → Risks
Electronic health records → Risks
Spontaneous ADR reports → Risks

Signal detection WP3
Signal evaluation WP2

Benefit-risk integration and representation – WP5

Reproducibility studies WP6
Training and education WP7
Partners (33)

**Public**

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

**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
- University of Aarhus

**Others:**
- WHO UMC
- GPRD (part of MHRA)
- IAPO
- CEIFE

**SMEs:**
- Outcome Europe
- PGRx

**Private**

**EFPIA companies:**
- GSK (Deputy Co-ordinator)
- Sanofi- Aventis
- Roche
- Novartis
- Pfizer
- Amgen
- Genzyme
- Merck Serono
- Bayer
- Astra Zeneca
- Lundbeck
- NovoNordisk
- Takeda
- Eli Lilly
## List of members of the External Advisory Board

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vries Corinne, PhD</td>
<td>Department of Pharmacy and Pharmacology, University of Bath, UK</td>
<td>Pharmacoepidemiology</td>
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<tr>
<td>Trevor Gibbs, MD</td>
<td>Former Head of Global Pharmacovigilance and Product Safety, GSK, UK</td>
<td>Pharmacovigilance</td>
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<td>Health Outcomes</td>
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<td>Public Health</td>
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<tr>
<td>David Haerry</td>
<td>European AIDS Treatment Group (EATG), Brussels, Belgium</td>
<td>Public Health</td>
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<td>Patients’ preference</td>
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<tr>
<td>Vicky Hogan, MSc</td>
<td>Associate Director General, Marketed Health Products Directorate (MHPD), Health Canada, Canada</td>
<td>Benefit-risk assessment</td>
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<tr>
<td>Michael Lewis, MD</td>
<td>EPES Epidemiology, Pharmcoepidemiology and Systems Research GmbH, Berlin, Germany</td>
<td>Pharmacoepidemiology</td>
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<tr>
<td>Allen Mitchell, MD</td>
<td>Slone Epidemiology Center, Boston, USA</td>
<td>Perinatal epidemiology</td>
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<tr>
<td>Marcus Müllner, MD</td>
<td>Head of AGES PharmMed (Austrian Medicines and Medical Devices Agency), Austria</td>
<td>Benefit-risk assessment</td>
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<td>Clinical epidemiology</td>
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<tr>
<td>Gerald Dal Pan, M.D., M.H.S.</td>
<td>Director Office of Drug Safety, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA</td>
<td>Pharmacovigilance</td>
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<td></td>
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<td>Drug development</td>
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<td>Public Health &amp; Risk management</td>
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<tr>
<td>Munir Pirmohamed, MD</td>
<td>Department of Pharmacology and Therapeutics, University of Liverpool, UK</td>
<td>Pharmacology</td>
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<td>Samy Suissa, PhD</td>
<td>Division of Epidemiology/Biostatistics, McGill University, Montreal, Canada</td>
<td>Biostatistics</td>
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<td>Pharmacoepidemiology</td>
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# Task Forces (TF) perform the following tasks:
- Data collection
- Software for B/R modelling & illustration
- Publications
WP1: Project Management and Administration

Objectives:
To create and maintain the conditions needed to achieve the objectives and deliverables of the PROTECT project.

- Scientific steer towards the overall project objectives and strategy
- Quality control and assurance measures
- Administrative, organisational and financial support
- Track of work progress in line with the work programme
- Knowledge management tools and strategies
- Financial monitoring and accountancy
WP2: 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
Art is made to disturb. Science reassures.

Georges Braque

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

<table>
<thead>
<tr>
<th>Statins only</th>
<th>Meier et al., 2000</th>
<th>Van Staa et al., 2011</th>
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</thead>
<tbody>
<tr>
<td>Current use</td>
<td>0.55 (0.44-0.69)</td>
<td>Current use</td>
</tr>
<tr>
<td>N prescriptions</td>
<td></td>
<td>Time since use</td>
</tr>
<tr>
<td>• 1-4</td>
<td>0.51 (0.33-0.81)</td>
<td>• 0-3 months</td>
</tr>
<tr>
<td>• 5-19</td>
<td>0.62 (0.45-0.85)</td>
<td>• 3-6 months</td>
</tr>
<tr>
<td>• 20</td>
<td>0.52 (0.36-0.76)</td>
<td>• 6-12 months</td>
</tr>
<tr>
<td>• &gt; 12 months</td>
<td>0.71 (0.50-1.01)</td>
<td>• &gt; 12 months</td>
</tr>
<tr>
<td>Recent use</td>
<td>0.67 (0.50-0.92)</td>
<td>Past use</td>
</tr>
<tr>
<td>Past use</td>
<td>0.87 (0.65-1.18)</td>
<td></td>
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<tr>
<td>Statins (current) and type of fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>0.12 (0.04-0.41)</td>
<td>Hip</td>
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<tr>
<td>Hand, wrist or arm</td>
<td>0.71 (0.52-0.96)</td>
<td>Radius/ulna</td>
</tr>
<tr>
<td>Vertebral</td>
<td>0.14 (0.02-0.88)</td>
<td>Vertebral</td>
</tr>
<tr>
<td>Other</td>
<td>0.43 (0.23-0.80)</td>
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### Why such a difference?

<table>
<thead>
<tr>
<th>Source population</th>
<th>Meier et al., 2000</th>
<th>Van Staa et al., 2011</th>
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<tbody>
<tr>
<td>370 GPRD practices</td>
<td>683 GPRD practices</td>
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</table>

<table>
<thead>
<tr>
<th>Study period</th>
<th>Through Sept 1998</th>
<th>Through July 1999</th>
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<table>
<thead>
<tr>
<th>Design</th>
<th>Selected case control (3 cohorts)</th>
<th>Conventional case-control</th>
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<table>
<thead>
<tr>
<th>N Cases</th>
<th>3,940</th>
<th>81,880</th>
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<table>
<thead>
<tr>
<th>N Controls</th>
<th>23,379</th>
<th>81,880</th>
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<table>
<thead>
<tr>
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<th></th>
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<th>&gt;85</th>
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<table>
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<th>BMI</th>
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<th>52.2%</th>
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<th>75.0%</th>
<th>75.6%</th>
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<th></th>
<th>57.3%</th>
<th>52.3%</th>
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</thead>
</table>

- 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

Work plan

• Three Working Groups (WG1-WG3)
  – Databases
  – Confounding
  – Drug Utilisation
WG1: Databases

Work Plan

- 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
  - Conduct studies and compare results
  - Identify sources of discrepancies

Databases

- Danish national registries
- Dutch Mondriaan database
- British GPRD database
- British THIN databases
- Spanish BIFAP project
- German Bavarian claims database
WG1: Databases

Progress status

- Selection criteria of key adverse events and drugs
  - 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
WG1: Databases

Progress status

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

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Condition</th>
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<tbody>
<tr>
<td>Antidepressants (incl. Benzodiazepines)</td>
<td>Hip Fracture</td>
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<tr>
<td>Antibiotics</td>
<td>Acute liver injury</td>
</tr>
<tr>
<td>Beta2 Agonists</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Suicide</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Cancer</td>
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</table>
WG1: Databases

Progress status

• Development of study protocols
  – Protocols for each DrugAE pair have been developed
  – Descriptive studies for the Drug AE pairs in all databases
  – 5 different study designs in selected databases
    ◦ Cohort design
    ◦ Nested case control design
    ◦ Case crossover
    ◦ Self controlled case series
    ◦ Population based case control
  – Harmonised approach across the 5 drug-event pairs (common standards, processes and template)
  – Blinding of results procedure
WG1: Databases

Progress status

• Conduct studies
  - First results of the descriptive studies have been delivered.
  - Cohort analysis are ongoing.
  - Manuscripts describing and explaining discrepancies in results between databases are planned in 2012.
WG2: Confounding

Work Plan

• 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, prior event rate ratio (PERR) adjustment, evaluation of measures of balance in real-life study
WG2: Confounding

Progress status

- Determine parameters of simulated cohorts/creation simulated cohorts (Sept 2009 – Sept 2010)
  - Sept 2010: Final protocol on how to conduct simulation studies is available
  - Sept 2010-Sept 2011: conduct of simulation studies on:
    - Propensity score/ balance measure methods to control for confounding
    - Normal distributed covariates, univariate measures of balance
    - Non-normal distributed covariates, multivariate measures of balance
  - Manuscripts
WG2: Confounding

Progress status

- Studies on propensity score / balance measure and propensity scores time dependent methods to control for observed confounding (Jan 2011 – Aug 2013)
  - Manuscripts:
    - Groenwold RHH, Klungel OH, Grobbee DE, Hoes AW. Selection of confounding variables should not be based on observed associations with exposure. Eur J Epidemiol 2011 - published
WG2: Confounding

Progress status

- Studies on Instrumental variables (IVs) / methods to control for unobserved confounding (Jan 2011 – Feb 2014)
  - Simulation studies on IVs
    • Performed simulation on validity of IV analysis in different settings with both continuous and binary instruments, exposures, and outcomes. Including cohort and case-control design. Currently finalizing simulations and writing report.
  - Identify potential IVs for each of the 5 ADRs
    • Unrealistic to identify IVs for all ADR pairs (inventory has been made). Aim is to start IV analysis using empirical data in beginning of 2012 on statins and cardiovascular events.
  - Report on application of IVs
    • Manuscripts:
WG2: Confounding

Progress status

- Multidatabase studies (Jun 2011 – Feb 2014)
  - Simulation studies:
    - Background: PROTECT → can we study adverse drug reaction using different European databases? Can we merge data / results from different European databases?
    - Different types of censoring in different databases:
      - Left censoring, i.e., no historic exposure information
      - Right censoring, i.e., no exposure and outcome information after loss to follow-up
    - Simulation studies are ongoing to evaluate the impact of different left and right censoring mechanisms on estimates of cumulative exposure effects, in the presence of time-varying exposure.
WG3: Drug utilisation data

Work Plan

• Elaborate an inventory of DU databases in Europe
  - From Outpatient healthcare sector & Inpatient healthcare sector
  - From National Drug Consumption Databases & IMS Health Inc

• Estimate the population attributable risk
  - Evaluate validity of DU data from the inventory and calculate prevalence of population exposed to drugs in National databases
  - Literature review of RCTs and OS and estimate the effect measures association drug-adverse effect

• Analysis of discrepancies of results
  - Compare drug exposure between clinical databases (WG1) and national drug consumption databases (WG3)
  - Compare results in databases (WG1) and RCTs/OS (WG3)
WG3: Drug utilisation data

Progress status

• Inventory of Drug Utilisation data
  - “Drug Consumption Databases in Europe” full report (latest version Aug 2011) is available on the PROTECT website http://www.imi-protect.eu/results.html
  - Goals:
    • To describe the characteristics of non-commercial drug consumption data providers in Europe, with special emphasis on pricing and reimbursement agencies.
    • To report the features of each country health policy systems and lists several pharmaceutical data sources. It includes a brief summary of data provided by Intercontinental Marketing Services (IMS Health).
    • To provides an updated list of national drug consumption databases in selected European countries, describing their main characteristics and accessibility.
    • To outlines the validity of these European national drug consumption databases.
    • To explores the availability of inpatient drug consumption data at national level.

• Work in progress:
  • Countries included : Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden and United Kingdom.
  • Further European countries will be included and the report is regularly updated.
  • Manuscript: Sabate et al. Research working groups on drug utilisation across Europe – submitted to Pharmacoepidemiological Drug Safety (under review)
WG3: Drug utilisation data

Progress status

• Literature Search of meta-analyses or syntheses available in the literature
  – Avoid duplication of work already done
  – Search for Meta-analysis and complete with observational studies published afterwards for the 5 drug AE pairs selected in WG1
  – Development of specific protocols for literature search - completed in December 2011
  – Literature search – started in January 2012 and final report planned in December 2012

• Calculate the prevalence of population exposed to the selected drugs in 8 European countries
  – Denmark, France, Germany, Netherlands, Norway, Spain, Sweden, and United Kingdom (databases from the inventory of drug utilization) – completed in July 2012
WG3: Drug utilisation data

Progress status

- Finalize the literature Search on Randomized Controlled Trials (RCT) and observational studies (OS) for the 5 drug AE pairs selected in WG1 (July 2012). Results (report / publication) with relative risk /odds ratio to calculate population attributable risk (PAR) are expected Dec 2012

- Public health impact of selected Drug AE pairs: Develop a protocol to calculate PAR (Dec 2012) and calculate PAR (Nov 2013). Report/publication (Feb 2014)

- Identification of discrepancies:
  - Comparison of prevalence to drug exposure between clinical databases (WG1) and national drug consumption databases (WG3) (November 2013
  - Identification of discrepancies: Comparison of results in databases (WG1) and RCTs/OS (WG3) (February 2014)
In summary, overview of WP2 milestones achieved to date (in blue) and planned (in grey)

**WG1 Databases**
- 5 drug AE pairs & 6 EU databases
- 6 protocols & data analysis plan
- First results of descriptive studies
  - Cohort studies ongoing
  - Other designs studies
- Analysis of discrepancies between databases is ongoing for descriptive results
- Multidatabase studies
- Application of PS and IV methods in empirical data from EU databases
- Comparison of prevalence of exposed population EU vs national DU databases & EU databases vs RCTs/OS

**WG2 Confounding**
- Protocol for simulation studies on PS and IV methods
- Studies on PS/balance measure and PS time dependent methods (observed confounding)
- Studies with simulated data on IV/ methods (unobserved confounding)

**WG3 Drug utilization**
- Inventory DU data, yearly updates
- Systematic literature review RCTs/OS studies ongoing
- Evaluate validity of data
- First results of prevalence of exposed population
- Effect measures association drug-adverse effect
- Estimation of population attributable risk
Objective:

To improve early and proactive signal detection from spontaneous reports, electronic health records, and clinical trials.
To improve early and proactive signal detection from spontaneous reports, electronic health records, and clinical trials.
Work Package 3: Signal Detection

Scope

- Develop new methods for signal detection in Individual Case Safety Reports.
- Develop Guidelines for signal detection and strengthening in Electronic Health Records.
- Implement and evaluate concept-based Adverse Drug Reaction terminologies as a tool for improved signal detection and strengthening.
- Evaluate different methods for signal detection from clinical trials.
- Recommendations for good signal detection practices.
### WP3 Sub-packages

<table>
<thead>
<tr>
<th>Sub-packages</th>
<th>Leader</th>
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<tbody>
<tr>
<td>3.01 Merits of disproportionality analysis</td>
<td>EMA</td>
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<tr>
<td>3.02 Concordance with risk estimates</td>
<td>AEMPS</td>
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<tr>
<td>3.03 Structured database of SPC 4.8</td>
<td>EMA</td>
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<td>3.04 Signal detection recommendations</td>
<td>AZ</td>
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<td>3.05 Better use of existing ADR terminologies</td>
<td>UMC</td>
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<td>3.06 Novel tools for grouping ADRs</td>
<td>INSERM</td>
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<td>3.07 Other information to enhance signal detection</td>
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<td>3.08 Subgroups and stratification</td>
<td>MHRA &amp; EMA</td>
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<td>3.09 Signal detection from clinical trials</td>
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<td>3.10 Signal detection in EHRs</td>
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<td>3.11 Drug-drug interaction detection</td>
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<tr>
<td>3.12 Duplicate detection</td>
<td>MHRA</td>
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3.01-Properties of disproportionality analysis

Scope

- Directly compare different statistical signal detection algorithms:
  - Within different databases
  - Between databases on same products

Current status

- All methods coded in SAS
- Implementations validated
3.02–Concordance with risk estimates

Progress to date

- Study Protocol adopted
- Selection of 78 Drug–ADR pairs from pharmacovigilance issues leading to European regulatory recommendations in the period 2007-2010

Future work

- Identification of published formal studies related to the above drug-ADR pairs
- Comparison with measures of disproportionality in EudraVigilance and AEMPS data
3.03–Structured db of SPC 4.8

- **Objective**
  Making available, in a *structured* format, already known ADRs to allow for:
  - Triaging out known ADRs
  - Automatic reduction of masking effects

- **Current status**
  - Database for centrally authorised products (CAP) fully implemented
  - Will provide gold standard for 3.01
  - Maintenance procedure agreed
  - Published on PROTECT website
  - Extension to non-CAP products being tested
**Structured database of SPC 4.8**

- Fuzzy text matching (automatic algorithm) to match MedDRA terms from manual extracted ADRs from the SPCs
  - Stemming, Stop words, Permutations, Synonyms and Spelling variations
  
  **Sensitivity of verbatim matching increased from 72% → 98%**

<table>
<thead>
<tr>
<th>Drug</th>
<th>SPC Term</th>
<th>Verbatim match</th>
<th>Fuzzy matching algorithm</th>
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<tbody>
<tr>
<td>Aclasta</td>
<td>FLU-LIKE SYMPTOMS</td>
<td>-</td>
<td>Flu symptoms</td>
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<tr>
<td>Advagraf</td>
<td>OTHER ELECTROLYTE ABNORMALITIES</td>
<td>-</td>
<td>Electrolyte abnormality</td>
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<tr>
<td>Advagraf</td>
<td>PAIN AND DISCOMFORT</td>
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</table>
3.04-Database survey

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

- **Focus**
  - # reports, # 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)

- **Current status**
  - Survey deployed and completed by most organisations
3.04-Overview of Databases

EBGM implementations via external vendor systems

Lack of comparability

General db info

metadata

AE coding

drug coding

db type

Therapeutics only

Mixed Therap./vaccines

Mixed Therap./vaccines

Mixed Therap./vaccines

WHO DDe

Custom

Custom

WHO DDe

MedDRA

MedDRA

MedDRA

1o WHO-ART

2o MedDRA
3.04-Data elements – demography SD

(% data available in all case reports)

<table>
<thead>
<tr>
<th>DB holder</th>
<th>Receipt Date</th>
<th>Age/DoB</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Country of case</th>
<th>Subject ID</th>
</tr>
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<tbody>
<tr>
<td>DKMA</td>
<td>✓</td>
<td>✓(unk)</td>
<td>✓(100%)</td>
<td>×</td>
<td>✓(100%)</td>
<td>✓(unk)</td>
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<tr>
<td>UMC</td>
<td>✓</td>
<td>✓(77%)</td>
<td>✓(94%)</td>
<td>✓(11%)</td>
<td>✓(100%)</td>
<td>✓(&gt;0%)</td>
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<tr>
<td>EMA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>✓</td>
<td>×</td>
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<tr>
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<td>✓(80%)</td>
<td>✓(97%)</td>
<td>×</td>
<td>✓(100%)</td>
<td>✓(57%)</td>
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<td>AEMPS</td>
<td>✓</td>
<td>✓(96%)</td>
<td>✓(99%)</td>
<td>×</td>
<td>✓(100%)</td>
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<tr>
<td>BSP</td>
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<td>✓(86%)</td>
<td>✓(10%)</td>
<td>✓(96%)</td>
<td>✓(59%)</td>
</tr>
</tbody>
</table>

High population of some common data elements, e.g. age, gender, country of case

Interim results 2011
3.04-Database size (no of spontaneous reports)

Interim results 2011

UMC
EMA
GSK
Bayer
AZ
MHRA
AEMPS
DKMA

Database size (no of spontaneous reports)

- Serious
- Non-serious
- Unknown
3.04-Database survey

Top 5 countries by count of reports used for signal detection (% of total spontaneous reports)

Interim results 2011
3.04-Database survey

Top 5 agents by count of all reports
(NB % of total for top 5, not total db)
Interim results 2011
3.05-Better use of existing terminologies

- **Scope**
  - Investigation of established adverse event coding groups for signal detection

- **Proof of concept**
  - Temozolomide
  - Not illustrating timeliness – VigiBase as of Feb 2009

<table>
<thead>
<tr>
<th>Term</th>
<th>Level of terminology</th>
<th># Reports</th>
<th>IC</th>
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<tr>
<td>Erythema Multiforme</td>
<td>PT</td>
<td>13</td>
<td>+0.30</td>
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<td>Stevens-Johnson Syndrome</td>
<td>PT</td>
<td>19</td>
<td>+0.68</td>
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<td>Toxic Epidermal Necrolysis</td>
<td>PT</td>
<td>6</td>
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<td>Bullous Conditions</td>
<td>HLT</td>
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<td>SMQ</td>
<td>47</td>
<td>-0.04</td>
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<td>WHO-ART HLT</td>
<td>35</td>
<td>+0.46</td>
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</tbody>
</table>
3.05-Better use of existing terminologies

- **Groups included:**
  - MedDRA Preferred Terms (PT, HTL, SMQ narrow or broad)
  - Ad hoc groupings (developed for the purpose of the study or existing proprietary groupings of one of the participating organisations)

- **Data sources:**
  - Medical concepts that are often drug-induced [Trifiro et al]
  - EU labeling changes [Alvarez et al]
  - WHO ICSR database, VigiBase
3.05-Preferred Terms Highlight Early!

• Results for 44 EMA labelling changes:

<table>
<thead>
<tr>
<th>Terminology level</th>
<th>Total</th>
<th>Before</th>
<th>After</th>
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</thead>
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<tr>
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<td>18</td>
<td>7</td>
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<tr>
<td>MedDRA HLT</td>
<td>23</td>
<td>17</td>
<td>6</td>
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<tr>
<td>SMQ narrow</td>
<td>19</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>CustomGroup</td>
<td>23</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

• Analysis at the level of individual MedDRA Preferred Terms trumps other groupings in terms of timeliness
  - Important distinctions may remain between PTs linked to the same medical concept
  - Alternatively, a result of the multiple comparisons inherent in looking separately at related terms
3.05-Better use of existing terminologies

• Tentative findings
  – Groupings of PTs slightly outperform predefined groupings (HLTs, SMQs)
  – Little indication that terminology-defined groupings are effective for screening in signal detection

• Limitations
  – Study has been limited largely to reasonably well-defined medical concepts
  – Are these results applicable to broader concepts (eg, bleeding, infection)?
3.06–Novel tools to group ADRs

• **Progress to date**
  - MedDRA terms related to 13 medical concept in 3.05 mapped to SNOMED-CT
  - MedDRA terms mapped to SNOMED-CT now collectively account for more than 97% of the reported adverse events in the last five years of the FOI database
  - Method for measuring semantic distance between MedDRA terms developed

• **Future work**
  - Comparison with standard MedDRA groupings for the 13 medical concepts from the 3.05 study
3.07–Other information to enhance SD

• **Progress to date**
  - Scope shifted to analysis of the impact of masking on disproportionality analysis (June 2011)
  - Conceptual framework developed for quantifying the masking effect on measures of disproportionality
  - Study conducted on EudraVigilance and Pfizer database
  - Paper drafted

• **Future work**
  - Refinement of framework based on feedback on draft paper
3.08–Subgroups and stratification

• Progress to date
  – Protocol agreed.
  – Literature search undertaken.
  – Product list from 3.01 extended to meet requirements of 3.08
  – Article on current perspectives on stratification drafted

• Future work
  – Further progress awaits analysis of 3.01
3.09–Signal detection from clinical trials

- **Progress to date**
  - Range of statistical methods to be evaluated agreed
  - Databases for analysis identified (Bayer) or under discussion (AZ and GSK)

- **Future work**
  - Internal protocols to be finalised
3.10–Signal detection in EHRs

• Progress to date
  – Computational framework for exploratory analysis of Electronic Health Records implemented
  – Study protocol finalised and approved by EPIC Scientific Review Committee
  – Selection of published epidemiological studies for methods evaluation and validation completed

• Future work
  – Comparison between results of method for exploratory analysis and published epidemiological studies
  – Prospective screening with the aim of characterising false positives and developing signal qualification strategies
3.11–Interaction detection

- **Progress to date**
  - Report from literature review drafted (incomplete as of yet)
  - Reference set of adverse drug interactions and non-adverse drug interactions initiated

- **Future work**
  - Literature review to be finalized
  - Reference set to be further developed
3.12–Duplicate detection

• Progress to date
  – Screen for suspected duplicates in VigiBase completed
  – Lists of suspected duplicates communicated to national centers in Spain, Denmark, and the UK
  – Evaluation of suspected duplicates completed by Spain

• Future work
  – Evaluation of suspected duplicates to be completed by Denmark and the UK
  – EMA to implement different methods for duplicate detection for head-to-head comparison in EudraVigilance
Work Package 4: Data collection from consumers

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
Issues with current methods

Using health care professionals to capture data

- Expensive and data capture relatively infrequent
- Will miss drug exposure before comes to attention of HCP
- Patients may not tell truth about “sensitive” issues
Issues with current methods

Using EHR records

- non prescription medicines, homeopathic and herbal medicines not captured
  - ? Women switch to “perceived safer” medicines
- Medicines prescribed/dispensed may not be medicines consumed – problem with p.r.n. medicines (i.e. dosage as needed)
- EHR may miss lifestyle and “sensitive” information
Project Definition

- Prospective, non interventional study which recruits pregnant women directly without intervention of health care professional
- Collect data from them throughout pregnancy using either web based or interactive voice response systems (IVRS):
  - medication usage, lifestyle and risk factors for congenital malformation (limited data set with IVRS)
- Compare data with that from other sources and explore differences
- Assess strengths and weaknesses of data collection and transferability to other populations
Objective

Assess the extent to which data collected directly from pregnant women via the internet and IVRS provides information on medication use and other potential risk factors throughout pregnancy and is suitable for research purposes.
Study population

- 4 countries:
  - Denmark
  - The Netherlands
  - Poland
  - United Kingdom

- 1400 pregnant women per country
  - Self identified as pregnant
  - Recruited directly, without intervention of HCP
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.
Key analyses

- Descriptive analyses
  - Characterise respondents
  - Compare study population with:
    - National or regional data
  - Characterise prescription medicine use
    - Chronic, pregnancy related, incidental/acute
    - Prescribed/dispensed vs consumed
    - Use of prn medicines
  - Describe use of OTC
  - Describe use of homeopathic/herbal
  - Medicines from other people
Key analyses

- Comparative analyses
  - Study population use of prescription medicines vs national and regional data
  - Characteristics of IVRS vs web population
  - For subgroups that can be linked:
    - Evaluate accuracy and completeness of self reported Rx medicines
Key contributions

• Can we get data earlier in pregnancy?

• Is information of sufficient quality to be used for PhV?

• How important are data not captured by EHR or pharmacy databases?

• Strengths and weaknesses of methods
  - Transferability to other population groups/countries
Achievements

- Protocol finalised
- Linkage workflow
- Questionnaires finalised
  - Screening
  - Enrolment
  - Baseline
  - Follow up
  - Pregnancy Outcome
  - Satisfaction
- Ethics Committee submission
- Ethics Approval
- Drug lists per country
Research Questions

- Compare whether the frequency of data collection affects the completeness and accuracy.

- Assess the extent to which women will provide “sensitive” information about lifestyle and other risk factors for congenital effects.

- Describe the differences between study countries.

- Generalisability to other patient populations and other countries.
Work Package 5: 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

➤ Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers

➤ From pre-approval through lifecycle of products
General objective of the WP

The overall objective of WP5 is to develop methods for use in benefit-risk (BR) assessment, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods.
Decision makers – who are they?

- **Patients**
  - Make decisions for themselves

- **Healthcare providers**
  - Make decisions based on prescribing lists

- **HTA institution**
  - Makes decisions on cost-effectiveness

- **EMA/MHRA etc.**
  - Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

- **Pharmaceutical companies**
  - Makes decisions on what to develop for which licenses to apply
The licensing challenge

- The task of regulators (EMA, FDA etc) is to take good decisions on which medicines should receive a license for which indications, based on the available evidence of risks and benefits.
- It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.
- Can more formal approaches of decision-making, and especially more modern methods of graphical display help regulators do these better?
Challenges in medical decision-making

• Should we formalise decision-making at all?
• Which quantitative approach(es) to use?
• Whose value preferences take priority – regulators, pharma, physicians or patients?
• How do we find these preferences – simple elicitation, decision conferencing, discrete choice experiments....?
• Do we need stakeholders’ preference a priori, or should we provide tools to allow individual decision-makers to explore their own preferences and the consequent decisions?
• How do we communicate benefits and risks?
Specific objectives

- Identify, characterise and test methods of collating data on benefits and risks from various data sources
- Integrating evidence with decision-criteria and formal assessment of values of patients, healthcare providers, regulators, the pharmaceutical industry
- Identify, test and compare modelling approaches that would allow continuous benefit-risk modelling along the lifecycle of the product, and support decision-making;
- Develop methods of graphical expression of the benefits and risks of the medicinal products for use by patients, healthcare providers, the pharmaceutical industry and regulators along the lifecycle of the product.
Methods

- Review the methods used in benefit risk assessment
- Test key methods via a case study approach
  - initially using cases where the drug was withdrawn
- Review the graphical/visual representations that could be used in presenting benefit risk information
- Use more complex case studies to further stretch BR methodologies and explore visual representation
  - Issues identified in the first wave of case studies to be followed up in more detail
- Take perspectives that include regulators, prescribers and patients
Classifications of B/R methods

- Benefit-risk assessment framework
  - PROACT-URL
  - ASF
  - BRAT
  - CMR-CASS
  - FDA
  - BRF

- Metric indices for B-R assessment
  - NNT
  - NNH
  - AE-NNT
  - RV-NNH
  - Impact numbers
  - MCE
  - RV-MCE
  - MAR
  - NEAR

- Health indices
  - QALY
  - DALY
  - HALE
  - Q-TWiST

- Threshold indices
  - UT-NNT
  - INHB
  - BRR
  - GBR
  - Principle of three
  - TURBO
  - Beckmann Model

- Main categories
  - Estimation techniques
    - DAGs
    - PSM
    - CPM
    - ITC
    - MTC
    - CDS

  - Utility survey techniques
    - SPM
    - CV
    - CA
    - DCE

- Sub-categories
  - Non-quantitative
  - Descriptive framework
  - Quantitative framework
Evaluation of techniques

1. Fundamental principles
   - Logically sound
   - Increased transparency
   - Statistical uncertainty estimate
   - Includes other sources of uncertainty
   - Principles easily understood
   - Incorporates value judgments
   - Handling of multiple options

2. Features
   - Balance of benefits and risks
   - Several benefit and risk criteria
   - May include multiple sources of evidence
   - Allows sensitivity analyses
   - Time dimension
   - Method can be formally updated
   - Any unique feature

3. Visual representation model
   - Potential visualisation techniques

4. Assessbility and accessibility
   - Parameters and results easily interpretable
   - How practical is the method when used in real-life decision-making
   - Perspectives the methods are useful for
   - Can the method lead to better decision-making
## Recommendations for further testing

<table>
<thead>
<tr>
<th>Framework</th>
<th>Metric</th>
<th>Estimation techniques</th>
<th>Utility survey techniques</th>
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<td>Descriptive</td>
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<td>• DCE</td>
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<td>• NNT</td>
<td>• MTC</td>
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</tr>
<tr>
<td></td>
<td>• NNH</td>
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<td>• Q-Twist</td>
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<td>• INHB</td>
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<td><em>Trade-off indices</em></td>
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<td>PrOACT-URL</td>
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<tr>
<td>MCDA</td>
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<td></td>
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</tr>
<tr>
<td>SMAA</td>
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## Visual Review – Recommendations table

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<tr>
<th>Approach</th>
<th>Visual representation of results</th>
<th>Other visual representations of special interest</th>
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<td>PrOACT-URL</td>
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<td>Tree diagram to represent model.</td>
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<td>MCDA</td>
<td>Bar graph, ‘difference display’</td>
<td>Table for evidence data, tree diagram to represent model, line graph for sensitivity analysis.</td>
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<tr>
<td>SMAA</td>
<td>Bar graph, forest plot</td>
<td>Table for evidence data, tree diagram and distribution plot to represent model, line graph and scatter plot for sensitivity analysis.</td>
</tr>
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The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines. This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.
# Wave 1 Case studies: Methodologies

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<td>DCE</td>
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<td>Decision conferencing</td>
<td>Decision conferencing</td>
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</table>
PrOACT-URL Framework

- A generic framework to structure the decision problem

1. **Problem**
   - Divide problem in criteria

2. **Objective**
   - Prioritise criteria using trade-offs

3. **Alternatives**
   - Assess uncertainty and linked consequence with decision made

- **Consequences**
- **Trade-off**
- **Uncertainty**
- **Risk tolerance**
- **Linked decisions**
BRAT Framework

Divide decision making process in the following 6 steps:

1. Define decision context
2. Identify outcomes
3. Identify data sources
4. Customise framework
5. Assess outcome importance
6. Display & interpret key B-R metrics

Decision & communication of B-R assessment
### Raptiva example

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Efalizumab</th>
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<tr>
<td>Indication</td>
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<tr>
<td>Severe side effects</td>
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<td>+ Decision conferencing to elicit value preference using swing-weighting</td>
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</tbody>
</table>
Raptiva: PrOACT-URL

Options

- Raptiva
- Placebo

Effects Tree
# Raptiva: PrOACT-URL effects Table

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Fixed Upper</th>
<th>Fixed Lower</th>
<th>Units</th>
<th>Raptiva</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASI75</td>
<td>Percentage of patients achieving 75% reduction in baseline PASI at week 12.</td>
<td>60.0</td>
<td>0.0</td>
<td>%</td>
<td>29.5</td>
<td>2.7</td>
</tr>
<tr>
<td>PASI50</td>
<td>Percentage of patients achieving 50% reduction in baseline PASI at week 12.</td>
<td>60.0</td>
<td>0.0</td>
<td>%</td>
<td>54.9</td>
<td>16.7</td>
</tr>
<tr>
<td>PGA</td>
<td>Percentage of patients achieving Physician’s Global Assessment clear/almost clear at week 12.</td>
<td>40.0</td>
<td>0.0</td>
<td>%</td>
<td>295</td>
<td>5.1</td>
</tr>
<tr>
<td>OLS</td>
<td>Percentage of patients with Overall Lesion Severity rating of minimal or clear at FT (day 84).</td>
<td>40.0</td>
<td>0.0</td>
<td>%</td>
<td>32.1</td>
<td>2.9</td>
</tr>
<tr>
<td>DLQI</td>
<td>Dermatology Life Quality Index. Mean percentage of patients showing an improvement.</td>
<td>10.0</td>
<td>0.0</td>
<td>Change score</td>
<td>5.8</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Unfavourable Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEs</td>
<td>Percentage of patients exhibiting injection site reactions, mild to moderate dose-related acute flu like symptoms.</td>
<td>50.0</td>
<td>20.0</td>
<td>%/100ptys</td>
<td>41.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Severe infections</td>
<td>Proportion of patients experiencing infections serious enough to require hospitalisation.</td>
<td>3.00</td>
<td>0.00</td>
<td>%/100ptys</td>
<td>2.83</td>
<td>1.4</td>
</tr>
<tr>
<td>Severe Thrombocytopenia</td>
<td>Number of cases exhibiting severe (grade 3 and above) thrombocytopenia.</td>
<td>10</td>
<td>0</td>
<td>number</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Psoriasis Severe Forms</td>
<td>Percentage of patients developing severe forms of psoriasis (erythrodermic, pustular).</td>
<td>4.0</td>
<td>0.0</td>
<td>%</td>
<td>3.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Hypersensitivity Reactions</td>
<td>Percentage of patients exhibiting hypersensitivity reactions, arthralgia, psoriatic arthritis, flares, back pain asthenia, ALT and Ph. Alk increase.</td>
<td>10.0</td>
<td>0.0</td>
<td>%</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>Number of cases of interstitial lung disease.</td>
<td>20</td>
<td>0</td>
<td>number</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory Polyaradiculopathy</td>
<td>Number of cases of inflammatory polyaradiculopathy.</td>
<td>5</td>
<td>0</td>
<td>Data</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td>Number of cases of haemolytic anemia.</td>
<td>25</td>
<td>0</td>
<td>number</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>PML</td>
<td>Number of cases of progressive multifocal leukoencephalopathy.</td>
<td>5</td>
<td>0</td>
<td>number</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Aseptic Meningitis</td>
<td>Number of cases of aseptic meningitis.</td>
<td>30</td>
<td>0</td>
<td>number</td>
<td>29</td>
<td>0</td>
</tr>
</tbody>
</table>
Raptiva: MCDA criteria contribution

- **FEs**: Raptiva 09: 305, Placebo: 87, Cumulative Weight: 77.8
- **UFEs**: Total: 392, Raptiva 09: 51, Placebo: 31, Cumulative Weight: 100.0

Criteria:
- PASI75: 25.5, 5.1
- PASI50: 20.4, 6.4
- PGA: 20.4
- OLS: 20.4
- DLQI: 0.5
- AEs: 2.6
- Serious Infections: 2.0
- Severe Psoriasis: 0.0
- Hprsnstvty Reactions: 0.0
- ILDs: 1.3
- Polyradiculopathy: 0.3
- Haemolytic anemia: 1.5
- PML: 12.8
- Aseptic Meningitis: 1.3

Total: 51, 31, 100.0
Raptiva: MCDA difference display

<table>
<thead>
<tr>
<th>Model Order</th>
<th>Cum Wt</th>
<th>Diff</th>
<th>Wtd Diff</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians’ ratings</td>
<td>PGA</td>
<td>20.4</td>
<td>61</td>
<td>12.4</td>
</tr>
<tr>
<td>Physicians’ ratings</td>
<td>PASI75</td>
<td>25.5</td>
<td>45</td>
<td>11.4</td>
</tr>
<tr>
<td>Patients’ ratings</td>
<td>DLQI</td>
<td>20.4</td>
<td>37</td>
<td>7.6</td>
</tr>
<tr>
<td>Physicians’ ratings</td>
<td>OLS</td>
<td>6.4</td>
<td>73</td>
<td>4.7</td>
</tr>
<tr>
<td>Physicians’ ratings</td>
<td>PASI50</td>
<td>5.1</td>
<td>64</td>
<td>3.2</td>
</tr>
<tr>
<td>SAEs</td>
<td>Severe Psoriasis</td>
<td>0.0</td>
<td>-45</td>
<td>0.0</td>
</tr>
<tr>
<td>SAEs</td>
<td>Hprsnsrvy Reactions</td>
<td>0.0</td>
<td>-50</td>
<td>0.0</td>
</tr>
<tr>
<td>Observational data</td>
<td>Polyradiculopathy</td>
<td>0.3</td>
<td>-80</td>
<td>-0.2</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>AEIs</td>
<td>0.5</td>
<td>-57</td>
<td>-0.3</td>
</tr>
<tr>
<td>Observational data</td>
<td>ILDs</td>
<td>1.3</td>
<td>-90</td>
<td>-1.1</td>
</tr>
<tr>
<td>SAEs</td>
<td>Serious Infections</td>
<td>2.6</td>
<td>-48</td>
<td>-1.2</td>
</tr>
<tr>
<td>Observational data</td>
<td>Aseptic Meningitis</td>
<td>1.3</td>
<td>-97</td>
<td>-1.2</td>
</tr>
<tr>
<td>Observational data</td>
<td>Haemolytic anemia</td>
<td>1.5</td>
<td>-96</td>
<td>-1.5</td>
</tr>
<tr>
<td>SAEs</td>
<td>Svre Thrombocytopeni</td>
<td>2.0</td>
<td>-90</td>
<td>-1.8</td>
</tr>
<tr>
<td>Observational data</td>
<td>PML</td>
<td>12.8</td>
<td>-95</td>
<td>-12.1</td>
</tr>
</tbody>
</table>

Diff: Difference between Raptiva 09 and Placebo
Wtd Diff: Weighted Difference
Sum: Total Weighted Difference
### Tysabri example

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Natalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Relapsing remitting multiple sclerosis</td>
</tr>
<tr>
<td><strong>Severe side effects</strong></td>
<td>Progressive Multifocal Leukoencephalopathy</td>
</tr>
</tbody>
</table>
| **Regulatory history** | Approved 2004  
License withdrawn 2005  
Re introduced because of patient demand 2006  
CHMP reassessed the PML risk and continue approval 2009 |
| **Data source**   | EPAR |
| **Methodologies tested** | PrOACT-URL, BRAT, MCDA, NNT & NNH, BRR, PSM, MTC  
+ Decision conferencing to elicit value preference directly |
Example of a wave 1 case study: Tysabri
Choice of methodology: Two methods applied by two teams

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Option</th>
<th>PrOACT/MCDA</th>
<th>BRAT/NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive guidelines</td>
<td>(1) PrOACT-URL guidelines.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2) Benefit Risk Action Team (BRAT) framework.</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Benefit-risk assessment frameworks</td>
<td>(3) Multi-Criteria Decision Analysis (MCDA).</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4) Stochastic Multi-criteria Acceptability Analysis (SMAA).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metric indices</td>
<td>(5) NNT and NNH.</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>(6) Impact numbers.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7) Quality Adjusted Life Years (QALY).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8) Q-TWiST.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(9) Incremental Net Health Benefit (INHB).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10) Benefit-Risk Balance.</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>(12) Mixed Treatment Comparison (MTC).</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Utility survey techniques</td>
<td>(13) Discrete Choice Experiment (DCE).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(14) Direct elicitation</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
The Benefit-risk is the product of the weight and the value.

Most of the Benefit-risk contribution is coming from prevention of relapses.

Infusion reactions are the worst risk.
Tysabri: MCDA criteria contribution
Stacked bar chart for Tysabri vs. all the other treatments

- Same information shown as a stacked bar chart.
- Positive incremental benefit-risk components above the x-axis and negative ones below.
- Total benefit-risk shown as the dark blue bar.
Tysabri: MCDA difference display
Incremental value scores for Tysabri compared to placebo
Like a horizontal bar chart, except that the end of the previous bar determines the start of the next bar.

End of the last bar gives the overall benefit-risk.

Green = positive BR

Red = negative BR
### Acomplia

<table>
<thead>
<tr>
<th><strong>Active drug</strong></th>
<th>Rimonabant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Weight loss in obese and overweight patients with co-morbidities in adults (&gt;18y)</td>
</tr>
<tr>
<td><strong>Regulatory history</strong></td>
<td>Approved June 2006, Voluntary withdrawal in January 2009</td>
</tr>
<tr>
<td><strong>Severe side effect</strong></td>
<td>Increased risk with depression</td>
</tr>
<tr>
<td><strong>Data source</strong></td>
<td>EPAR Published clinical trials</td>
</tr>
<tr>
<td><strong>Methodologies tested</strong></td>
<td>PrOACT-URL, BRAT, MCDA, SMAA, NNT&amp;NNH, Impact numbers, INHB, BRR, PSM + direct utility elicitation via survey</td>
</tr>
</tbody>
</table>
Remarks

- Frameworks are important to govern B-R assessment process and to ensure transparency.
- Stakeholders’ value preference may influence the benefit-risk balance.
- Benefits and risks need to be on common scales to be traded off.
- Uncertainties must be taken into account especially when data are skewed.
- Methodologies only aid decision-making, not make the decisions.
On-going work

- Review of and applications of modern visual representation of benefits and risk
- Wave 2 case studies
  - Two extended from wave 1 to investigate more into benefit-risk methodologies used and visual representations (Tysabri and Acomplia)
  - Two new case studies looking at more complex benefit-risk questions (Warfarin and Rosiglitazone)
Work Package 6: Validation

Objectives:

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

• To determine the added value of using other data sources as a supplement or alternative to those generally used for drug safety studies, in order to investigate specific aspects or issues.

Started in September 2010
Work Package 6 – Reproducibility studies

Objectives:

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

• To determine the added value of using other data sources as a supplement or alternative to those generally used for drug safety studies, in order to investigate specific aspects or issues.

Started in September 2010 (Year 2)
# WP6 Research Plan for WP2 studies: Study Objectives, Rationale and Design

<table>
<thead>
<tr>
<th>Defined Study Objective</th>
<th>Scientific Question</th>
<th>DB identification</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective 1</strong>&lt;br&gt;Replication study in same database</td>
<td>Is the study replicable when conducted independently in the same database?</td>
<td>• GPRD&lt;br&gt;• Danish Psychiatric, Somatic Hospital Discharge &amp; Mortality Registers (DKMA)</td>
<td>Population case control</td>
</tr>
<tr>
<td><strong>Objective 2</strong>&lt;br&gt;Replication study in different database</td>
<td>Do the results have external validity?</td>
<td>• LabRx/Premier&lt;br&gt;• MarketScan and Medicare&lt;br&gt;• E3N&lt;br&gt;• LA-SER PGRx&lt;br&gt;• UPOD</td>
<td>• Nested case control&lt;br&gt;• Population case control&lt;br&gt;• Cohort&lt;br&gt;• Descriptive study</td>
</tr>
</tbody>
</table>
# WP6 Research Plan for WP2 studies:
Study Objectives, Rationale and Design

<table>
<thead>
<tr>
<th>Defined Study Objective</th>
<th>Scientific Question</th>
<th>DB identification</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective 3</strong></td>
<td>Does a study using the same protocol provide absence of evidence of an association where the exposure is such that the expected result is one of no association?</td>
<td>• LabRx/Premier</td>
<td>• Nested case control (AMI)</td>
</tr>
<tr>
<td><strong>Negative control study</strong></td>
<td></td>
<td>• GPRD</td>
<td>• Self-controlled-series (hip fracture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LA-SER PGRx</td>
<td>• Population case control</td>
</tr>
<tr>
<td><strong>Objective 4</strong></td>
<td>What is the impact of different levels of certainty of the outcome (e.g. definite, probable, possible) on the effect estimate?</td>
<td>• GPRD</td>
<td>• Population case control</td>
</tr>
<tr>
<td><strong>Use of alternative outcome definition</strong></td>
<td></td>
<td>• LA-SER PGRx</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DKMA</td>
<td></td>
</tr>
</tbody>
</table>
## WP6 Research Plan for WP2 studies: Study Objectives, Rationale and Design

<table>
<thead>
<tr>
<th>Defined Study Objective</th>
<th>Scientific Question</th>
<th>DB identification</th>
<th>Study design</th>
</tr>
</thead>
</table>
| **Objective 5**  
Validation of outcome | Has the outcome of interest been validated through clinical record review? What is the impact of validation on the effect estimate? | • GPRD  
• LabRx/Premier  
• UPOD  
• DKMA  
• GPRD | • Population case control  
• Nested case control  
• Descriptive study |
| **Objective 6**  
Assessment of confounders | Has confounding been adequately taken into consideration? Are there additional confounders that need to be assessed? How does better control for confounding impact the effect estimate? | • UPOD  
• LA-SER PGRx  
• DKMA | • Descriptive study  
• Population case control |
# WP6 Research plan and timelines

<table>
<thead>
<tr>
<th>Study</th>
<th>Status</th>
<th>Start of analysis</th>
<th>Results Report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics and ALI: replication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in LabRx (Sanofi)</td>
<td>Final protocol, sanofi internal approval pending</td>
<td>April/May 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td>in GPRD (Takeda)</td>
<td>Final protocol, ISAC approval pending</td>
<td>April/May 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td>in UPOD (Utrecht university)</td>
<td>Protocol being reviewed</td>
<td>April/May 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td><strong>Antibiotics and AMI: negative control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in LabRx (sanofi)</td>
<td>Final protocol, sanofi internal approval pending</td>
<td>April/May 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td>in LA-SER-PGRx</td>
<td>Final protocol approved</td>
<td>April/May 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td><strong>Beta2 agonists and AMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in LA-SER-PGRx</td>
<td>Final protocol approved</td>
<td>April 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td>in LabRx (Sanofi)</td>
<td>Final protocol, workload issues identified</td>
<td>Delayed to be provided</td>
<td>To be provided</td>
</tr>
</tbody>
</table>
## WP6 Research plan and timelines

<table>
<thead>
<tr>
<th>Study</th>
<th>Status</th>
<th>Start of analysis</th>
<th>Results Report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiepileptics and suicide related events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danish register (Aarhus university)</td>
<td>Final protocol Issue regarding CDC ICD 10 codes proposed in WP2 being solved</td>
<td>February 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td>in GPRD (GSK)</td>
<td>Protocol not prepared yet, waiting for assessment of final numbers of events, which depends on the analyses in WP2</td>
<td>January 2013</td>
<td>March 2013</td>
</tr>
<tr>
<td>LA-SER PGRx</td>
<td>Final protocol approved</td>
<td>March/April 2012</td>
<td>Sept/October 2012</td>
</tr>
<tr>
<td><strong>Calcium channel blockers and cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in E3N (LA-SER)</td>
<td>Protocol to be released in June 2012</td>
<td>July/August 2012</td>
<td>January 2013</td>
</tr>
<tr>
<td>in Medstat (GSK)</td>
<td>Protocol to be released in May 2012</td>
<td>March/April 2013</td>
<td>Sept/October 2013</td>
</tr>
</tbody>
</table>
WP6: Additional studies for WP5

Possible scenarios once Wave 1 Studies are completed:

• Replication of Phase 1 study(ies) (Tysabri, Acomplia, Ketek, Raptiva)
• Stochastic sensitivity analysis (e.g. Tysabri)
• Time dependency issue for risk-benefit analysis (Phase 2 study or paper)
• Patient reported outcomes study
Work Package 7: Training and education

Objective:
To identify training opportunities and support training programmes to disseminate the results achieved in PROTECT.
Work Package 7: Scope

- Development of a Platform of Training Opportunities
  - Launched.
- Regular interaction with Eu2P Consortium
  - Mechanism in place to ensure timely input from PROTECT WPs 2-5 into Eu2P training programmes.
Work Package 7: Training Platform

- Available at https://w3.icf.uab.es/trainingopp (or through link from PROTECT homepage)
- Launched in July 2011
- Extended to EU2P in July 2011
- Extension to ENCePP as of Nov 2011
PROTECT: Dissemination of Results

The Project will generate a number of reports providing standards and recommendations which will be widely disseminated through:

**PROTECT web portal**
Includes a webpage accessible to the general public where relevant deliverables for public use are posted [http://www.imi-protect.eu/index.html](http://www.imi-protect.eu/index.html), eg.

- Inventory of drug consumption databases in Europe
- SPC ADR database (forthcoming)

**Publications**
Most deliverables of the project presented at scientific conferences, published and disseminated through other appropriate mediums.

**ENCePP network**
The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is a project led by the EMEA intended to further strengthen the post-authorisation monitoring of medicinal products in Europe. The results of the PROTECT programme will be made available to all ENCePP members.

**Regulatory activities and guidelines**
Eg. signal detection, PASS studies, methods for benefit-risk evaluation and visualisation
More information?

Website: www.imi-protect.eu

Email: Protect_Support@ema.europa.eu