ENGELBERG CENTER for Health Care Reform at BROOKINGS

European Medicines Agency's Postmarket Drug Safety Activities: Overview of PROTECT

Xavier Kurz, Principal Scientific Administrator, Post-Authorisation, Pharmacovigilance and Risk Management Sector, European Medicines Agency

June 20, 2012

Brookings Roundtable on Active Medical Product Surveillance

Some Initial Housekeeping

- To minimize feedback, please confirm that the microphone on your telephone is muted.
- To mute your phone, press the mute button or '*6'. (To unmute, press '*7' as well.)
- **There will be several opportunities for questions and discussion throughout today's session. Please use the chat box at the right side of your screen to submit your questions into the queue at any point and we will call upon you to state your question.**
- We will open up the lines for questions from those participating only by phone at the end of each Q&A session.
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PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

The PROTECT project

Xavier Kurz,

European Medicines Agency

Brookings Institution webinar

20 June 2012

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

The Innovative Medicines Initiative (IMI)

- Mission
  - The Innovative Medicines Initiative (IMI) is Europe's largest public-private partnership aiming to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients.
  - 30 projects funded through 5 Calls (1st call in 2008)
  - 6th Call ("Combating antibiotic resistance") on-going
  - PROTECT funded through 1st Call

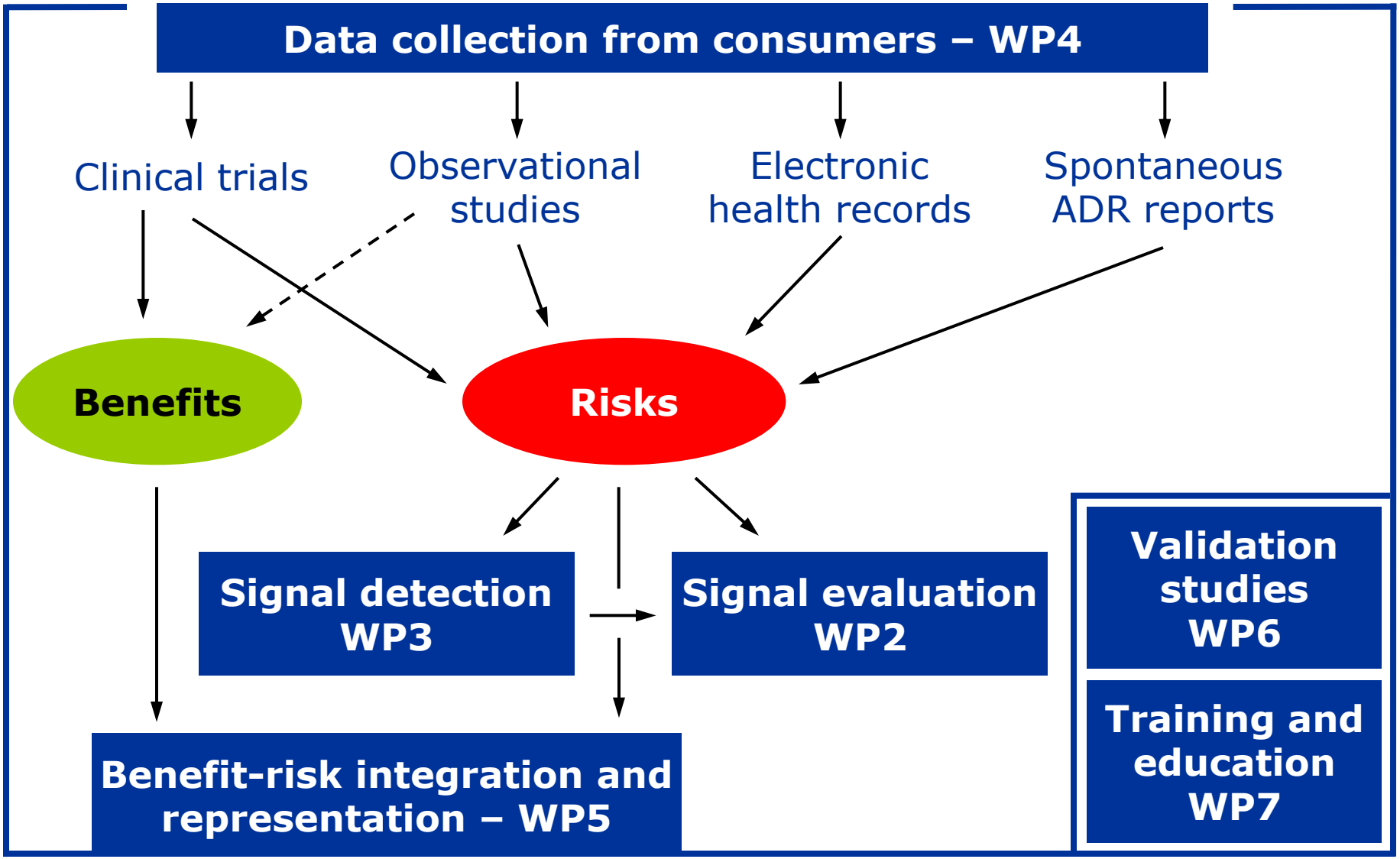
PROTECT Goal

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.


Data collection from consumers – WP4
Clinical trials
Observational studies
Electronic health records
Spontaneous ADR reports
Benefits
Risks
Signal detection WP3
Signal evaluation WP2
Validation studies WP6
Training and education WP7
Benefit-risk integration and representation – WP5

Partners (32)

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

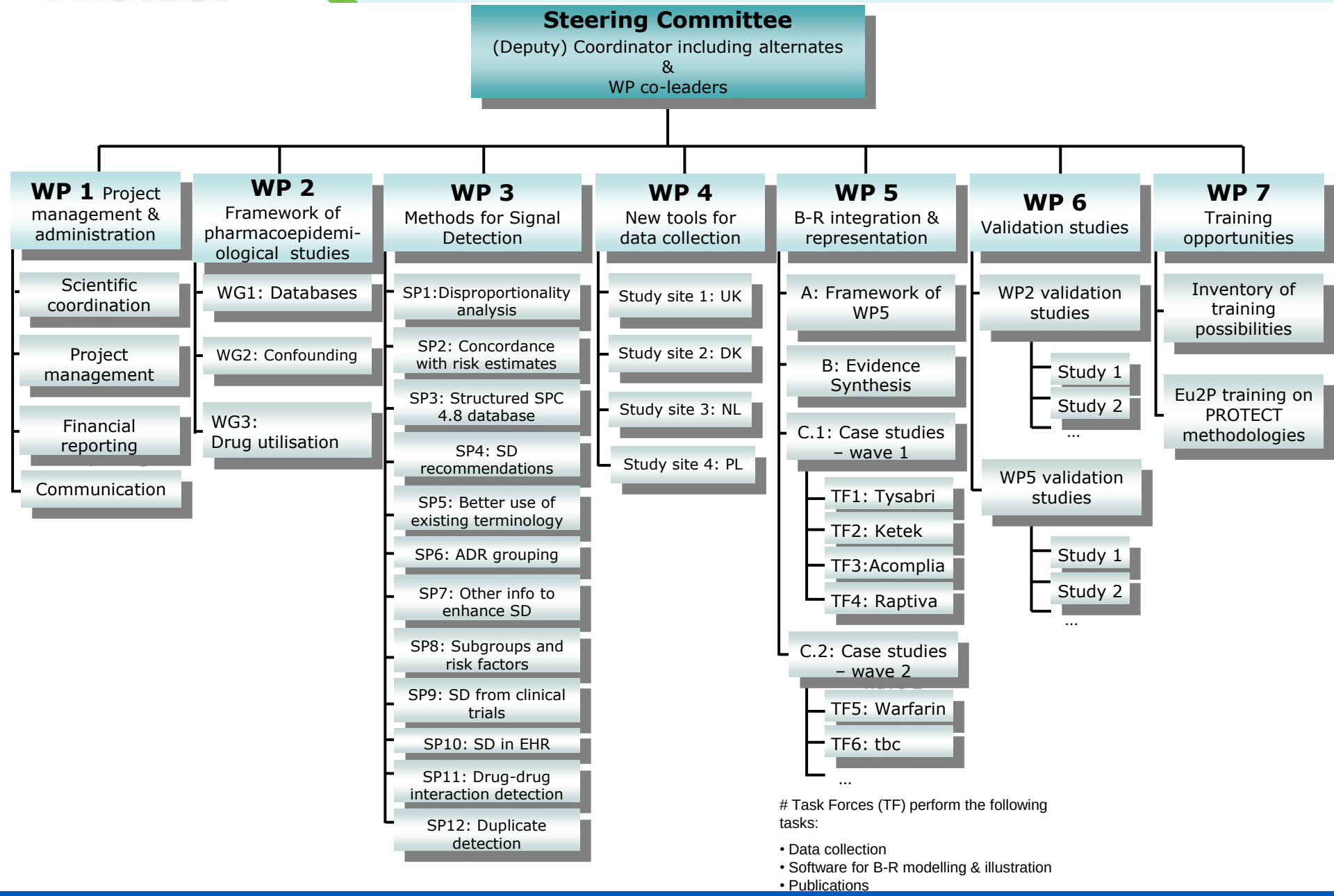
SMEs:
Outcome Europe
PGRx

Others:
WHO UMC
GPRD
IAPO
CEIFE

Private

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

PROTECT



Task Forces (TF) perform the following tasks:

- Data collection
- Software for B-R modelling & illustration
- Publications

WP 2: 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 the General Practice Research Database (GPRD) around the same period by two different groups.

	Meier et al., 2000		Van Staa et al., 2001	
Statins only	*Current use*	0.55 (0.44-0.69)	*Current use*	1.01 (0.88-1.16)
	N prescriptions		Time since use	
	- 1-4	0.51 (0.33-0.81)	- 0-3 months	0.71 (0.50-1.01)
	- 5-19	0.62 (0.45-0.85)	- 3-6 months	1.31 (0.87-1.95)
	- 20	0.52 (0.36-0.76)	- 6-12 months	1.14 (0.82-1.58)
			- > 12 months	1.17 (0.99-1.40)
	Recent use	0.67 (0.50-0.92)		
	Past use	0.87 (0.65-1.18)	*Past use*	1.01 (0.78-1.32)
Statins (current) and type of fractures	Femur	0.12 (0.04-0.41)	Hip	0.59 (0.31-1.13)
	Hand, wrist or arm	0.71 (0.52-0.96)	Radius/ulna	1.01 (0.80-1.27)
	Vertebral	0.14 (0.02-0.88)	Vertebral	1.15 (0.62-2.14)
	Other	0.43 (0.23-0.80)		

Why such a difference ?

		Meier et al., 2000		Van Staa et al., 2001
Source population		370 GPRD practices		683 GPRD practices
Study period		through Sept 1998		through July 1999
Design		Selected case control (3 cohorts)		Conventional case-control
N Cases		3,940		81,880
N Controls		23,379		81,880
Age	*50-69*	52.2%	*50-69*	47.9%
	70-79	28.9%	*70-84*	38.9%
	80-89	18.9%	*≥85*	13.2%
Sex	*Female*	75.0%	*Female*	75.6%
BMI	*≥25*	57.3%	*≥25*	52.3%

- 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

Work Package 2 – 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
  - Compare results of studies
  - Identify sources of discrepancies and issue recommendations

Databases

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

Work Package 2 – WG1: Databases

➲ Selection of 5 key adverse events and drugs

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

Antidepressants (incl. Benzodiazepines) **- Hip Fracture**
Antibiotics - **Acute liver injury**
Beta2 Agonists **- Myocardial infarction**
Antiepileptics - **Suicide**
Calcium Channel Blockers - **Cancer**

Stepwise approach

- Descriptive studies
- Cohort studies
- Other designs as applicable (case-control, case-crossover, SCCS,…)

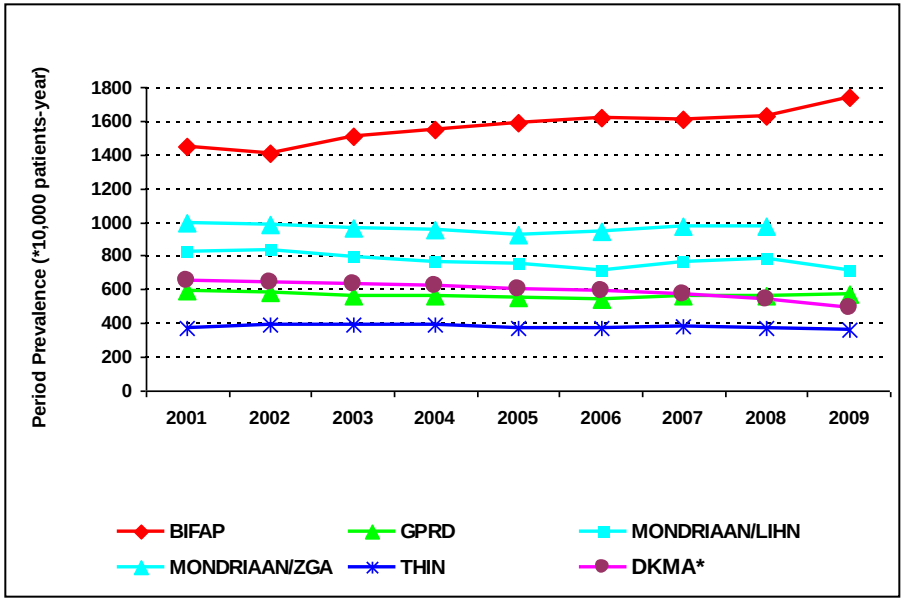
WG1 Progress status – COHORT STUDIES
last update: 16 April 2012

COHORT STUDY	Crude result tables from databases*		Draft reports compiling key results from databases	Preliminary draft manuscript
	Delivered April 2012	Pending April 2012		
Antibiotics/liver injury	Complete: BIFAP	GPRD (Amgen)	Delivered April 2012	Planned June 2012
Antiepileptics / Suicidality	None	DKMA GPRD (Roche)	Planned End April 2012	Planned June 2012
Antidepressants/Hip fracture	Mondriaan - interim THIN –interim	BIFAP Bavaria claims **	Delivered April 2012	Planned June 2012
Benzodiazepines/Hip fracture	None	BIFAP GPRD (Merck) Mondriaan Bavaria claims**	Planned End April 2012	Planned June 2012
Calcium channel blockers/Cancer	None	DKMA GPRD (Laser) **	Planned End April 2012	Planned June 2012
Inhaled Beta2 agonists / Myocardial infarction	None ***	BIFAP DKMA GPRD (Novartis) Mondriaan Bavaria claims**	Expected May/June 2012	To be defined

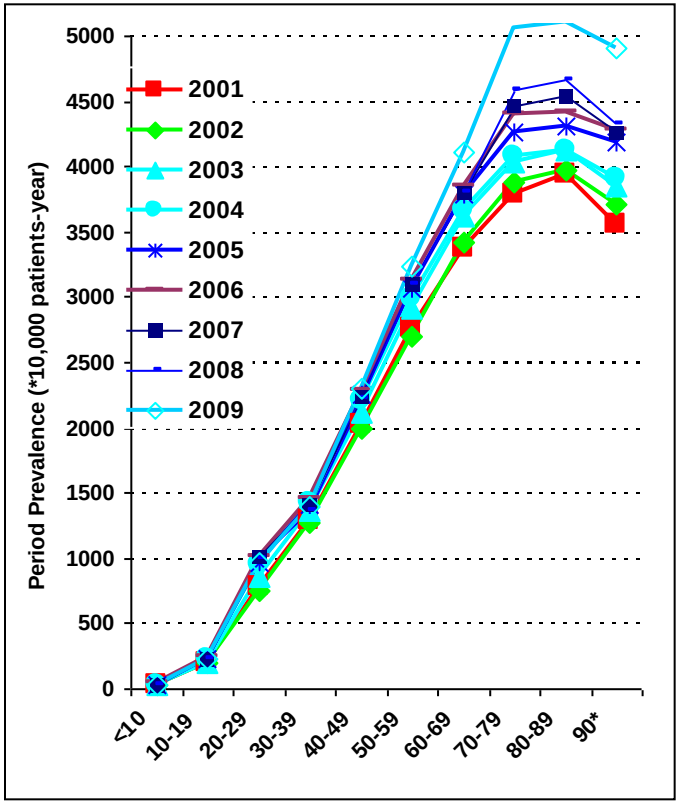
* Databases: Bavaria claims (Germany); BIFAP (Spain); DKMA (Denmark); Mondriaan (The Netherlands); GPRD (UK); THIN (UK)
** Due to delay in obtaining the data
*** due to delay in finalization of the protocol. Final protocol version delivered on 30 March 2012

WG1 Preliminary results - DESCRIPTIVE STUDIES Benzodiazepines (BZDs)

Period prevalence of BZD use by year

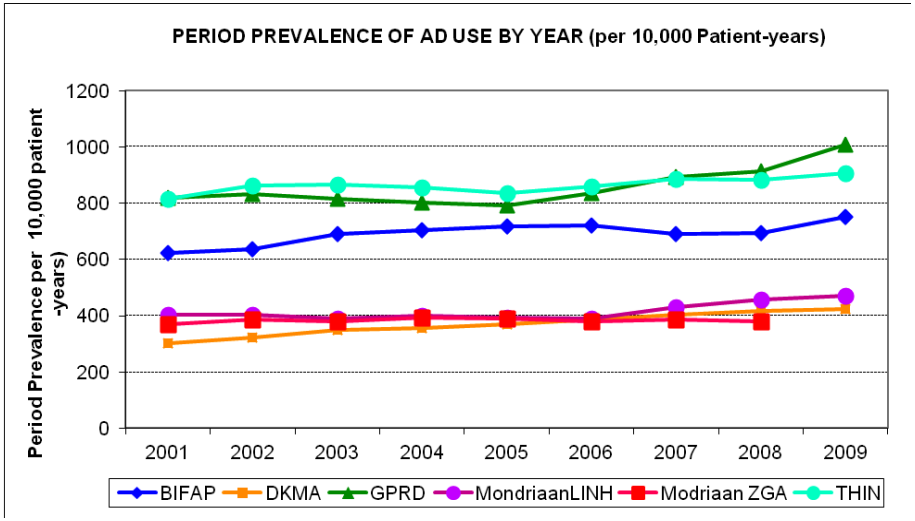


Period prevalence of BZD use by age and calendar year in BIFAP

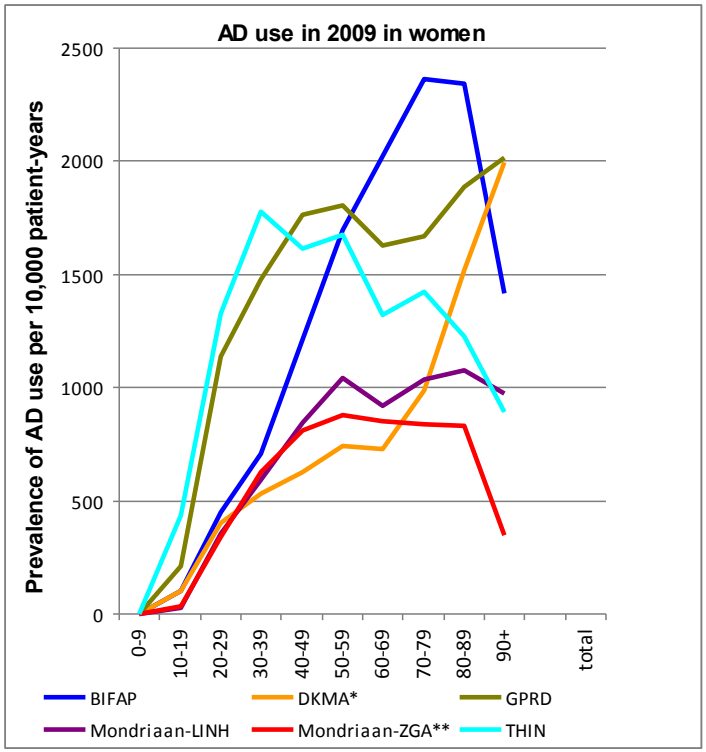


WG1 Preliminary results - DESCRIPTIVE STUDIES Antidepressants (ADs)

Period prevalence of AD use by year

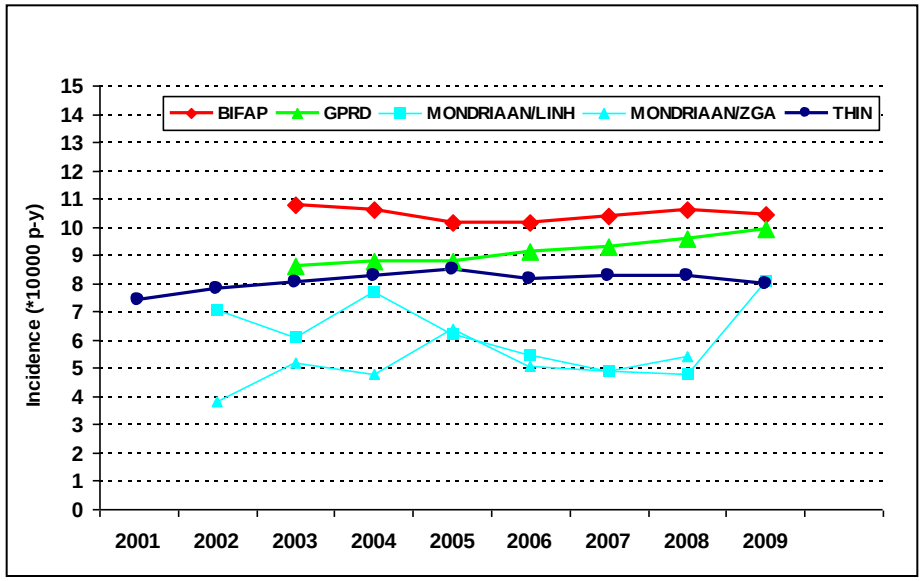


Period prevalence of AD use in women by age (2009)

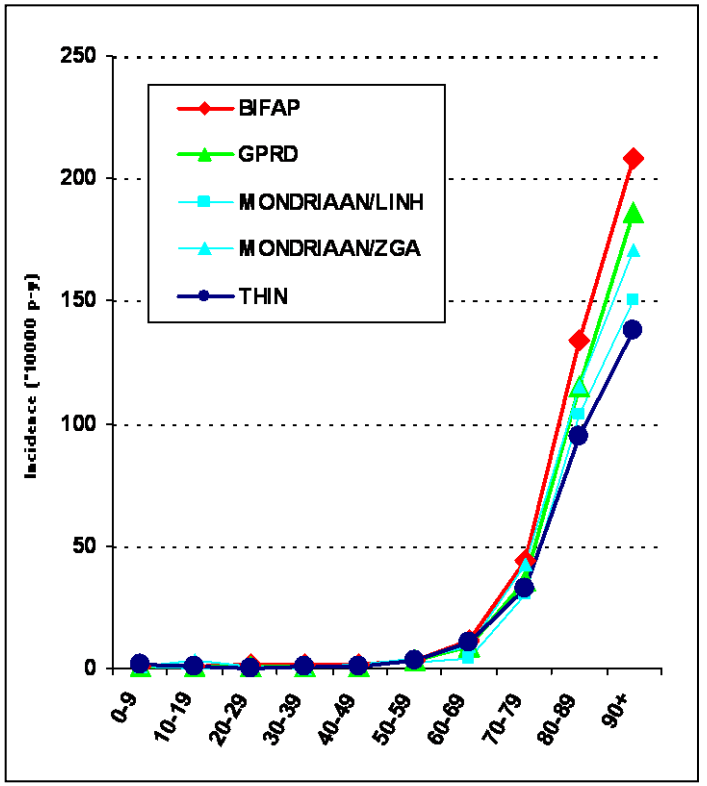


WG1 Preliminary results - DESCRIPTIVE STUDIES
Hip fracture

Incidence of hip fracture by year



Incidence of hip fracture by age (2003)



WG2 Confounding

1. Conduct of simulation studies:

- Propensity score/ balance measure methods to control for confounding
  - Normal distributed covariates, univariate measures of balance
  - Non-normal distributed covariates, multivariate measures of balance
- Studies on propensity score / balance measure and propensity scores time dependent methods to control for observed confounding
- Studies on Instrumental variables (Ivs) / methods to control for unobserved confounding
- Multi-database studies: 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.

2. Use of methods in real-life data (5 AE-drug pairs)

WG3 Drug Utilisation data

1. Inventory of Drug Utilisation data in Europe

- "Drug Consumption Databases in Europe" full report (latest version Aug 2011) is available on the PROTECT website http://www.imi-protect.eu/results.html
  - 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.
  - Goals:
    - To describe the characteristics of non-commercial drug consumption data providers in Europe
    - To report the features of each country health policy systems
    - 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.

2. Inventory of research working groups on drug utilisation in Europe

PROTECT WP3 Methods for signal detection

To improve early and proactive signal detection from spontaneous reports, electronic health records, and clinical trials

WP3 Sub-packages

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

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

- Progress to date
  - Database for centrally authorised products (CAP) fully implemented
  - Will provide gold standard for 3.01
  - Maintenance procedure agreed
  - To be published on PROTECT website
  - Extension to national products being tested

- Stepwise approach with proof-of-concept analysis of free text extraction algorithm from SPC section 4.8 to MedDRA PT
  - Initial match rate increased from 72% to 98%

Work Package 3 – 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

PROTECT WP4: New tools for data collection from consumers

New methods of data collection in pharmacovigilance including methods for collecting data in the natural language and research on how to simplify data collection from reporters whoever they are.

An exploratory study of self-reported medication use in pregnant women

Work Package 4 - 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

Work package 4 - Study population

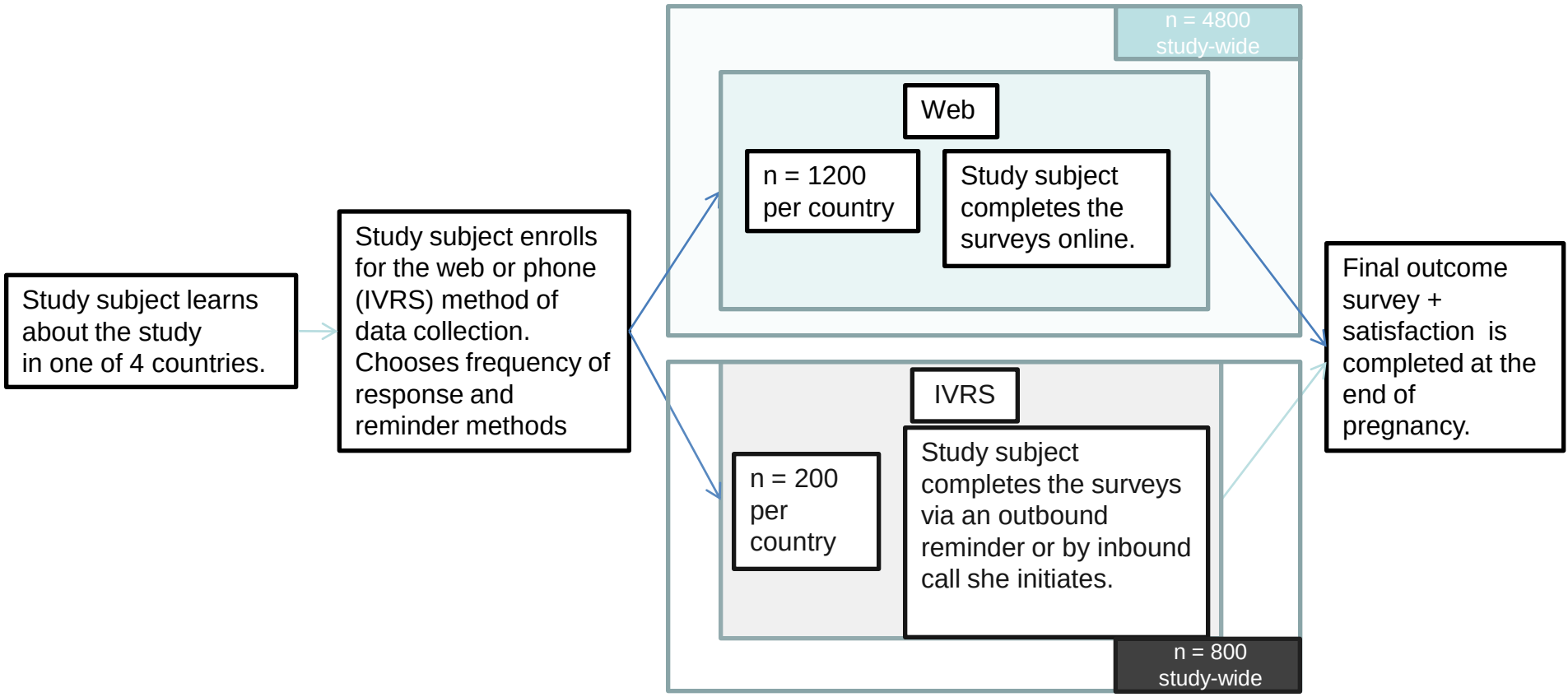
- 4 countries:

Denmark   Poland

The Netherlands   United Kingdom

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

Study Outline



Research Questions

Objective is not to evaluate pregnancy outcomes!

- Compare whether the frequency of data collection affects the completeness and accuracy.
- Comparison with other sources of information
  - eg GPRD in the UK, Danish registries
  - comparison limited to available data
- 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.

PROTECT WP5: Benefit-risk assessment

The overall objective of WP5 is to **develop methods for use in benefit-risk (B-R) assessment, including both the underpinning modeling and the presentation of the results**, with a particular emphasis on **graphical methods.**

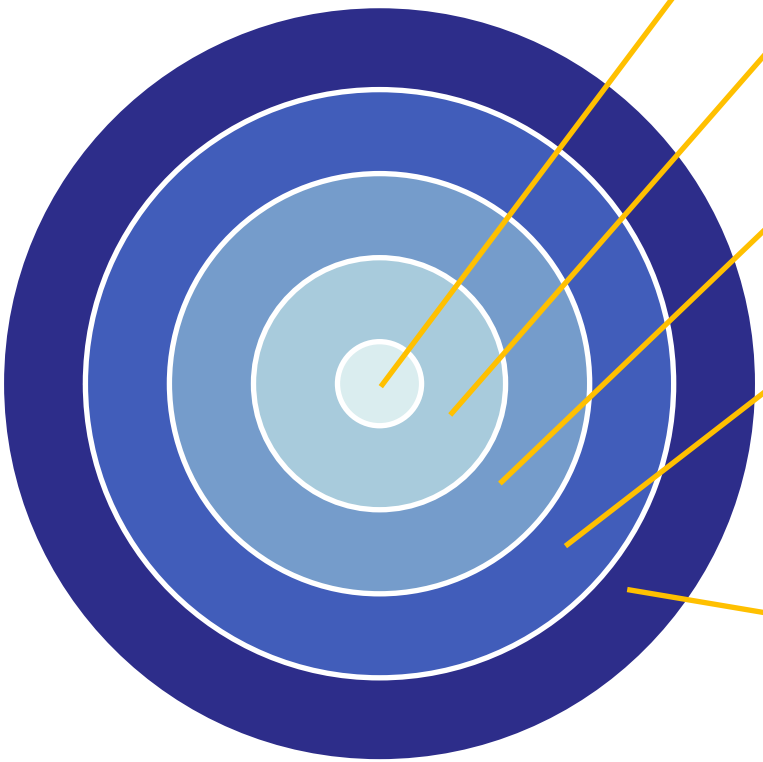
The licensing challenge

- The task of regulators (EMA, FDA etc) is to make 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 this 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?

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/NCAs etc.

- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

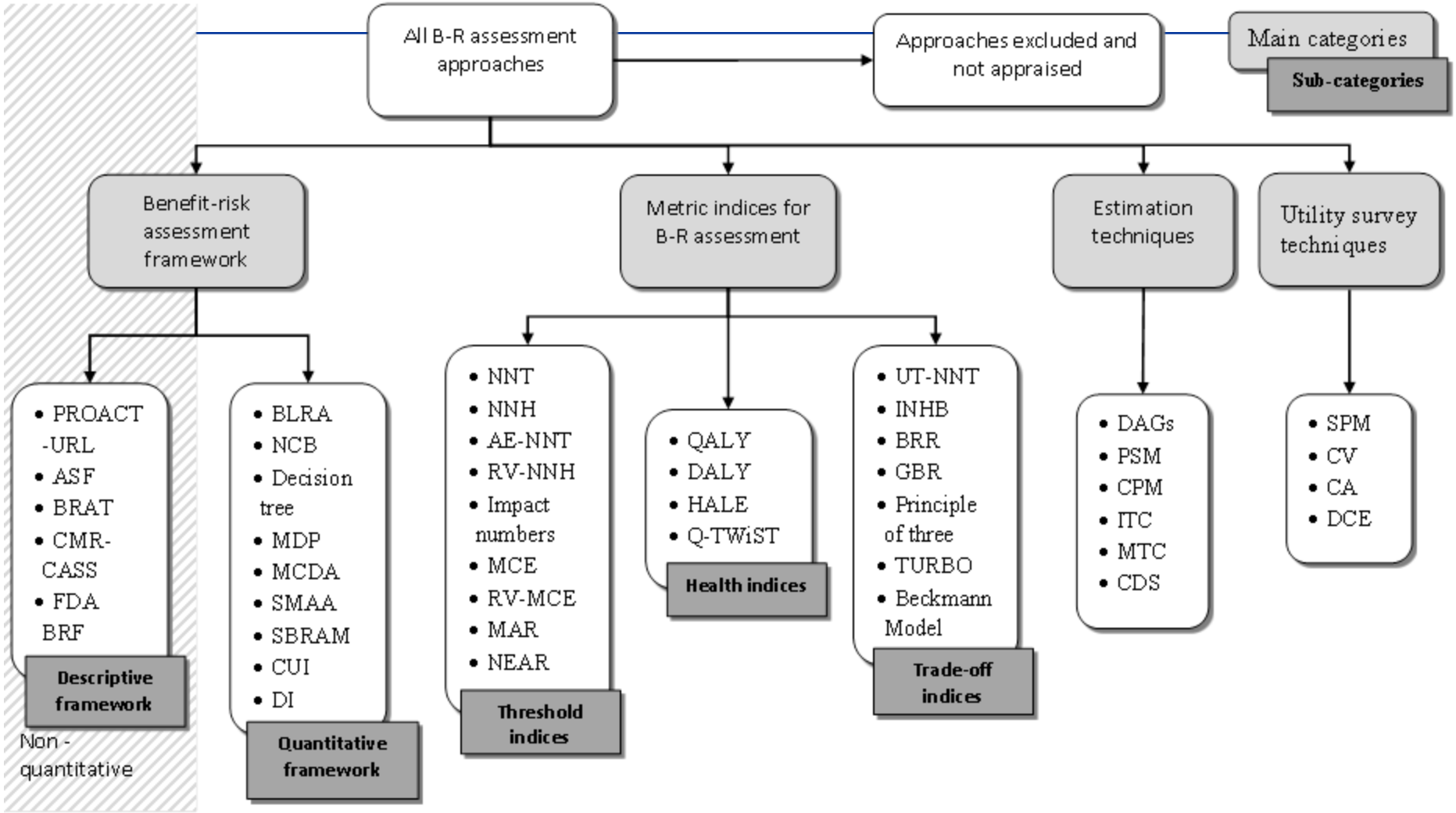
Pharmaceutical companies

- Makes decisions on what to develop, and for which licenses to apply

Methods

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

1. Classifications of B-R methods



Recommendations for further testing

Framework	Metric	Estimation techniques	Utility survey techniques
Descriptive • PrOACT-URL • BRAT *Comprehensive* • MCDA • SMAA	*Threshold indices* • NNT • NNH • Impact number *Health indices* • QALY • Q-Twist • INHB *Trade-off indices* • BRR	• PSM • MTC	•DCE

Visual Review – Recommendations table

Approach	Visual representation of results	Other visual representations of special interest
PrOACT-URL	'Effects' table	n/a
PhRMA BRAT	Table, forest plot, bar graph	Tree diagram to represent model.
MCDA	Bar graph, 'difference display'	Table for evidence data, tree diagram to represent model, line graph for sensitivity analysis.
SMAA	Bar graph, forest plot	Table for evidence data, tree diagram and distribution plot to represent model, line graph and scatter plot for sensitivity analysis.
BRR	Bar graph, forest plot, line graph	Scatter plot or contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.
NNT	Forest plot, line graph, scatter plot	Contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.
Impact Numbers	Forest plot, line graph, scatter plot	Contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.
QALY	Bar graph, forest plot	Line graph or scatter plot for sensitivity analysis.
Q-TWiST	Bar graph, forest plot	Line graph or scatter plot for sensitivity analysis.
INHB	Line graph, scatter plot	Contour plot for sensitivity analysis.
PSM	n/a	Network graph to represent model.
MTC	n/a	Network graph to represent model.
DCE	Bar graph	Line graph or scatter plot for sensitivity analysis.

Disclaimers

"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

	Acomplia	Ketek	Raptiva	Tysabri
PrOACT-URL	✓	✓	✓	✓
BRAT	✓	✓	✓	✓
MCDA	✓	✓	✓	✓
SMAA	✓	✓		
NNT & NNH	✓			✓
Impact Number	✓			
QALY				
Q-TWiST				
INHB	✓			
BRR	✓	✓	✓	✓
PSM	✓	✓		✓
MTC				✓
DCE				
Other:	Direct utility elicitation	SBRAM, Swing-weighting	Decision conferencing	Decision conferencing

Tysabri example

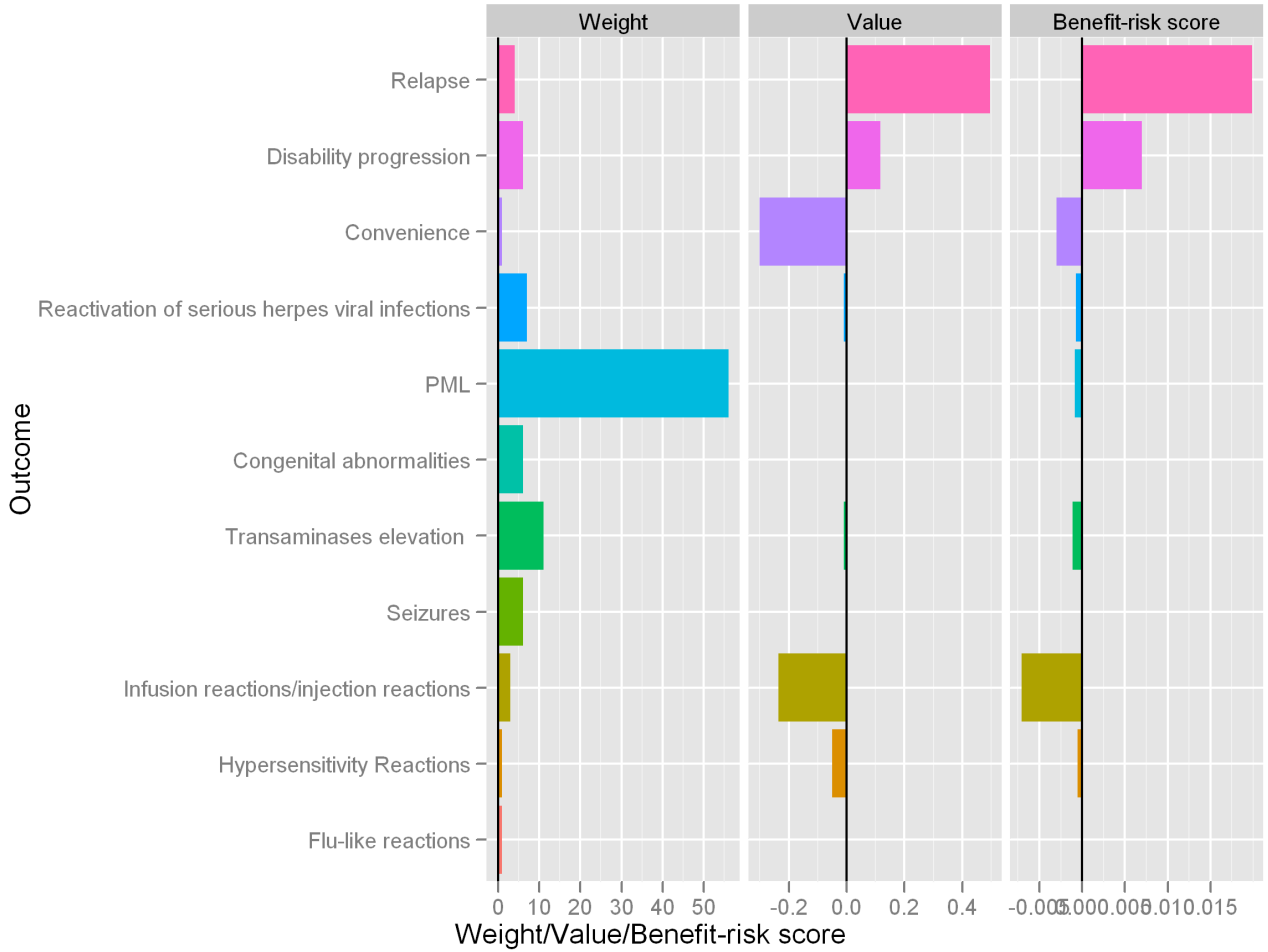
Active drug	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effects	Progressive Multifocal Leukoencephalopathy
Regulatory history	Approved 2004 License withdrawn 2005 Reintroduced because of patient demand 2006 CHMP reassessed the PML risk and continue approval 2009
Data source	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 sets of methods applied by two teams

Aspect	Option	PrOACT/ MCDA	BRAT/ NNT
Descriptive guidelines	(1) PrOACT-URL guidelines.	X	
	(2) Benefit Risk Action Team (BRAT) framework.		X
Benefit-risk assessment frameworks	(3) Multi-Criteria Decision Analysis (MCDA).	X	
	(4) Stochastic Multi-criteria Acceptability Analysis (SMAA).		
Metric indices	(5) NNT and NNH.		X
	(6) Impact numbers.		
	(7) Quality Adjusted Life Years (QALY).		
	(8) Q-TWiST.		
	(9) Incremental Net Health Benefit (INHB).		
	(10) Benefit-Risk Balance.	X	
Estimation techniques	(11) Probabilistic Simulation Method (SPM).	X	
	(12) Mixed Treatment Comparison (MTC).	X	X
Utility survey techniques	(13) Discrete Choice Experiment (DCE).		
	(14) Direct elicitation	X	X

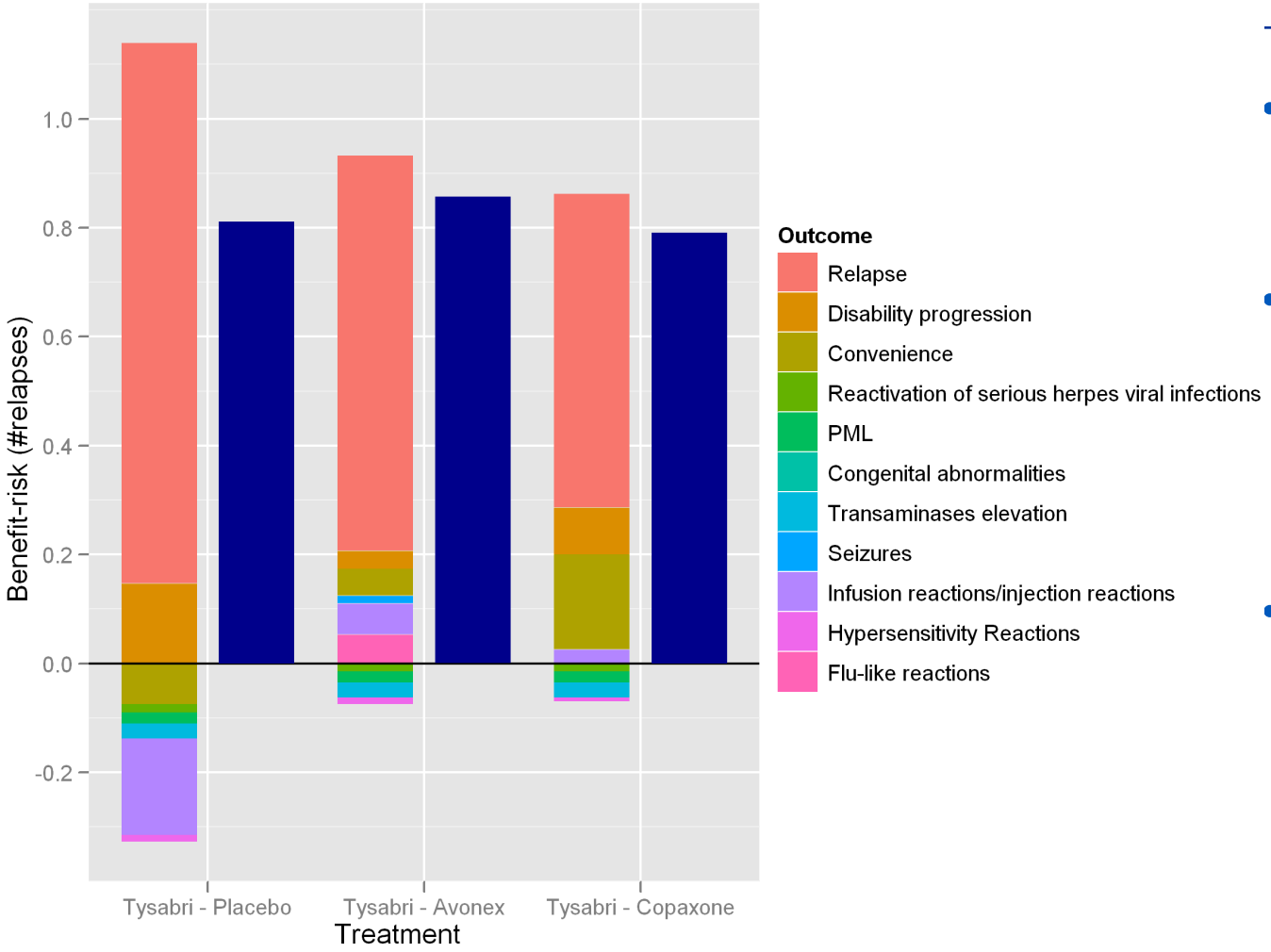
Find the B-R contribution of each outcome for Tysabri - placebo



- 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

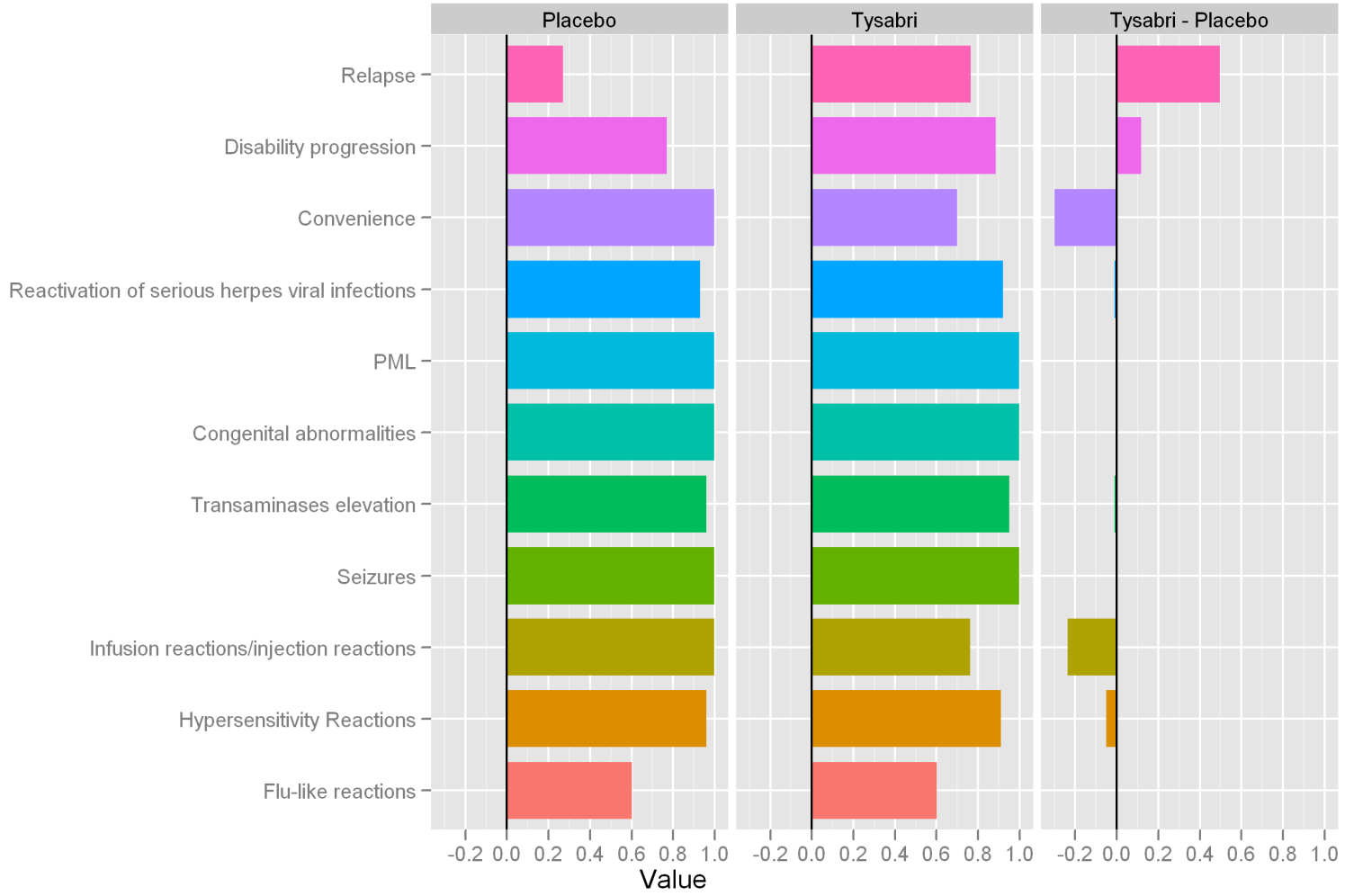
Stacked bar chart for Tysabri vs. all the other treatments.



- 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.

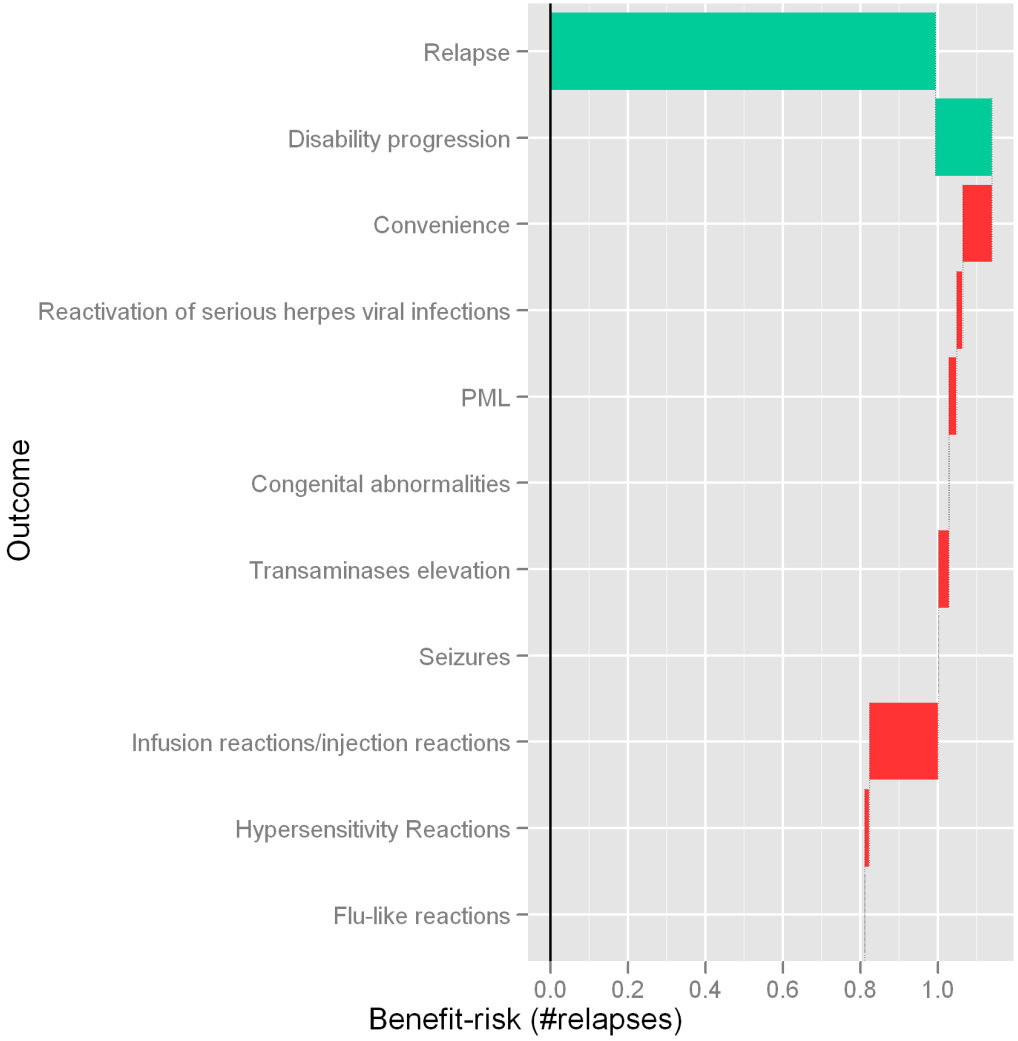
Tysabri: MCDA difference display

Incremental value scores for Tysabri compared to placebo



Tysabri: MCDA waterfall plot criteria contribution

Waterfall plot for Tysabri - 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 B-R
- Red =negative B-R

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)

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, 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


MERCURY

Thank you !

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Roundtable Discussion and Questions

View this and past Active Medical Product Surveillance webinars at:

http://www.brookings.edu/health/Projects/surveillance/roundtables.aspx