The PROTECT project

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

Latest update: April 2013
PROTECT is receiving support from the Innovative Medicines 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.
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.
Clinical trials

Observational studies

Electronic health records

Spontaneous ADR reports

Benefits

Signal detection WP3

Signal evaluation WP2

Risks

Benefit-risk integration and representation – WP5

Data collection from consumers – WP4

Reproducibility studies WP6

Training and education WP7
Partners (33)

Public

Regulators:
- EMA (Co-ordinator)
- DHMA (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

Private

EFPIA companies:
- GSK (Deputy Co-ordinator)
- Sanofi- Aventis
- Roche
- Novartis
- Pfizer
- Amgen
- Genzyme
- Merck Serono
- Bayer
- Astra Zeneca
- Lundbeck
- NovoNordisk
- Takeda
- Eli Lilly

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

SMEs:
- Outcome Europe
- PGRx Laser
# 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>Helen Dolk, MD</td>
<td>Epidemiology and Health Services Research Centre for Maternal, Fetal and Infant Research, the University of Ulster, UK</td>
<td>Epidemiology and Health Services Research Maternal, Fetal and Infant Research</td>
</tr>
<tr>
<td>Trevor Gibbs, MD</td>
<td>Former Head of Global Pharmacovigilance and Product Safety, GSK, UK</td>
<td>Pharmacovigilance, Health Outcomes, Public Health</td>
</tr>
<tr>
<td>David Haerry</td>
<td>European AIDS Treatment Group (EATG), Brussels, Belgium</td>
<td>Public Health, Patients’ preference</td>
</tr>
<tr>
<td>Vicky Hogan, MSc</td>
<td>Associate Director General, Marketed Health Products Directorate (MHPD), Health Canada, Canada</td>
<td>Benefit-risk assessment</td>
</tr>
<tr>
<td>Michael Lewis, MD</td>
<td>EPES Epidemiology, Pharmacoepidemiology and Systems Research GmbH, Berlin, Germany</td>
<td>Pharmacoepidemiology</td>
</tr>
<tr>
<td>Allen Mitchell, MD</td>
<td>Slone Epidemiology Center, Boston, USA</td>
<td>Perinatal epidemiology, Pharmacoepidemiology</td>
</tr>
<tr>
<td>Marcus Müllner, MD</td>
<td>Head of AGES PharmMed (Austrian Medicines and Medical Devices Agency), Austria</td>
<td>Benefit-risk assessment, Clinical epidemiology, Pharmacovigilance</td>
</tr>
<tr>
<td>Gerald Dal Pan, MD</td>
<td>Director Office of Drug Safety, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), USA</td>
<td>Pharmacovigilance, Drug development, Public Health &amp; Risk management</td>
</tr>
<tr>
<td>Munir Pirmohamed, MD</td>
<td>Department of Pharmacology and Therapeutics, University of Liverpool, UK</td>
<td>Pharmacology, Pharmacovigilance</td>
</tr>
<tr>
<td>Samy Suissa, PhD</td>
<td>Division of Epidemiology/Biostatistics, McGill University, Montreal, Canada</td>
<td>Biostatistics, Pharmacoepidemiology</td>
</tr>
</tbody>
</table>
# 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>
</tr>
</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></td>
</tr>
<tr>
<td>• 1-4</td>
<td>0.51 (0.33-0.81)</td>
<td>Time since use</td>
</tr>
<tr>
<td>• 5-19</td>
<td>0.62 (0.45-0.85)</td>
<td>• 0-3 months</td>
</tr>
<tr>
<td>• 20</td>
<td>0.52 (0.36-0.76)</td>
<td>• 3-6 months</td>
</tr>
<tr>
<td>Recent use</td>
<td>0.67 (0.50-0.92)</td>
<td>• 6-12 months</td>
</tr>
<tr>
<td>Past use</td>
<td>0.87 (0.65-1.18)</td>
<td>• &gt; 12 months</td>
</tr>
<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>
</tr>
<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>
<td></td>
</tr>
</tbody>
</table>
Why such a difference?

<table>
<thead>
<tr>
<th>Source population</th>
<th>Meier et al., 2000</th>
<th>Van Staa et al., 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>370 GPRD practices</td>
<td>683 GPRD practices</td>
</tr>
<tr>
<td>Study period</td>
<td>Through Sept 1998</td>
<td>Through July 1999</td>
</tr>
<tr>
<td>Design</td>
<td>Selected case control (3 cohorts)</td>
<td>Conventional case-control</td>
</tr>
<tr>
<td>N Cases</td>
<td>3,940</td>
<td>81,880</td>
</tr>
<tr>
<td>N Controls</td>
<td>23,379</td>
<td>81,880</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-69</td>
<td>52.2%</td>
<td>50-69</td>
</tr>
<tr>
<td>70-79</td>
<td>28.9%</td>
<td>70-84</td>
</tr>
<tr>
<td>80-89</td>
<td>18.9%</td>
<td>&gt;85</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75.0%</td>
<td>Female</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 25</td>
<td>57.3%</td>
<td>≥ 25</td>
</tr>
</tbody>
</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

• 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

• Initial list of 55 events and >55 drugs
• Final selection based on literature review and consensus meeting
WG1: Databases

Work Plan

- Conduct of drug-adverse event (AE) pair studies in different EU databases
  - Antidepressants/Benzodiazepines and hip fracture
  - Inhaled long-acting B2-agonists and acute myocardial infarction
  - Antiepileptics and suicide
  - Antibiotics and acute liver injury
  - Calcium channel blockers and cancer

Databases

- Danish national registries DKMA
- Dutch Mondriaan database
- British CPRD database (formerly known as GPRD)
- British THIN databases
- Spanish BIFAP project
- German Bavarian claims database
Progress status

- Development of study protocols
  - Protocols for each drug-AE pair have been developed
  - Descriptive studies for the drug-AE pairs in all databases
  - 4 different study designs in selected databases
    - Cohort design
    - Nested case control design
    - Case crossover
    - Self controlled case series
  - Harmonised approach across the 6 drug AE pairs (common standards, processes and template)
  - Blinding of results procedure
  - Submission of protocols to ENCePP registry of studies
## WG1: Methods: Overview of planned studies

<table>
<thead>
<tr>
<th>Drug-AE pair</th>
<th>Descriptive</th>
<th>Cohort</th>
<th>Nested case control</th>
<th>Case crossover</th>
<th>Self-Controlled case series</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB-ALI</td>
<td>All Databases</td>
<td>CPRD BIFAP</td>
<td>CPRD BIFAP</td>
<td>CPRD BIFAP</td>
<td>CPRD BIFAP</td>
</tr>
<tr>
<td>AED-Suicide</td>
<td>All Databases</td>
<td>CPRD DKMA</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>AD-Hip</td>
<td>All Databases</td>
<td>THIN Mondriaan BIFAP</td>
<td>THIN Mondriaan BIFAP</td>
<td>THIN Mondriaan BIFAP</td>
<td>THIN Mondriaan BIFAP</td>
</tr>
<tr>
<td>BZP-Hip</td>
<td>All Databases</td>
<td>CPRD BIFAP Mondriaan</td>
<td>CPRD BIFAP Mondriaan</td>
<td>CPRD BIFAP</td>
<td>CPRD BIFAB</td>
</tr>
<tr>
<td>B2A-AMI</td>
<td>All Databases</td>
<td>CPRD Mondriaan</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>CCB-Cancer</td>
<td>All Databases</td>
<td>CPRD DKMA</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
# WG1: Progress of studies

<table>
<thead>
<tr>
<th>Drug-AE pair</th>
<th>Descriptive</th>
<th>Cohort</th>
<th>Nested case control</th>
<th>Case crossover</th>
<th>Self-Controlled case series</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB-ALI</td>
<td>Completed</td>
<td>Completed</td>
<td>March 2013</td>
<td>May 2013</td>
<td>March 2013</td>
</tr>
<tr>
<td>AED-Suicidality</td>
<td>Completed</td>
<td>March 2013</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>AD-Hip</td>
<td>Completed</td>
<td>Completed</td>
<td>Aug 2013</td>
<td>Dec 2013</td>
<td>n/a</td>
</tr>
<tr>
<td>BZP-Hip</td>
<td>Completed</td>
<td>Completed</td>
<td>Sept 2013</td>
<td>Sept 2013</td>
<td>Sept 2013</td>
</tr>
<tr>
<td>B2A-AMI</td>
<td>Completed</td>
<td>March 2013</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>CCB-Cancer</td>
<td>Completed</td>
<td>April 2013</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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</tbody>
</table>
WG1: Examples of descriptive results
Prevalence of antibiotic prescribing

[Graph showing prevalence of antibiotic prescribing from 2004 to 2009 for different datasets and countries, such as CPRD (UK), THIN (UK), BIFAP (Spain), Bavarian Claims Database (Germany), Mondriaan NPCRD (The Netherlands), Mondriaan AHC (The Netherlands), and DKMA (Denmark).]
WG1: Examples of descriptive results

Prescribing of BZD by age

Prevalence use rates of benzodiazepines and related drugs in Females for 2008

Prevalence use rates of benzodiazepines and related drugs in Males for 2008
WG1: Examples of descriptive results

Incidence of hip fracture

Incidence of Hip/femur fractures in Males for 2008

Incidence of Hip/femur fractures in Females for 2008
WG1: Publications

1. Abbing et al. Bridging differences in findings from pharmacoepidemiological studies: The PROTECT project (**Current Clinical Pharmacology, prov. accepted**)
4. Abbing et al. Antidepressant prescribing in five European countries: application of common definitions to assess prevalence of use. (**in preparation**)
5. Huerta et al. Prevalence of use of benzodiazepine and related drugs in seven European databases: A cross-national descriptive study from the PROTECT-EU Project (**in preparation**)
6. Rottenkolber/Voogd et al. Time trends in prevalence of inhaled long-acting beta-2-adrenoceptor agonist in persons with asthma or COPD - a comparison of seven European electronic health record databases (**in preparation**)

- 5 presentations at ICPE 2011-2012, 1 other presentation
- 11 abstracts submitted for ICPE 2013 (incl. 1 abstract for WP2/WP6 symposium)
Next steps

- Conduct of studies
  - Finalise cohort analysis for the 6 drug-AE pairs – Spring 2013
  - Conduct analysis on other designs (i.e.: nested case control, case crossover and self controlled case series) – Dec 2013
  - Finalise papers with comparison/analysis of discrepancies across designs/databases – Feb 2014
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

Results

- Guideline for conduct of simulation studies (PS, IV)
- Propensity scores
  - Review of current status of conducting PS analysis
  - Usefulness of measures for balance for reporting of the amount of balance reached in PS analysis and selecting the final PS model (2 simulation studies, 1 application)
  - Comparison of methods to control for time-dependent confounding (1 application)
- Instrumental variables
  - Review of IV analysis methods
  - Evaluation of IV in case-control and cohort studies (1 simulation study)
  - Use of measures for balance to test IV assumption (1 simulation study)
  - Evaluation of different IVs to assess association between LABA and MI (1 application in 1 Dutch GP database)
- Multi database analysis
  - Simulation study on impact of left/right censoring
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

- 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

- 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 drug-AE pairs
    - 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:
• 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.
Next Steps

- Finalise comparison of methods to control for time-dependent confounding
  - LABA and MI in CPRD/Mondriaan
- Finalise multi database analysis
  - Pooling versus step-wise analysis
- Finalise analysis of instrumental variables (IV) in Drug AE pairs
  - LABA and MI in CPRD/Mondriaan
WG2: Confounding

Publications


- 5 presentations at ICPE 2011-2012, 2 other
- 5 abstracts submitted to ICPE 2013
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

• 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

- 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

Results

• Inventory of DU databases in Europe
  – Published in the IMI-PROTECT website. Updated yearly (Aug 2011 and Oct 2012). In the last update:
    ✤ Executive summary
    ✤ Master document “Drug Consumption databases in Europe”
    ✤ Countries profiles (NEW)

http://www.imi-protect.eu/drugConsumption.shtml
WG3: Drug utilisation data

Next steps

• Finalise the literature Search on Randomized Controlled Trials (RCT) and observational studies (OS) for the 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).
WG3: Drug utilisation data

Publications


21. Sabate et al. Research working groups on drug utilization across Europe. European working groups on drug utilization. The PROTECT project (submitted)

22. Ferrer et al. Sources of medicines consumption data in Europe (in preparation)

• 6 presentations at ICPE 2011-2012, 2 other
• 4 abstracts submitted to ICPE 2013
WG3: Drug utilisation data

Next Steps

- Yearly update of the inventory of DU databases (Aug 2013)
- Finalise publications on Systematic / literature reviews on Drug-AE pairs.
- Assess validity of drug consumption data collected (17 countries from National sources and 10 countries from IMS data for the 6 Drug-AE pairs) – Nov 2013
- WG1-WG3 collaboration: compare results of the systematic reviews (WG3) and prevalence of drug exposure in databases (WG1) – Feb 2014
- Collaboration EuroDURG-CNC group and PROTECT-WG3 to develop recommendations on Cross National Comparison studies as part of the PROTECT guidelines on DU research – Aug 2014.
Overview of WP2 activities and milestones

**WG1** Databases
- 5 drug AE pairs & 6 EU databases
- 6 protocols & data analysis plan
- Descriptive studies
- Cohort studies
- Other designs studies
- Analysis of discrepancies between databases for descriptive and association studies
- Multidatabase studies

**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)
- Application of PS and IV methods in empirical data from EU databases

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

Aug 2009 – Project starts
Aug 2014 – Project ends

Guidelines and standards for PE studies and DU studies

WG1: blue = complete or ongoing tasks; grey = planned tasks; red = interaction between WGs
Objective:

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

Scope

- Directly compare different statistical signal detection algorithms:
  - Within different databases
  - Between databases on same products
Merits of disproportionality analysis

**Progress to date**
- Mapping of medicinal products completed
- Evaluation of measures of disproportionality
  - Completed for EMA, Bayer, GSK, and MHRA
  - Nearly completed for UMC and AstraZeneca
- Abstract submitted to ICPE 2013

**Future work**
- Complete analysis for remaining data sets
- Compare results across data sets
- Draft paper
- Pursue sub-groups and stratification sub-package
Preliminary results for EudraVigilance
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>
</tr>
</thead>
<tbody>
<tr>
<td>Aclasta</td>
<td>FLU-LIKE SYMPTOMS</td>
<td></td>
<td>Flu symptoms</td>
</tr>
<tr>
<td>Advagraf</td>
<td>OTHER ELECTROLYTE ABNORMALITIES</td>
<td>-</td>
<td>Electrolyte abnormality</td>
</tr>
<tr>
<td>Advagraf</td>
<td>PAIN AND DISCOMFORT</td>
<td>-</td>
<td>Pain and discomfort NEC</td>
</tr>
<tr>
<td>Advagraf</td>
<td>PRIMARY GRAFT DYSFUNCTION</td>
<td>-</td>
<td>Primary graft dysfunction*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>PRURITUS</td>
<td>PRURITUS</td>
<td>Pruritus*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>PSYCHOTIC DISORDER</td>
<td>PSYCHOTIC DISORDER</td>
<td>Psychotic disorder*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>PULSE INVESTIGATIONS ABNORMAL</td>
<td>-</td>
<td>Investigation abnormal</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RASH</td>
<td>RASH</td>
<td>Rash*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RED BLOOD CELL ANALYSES ABNORMAL</td>
<td>-</td>
<td>Red blood cell analyses*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RENAL FAILURE</td>
<td>RENAL FAILURE</td>
<td>Renal failure*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RENAL FAILURE ACUTE</td>
<td>RENAL FAILURE ACUTE</td>
<td>Acute renal failure, Renal failure acute*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RENAL IMPAIRMENT</td>
<td>RENAL IMPAIRMENT</td>
<td>Renal impairment*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RENAL TUBULAR NECROSIS</td>
<td>RENAL TUBULAR NECROSIS</td>
<td>Renal tubular necrosis*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RESPIRATORY FAILURES</td>
<td>-</td>
<td>Respiratory failure, Failure respiratory</td>
</tr>
<tr>
<td>Advagraf</td>
<td>RESPIRATORY TRACT DISORDERS</td>
<td>-</td>
<td>Respiratory tract disorders NEC</td>
</tr>
<tr>
<td>Advagraf</td>
<td>SEIZURES</td>
<td>-</td>
<td>Seizure, Seizures*</td>
</tr>
<tr>
<td>Advagraf</td>
<td>SHOCK</td>
<td>SHOCK</td>
<td>Shock*</td>
</tr>
</tbody>
</table>

Better option: Red blood cell abnormal
Structured database of SPC 4.8 – published

http://www.imi-protect.eu
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 results presented as poster at ICPE, Barcelona, August 2012
Lack of comparability in EBGM implementations via external vendor systems.

3.04-Overview of Databases

General db info

- **Drug coding**
  - AZ/GSK: Therapeutics only
  - Pharma: Mixed Therap./vaccines
  - GSK: Mixed Therap./vaccines

- **Metadata**
  - National
  - Multinational

- **AE coding**
  - National
  - MedDRA

DME, IME, TME, Listedness

- AZ: None
- BSP: AEMPS
- GSK: None
- MHRA: None
- EMA: None
- UMC: None
### 3.04 - Data elements – demography SD

<table>
<thead>
<tr>
<th></th>
<th>Receipt Date</th>
<th>Age/DoB</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Country of case</th>
<th>Subject ID</th>
<th>Time to onset²</th>
</tr>
</thead>
<tbody>
<tr>
<td>DKMA</td>
<td>✓</td>
<td>✓ (unk)</td>
<td>✓ (100%)</td>
<td>x</td>
<td>✓ (100%)</td>
<td>✓ (unk)</td>
<td>x</td>
</tr>
<tr>
<td>UMC</td>
<td>✓</td>
<td>✓ (77%)</td>
<td>✓ (94%)</td>
<td>✓ (11%)</td>
<td>✓ (100%)</td>
<td>✓ (&gt;0%)</td>
<td>✓ (54%)</td>
</tr>
<tr>
<td>EMA</td>
<td>✓</td>
<td>✓ (unk)</td>
<td>✓ (unk)</td>
<td>x</td>
<td>✓ (unk)</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MHRA</td>
<td>✓</td>
<td>✓ (80%)</td>
<td>✓ (97%)</td>
<td>x</td>
<td>✓ (100%)</td>
<td>✓ (57%)</td>
<td>✓ (5%)</td>
</tr>
<tr>
<td>AEMPS</td>
<td>✓</td>
<td>✓ (96%)</td>
<td>✓ (99%)</td>
<td>x</td>
<td>✓ (100%)</td>
<td>x</td>
<td>✓ (59%)</td>
</tr>
<tr>
<td>BSP</td>
<td>✓</td>
<td>✓ (74%)</td>
<td>✓ (97%)</td>
<td>✓ (58%)</td>
<td>✓ (100%)</td>
<td>✓ (83%)</td>
<td>✓ (37%)</td>
</tr>
<tr>
<td>AZ</td>
<td>✓</td>
<td>✓ (73%)</td>
<td>✓ (92%)</td>
<td>✓ (26%)</td>
<td>✓ (100%)</td>
<td>✓ (41%)</td>
<td>✓ (37%)</td>
</tr>
<tr>
<td>GSK</td>
<td>✓</td>
<td>✓ (79%)</td>
<td>✓ (86%)</td>
<td>✓ (10%)</td>
<td>✓ (96%)</td>
<td>✓ (59%)</td>
<td>✓ (32%)</td>
</tr>
</tbody>
</table>

1. x - not recorded; value present in ≤ 5% of reports
2. First dose to event first occurrence

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

Final results 2012
3.04-Database size (no of spontaneous reports)

- **UMC**: Total Serious (1.5M), SPONTANEOUS (0.5M)
- **EMA**: Total Serious (1.2M), SPONTANEOUS (0.8M)
- **GSK**: Total Serious (0.5M), SPONTANEOUS (1.0M)
- **BSP**: Total Serious (0.2M), SPONTANEOUS (0.3M)
- **MHRA**: Total Serious (0.1M), SPONTANEOUS (0.1M)
- **AZ**: Total Serious (0.01M), SPONTANEOUS (0.01M)
- **AEMPS**: Total Serious (0.001M), SPONTANEOUS (0.001M)
- **DKMA**: Total Serious (0.0001M), SPONTANEOUS (0.0001M)

Legend:
- **Blue**: Total Serious
- **Red**: SPONTANEOUS
- **Green**: Unknown Seriousness
3.04 - Spontaneous reports by reporter type

Percentage of spontaneous reports for each reporter occupation

*counts of AE report for AZ and MHRA are not based on unique reports for each category of reporter

- Physician
- Pharmacist
- Other health professional
- Lawyer
- Consumer
- Unknown
- Other
3.04-Database survey

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

Top 5 agents by count of all reports
(NB % of total for top 5, not total db)
3.05 Better use of existing terminology

• To what extent does grouping relevant medical terms expedite detection of historical safety signals

• Background
  – Different terms can be used to describe the same suspected adverse drug reaction (ADR)
  – We need a large enough number of reports on the ADR before an association can be detected
3.05 Retrospective study

- 13 medical concepts with medium to high probability of being drug-related (Trifirò et al, Pharmacoepidemiology and Drug Safety 2009)
- 44 EMA labelling changes (Alvarez et al, Drug Safety 2010)

Scope of study
- Sets of individual Preferred Terms
- High-Level Terms
- Narrow SMQs
- Groupings of manually selected Preferred Terms (custom groups)
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>
</tr>
</thead>
<tbody>
<tr>
<td>MedDRA PT</td>
<td>25</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>MedDRA HLT</td>
<td>23</td>
<td>17</td>
<td>6</td>
</tr>
<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

• 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)?
Acute renal failure with Hydrochlorothiazide/Telmisartan

- Highlighted by the first PT in 2\textsuperscript{nd} quarter 2008
Acute renal failure with Hydrochlorothiazide/Telmisartan

- Highlighted by the HLT in 2nd quarter 2006
Peripheral neuropathy with efalizumab

- Highlighted by two PTs in 4th quarter 2008
Peripheral neuropathy with efalizumab

- Not highlighted by the HLT at all
Peripheral neuropathy with efalizumab

- High expected count for HLT due to another PT
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
  - Comparison with standard MedDRA groupings for the 13 medical concepts from the 3.05 study
3.06–Novel tools to group ADRs

- Endorsed by PROTECT Steering Committee in December 2012

- Scope
  - Collaboration with MSSO (MedDRA maintenance organisation)
  - More narrow groupings of MedDRA terms based on semantic reasoning that may bring value to signal detection
  - Work on-going
Progress to date

- Developed a mathematical algorithm aimed at detecting the presence, direction and magnitude of the masking effect associated with the quantitative methods of signal detection on SRS databases.

- Algorithm developed and validated for the measures of disproportionality (ROR, PRR and RRR).

- Algorithm developed for the corresponding confidence intervals (Lower bounds of the 95% CI for the ROR, PRR and RRR).

- Assessed the influence of method of computation and allocation of reports containing both the product of interest and the masking product.
3.07–Other information to enhance SD

- Events rarely reported were mostly affected by masking in EudraVigilance and Pfizer (PfAST) databases
- Differences observed due to structural differences (products covered in the database)

<table>
<thead>
<tr>
<th>Reaction PT</th>
<th>Approx. MR EV</th>
<th>Approx. MR Pfizer db</th>
<th>Difference</th>
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</thead>
<tbody>
<tr>
<td>Acute hepatic failure</td>
<td>1.653</td>
<td>1.250</td>
<td>-0.383</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1.743</td>
<td>1.244</td>
<td>-0.500</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1.130</td>
<td>1.180</td>
<td>0.050</td>
</tr>
<tr>
<td>Anaphylactic shock</td>
<td>1.042</td>
<td>1.072</td>
<td>0.030</td>
</tr>
<tr>
<td>Anterograde amnesia</td>
<td>1.655</td>
<td>6.781</td>
<td>5.126</td>
</tr>
<tr>
<td>Anti-erythropoietin antibody positive</td>
<td>6.518</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Apalastic anaemia</td>
<td>1.046</td>
<td>1.122</td>
<td>0.075</td>
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<tr>
<td>Bone debridement</td>
<td>5.331</td>
<td>1.560</td>
<td>-3.773</td>
</tr>
<tr>
<td>Bone marrow reticulin fibrosis</td>
<td>8.556</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Bronchitis</td>
<td>1.190</td>
<td>1.410</td>
<td>-0.220</td>
</tr>
<tr>
<td>Cardiac valve disease</td>
<td>1.224</td>
<td>12.052</td>
<td>10.827</td>
</tr>
<tr>
<td>Confusional state</td>
<td>1.021</td>
<td>1.100</td>
<td>0.080</td>
</tr>
<tr>
<td>Convulsion</td>
<td>1.036</td>
<td>1.143</td>
<td>0.107</td>
</tr>
<tr>
<td>Crobotyphlogiroma</td>
<td>6.294</td>
<td>6.500</td>
<td>0.207</td>
</tr>
<tr>
<td>Depression</td>
<td>1.126</td>
<td>1.226</td>
<td>0.100</td>
</tr>
<tr>
<td>Dermatitis bullosus</td>
<td>1.048</td>
<td>1.119</td>
<td>0.071</td>
</tr>
<tr>
<td>Drug specific antibody present</td>
<td>1.687</td>
<td>2.936</td>
<td>1.248</td>
</tr>
<tr>
<td>Dupuytren's contracture</td>
<td>1.193</td>
<td>1.159</td>
<td>-0.034</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>1.116</td>
<td>1.368</td>
<td>0.252</td>
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<td>Episcleritis</td>
<td>4.819</td>
<td>9.978</td>
<td>5.159</td>
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<td>Extrapyramidal disorder</td>
<td>1.256</td>
<td>1.462</td>
<td>0.205</td>
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<tr>
<td>Factor IX inhibition</td>
<td>2.625</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Factor VIII inhibition</td>
<td>2.063</td>
<td>N/A</td>
<td></td>
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<tr>
<td>Fanconi syndrome</td>
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<td>1.481</td>
<td>-0.149</td>
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<td>Fanconi syndrome acquired</td>
<td>1.630</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Gambling</td>
<td>2.605</td>
<td>3.336</td>
<td>0.731</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>1.081</td>
<td>1.065</td>
<td>-0.016</td>
</tr>
<tr>
<td>Intrasuccion</td>
<td>2.523</td>
<td>1.600</td>
<td>-0.923</td>
</tr>
<tr>
<td>Jaw operation</td>
<td>1.082</td>
<td>2.126</td>
<td>1.044</td>
</tr>
<tr>
<td>Mania</td>
<td>1.089</td>
<td>1.290</td>
<td>0.201</td>
</tr>
<tr>
<td>Micronuclear toxicity</td>
<td>1.172</td>
<td>1.600</td>
<td>0.428</td>
</tr>
<tr>
<td>Nephrogenic systemic fibrosis</td>
<td>2.521</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Neopapathy peripheral</td>
<td>1.195</td>
<td>1.245</td>
<td>0.050</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>1.097</td>
<td>1.184</td>
<td>0.087</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome</td>
<td>1.573</td>
<td>1.560</td>
<td>-0.013</td>
</tr>
<tr>
<td>Pancreatitis acute</td>
<td>1.064</td>
<td>1.200</td>
<td>0.136</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1.102</td>
<td>1.501</td>
<td>0.399</td>
</tr>
<tr>
<td>Pathological gambling</td>
<td>2.072</td>
<td>2.737</td>
<td>0.665</td>
</tr>
<tr>
<td>Polymavirus-associated nephropathy</td>
<td>3.326</td>
<td>2.600</td>
<td>-0.726</td>
</tr>
<tr>
<td>Pregnancy with contraceptive patch</td>
<td>4.936</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Progressive external ophthalmoplegia</td>
<td>11.991</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>1.647</td>
<td>1.633</td>
<td>-0.014</td>
</tr>
<tr>
<td>Rapid correction of hyponatraemia</td>
<td>21.999</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>1.050</td>
<td>1.072</td>
<td>0.022</td>
</tr>
<tr>
<td>Renal failure acute</td>
<td>1.134</td>
<td>1.101</td>
<td>0.033</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.097</td>
<td>1.777</td>
<td>0.680</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.259</td>
<td>2.040</td>
<td>0.781</td>
</tr>
<tr>
<td>Rosai-Dorfman syndrome</td>
<td>1.187</td>
<td>1.500</td>
<td>0.313</td>
</tr>
<tr>
<td>Scleroderma-junction syndrome</td>
<td>1.111</td>
<td>1.356</td>
<td>0.245</td>
</tr>
<tr>
<td>Sudden onset of sleep</td>
<td>1.908</td>
<td>2.300</td>
<td>0.392</td>
</tr>
<tr>
<td>Suicide behaviour</td>
<td>1.143</td>
<td>1.590</td>
<td>0.447</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1.061</td>
<td>1.203</td>
<td>0.142</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.046</td>
<td>1.085</td>
<td>0.040</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>1.088</td>
<td>1.072</td>
<td>-0.016</td>
</tr>
<tr>
<td>Upper gastrointestinal haemorrhage</td>
<td>1.104</td>
<td>1.271</td>
<td>0.167</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1.065</td>
<td>1.112</td>
<td>0.047</td>
</tr>
</tbody>
</table>
3.07–Other information to enhance SD

- We have established a direct mathematical link between the masking for the PRR and its 95% confidence interval:

\[ \ln(MRCI) \approx \ln(MR) + 1.96 \left( \sqrt{\frac{1}{n_1}} - 1 - \sqrt{\frac{1}{n_1 - n_{01}}} \right) \]

- The extent of the masking observed with the PRR (left hand side) and with the Lower95CI (right hand side) is very similar.
3.07–Other information to enhance SD

- The removal of the masking for the two methods reveals an important proportion of identical SDRs, the proportion of SDRs revealed unmasked increases with the magnitude of the masking.
3.07–Other information to enhance SD

- Future direction
- 4th article in preparation (validation of the proposed approximate approach in EudraVigilance)
- Test the algorithm on smaller SRS databases (collaboration with INSERM / University Bordeaux Victor Segalen under discussion with A. Pariente)
- Public Health impact of masking on prospective signal detection activities (true effects unravelled, time gained)
3.07–Other information to enhance SD

- Publications
  - FRANCOIS MAIGNEN, MANFRED HAUBEN, ERIC HUNG, LIONEL VAN HOLLE, JEAN MICHEL DOGNE. A conceptual approach to the masking effect of measures of disproportionality (submitted to Pharmacoepidemiology and Drug Safety)
  - FRANCOIS MAIGNEN, MANFRED HAUBEN, ERIC HUNG, LIONEL VAN HOLLE, JEAN MICHEL DOGNE. Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases (submitted to Pharmacoepidemiology and Drug Safety)
  - FRANCOIS MAIGNEN, MANFRED HAUBEN, ERIC HUNG, LIONEL VAN HOLLE, JEAN MICHEL DOGNE. A mathematical framework to quantify the masking effect associated with the confidence intervals of measures of disproportionality (internal review before submission to Pharmacoepidemiology and Drug Safety)
  - 4th article in preparation (validation of algorithm in EV and PfAST)
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**
  - Legal hurdles cleared
  - Company-specific analysis plans finalized
  - High-level presentation held at DIA Euro 2013

- **Future work**
  - Complete hierarchical model analysis of Bayer data
  - Complete extreme value modeling of AZ laboratory data
  - Write papers and prepare presentations
3.10–Signal detection in EHRs

• Progress to date
  – Study I completed: Comparison to published epidemiological papers
  – Study II in progress: Broad screening – characterize false positives and develop signal qualification strategies
  – Oral presentation held at ISPE Asia 2012
  – Abstract submitted to ICPE 2013

• Future work
  – Complete Study II (Aug 2013)
  – Initiate and complete Study III (Aug 2013): comparison between EHRs and spontaneous reports
  – Write papers and prepare presentations
3.10—Signal detection in EHRs

### IC delta screening

<table>
<thead>
<tr>
<th>Selection Type</th>
<th>Therapy Name</th>
<th>Medical Event Name</th>
<th>Matched subordinate terms</th>
<th>Window type</th>
<th>ICdelta</th>
<th>ICdelta/expected</th>
<th>Observed</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Disseminated lupus erythematosus</td>
<td></td>
<td>2-6 months</td>
<td>2.46</td>
<td>1.92</td>
<td>9</td>
<td>0.0</td>
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<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Cardiomegaly</td>
<td></td>
<td>2-4 months</td>
<td>2.84</td>
<td>1.01</td>
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<td>Daraprim</td>
<td>Cardiorespiratory disease</td>
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<td>1 month</td>
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<td>1.00</td>
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<td>11.0</td>
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<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Terminal illness</td>
<td></td>
<td>2-0 months</td>
<td>2.81</td>
<td>0.76</td>
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<td>0.3</td>
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<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Refused to cheat physician</td>
<td></td>
<td>2-6 months</td>
<td>2.81</td>
<td>0.76</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Drug treatment not indicated</td>
<td></td>
<td>2-7 months</td>
<td>3.23</td>
<td>0.71</td>
<td>3</td>
<td>0.7</td>
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<tr>
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<td>Daraprim</td>
<td>Haemorrhage</td>
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<td>1.38</td>
<td>0.63</td>
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<td>6.6</td>
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<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Acute myocardial infarction</td>
<td></td>
<td>1 month</td>
<td>1.71</td>
<td>0.34</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>View statistics</td>
<td>Daraprim</td>
<td>Volume depletion</td>
<td></td>
<td>2-0 months</td>
<td>1.05</td>
<td>0.32</td>
<td>10</td>
<td>3.1</td>
</tr>
</tbody>
</table>

### Chronograph

**Nifedipine - Flushing/goes red 1672**

Number of events:
- **Observed**: 64
- **Expected**: 30.7

**Nifedipine - Ankle swelling 1832**

Number of events:
- **Observed**: 27
- **Expected**: 14.4
3.11–Interaction detection

• Progress to date
  – Report from literature review completed
  – Reference set of adverse drug interactions and non-adverse drug interactions completed
  – Draft protocol available

• Future work
  – Analysis of different methods as per protocol
  – Submitting a summary of literature review for publication
3.12–Duplicate detection

• Progress to date
  – Screen for suspected duplicates in VigiBase completed
  – Evaluation of suspected duplicates completed by Spain, Denmark, and the UK
  – Abstract submitted to ICPE 2013

• Future work
  – Paper to be written up
  – Evaluation of duplicate detection with probabilistic record matching directly on national databases
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 learns about the study in one of 4 countries.

Study subject enrols for the web or phone (IVRS) method of data collection. Chooses frequency of response and reminder methods.

Web

n = 1200 per country

Study subject completes the surveys online.

Final outcome survey + satisfaction is completed at the end of pregnancy.

IVRS

n = 200 per country

Study subject completes the baseline survey

n = 800 study-wide

n = 4800 study-wide

Study subject completes the surveys online.

n = 200 per country

Web

n = 1200 per country
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
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.
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
Planned timescale October 2012
IMPORTANT MILESTONES

- 1st October Website went live
- 10th October – recruitment started in Denmark
- 19th October - Leaflets shipped to NL
- 24th October – Leaflets shipped to UK
- 29th October recruitment start in NL and UK
Original Recruitment Strategies

- Original recruitment strategies were similar for each country and consisted of the following

<table>
<thead>
<tr>
<th>Country</th>
<th>Recruitment Tactic #1</th>
<th>Recruitment Tactic #2</th>
<th>Recruitment Tactic #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Leaflets/Posters in Thin specific areas</td>
<td>Facebook/Twitter</td>
<td>Free advertisement on pregnancy websites and forums i.e. community.babycentre.co.uk, netdoctor.co.uk/forum, patient.co.uk/forum,</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Leaflets/Posters in identified pharmacies, gynecologists in North Holland</td>
<td>Facebook</td>
<td>Free advertisement on pregnancy websites and forums i.e. zwanger.nl, babybytes.nl</td>
</tr>
<tr>
<td>Poland</td>
<td>Leaflets/Posters distributed to a number of destinations</td>
<td>Facebook</td>
<td>Free advertisement on pregnancy websites and forums i.e. twojaciazaz.com.pl/forum/index.php,babyboom.pl/forum</td>
</tr>
<tr>
<td>Denmark</td>
<td>via Netdoktor.dk by adds or through news letters.</td>
<td>It not yielding enough participants from netdoktor.dk ad on google.com</td>
<td>Facebook</td>
</tr>
</tbody>
</table>
Recruitment Strategies (Leaflets)

- Overview of number of posters leaflets generated
- Example of UK Posters, leaflets.

<table>
<thead>
<tr>
<th>Country</th>
<th>PL numbers</th>
<th>PL Packing units</th>
<th>UK numbers</th>
<th>UK Packing units</th>
<th>NL numbers</th>
<th>NL Packing units</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Posters A3</td>
<td>500</td>
<td>50</td>
<td>500</td>
<td>50</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td># of Posters A4</td>
<td>500</td>
<td>50</td>
<td>500</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td># of Leaflets</td>
<td>30 000</td>
<td>1000</td>
<td>15 000</td>
<td>1000</td>
<td>10 000</td>
<td>1000</td>
</tr>
</tbody>
</table>
Recruitment Strategies (Social Media)

• 3 Facebook pages generated for UK, NL, PL. DK in the pipeline.
• Difficult to build an audience
• Therefore traffic to page is small but working on this with assistant from IAPO
• Twitter initiated in UK but again difficult to build audience. Abandoned for time being
Some new recruitment strategies

- UK – Bounty “Discover Bounty, your one-stop pregnancy, baby and parenting club for mums-to-be and ... Find news and advice on pregnancy and being a parent at Bounty.com.

Join the PROTECT pregnancy study – Answering questions today for the pregnancies of tomorrow

Women who are pregnant often need advice about health and lifestyle choices, including for example use of alcohol, tobacco and medicines.

In order for medical professionals to have the most up to date information available to provide this advice, it is important to collect details about the health and lifestyle of our pregnant population.

To do this, we need YOUR HELP.

If you are:

✓ Pregnant
✓ Living in the UK
✓ Able to spend a short amount of time completing questionnaires by phone or on-line from the comfort of your own home

Then we need to hear from you TODAY!

What you will need to do?

If you would like to learn more or you would like to get involved today, then please visit our website:

www.pregnancystudy4.eu
Recruitment Conclusions

- Social Media: It is extremely difficult to build an audience via facebook and twitter.
- From early evidence it seems paid advertisement yields best results.
- It helps to make our website https://www.pregnancystudy4.eu/ as enticing as possible to encourage recruitment.
- Efforts are in place to make certain changes to the website to make it more enticing to enroll.
Adjustment of the timelines

1st Participants in:
DK: 12-Oct-2012
UK: 29-Oct-2012
NL: 05-Nov-2012

Recruitment and follow up

- Test Data Set to Imperial College 15-Sep-2013
- Final Data Set to Imperial College 14-Apr-2014
- 31-Aug-2013: 1. Last woman recruited 2. Linkage to Thin and Danish data to commence
- Stop Data Collection 31-Mar-2014
- Report to IMI 31-Aug-2014

Data Cleaning

Data Linkage

Analysis and Report Generation

Publications

Publication Preparations

Time in months

0 6 11 18 20 23
Recruitment, although on the increase, needs to improve dramatically to reach our study goals:
Conclusion

- No participants to IVRS arm of the study after 5 months of recruitment efforts.

- Social media is not yielding much result but efforts in place to activity on pages but difficult to build an audience.

- Advertisements on websites where a payment for a pay per conversion, pay per click method is used or specific e-mailing with a ready made audience seems to be the way forward; however, it is expensive.
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.
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 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

- All B-R assessment approaches
  - Approaches excluded and not appraised

- Benefit-risk assessment framework
  - PROACT, URL, ASF, BRAT, CMR-CASS, FDA, BRF
- Descriptive framework
- Non-quantitative

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

- Main categories
  - Estimation techniques
    - UT-NNT, INHB, BRR, GBR, Principle of three, TURBO, Beckmann Model
  - Utility survey techniques
    - DAGs, PSM, CPM, ITC, MTC, CDS
- Sub-categories
- Health indices
- Trade-off indices
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. Assesibility 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive</strong></td>
<td><em>Threshold indices</em></td>
<td>• PSM</td>
<td>• DCE</td>
</tr>
<tr>
<td>• PrOACT-URL</td>
<td>• NNT</td>
<td>• MTC</td>
<td></td>
</tr>
<tr>
<td>• BRAT</td>
<td>• NNH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Impact number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comprehensive</strong></td>
<td><em>Health indices</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MCDA</td>
<td>• QALY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• SMAA</td>
<td>• Q-Twist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• INHB</td>
<td>• Trade-off indices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• BRR</td>
<td></td>
<td></td>
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</table>
### Visual Review – Recommendations table

<table>
<thead>
<tr>
<th>Approach</th>
<th>Visual representation of results</th>
<th>Other visual representations of special interest</th>
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<tbody>
<tr>
<td>PrOACT-URL</td>
<td>‘Effects’ table</td>
<td>n/a</td>
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<tr>
<td>PhRMA BRAT</td>
<td>Table, forest plot, bar graph</td>
<td>Tree diagram to represent model.</td>
</tr>
<tr>
<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>
</tr>
<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>
<tr>
<td>BRR</td>
<td>Bar graph, forest plot, line graph</td>
<td>Scatter plot or contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.</td>
</tr>
<tr>
<td>NNT</td>
<td>Forest plot, line graph, scatter plot</td>
<td>Contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.</td>
</tr>
<tr>
<td>Impact Numbers</td>
<td>Forest plot, line graph, scatter plot</td>
<td>Contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.</td>
</tr>
<tr>
<td>QALY</td>
<td>Bar graph, forest plot</td>
<td>Line graph or scatter plot for sensitivity analysis.</td>
</tr>
<tr>
<td>Q-TWiST</td>
<td>Bar graph, forest plot</td>
<td>Line graph or scatter plot for sensitivity analysis.</td>
</tr>
<tr>
<td>INHB</td>
<td>Line graph, scatter plot</td>
<td>Contour plot for sensitivity analysis.</td>
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<tr>
<td>PSM</td>
<td>n/a</td>
<td>Network graph to represent model.</td>
</tr>
<tr>
<td>MTC</td>
<td>n/a</td>
<td>Network graph to represent model.</td>
</tr>
<tr>
<td>DCE</td>
<td>Bar graph</td>
<td>Line graph or scatter plot for sensitivity analysis.</td>
</tr>
</tbody>
</table>
Disclaimer

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 2 Case studies: Applications

<table>
<thead>
<tr>
<th>Method</th>
<th>Acomplia</th>
<th>Tysabri</th>
<th>Rosiglitazone</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrOACT-URL</td>
<td>✓ (jointly)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>BRAT</td>
<td>✓ (jointly)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>MCDA</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>SMAA</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSM</td>
<td></td>
<td>✓</td>
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<td>MTC/ITC</td>
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<td>AHP</td>
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<td>✓</td>
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<td>Swing-weighting</td>
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<td>✓</td>
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<tr>
<td>MACBETH</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
PrOACT-URL Framework

- Problem
- Objective
- Alternatives
- Consequences
- Trade-off
- Uncertainty
- Risk tolerance
- Linked decisions

- A generic framework to structure the decision problem
- Divide into 8 steps
- Emphasis on uncertainty via sensitivity analysis
BRAT Framework

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

- A framework to assist benefit-risk assessment and communication
- Divide into 6 steps
- Emphasis on uncertainty in the confidence intervals when presenting results
### Raptiva example

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Efalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Severe side effects</td>
<td>Progressive Multifocal Leukoencephalopathy</td>
</tr>
<tr>
<td>Regulatory history</td>
<td>Approved 2004</td>
</tr>
<tr>
<td></td>
<td>License withdrawn 2009</td>
</tr>
<tr>
<td>Data source</td>
<td>EPAR</td>
</tr>
<tr>
<td></td>
<td>SPC</td>
</tr>
<tr>
<td></td>
<td>PSUR10</td>
</tr>
<tr>
<td>Methodologies tested</td>
<td>PrOACT-URL, BRAT, MCDA, BRR</td>
</tr>
<tr>
<td></td>
<td>+ Decision conferencing to elicit value preference using swing-weighting</td>
</tr>
</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>% / 100 ptyrs</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>% / 100 ptyrs</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 Polyradiculopathy</td>
<td>Number of cases of inflammatory polyradiculopathy.</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
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 PGA</td>
<td>20.4</td>
<td>61</td>
<td>12.4</td>
<td>12.4</td>
</tr>
<tr>
<td>Physicians' ratings PASI75</td>
<td>25.5</td>
<td>45</td>
<td>11.4</td>
<td>23.8</td>
</tr>
<tr>
<td>Patients' ratings DLQI</td>
<td>20.4</td>
<td>37</td>
<td>7.6</td>
<td>31.4</td>
</tr>
<tr>
<td>Physicians' ratings OLS</td>
<td>6.4</td>
<td>73</td>
<td>4.7</td>
<td>36.1</td>
</tr>
<tr>
<td>Physicians' ratings PASI50</td>
<td>5.1</td>
<td>64</td>
<td>3.2</td>
<td>39.3</td>
</tr>
<tr>
<td>SAEs Severe Psoriasis</td>
<td>0.0</td>
<td>-45</td>
<td>0.0</td>
<td>39.3</td>
</tr>
<tr>
<td>SAEs Hprnsntvty Reactions</td>
<td>0.0</td>
<td>-50</td>
<td>0.0</td>
<td>39.3</td>
</tr>
<tr>
<td>Observational data Polyradiculopathy</td>
<td>0.3</td>
<td>-80</td>
<td>-0.2</td>
<td>39.1</td>
</tr>
<tr>
<td>Clinical Trials AEs</td>
<td>0.5</td>
<td>-57</td>
<td>-0.3</td>
<td>38.8</td>
</tr>
<tr>
<td>Observational data ILDs</td>
<td>1.3</td>
<td>-90</td>
<td>-1.1</td>
<td>37.7</td>
</tr>
<tr>
<td>SAEs Serious Infections</td>
<td>2.6</td>
<td>-48</td>
<td>-1.2</td>
<td>36.4</td>
</tr>
<tr>
<td>Observational data Aseptic Meningitis</td>
<td>1.3</td>
<td>-97</td>
<td>-1.2</td>
<td>35.2</td>
</tr>
<tr>
<td>Observational data Haemolytic anemia</td>
<td>1.5</td>
<td>-96</td>
<td>-1.5</td>
<td>33.7</td>
</tr>
<tr>
<td>SAEs Svre Thrombocytopeni</td>
<td>2.0</td>
<td>-90</td>
<td>-1.8</td>
<td>31.9</td>
</tr>
<tr>
<td>Observational data PML</td>
<td>12.8</td>
<td>-95</td>
<td>-12.1</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Total: 100.0  19.8
# Tysabri example

<table>
<thead>
<tr>
<th>Active drug</th>
<th>Natalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Relapsing remitting multiple sclerosis</td>
</tr>
<tr>
<td>Severe side effects</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 |
| Comparators | Placebo, Avonex, Copaxone |
| Methodologies tested | PrOACT-URL, BRAT, MCDA, NNT & NNH, BRR, PSM, MTC  
+ Decision conferencing to elicit value preference directly |
Tysabri: Structure by value tree

Benefit-risk balance

Benefit
- Reduction in relapse rate
- Slowdown in disability progression

Administration

Risks
- Severe side effects
  - PML
    - Reactivation of serious herpes viral infections
    - Seizures
    - Abortion or congenital abnormalities
  - Transaminases elevation
  - Infusion or injection reactions
  - Hypersensitivity reactions
  - Flu-like reactions

Mild side effects
### 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>X</td>
<td></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>X</td>
<td></td>
</tr>
<tr>
<td>Metric indices</td>
<td>(5) NNT and NNH.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6) Impact numbers.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7) Quality Adjusted Life Years (QALY).</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(8) Q-TWiST.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(9) Incremental Net Health Benefit (INHB).</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Estimation techniques</td>
<td>(10) Benefit-Risk Balance.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11) Probabilistic Simulation Method (SPM).</td>
<td>X</td>
<td></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>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>(14) Direct elicitation</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Tysabri: MCDA calculating weighted utility

For each criterion (outcome)

Outcome: Disability Progression

Measure = 11%

Value (measure) = 0.89

Elicited Weight = 5%

BR Contribution = 0.045
Let $S_{ij} =$ utility score for criterion $j$ in alternative $i$

$w_j =$ preference weight for criterion $j$

With constraint $\sum_{j=1}^{k} w_j = 1$ for $k$ number of criteria

Then, the overall expected utility for alternative $i$ is

$$U_i = \sum_{j=1}^{k} w_j S_{ij} = w_1 S_{i1} + w_2 S_{i2} + \cdots + w_k S_{ik}$$
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: 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
The base case value of the weight for each outcome is shown under each bar.

The low values and high values of ±20% change in weight are shown at the ends of the bars.

The incremental benefit-risk at the base case is the x-axis value at the middle.

How this changes with each weight is shown by the position of the bar ends.

From this plot we see that changes in the weight of relapse has the most influence on the benefit-risk score.
Tysabri: MCDA comments

• In its current form, only point values are taken into account
• For Gaussian shaped data, may reflect average
• Skewed data may be misrepresented
• What about uncertainty in data?
• What about uncertainty in value preferences?
• What about missing value preferences?
Quantitative B-R: SMAA-2

- Similar to MCDA (MAUT)
- Requires utilities, probabilities, weights
- Allows uncertainty and missing weights
- There is no formal framework but could be combined with PrOACT-URL or BRAT
- Stochastic analysis
## Acomplia

<table>
<thead>
<tr>
<th>Active drug</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>Comparator</strong></td>
<td>Placebo, Orlistat (Wave 2), Meridia (Wave 2)</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>
Acomplia: Structure by value tree

Benefit-risk Balance

Benefit
- Achieving 10% weight loss
- Improvement in HDL cholesterol

Risk
- Cardiovascular disorders
- Psychiatric disorders
- Gastrointestinal disorders
Acomplia: SMAA calculating weighted utility
For each criterion (outcome)

Outcome: Achieved 10% weight loss

Measure: 40% (range 24% - 59%)

Value(measure): 50% (range 29% - 74%)

Weight space: 57% (range 21% - 100%)

BR Contribution 29% (range 9% - 68%)
Let $f_X(\xi) = \text{density function on the space of all consequence } X$
$f_W(w) = \text{density function of weight space } W$
$W_i^1(\xi) = \text{alternative } i \text{ favourable weight space}$

For $X \subset R^{i \times j}$ (i alternatives and j criteria) and $w \in W_i^1(\xi)$
Then the probability of alternative $i$ ranked first is

$$b_i^1 = \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} f_W(w) \, dw \, d\xi$$
Acomplia: Calculating central weight

The expected centre of gravity for \( W_i^1(\xi) \) is

\[
 w_i^c = \frac{1}{b_i^1} \int_{\xi \in X} f_X(\xi) \int_{w \in W_i^1(\xi)} w f(w) dw \, d\xi
\]
Acomplia: SMAAA (Wave 1)
Preference-free model

Acceptability index
alternative $i$ is ranked $r$

<table>
<thead>
<tr>
<th>Alternative</th>
<th>Rank 1</th>
<th>Rank 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acomplia 20mg</td>
<td>0.70</td>
<td>0.30</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.30</td>
<td>0.70</td>
</tr>
</tbody>
</table>
Acomplia: SMAA (Wave 2)
Probabilities achieving rank 1, 2, 3 or 4

- Non-missing weights model
- Drugs
  - Placebo
  - Orlistat
  - Meridia
  - Acomplia
Acomplia: SMAA (Wave 2)
Utility distributions for a set of decision-maker’s weights

- Drugs
  - Placebo
  - Orlistat
  - Meridia
  - Acomplia

- Online interactive version allows own weights is available

http://public.tableausoftware.com/views/wave2rangeweight/Dashboard2?:embed=y
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
Results...progression,

Wave 1 case studies testing methodologies

Methodology review

Wave 2 case studies further testing methodologies and visual representation

Visual review (1&2)

Recommendations for BR analyses and representation

Patient public involvement
On-going work (Wave 2)

- Interactive benefit-risk visual representation and recommendations
- Individualised benefit-risk assessment (Warfarin case study)
- Bayesian modelling of MCDA
- Various methods of value preference elicitation directly from patients
  - DCE, AHP, Swing-weighting, MACBETH
  - Uncertainty in value preferences
Communications (incl. publications)

- Eleven reports expected to be made public in the near future
- A further two reports planned, summaries of wave 1 and of wave 2 case study results
- All likely to generate academic manuscripts
- Multiple invitations to present at conferences attended by members of the pharmaceutical industry, academics and regulators
- Working with IAPO to generate patient/public related communications
Work plan until August 2014

- Patient public involvement team due to deliver final report by end 2013
- Recommendations subteam due to deliver first draft spring 2013
  - Paper/2D recommendations
  - Pragmatic, summary document with multiple hyperlinks and supporting documentation
  - Interactive web based recommendations
  - Due late 2013
- Publications subteam to oversee publications for the remainder of the project
- Bridge to WP6 formed via WP5 co-lead attending/participating in WP6 meetings
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)
Two replication programmes planned

- First replication programme of the studies in WP
- Second replication programme of the methods and tools developed in WP5
## WP6 Research Plan for WP2 studies replication

### Study Objectives, Rationale and Design

<table>
<thead>
<tr>
<th>Objective</th>
<th>Defined Study Objective</th>
<th>Scientific Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective 1</strong></td>
<td>Replication study in same database</td>
<td>Is the study replicable when conducted independently in the same database?</td>
</tr>
<tr>
<td><strong>Objective 2</strong></td>
<td>Replication study in different database</td>
<td>Do the results have external validity?</td>
</tr>
<tr>
<td><strong>Objective 3</strong></td>
<td>Negative control study</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>
</tr>
<tr>
<td><strong>Objective 4</strong></td>
<td>Use of alternative outcome definition</td>
<td>What is the impact of different levels of certainty of the outcome (e.g. definite, probable, possible) on the effect estimate?</td>
</tr>
<tr>
<td><strong>Objective 5</strong></td>
<td>Validation of outcome</td>
<td>Has the outcome of interest been validated through clinical record review? What is the impact of validation on the effect estimate?</td>
</tr>
<tr>
<td><strong>Objective 6</strong></td>
<td>Assessment of confounders</td>
<td>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?</td>
</tr>
</tbody>
</table>
## WP6 Research Plan for WP2 studies replication

**Objective(s) per drug/event pair and data source**

<table>
<thead>
<tr>
<th>Drug / Adverse event pair</th>
<th>WP6 Partner</th>
<th>Data sources</th>
<th>Obj 1 same DB</th>
<th>Obj 2 different database</th>
<th>Obj 3 negative control study</th>
<th>Obj 4 alternative outcome</th>
<th>Obj 5 valid. of outcome</th>
<th>Obj 6 confound ers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics &amp; ALI</td>
<td>TAKEDA</td>
<td>GPRD</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>SANOFI</td>
<td>Invision Datamart</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Utrecht U</td>
<td>UPOD</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Antiepileptic &amp; suicidality</td>
<td>LA-SER</td>
<td>PGRx</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>AARHUS</td>
<td>Danish Register</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta2 agonists &amp; AMI</td>
<td>SANOFI</td>
<td>Invision Datamart</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LA-SER</td>
<td>PGRx</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Negative control ATB &amp; MI</td>
<td>SANOFI</td>
<td>Invision Datamart</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LA-SER</td>
<td>PGRx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CCB &amp; Cancer</td>
<td>LA-SER</td>
<td>E3N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
WP6 Research Plan for WP2 studies replication
Progress status, March 2013 (1)

- **WP2 drug-adverse event** studies have been considered:
  - Antibiotics and drug induced liver injury
  - Inhaled beta-2 agonists and acute myocardial infarction
  - Negative control Antibiotics & acute myocardial infarction
  - Antiepileptic & suicidality
  - Calcium channel blockers and cancer

- **Data sources** have been identified:
  - PGRx (LA-SER), GPRD (UK), Danish psychiatric registry, UPOD (NL), Invision Datamart/Premier (US), E3N (France).

- Cancelled studies:
  - Antidepressants or benzodiazepines and hip/femur fracture in GPRD
  - Calcium channel blocker & Cancer in Marketscan/Medicaid
  - Antiepileptic & suicidality in GPRD
WP6 Research Plan for WP2 studies replication
Progress status, March 2013 (2)

- 6 studies completed
  - Danish register - Suicidality & anticonvulsants
    - Gasse C - Impact of previous suicide attempts and family history of psychiatric disease on the size of the association between antiepileptic drugs and suicide related events
    - Astrup A - Impact of censoring at or truncating risk time of hospitalizations on the effect measure of the association between antiepileptic drugs (AED) and suicide attempt
  - PGRx - Suicidality & anticonvulsants
    - Grimaldi-Besouda L - Risk of suicide attempts associated with antiepileptic drugs: a case-control study looking at the effect of differing design options
  - PGRx - MI and Beta 2 agonists
    - Risk of acute myocardial infarction associated with inhaled long acting beta2 adrenoceptor agonists: a case-control study looking at the effect of differing design options
  - Invision Datamart – Antibiotics & ALI
    - Tcherny-Lessenot S - WP6 replication study on the risk of liver injury associated with the use of antibiotics using a US database with linkage with hospital data
  - UPOD – Antibiotics & ALI
    - Udo R - Validation of hospital discharge diagnoses and liver related laboratory measurements to identify patients with idiopathic acute liver injury
**WP6-WP5 activities**

**Activity 1**
Test how B/R methods adapt in a real-life setting

**Activity 2**
Validate visualisation tools recommended by WP5 to the targeted audience

Lead: LASER

Lead: EMA
Activity 1: Assessing the relevance of RCT-based B/R methodology in the real-life setting

- Consider the various sources of data
- Consider the time factor
- Consider the real-world factors that may impact
- Consider uncertainty as key input in the decision making

Three assessment areas

- Effect of time horizon, time dependency
- Early uncertainty assessment, prior expert judgement
- Use of real-world/observational data vs. clinical only
Activity 2: Validation of visualisation tools

1. Validation of Methods to Present BR data
   Research questions:
   - What graphical presentation methods are most useful for regulators/physicians in evaluating benefit-risk trade-offs?
   - What graphical presentation methods are most useful for communicating benefit-risk trade-offs to physicians/patients?

2. Extension of Methodology to Elicit Patient Preferences
   Research questions:
   - Do the 3 different methods currently used for eliciting preferences produce the same results?
   - What are the differences in preferences for treatment outcomes among stakeholders (regulators, health care professionals, patients)?
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.
WP7 Progress so far and next steps

- Potential training topics are identified based on:
  - The PROTECT Project Plan and expected deliverables,
  - Contents of Consortium meetings,
  - Follow-up of PROTECT publications and presentations, and
  - Regular monitoring of the information posted on the e-room
Identify potential training topics

- Review of documents made public through the PROTECT website
- Review of e-room documents
- Approaching co-leaders of each WP at regular intervals
- Agreeing training materials with WP co-leaders

Liaise with EU2P

- Identify the competency area at EU2P for each training topic of interest
- Establish general agreement with EU2P for knowledge transfer
- Agree each training topic of interest with EU2P co-leaders

Follow up

- Follow up of new training topics and training materials produced by PROTECT and included in the EU2P training programmes
Work Package 7: Training Platform

- Available at [https://w3.icf.uab.es/trainingopp](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
- First applications in October 2012
  - 10 training positions posted by two PROTECT consortium members
  - 14 inquiries received by the two institutions (12+2)
    - 3 submitted by Eu2P students
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](http://www.imi-protect.eu)

Email: Protect_Support@ema.europa.eu