Quality • NHS Clinical • Linkage • Real world • Randomised • PROs • Population 52M+

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Methods for harm-benefit modelling

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MHRA Medicines and Healthcare products Regulatory Agency

NHS National Institute for Health Research

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Disclosures

CPRD is owned by the UK Department of Health and operates within the Medicines and Healthcare products Regulatory Agency (MHRA). CPRD has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies.

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Outline of presentation

- General background
- PROTECT work on harm-benefit methodologies
- Individualised harm-benefit modelling
- Some reflections (personal points of view)

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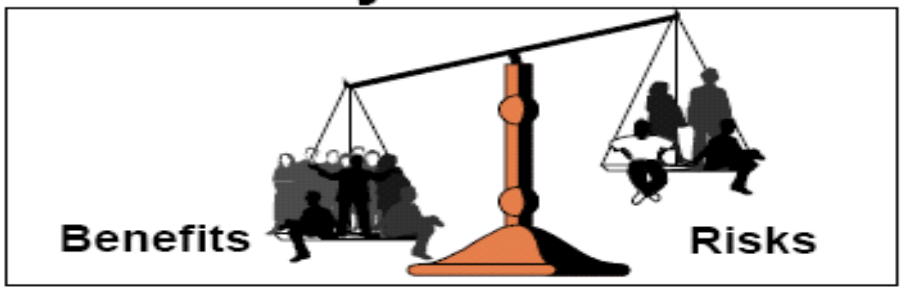
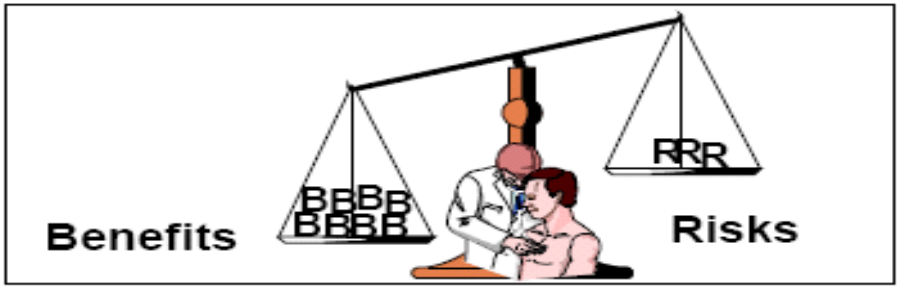
Institute of Medicine: benefits and risks

Benefit/Risk is in the eyes of the beholder:

FDA
evaluates
benefits/risks
for the population



Provider
evaluates
benefits/risks
for a patient



Patient
evaluates
benefits/risks
in terms of
personal values

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Benefit-harm: what is it?
a patient perspective

This drug helped me a lot in reducing my pain; other than my osteoarthritis, I am otherwise healthy and am at low risk of myocardial infarction; my pain reduction is *more important* to me than this *small increase* in the risk of myocardial infarction

=> What is harm-benefit assessment?

- 1. measurement of probabilities of various outcomes
- 2. magnitude of effects of drug
- 3. weighing of outcomes / preferences

The IMI-PROTECT (Consortium)

Objectives of PROTECT (http://www.imi-protect.eu)

The overall objective of PROTECT is to strengthen the monitoring of the benefit-risk of medicines in Europe. In order to achieve this overall goal, PROTECT has been designed as a comprehensive and integrated project aiming to develop and validate a set of innovative tools and methods that will:

- Enhance data collection directly from consumers of medicines in their natural language in several European Union countries, using modern tools of communication;
- Improve early and proactive signal detection from spontaneous reports, electronic health records and clinical trials;
- Develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies applicable to different safety issues and using different data sources;
- Develop methods for continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods;
- Test and validate various methods developed in PROTECT using a large variety of different sources in the European Union (e.g. clinical registries) in order to identify and help resolve operational difficulties linked to multi-site investigations.

Acknowledgments

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.
- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, 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.

Disclaimers

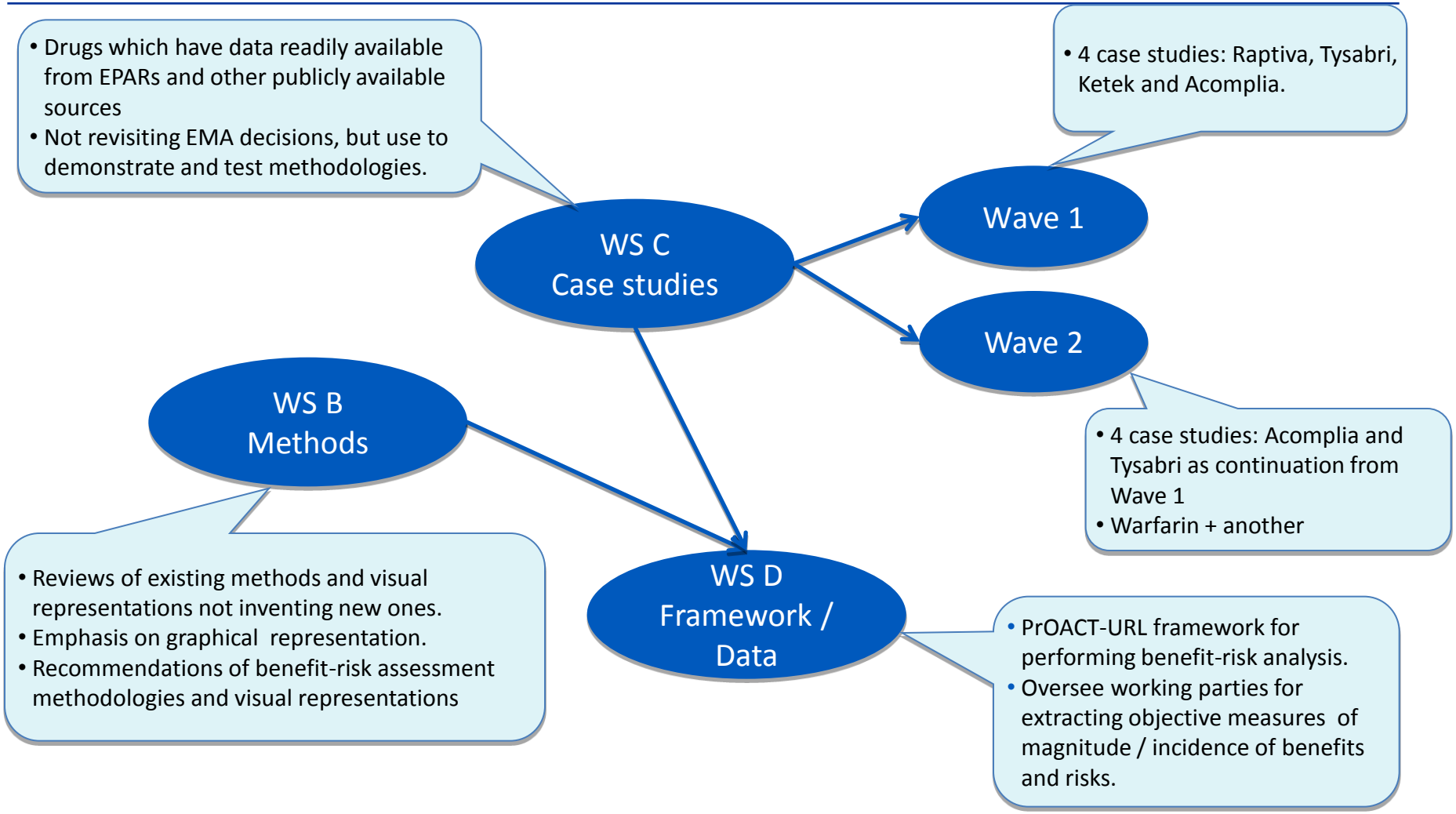
"The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

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."

Work Package 5 of PROTECT (membership)

Public	Private
EMA	AstraZeneca
DKMA	Bayer
AEMPS	GSK
MHRA	Lundbeck
Imperial College (co-leader)	Merck KGaA (co-leader)
Mario Negri Institute	Novartis
CPRD	Novo Nordisk
IAPO	Pfizer
	Roche
	Sanofi-Aventis
	Takeda Eli Lilly Amgen

Work Package 5: Overview



Other Benefit–Risk Initiatives

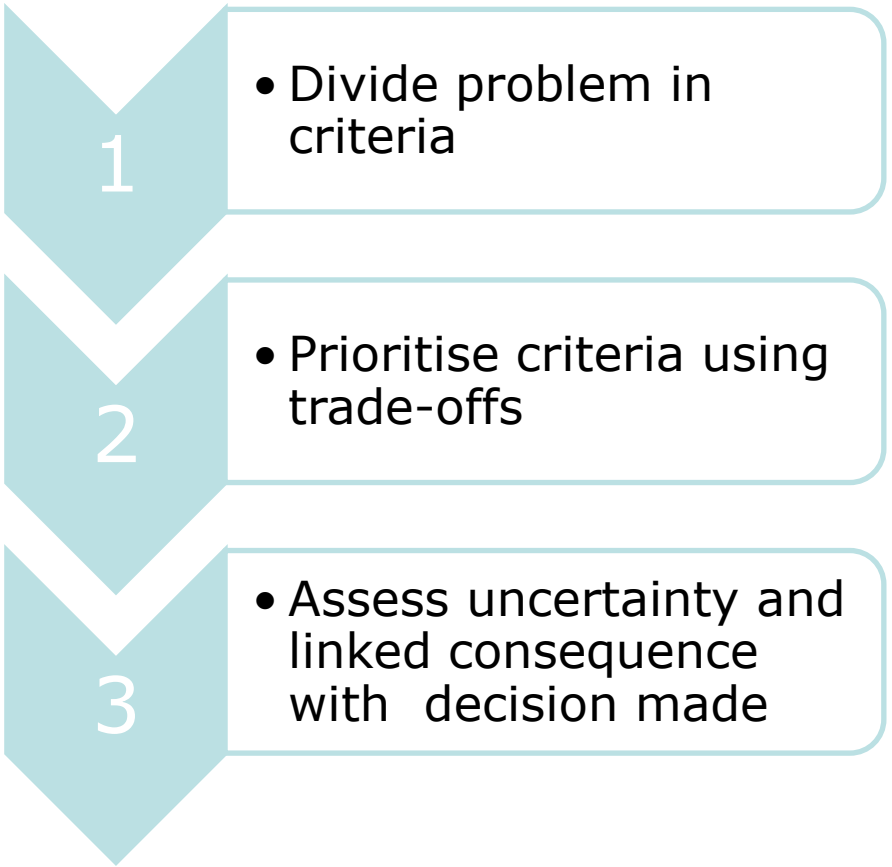
- **Regulatory:**
  - **EMA's project to increase consistency and transparency of B/R assessment for medicinal products (qualitative component being implemented)**
  - **FDA very active, including meeting on 'Risk-Benefit Considerations in Drug** Regulatory Decision-Making' April 2010
- **Pharma:**
  - Pharmaceutical Research and Manufacturers of America's Benefit-Risk Action Team's (PhRMA BRAT) developing a quantitative framework
  - Novo Nordisk developed comprehensive framework with MCDA rigour – Data-Driven Clinical Benefit-Risk Assessment
- **'Academic':**
  - Many papers, reviews and books are emerging

Benefit risk methodologies

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

PrOACT-URL

- A generic framework to structure the decision problem
- The acronym PrOACT-URL represents the following steps:



PrOACT-URL

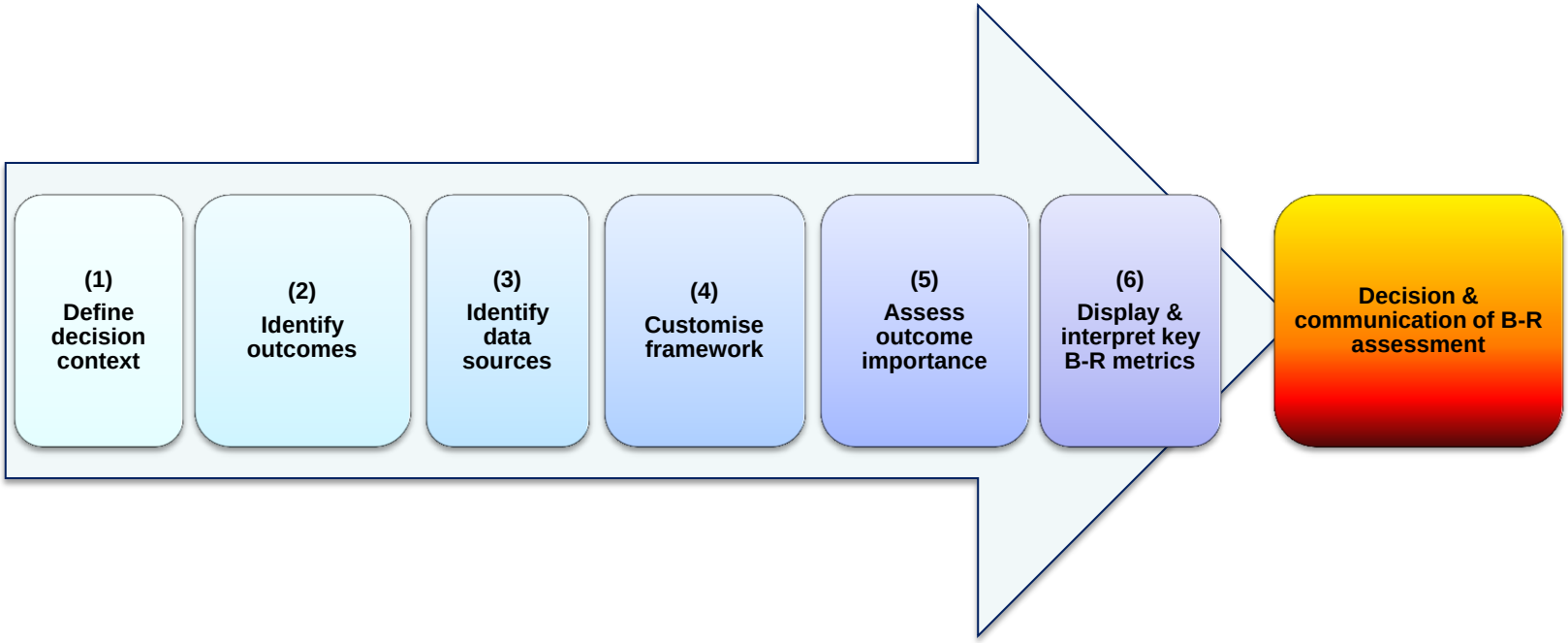
Problem	Determine the decision context and frame the problem
Objective	Establish objectives and identify criteria
Alternatives	Identify options and alternatives
Consequences	Evaluate the expected consequences of the options for each criterion
Trade-off	Assess trade-offs of risk and benefit
Uncertainty	Report uncertainty in benefit and risk and impact of uncertainty
Risk tolerance	Assess relative importance and risk attitude of decision makers
Linked decisions	Assess consistency with other linked decision in the pass and its impact on future decision

BRAT

- Developed by Pharmaceutical Research and Manufacturers of America (PhRMA) ***benefit-risk action team***
- Emphasis on
  - Value tree build up
  - Data Selection
  - Data Preparation

BRAT

- Divide decision making process in the following 6 steps



Number needed to treat approach

NNT=$1/\Delta_p$ patients to be treated to observe one beneficial effect

NNH=$1/\Delta_q$ patients to be treated to observe one adverse event

NNT<NNH is desirable

Impact numbers

Metric index	Definition	Formula
Attributable risk (AR)	the difference in risk between exposed and unexposed cases	$I_u \times (RR - 1)$
Population attributable risk (PAR)	the attributable risk in the whole population	$\frac{P_e \times (RR - 1)}{1 + P_e \times (RR - 1)}$
Attributable fraction among exposed (AFE)	the attributable risk of exposure among exposed cases	$\frac{RR - 1}{RR}$
Disease impact number (DIN)	the number of people with the medical condition in question amongst whom one event is attributable to exposure to the risk factor	$\frac{1}{\mathrm{AR} \times P_e}$
Population impact number (PIN)	the number of people in the whole population amongst whom one case is attributable to exposure to the risk factor	$\mathrm{DIN} \times \frac{1}{P_d}$
Case impact number (CIN)	the number of people with the case for whom one case will be attributable to the exposure or risk factor	$\frac{1}{\mathrm{PAR}}$
Exposure impact number (EIN) or NNT	the number of people with the exposure amongst whom one excess case is due to the exposure	$\frac{1}{\mathrm{AR}}$
Exposed cases impact number (ECIN)	the number of exposed cases amongst whom one case is due to the exposure	$\frac{1}{\mathrm{AFE}}$
Population impact number of eliminating a risk factor over time t (PIN-ER-t)	the potential number of cases prevented in the study population over the next years by eliminating a risk factor	$n_S \times I_u \times \mathrm{PAR}$
Number of events prevented in a population (NEPP)	the number of cases prevented by the intervention in the study population	$n_S \times P_e \times P_d \times I_u \times (RR - 1)$

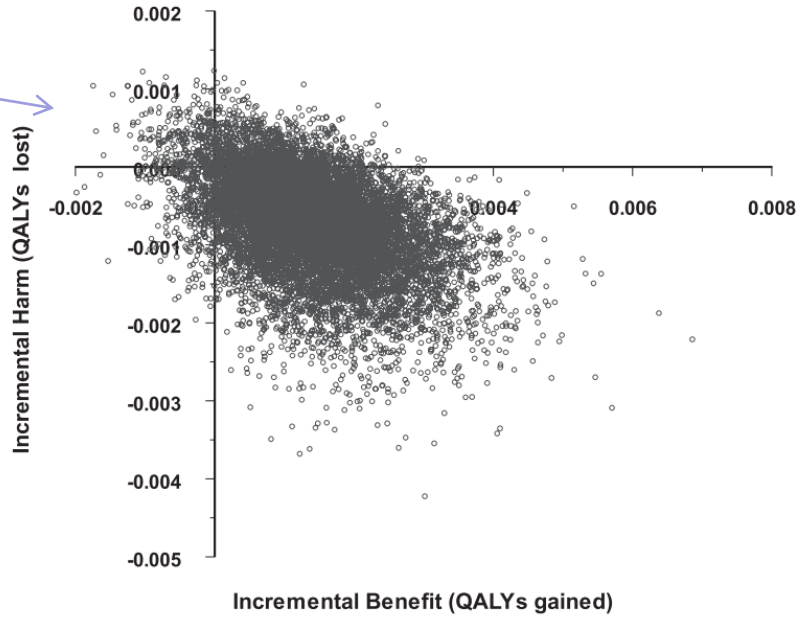
QALY

- ***Quality-Adjusted Life-Years***
  - A measure of life time with quality of life incorporated into the measurement
  - For example
    - A subject lives four years in QoL (quality of life) 0.75 has QALY = 4 x 0.75 =3

QALY

Negative incremental harm

This represents fewer QALYs lost due to harm associated between two treatment options



MCDA

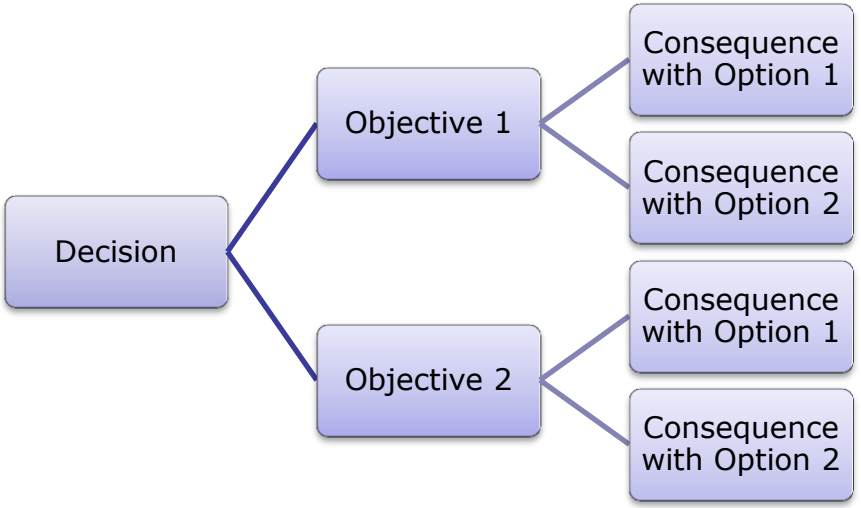
- ***Multi Criteria Decision Analysis***
  - Decision making model to manage multiple conflicting criteria
  - Decision making approaches are realisations of the multi-attribute utility theory (MAUT) .
  - Combines multiple criteria in a logical way.

MCDA

- Decision problem
- Decision problem divide into criteria for assessment
- Each option are assessed against each criterion and create an utility score
- Utility score from each criteria are weighted using preference information obtained prior to analysis
- A weighted assessment of each option

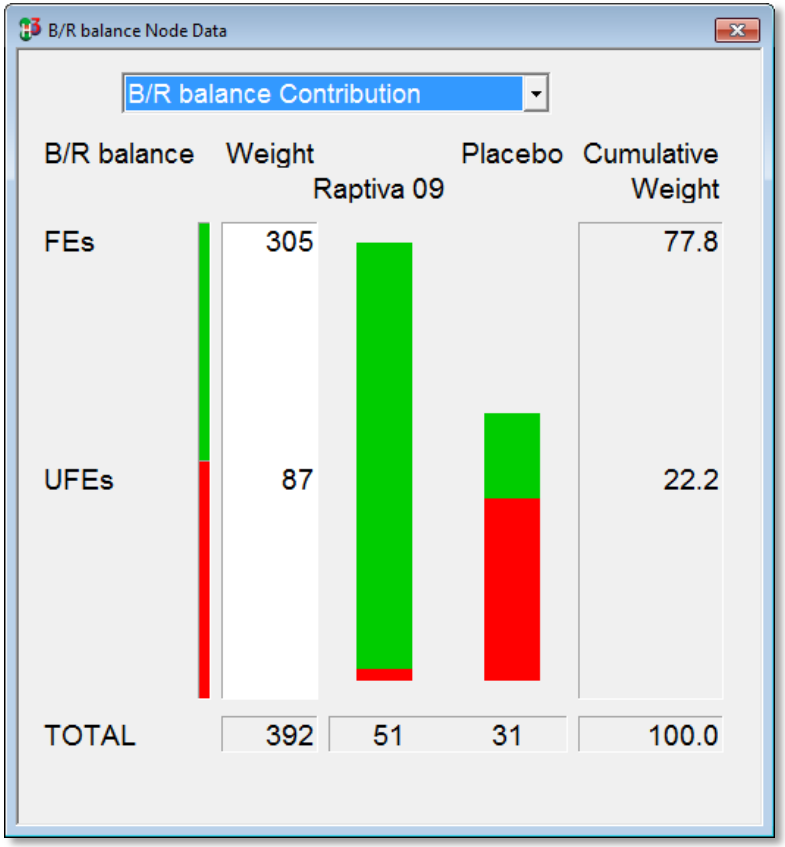
Decision tree

- Criteria depicted in a value tree
- Nodes representing objectives
- Branches emanating from notes showing criteria represents realisation of the objectives



MCDA

- Uncertainty is taken into account and reflected as utility function.
- Importance on each criterion is reflected as weight.
- Result is an overall weighted preference value for each option.



A Simple Example of MCDA

[adopted from benefit-risk appraisal of medicines Mussen et al]

values	Criteria (worst to best)	Actual score (0-100)	Weight of each criterion
1. Criteria for benefit			
efficacy versus comparator	RR=1 to RR=0.50	50	100
patient compliance	50 to 100%	50	20
2. Criteria for risks:			
incidence of ADRs	35% to 5%	50	50
discontinuation rate due to ADR	100 to 0%	50	10

Tysabri

Active drug	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effects	Progressive Multifocal Leukoencephalopathy
Regulatory history	Approved 2004 License withdrawn 2005 Re introduced because of patient demand 2006 CHMP reassessed the PML risk and continue approval 2009
Data source	EPAR
Methodologies tested	PrOACT-URT BRAT MCDA NNT/NNH BRR, PSM MTC Direct Utility Elicitation

BRAT step 1:Define the decision context

Identify the fundamental problem

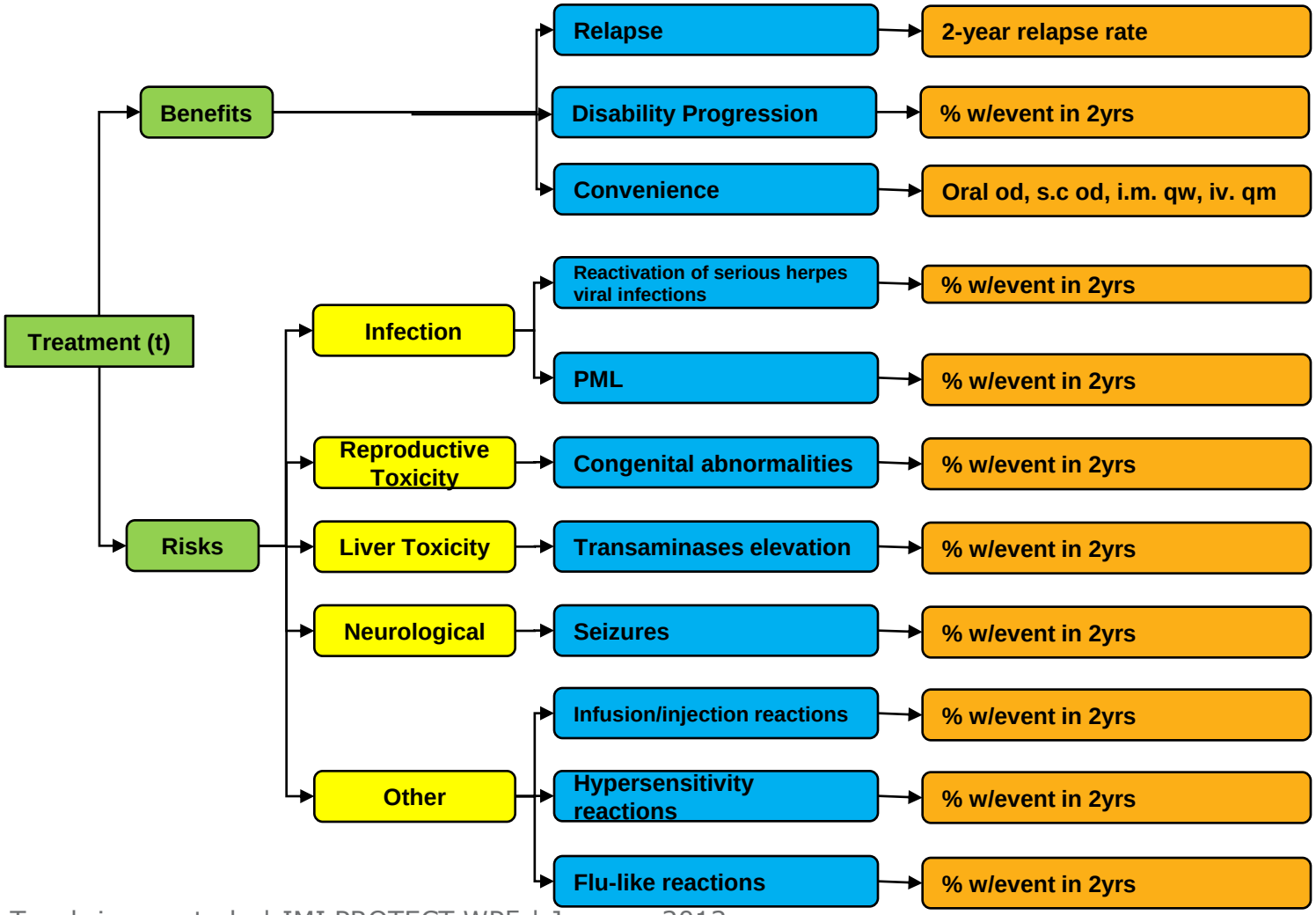
- Decision question:
  - Should Tysabri be given marketing approval at the time of first registration?
  - Should Tysabri be kept on the market given that episodes of PML are *observed* at the time that these episodes were observed?
- Indication: Relapsing remitting multiple sclerosis
- Drug to compare
  - Tysabri (Natalizumab), Avonex (Interferon beta-1a), Copaxone (Glatiramer acetate), Placebo
- Decision perspective: EMA, taking the patient perspective.
  - The regulator makes the decision, but using the values and weights of a patient.
- Time frame: two-years
  - This is the time frame of the pivotal studies, but the time frame for safety events may be longer as these take longer to manifest.

BRAT step 1: Define the decision context

Identify the possible decisions to be evaluated against the criteria

- Generally in decision analysis there are multiple decisions to be made.
- This leads to many combinations of possible decisions (strategies).
- Regulators question is to approve Tysabri/keep it on the market as an alternative option.

BRAT step 2: Identify benefit and risk outcomes



PROTECT

BRAT step 3: Extract source data

What are the observations relevant to the criteria? Source data

We considered data only from the pivotal Phase III studies

Study ID	Value Tree Category	Outcome	Measure	Study Drug	Study Drug Estimate	Ref Group	Ref Group Estimate	Study/Reference Estimate
Polman 2006/ EPAR	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Tysabri	0.23 [0.19-0.28]	Placebo	0.73 [0.62 –0.87]	0.32 [0.26 – 0.40]
Jacobs 1996	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Avonex	0.67 [n.a.]	Placebo	0.82 [n.a.]	0.82 [0.56 – 1.20]
Johnson 1998	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Copaxone	0.65 [n.a.]	Placebo	0.91 [n.a.]	0.71 [0.47 – 1.08]
...								
Polman 2006	Liver Tox	ALT>5x ULN	n/N (%)	Tysabri	31/627 (5%)	Placebo	12/312 (4%)	RR = 1.25
Jacobs 1996	Liver Tox	ALT>5x ULN	n/N (%)	Avonex	Not reported	Placebo	Not Reported	RR = 1
Johnson 1998	Liver Tox	ALT>5x ULN	n/N (%)	Copaxone	Not reported	Placebo	Not Reported	RR = 1
...								

BRAT step 4: Customize the framework

- From a structured data source table a comparison table and a forest plot were generated by the tool.
- Data were discussed and the value tree was confirmed.
- Filter defined in the source table allowed presentation of the data based on the PML occurrence assumed at time of approval as well as at time of re-evaluation.

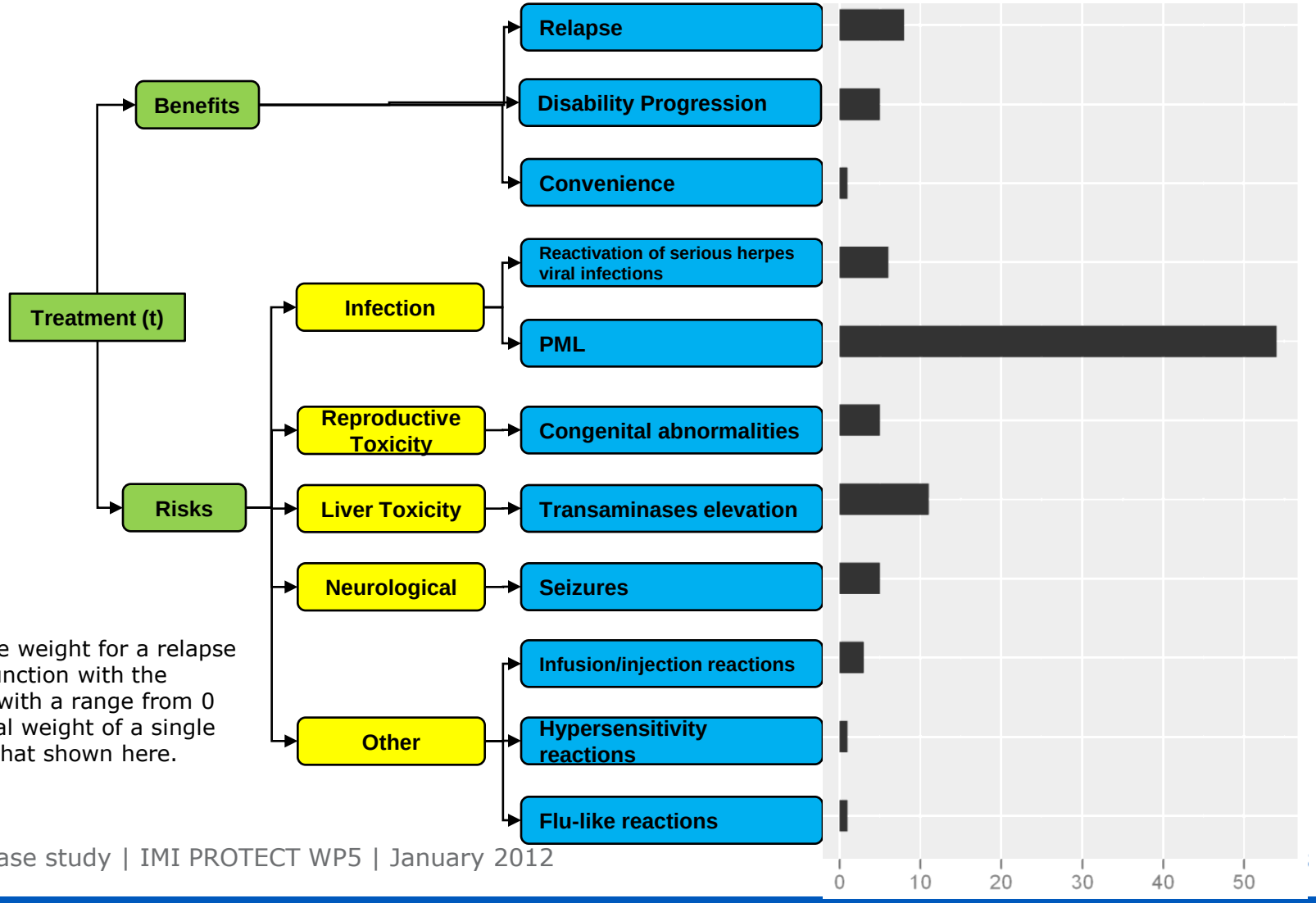
BRAT step 5: Assess outcome importance

Process overview

- Outcomes have different measurement scales and need to be mapped to a common scale
  - Elicit value functions (a type of utility function)
- Assign weights to the outcomes according to their importance
- The BRAT framework by intention does not suggest any particular method for assessing importance or even require the use of it but leaves the choice to the user.
  - However, depending on the method chosen, weighing is possible and weights can also be displayed in the tool.

BRAT step 5: Assess outcome importance

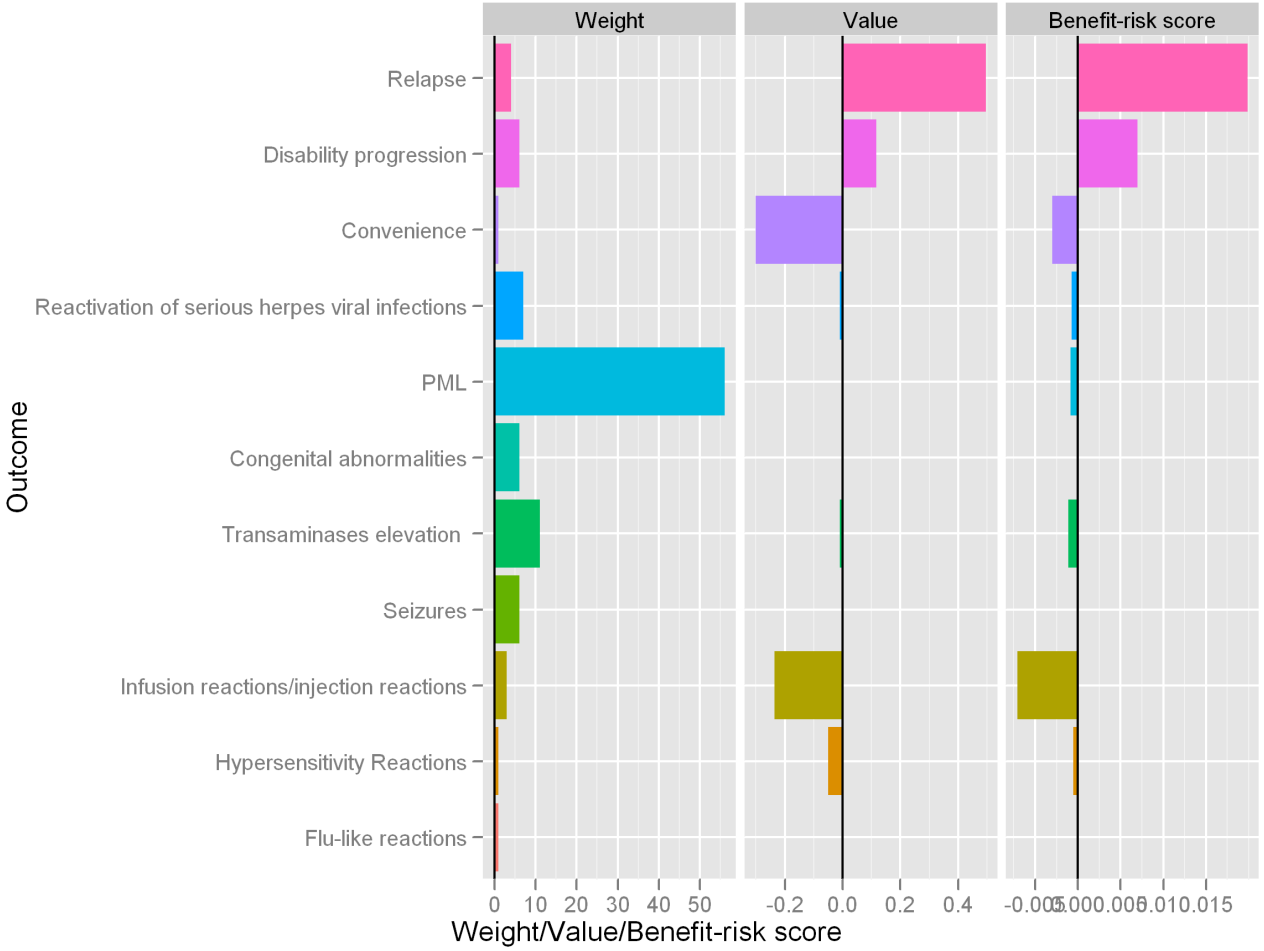
Results



Note that as the weight for a relapse is for a value function with the measure scale with a range from 0 to 2, then actual weight of a single relapse is half that shown here.

MCDA: Trade-offs

Find the BR 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

=> Incremental benefits of Tysabri are greater than the incremental risks

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How can we epidemiologists contribute to harm-benefit modelling?

- RCT Populations ≠ Population in actual clinical practice
- Most Harm-Benefit models use <u>average</u> rates, but very few patients are average….=> individualised harm-benefit assessment

Example: 10-year cardiovascular risks:

	Average risk	5th percentile	95% percentile
age 35-49	1.6	0.1	5.5
age 50-64	5.8	0.8	15.7
age 65+	12.2	4.3	24.5

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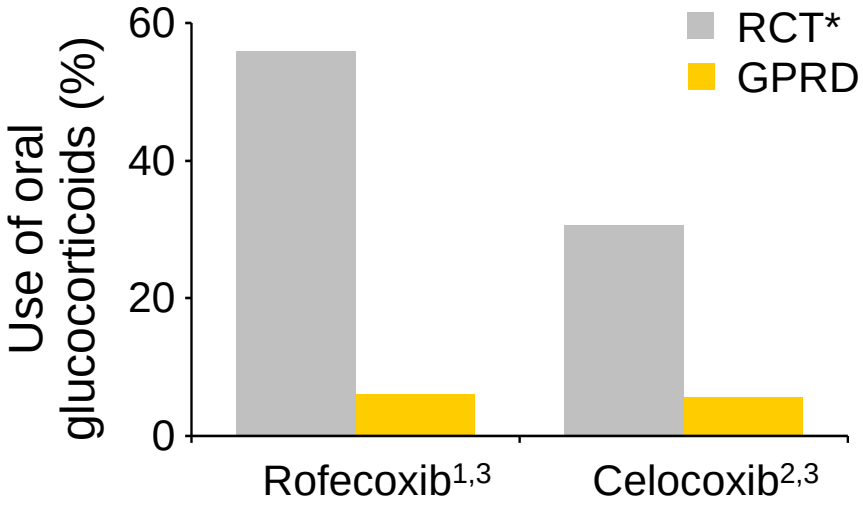
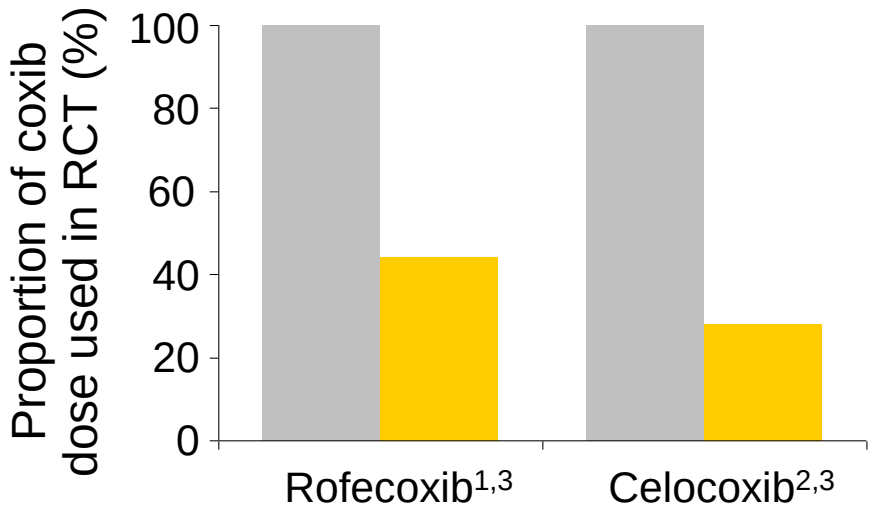
Trial population ≠ population in actual clinical practice





1. Bombardier C, et al. *N Engl J Med* 2000;343:1520-28.
2. Silverstein FE, et al. *J Am Med Assoc* 2000;284:1247-55.
3. Van Staa et al Plos Medicine.

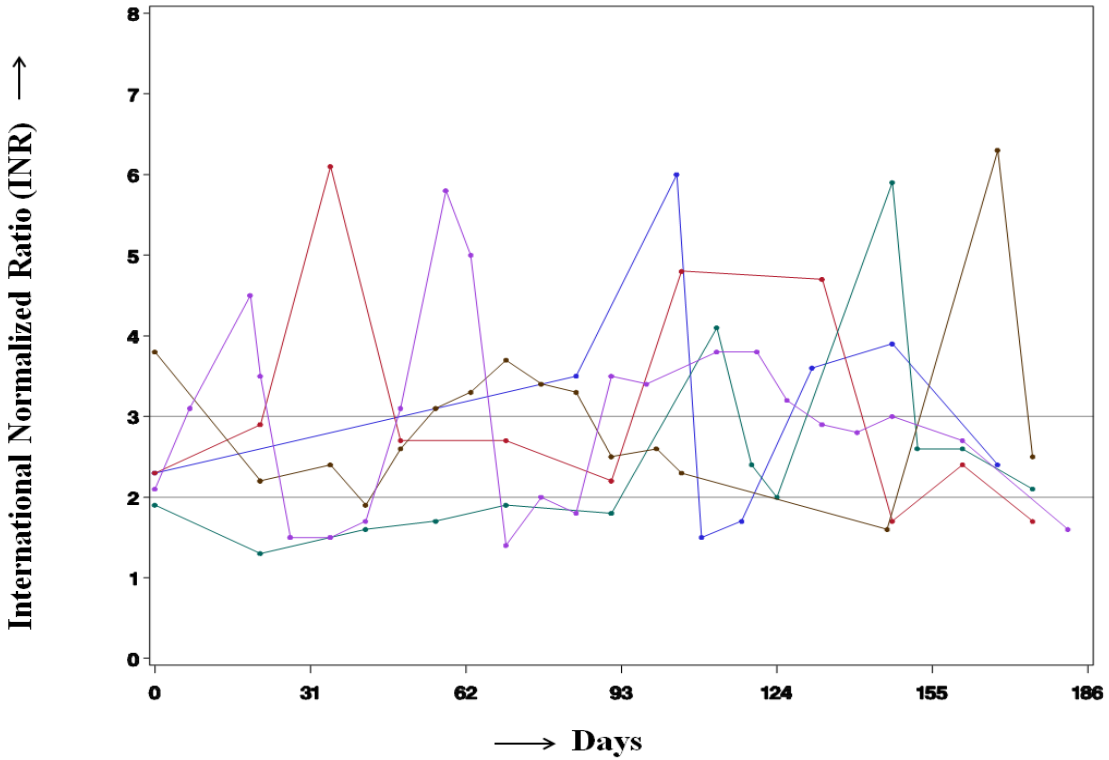
The patterns of anticoagulation control and the risk of stroke, bleeding and mortality in patients with non-valvular atrial fibrillation

24 August 2012, Barcelona

Rianne van den Ham
Dr. Olaf Klungel, Prof. dr. Bert Leufkens, Prof. dr. Tjeerd van Staa

Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University

Cluster 6



Outcome	OR (95% CI)
CPRD Death	10.7(8.27-13.85)
CPRD Stroke	3.42(2.08-5.63)
CPRD Major bleed	1.60(1.13-2.26)
CPRD Minor bleed	2.13(1.39-3.27)

The probabilities of different pathways of anticoagulation patterns in the first two year

Time spent within therapeutic range			
Pattern in month 0-6	Pattern in month 6-12	Pattern in month 12-24	Probability of pattern in overall study population
3.>=80	1.< 60	1.< 60	3.0%
	1.< 60	2.60-80	2.0%
	1.< 60	3.>=80	1.9%
	2.60-80	1.< 60	1.7%
	2.60-80	2.60-80	1.9%
	2.60-80	3.>=80	3.0%
	3.>=80	1.< 60	2.1%
	3.>=80	2.60-80	3.1%
	3.>=80	3.>=80	7.5%

Protect: individualised harm-benefit for warfarin versus newer anticoagulants

- Objective is to estimate individual risks for adverse and beneficial effects of anticoagulants
- Obtain effect estimates of anticoagulants from systematic review
- Combine individual risks with effect estimates to obtain individual harm-benefit
- Visualise results

•Rianne van den Ham (Protect team lead: Lesley Wise)

What is the harm–benefit ratio of Cox-2 inhibitors?

T P van Staa,[1,2]* L Smeeth,[3] I Persson,[4] J Parkinson[1] and H G M Leufkens[2]

Accepted 19 December 2007

Background Selective cyclooxygenase-2 (Cox-2) inhibitors, developed to reduce the risk of NSAID-related gastrointestinal (GI) complications, have been associated with an increased risk of cardiovascular events. Our objective was to determine the balance of potential harm and benefit related to Cox-2 inhibitors' exposure.

Methods The study population included patients aged 40+ years who received a prescription for Cox-2 inhibitors and were included in the General Practice Research Database. The incidence of upper GI events, myocardial infarction (MI) and stroke was estimated in this cohort. It was assumed that patients had experienced the upper GI and cardiovascular effects, as observed in clinical trials [relative rate (RR) of 0.49 for upper GI and 1.86 for MI]. Simulation methodology was used to estimate attributable risks, i.e. the difference between exposed and unexposed event probabilities.

Results The study population included 155 439 Cox-2 users. The number of upper GI events prevented by Cox-2 inhibitors was 179, while the number of excess MI cases was 83 per 10 000 patients treated for 4 years. A strong association was found between extent of GI benefit and cardiovascular harm. There was a large difference in the frequency of benefit over harm in only 6% of the patients (difference of 1% or more); 23% of the patients had more harm than benefit, including those with a history of ischaemic heart disease.

Conclusions The benefit of Cox-2 inhibitors in reducing the frequency of upper GI events may be offset by their cardiovascular harm, particularly in patients with risk factors for cardiovascular disease.

Methods Individualised Harm-Benefit modelling

1. Estimate *individualised* risks in EHR database
    a. in target population (e.g. users of traditional NSAIDs)
    b. in users of drug of interest (e.g. coxibs)
2. Relative rate=rate exposed to drug of interest / rate unexposed
    a. RRs from RCTs
    b. RRs from any other source
3. Using RR and rate unexposed, one can derive rate exposed and estimate attributable risk for each patient

Example: -50 year coxib user with RA: in EHR, rate of GI event=2%

-Coxibs reduce GI by 25% (RR=0.75) according to RCTs

=> Patient's rate would have 2.67% if using traditional NSAID

Methods Individualised Harm-Benefit modelling

4. Weighing of outcomes (e.g. one MI not equivalent to one GI)
    a. by case fatality rate (used in presented examples)
    b. QALYs
    c. Willingness to trade or other methods
5. Use of modelling methods used in Pharmacoeconomics
    a. inclusion uncertainty (e.g. 95% CI around RR of drug effect)
    b. bootstrapping for confidence intervals around results
6. Presentation and visualisation of individual results

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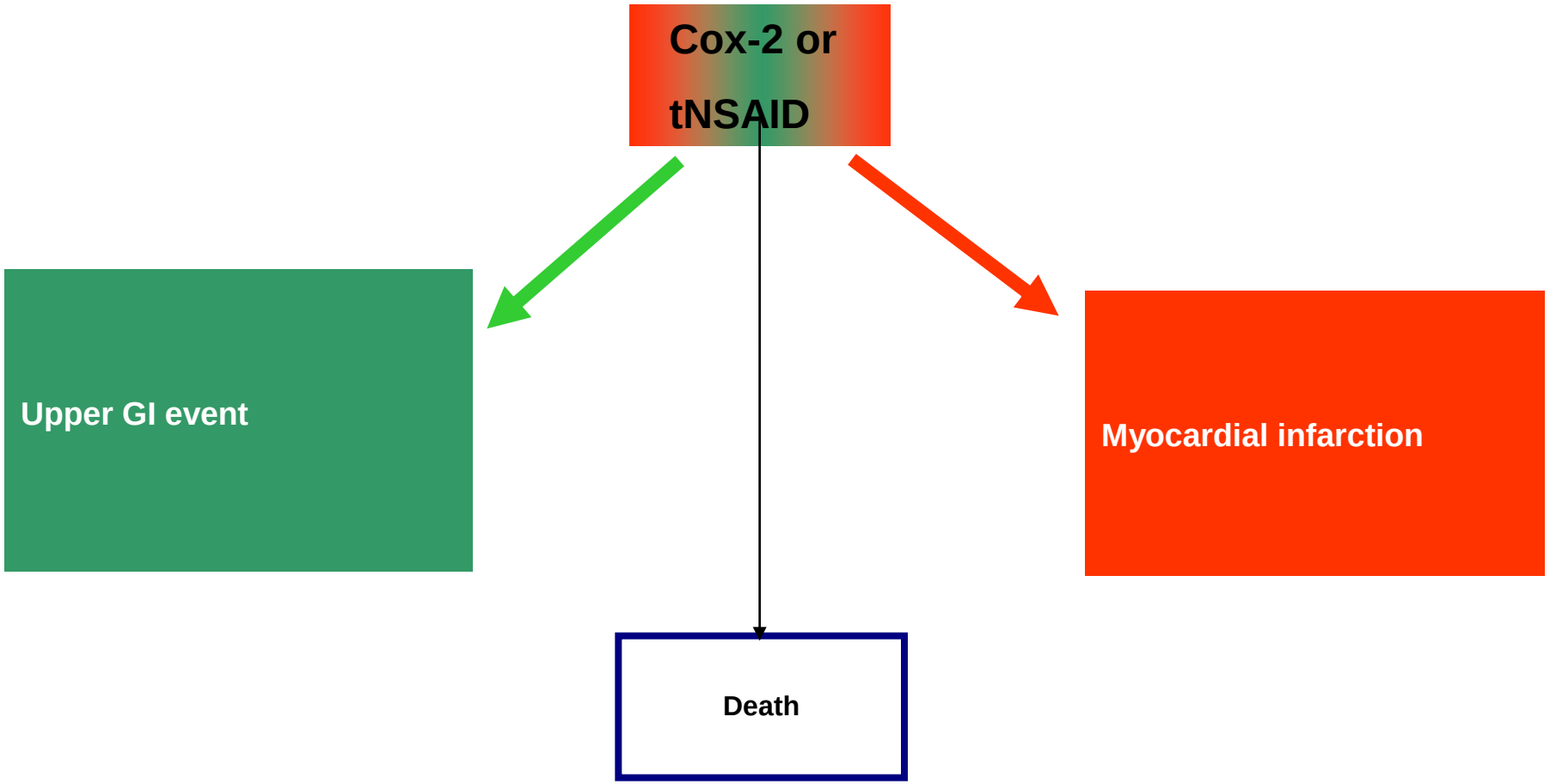
Cox-2 Harm-Benefit model



Excess MI and stroke and GI prevented with coxibs (N cases per 10,000 treated for 4 years)

		Excess MI	Excess stroke	GI prevented	Benefits minus risks (95% CI)*
Overall		83	39	186	16 (-60 – 126)
GI	Lowest	64	33	127	-1 (-65 – 56)
Probability	Lower	71	38	146	1 (-70 – 68)
(quintiles)	Middle	82	40	163	1 (-70 – 75)
	Higher	91	43	183	4 (-82 – 68)
	Highest	105	46	274	51 (-57 – 171)

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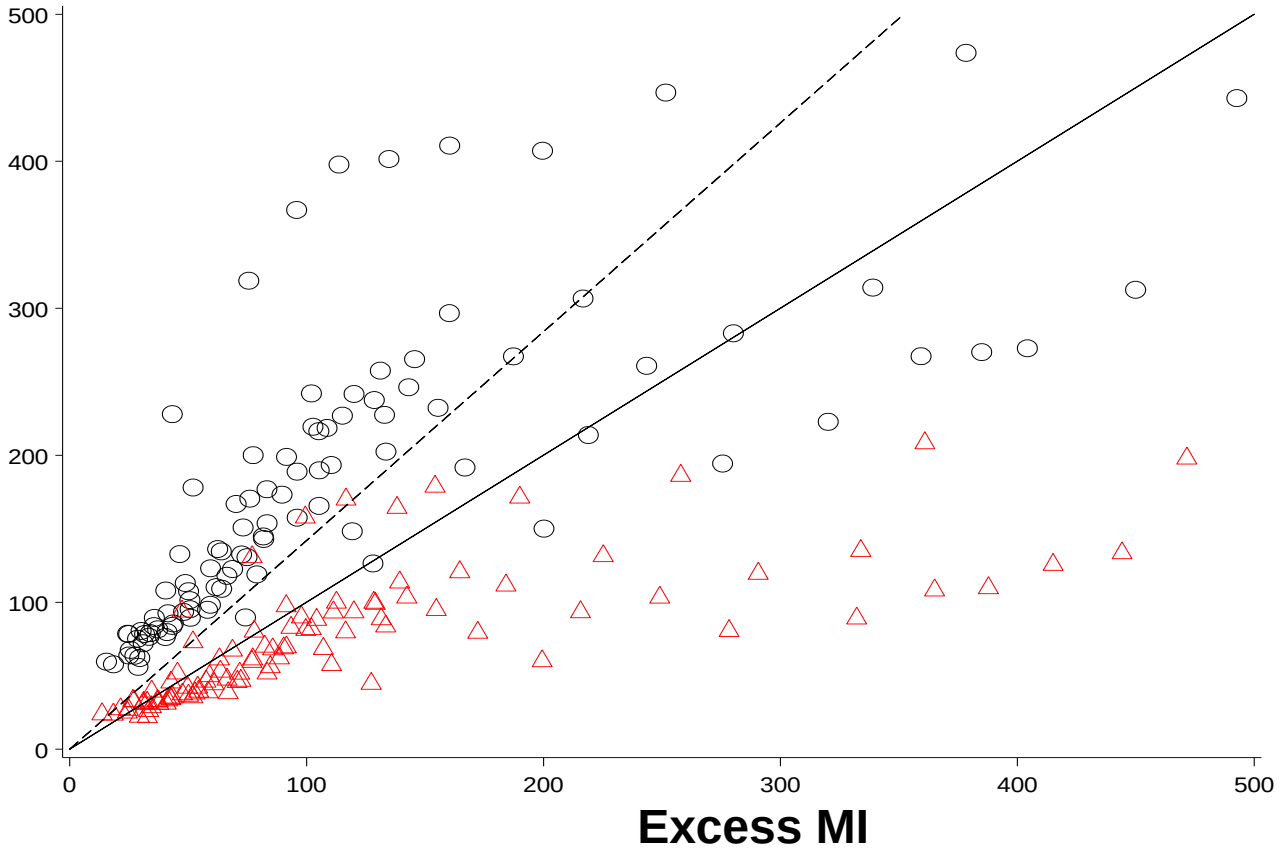
Excess MI and stroke and GI prevented with coxibs (N cases per 10,000 treated for 4 years)

No GI prevented



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Predictors for benefit minus harm (per 10,000 treated for four years)

Risk factor	Prevalence in Cox-2 cohort	RCT GI efficacy (RR=0.49) No of benefits minus risks*
History of ischemic heart disease (compared to no history)	14.0%	-144
Age 80+ (compared to age 40-49)	15.1%	12
History of diabetes (compared to no history)	7.9%	-35
History of renal failure (compared to no history)	0.7%	-39
History of upper GI events (compared to no history)	6.6%	97
Age 70-79 (compared to age 40-49)	23.7%	9
Users of anticoagulants (compared to non-users)	1.7%	37
Men (compared to women)	35.5%	-4
Current smokers (compared to non-smokers)	23.8%	-2
Age 60-69 (compared to age 40-49)	24.2%	7

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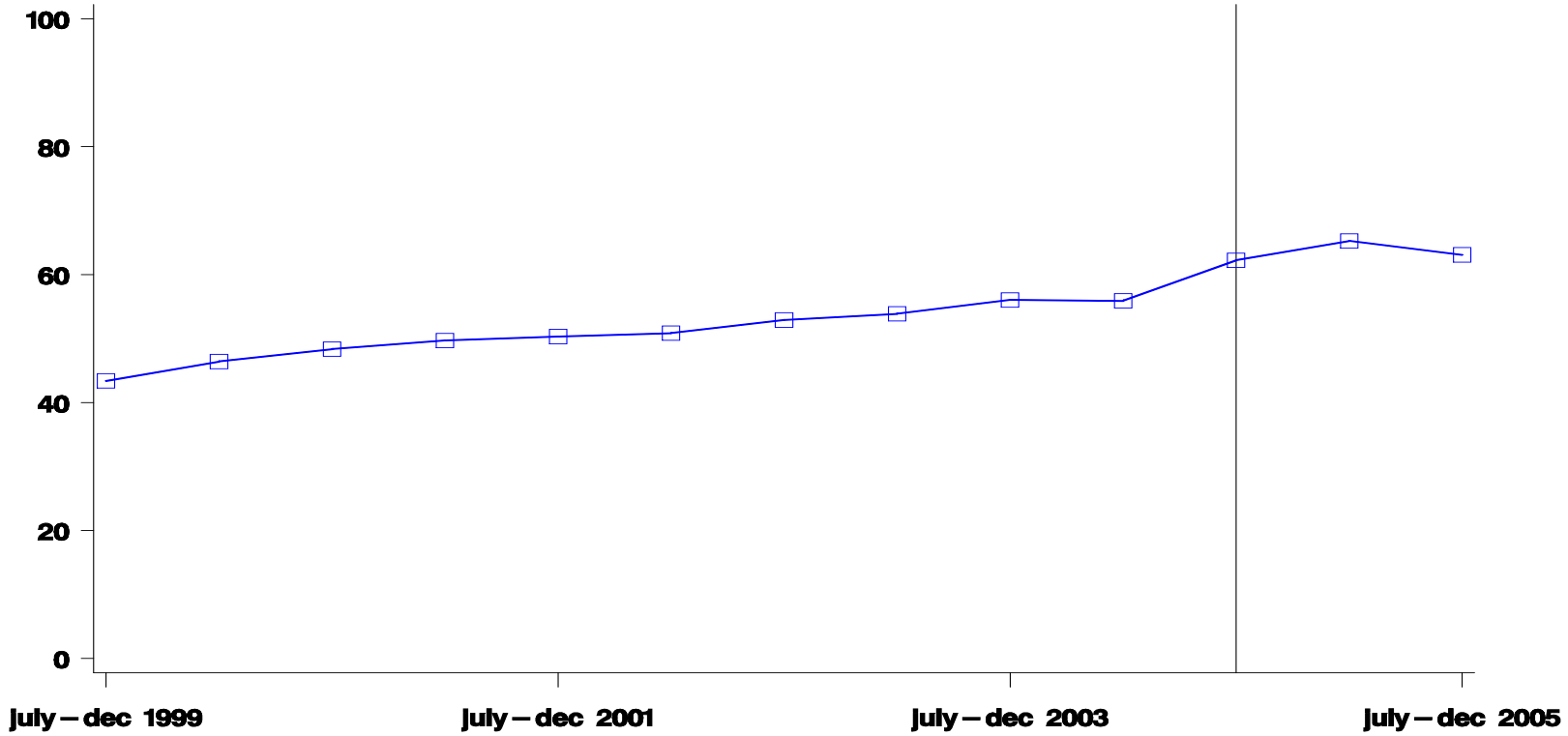
Percentage of patients stopping Cox-2 therapy within 1 month of starting



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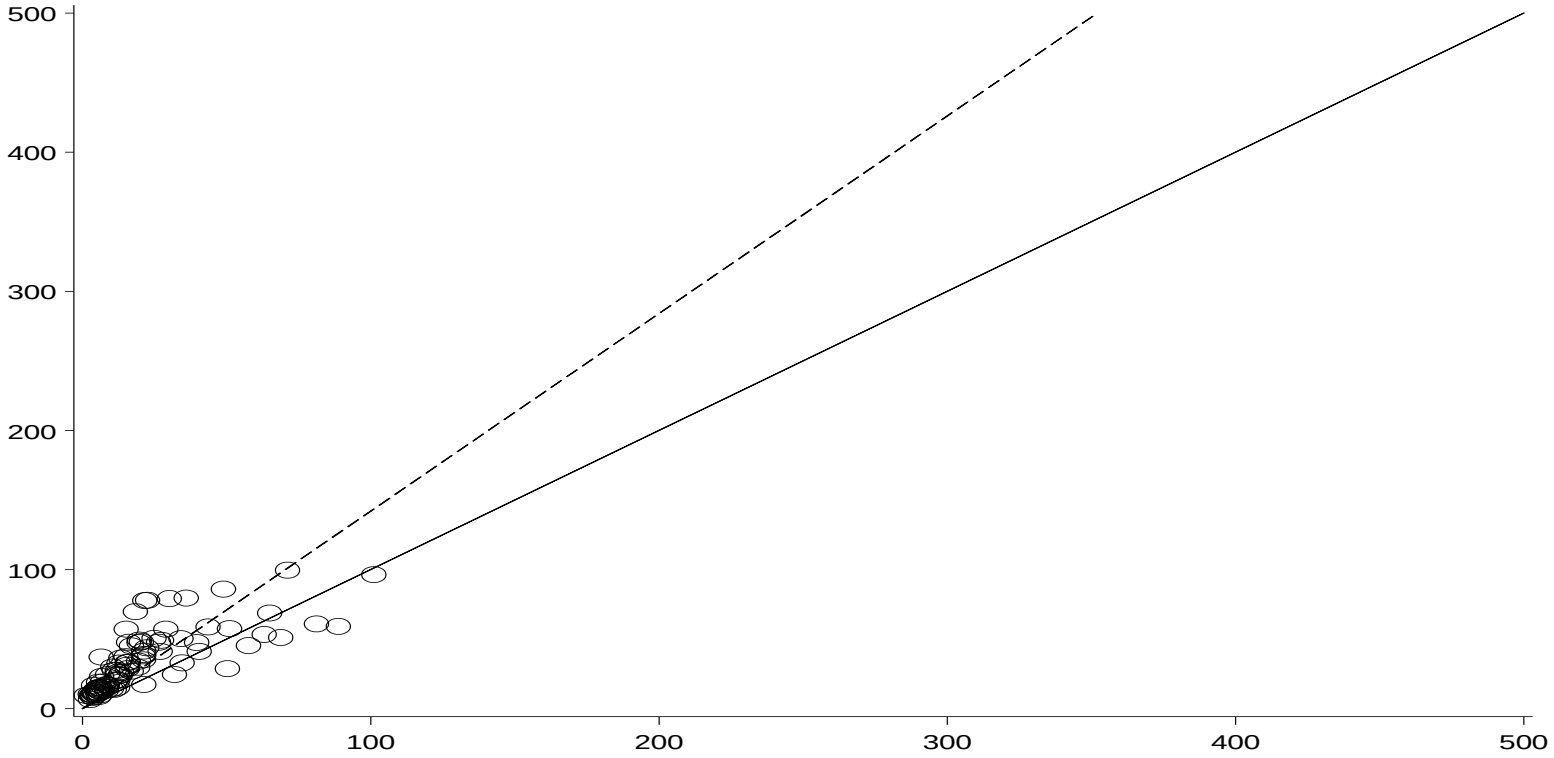
Excess MI and stroke and GI prevented with coxibs based on actual use (N cases per 10,000

No GI prevented



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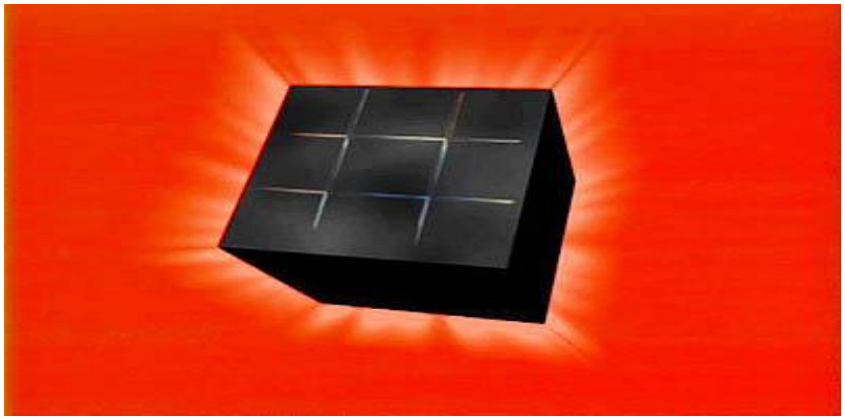
Should harm-benefit modelling replace the regulators?



Advantages of the black box:

- Human uncertainty with decision-making and subjectivity is replaced with clear answers
- Consistent
- Cheap and cheerful!
- Sensitivity analyses can address any limitations in evidence used for the black box

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BUT…….credit crunch and statistical modelling (Blame the models: Danielsson LSE 2008)

The quality of statistical risk models is much lower than often assumed. Such models are useful for measuring the risk of frequent small events, such as in internal risk management, but not for systematically important events. Unfortunately, it is common to see unrealistic demands placed on risk models. Having a number representing risk seems to be more important than having a number which is correct. Here, it is demonstrated that even in what may be the easiest and most reliable modeling exercise, Value–at–Risk forecasts from the most commonly used risk models provide very inconsistent results.

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"Wrong data in – wrong answer out":

Cost per GI case avoided with coxibs [van Staa PlosMed]

	Mean cost (95 % CI)	% of Rx below 50k threshold
Event probabilities based on GPRD		
Overall	52k (39-73k)	30.4%
Onset of coxib upper GI effects: 1 month	106k (78-148k)	14.8%
6 months	> 1 million	0%
Event probabilities based on RCTs		
VIGOR RCT	8k (6-10k)	99.0%
CLASS RCT	10k (8-13k)	98.8%
Rofecoxib meta-analysis	14k (11-19k)	98.0%
Celecoxib meta-analysis	21k (17-27k)	96.3%
Etoricoxib meta-analysis	14k (12-20k)	97.9%

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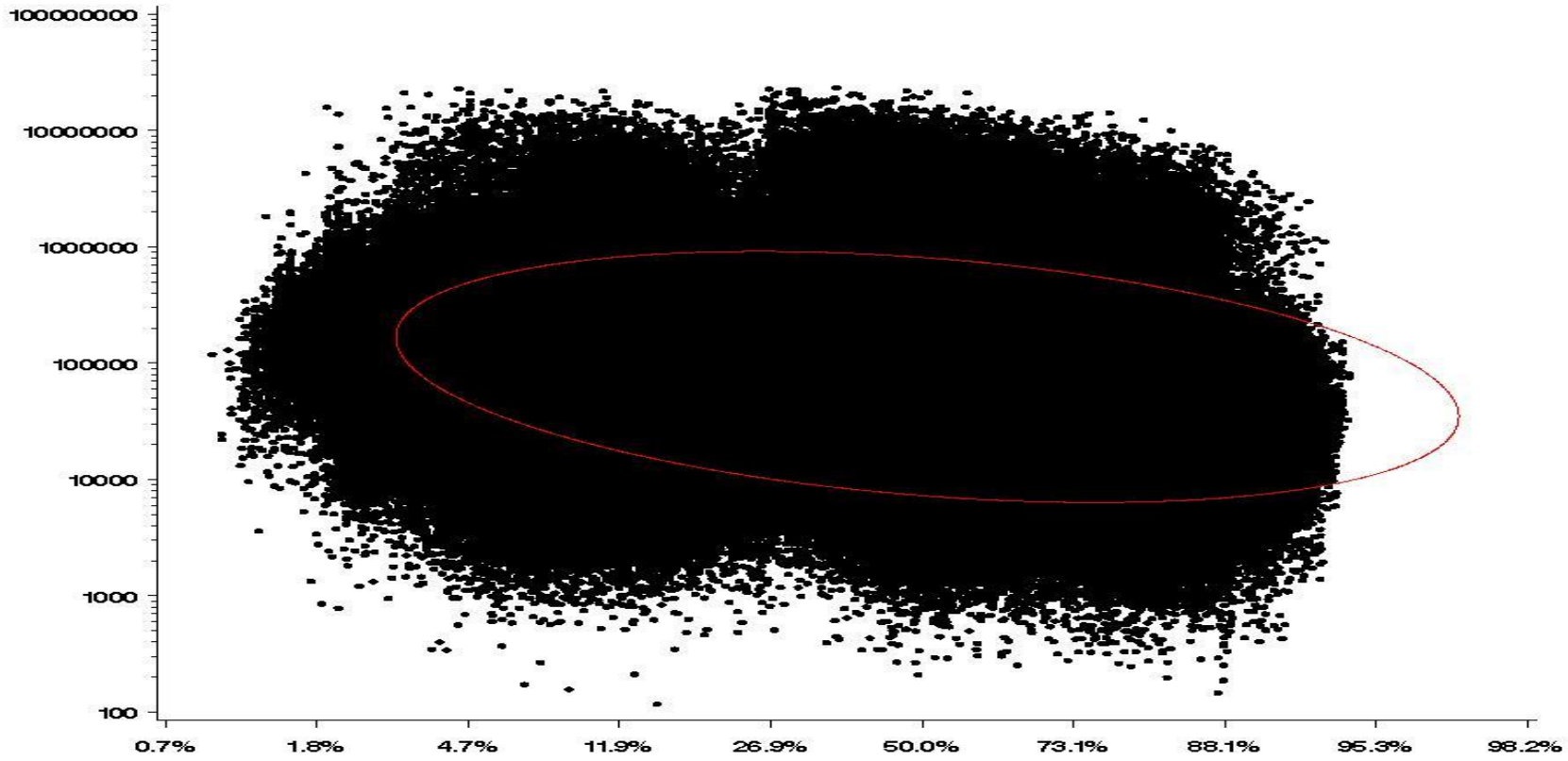
MORE DIMENSIONS TO DATA

"Wrong data in – wrong answer out":

Cost per GI case avoided with coxibs for each patient

cost per case avoided (£)



probability of repeat prescribing

Discussion

- Harm-benefit modelling: several initiatives ongoing to develop methods
- One major benefit is the systematic assessment and quantification of evidence
- Epidemiologists can help to provide data to these assessments:
  - Information on target population
  - Information on use in actual practice
- Identification of scenarios that could substantially change harm-benefit ratio => gather more evidence