PROTECT Work Package 5

Benefit-Risk Integration and Representation

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The PROTECT project (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.

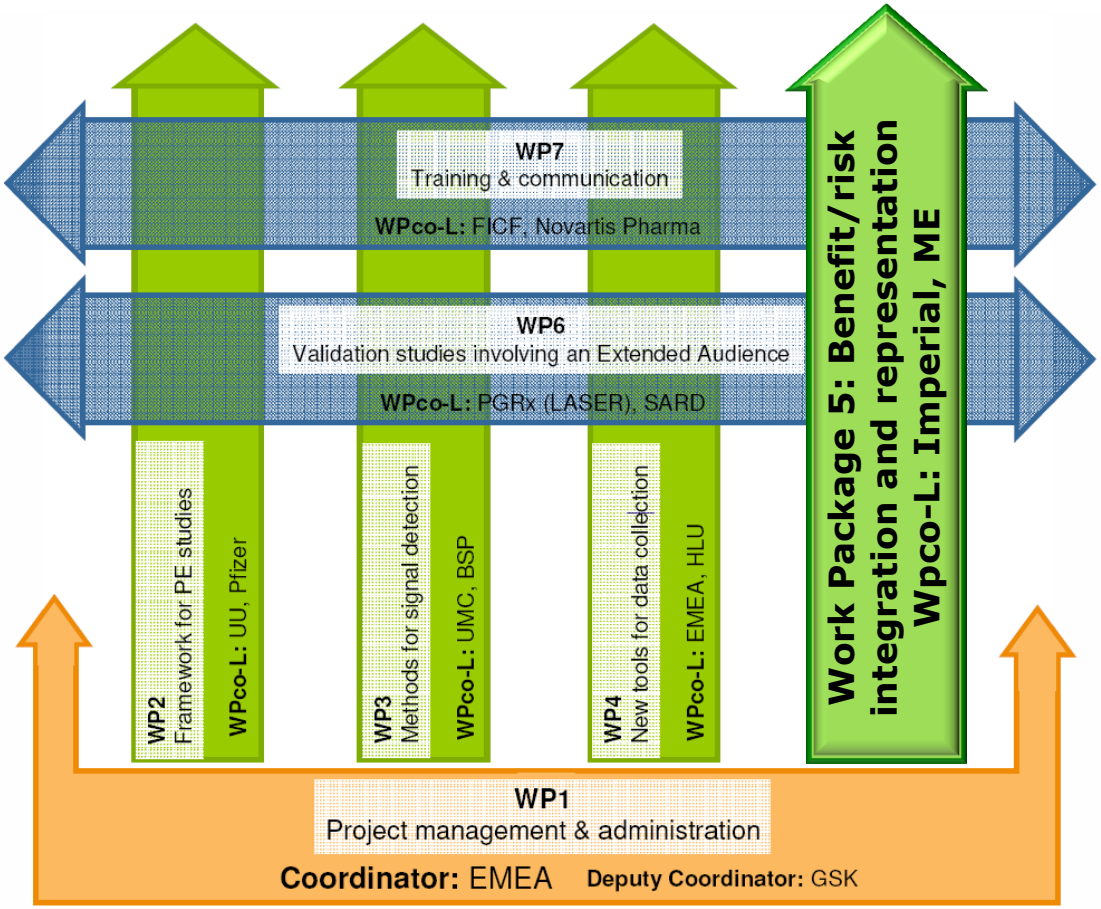
Public Partners

Agencia Espanola de Medicamentos y Productos Sanitarios	Ludwig-Maximilians-Universität-München
European Medicines Agency	Medicines and Healthcare products Regulatory Agency / General Practice Research Database
Fundació Institut Català de Farmacologia	Mario Negri Institute for Pharmacological Research
Fundación Centro Español de Investigación Farmacoepidemiológica	Outcome Europe Sarl / Outcome Sciences, Inc.
Imperial College of Science, Technology and Medicine	Poznan University of Medical Sciences Polish Registry of Congenital Malformations (acceded after Sep 2009)
Institut National de la Sante et de la Recherche Medicale	Rijksuniversiteit Groningen
International Alliance of Patients' Organizations	Stiftelsen WHO Collaborating Centre for International Drug Monitoring
L.A. Sante Epidemiologie Evaluation Recherche	Universiteit Utrecht
Lægemiddelstyrelsen (Danish Medicines Agency)	University of Newcastle upon Tyne

Private partners and subcontractors*

Amgen NV	Novartis Pharma AG
AstraZeneca AB	Novo Nordisk A/S
Bayer Schering Pharma AG	Pfizer Ltd
F.Hoffmann-La Roche AG	Sanofi-Aventis Research and Development
Genzyme Europe B.V.	Takeda Global Research and Development Centre (Europe) Ltd (acceded after Sep 2009)
GlaxoSmithKline Research and Development LTD	Consulting & Coaching*
H. Lundbeck A/S	EPIC Database Research Co Ltd*
Merck KGaA	Innovative Medicines Initiative ** (Funder)

Work Packages



- One WP concerned with all aspects of the organisation and management of PROTECT
- Four "vertical" WPs targeting the specific objectives and methodological developments
- Two "horizontal" WPs concerned with the communication, validation and integration of the scientific work into an integrated and cohesive European activity

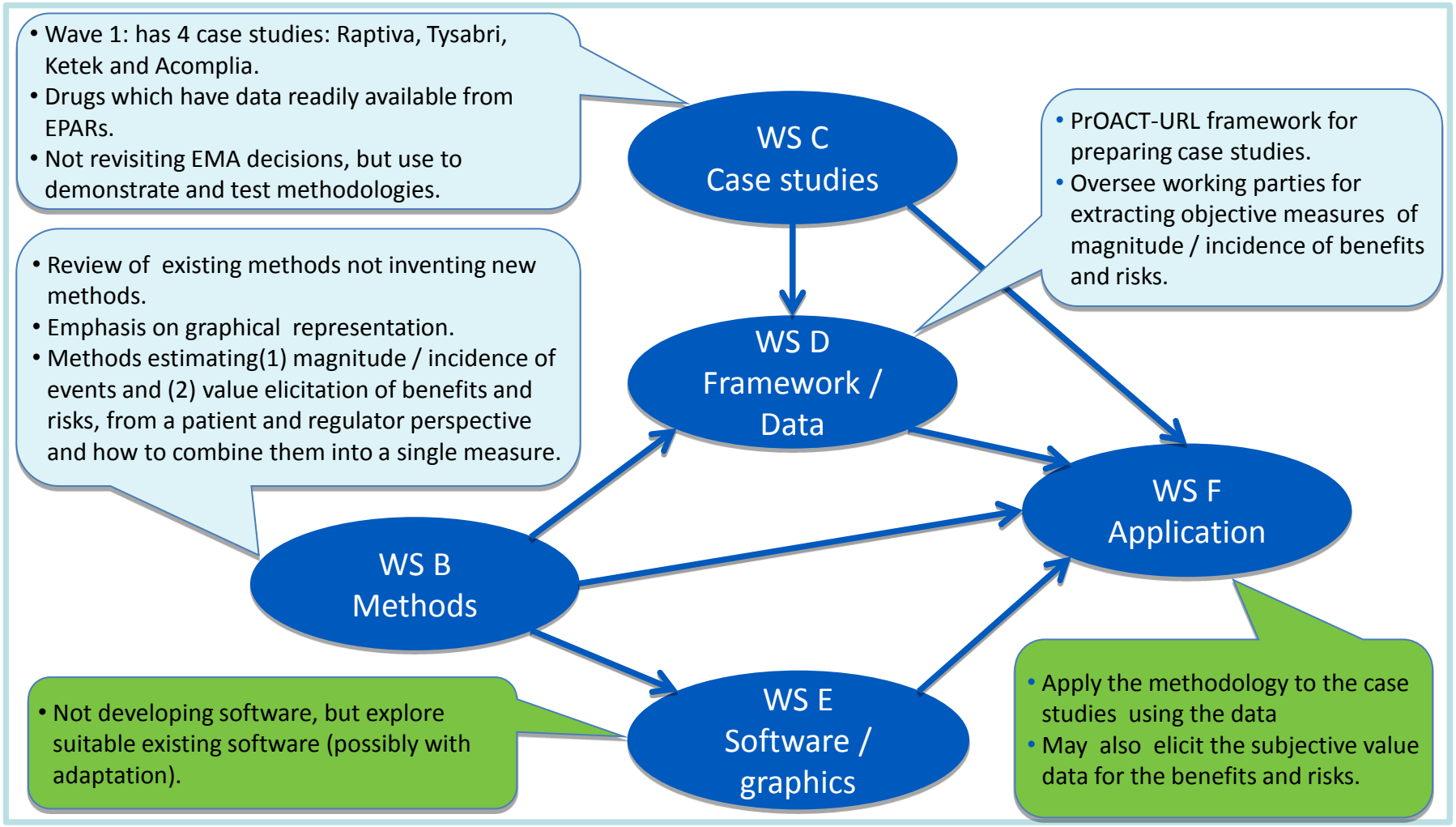
Work Package 5 of PROTECT (membership)

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

Work Package 5 of PROTECT

- Charter
  - Scope
    - Submission and post-approval, while recognising the relevance of pre-approval B-R assessment
    - individual and population-based decision making
    - the perspectives of patients, physicians, regulators and other stakeholders such as societal views needed for HTA
    - possible interdependencies with other PROTECT Work Packages as well as other relevant external initiatives.
  - Review and selection of methodologies and of visualisation methods
  - Choice and implementation of case studies
  - Visualisation
  - Communication (publications)

Work Package 5: Overview



Example: Trastuzumab for early breast cancer*

Decision-maker	The woman
Possible decisions	• Take trastuzumab • Not take trastuzumab
Uncertain consequences	• Breast cancer recurrence • Death • Cardiotoxicity
Sources of evidence	A pivotal trial
Utility assessment	Increased disease-free survival and cardiotoxicity

(*European Medicines Agency (2006). Scientific discussion on Herceptin. Report reference EMEA/H/C/278/II/0026)

Trastuzumab:

Benefit-Risk captured with a single parameter

- Pivotal study: randomised, open-label comparing Herceptin and placebo in women with non-metastatic, operable primary invasive breast cancer over-expressing HER2 who had completed … therapy… for primary breast cancer.
- Benefit: Disease-free survival (Placebo vs. Herceptin)
  - proportion with either disease progression or death (due to any cause) 22% vs. 13.9%
  - Death (due to any cause) 2.4% vs. 1.8%
- Risk: Cardiotoxicity (Placebo vs. Herceptin)
  - significant asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) cardiac dysfunction 0.53% vs. 3.04%
  - symptomatic congestive heart failure of NYHA class III or IV or cardiac death 0.06% vs. 0.6%

PROTECT

Number needed to treat approach for trastuzumab

- NNT=$1/\Delta_p$ patients to be treated to observe one benefit (or to prevent an adverse event)
- NNH=$1/\Delta_q$ patients to be treated to observe an adverse event (or to prevent a benefit)
- $\mathrm{NNT} = \frac{1}{0.861-0.780} = 12.3$
  = for every 13 patients treated, one will benefit from progression-free survival
- $\mathrm{NNH} = \frac{1}{0.0304-0.0053} = 39.8$
  = for every 40 patients treated, one will experience cardiotoxicity

NNT<NNH is desirable

Treating menopausal symptoms*

Decision-maker	The woman
Possible decisions	• HRT or not? • For how long?
Uncertain consequences	• Heart attack/stroke • Breast cancer • Osteoporosis/fractures • Vasomotor symptoms • Skin • Weight Change
Sources of evidence	Epidemiological studies Trials
Utility assessment	Woman's trade off between long and short term consequences

(*Medicines and Healthcare Regulatory Agency (2007). Hormone-replacement therapy: safety update. UK Public Assessment Report MHRA/2032228)

Hormone-replacement therapy: safety update*

- 5 years' HRT use in women younger than age 60 years

Type of HRT	Baseline	Absolute risk	Attributable risk
Oestrogen-only (no uterus)	*42*	*47 (44-52)*	*5 (2-10)*
Oestrogen-only (with uterus)	*44*	*53 (49-59)*	*9 (5-15)*
Combined HRT	*37*	*51 (48-56)*	*14 (11-19)*

(similar tables for 60-69s, and for 10 years' HRT use)

(*UK Public Assessment Report, MHRA
See http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2032228.pdf)

Hormone-replacement therapy: safety update

- Baseline rate: Obtained by adding the baseline rates for breast cancer, endometrial cancer (in women with a uterus), ovarian cancer, colorectal cancer, venous thromboembolism, CHD, stroke and fracture of femur in non-HRT users.
- Absolute risk: Obtained by subtracting the number of cases of colorectal cancer and fracture prevented from the total number of cases of breast cancer, endometrial cancer (in women with a uterus), ovarian cancer, venous thromboembolism, CHD, stroke in HRT users.
- Attributable risk: Obtained by subtracting the baseline risk in non-HRT users from the absolute risk in HRT users.

Hormone-replacement therapy: safety update

"A key drawback of this approach is that the benefits of vasomotor symptom relief—the main indication for HRT—are difficult to quantify and have been not taken into consideration. Because the efficacy of oestrogen-only HRT and combined HRT in relief of vasomotor symptoms is similar, however, the safety profile of these two types of HRT can justifiably be compared."

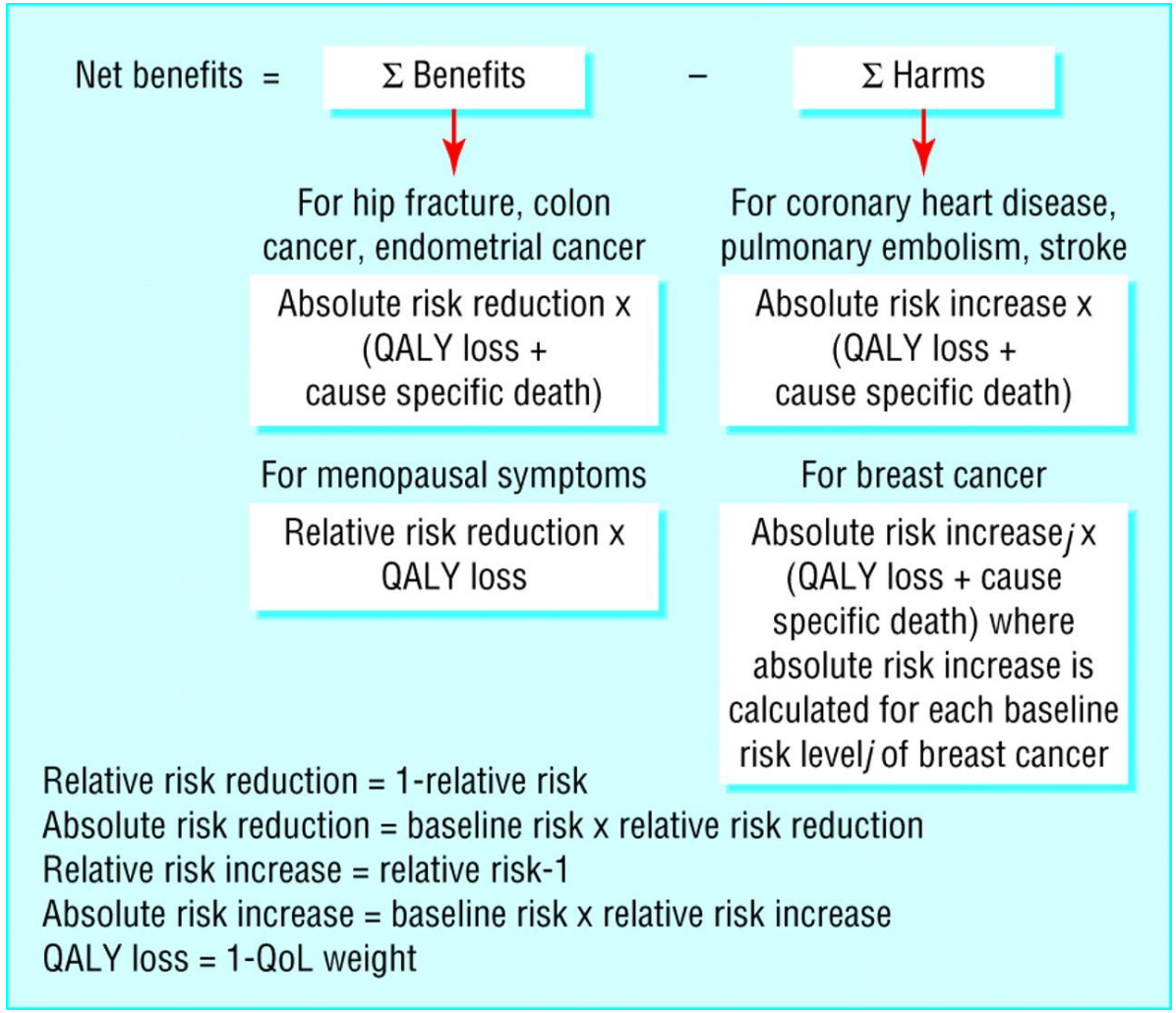
BUT

- not very helpful in deciding whether to use HRT or not for its licensed indications
- Utilities are implicit – that all other endpoints are equally serious

cf data-monitoring for WHI (Freedman et al, CCT, 1996;

Ashby & Tan, Clinical Trials, 2005)

Fig 1 Structure of net benefit decision model



Minelli, C. et al.
BMJ 2004;328:371

Benefits and Harms of HRT*

- Conclusion: "*Women with menopausal symptoms on average benefit from HRT,…which concur[s] with the recommendations of the UK MHRA. The results depend on the QoL attributed to symptoms, which in turn vary greatly,….. Thus a decision analysis tailored to individual women would be more appropriate in clinical practice than a population based approach*"

(*Minelli C et al, BMJ, 2004)

Example: Rizatriptan for acute migraine attacks*

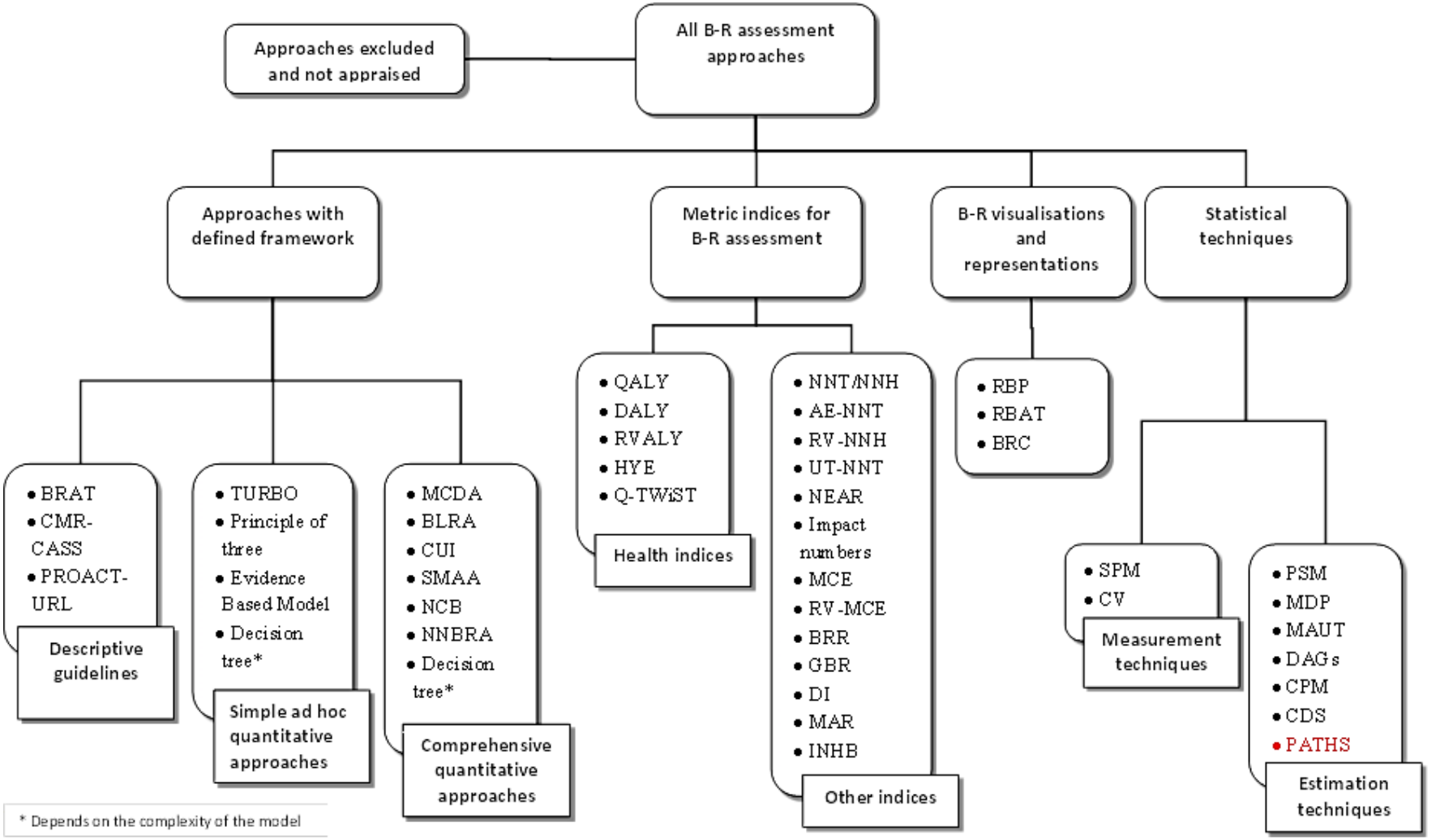
Decision-maker	Physicians
Possible decisions	• Administer rizaptriptan • Administer sumatriptan • Do nothing
Uncertain consequences	• Benefits – pain relief at 2hr, efficacy in subgroups (men vs. women), anticipated compliance in trials • Risks – dizziness, somnolence, asthenia/fatigue, chest pain, potential off-label use leading to safety hazards
Sources of evidence	Three pivotal trials from MA application
Utility assessment	Physicians' value judgments and weightings for each uncertain consequence

(*See Mussen F. et al. (2009). Development and Application of a Benefit-Risk Assessment Model Based on Multi-Criteria Decision Analysis. In Benefit-Risk Appraisal of Medicines. pp. 111-149, John Wiley & Sons, Ltd.)

Multi-Criteria Decision Analysis (MCDA)

Steps in MCDA	Application to rizatriptan example
1. Establish decision context	Rizatriptan treatment in acute migraine attacks in over 18 using pivotal MA application data from physicians' view
2. Identify options to appraise	Rizatriptan vs. sumatriptan vs. placebo
3. Identify objectives and criteria	High-level criteria are benefits and risks
4. Score options	Least preferred benefits and most preferred risks = placebo rates.
5. Weight criteria	Swing-weighting and using authors' view
6. Combine weights and scores	Weights are normalised and given as cumulative weights and weighted utilities
7. Examine results	Rizatriptan: 27.8 benefits, 39.0 risks. Total=67 Sumatriptan: 26.2 benefits, 35.0 risks. Total=61 Placebo: 0 benefits, 50 risks. Total=50
8. Conduct sensitivity analysis	Placebo is favoured if weights on benefit <30 or weights on risks > 70

Classifications of B-R approaches



Comparison of technologies (legend)

- π = probability;
- S = Scoring;
- U = Utility;
- w = weights;
- I = Integrated risk and benefit;
- T = integrate time trade-off;
- ζ = explicit sensitivity analysis;
- G = Graphical methods readily available;
- M = The resultant B-R metric
- X indicates required parameters; O indicates optional parameters.

Comparison of technologies (table)

	BRAT	CMR-CASS	PrOACT-URL	TURBO	Principle of three	EBM	MCDA	Decision tree	NNBRA	BLRA	NCB	SMAA	CUI / DI	CPM	QALY (DALY)	Q-TWiST	BRR	GBR	NNT/NNH	AE-NNT	NEAR	UT-NNT	RV-NNT	Impact numbers	MCE	RV-MCE	MAR	INHB	RBP / RBAT	BRC	SPM	CV	MAUT	MDP	PSM	CDS	PATHS
π	-	-	-				X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X	X			X	X	X	O	?
U	-	-	-				X	X		X	X	X	X	O	X	X						X	X			X	X	X			X	X	X	X	O	O	?
S	-	-	-	X	X	X	X		X	X		X			X	X												X			X	X			O	O	?
w	-	-	-			X	X	O	X	X		X	X		X	X												X	X				X	X	O	O	?
I	-	-	-	X			X	X		X		X	X	X		X		X		X	X				X	X	X	X						X	O	O	?
T	-	-	-				O	O		O		O	O	O	X	X												X						O	O	O	?
ζ	-	-	-				X			X		X	X															X	X						O	O	?
G	-	-	-	X			X	X	X			X	X	X													X		X	X				O	O	O	?
M	-	-	-	ψ_w	ψ	ψ_w	U_w	U_w	ψ_w	U_w	U_ρ	U_w	U_w	ψ_w	U_w	U_w	Δ_ρ	Δ_w	Δ_ρ	Δ_ρ	Δ_ρ	U_ρ	U_ρ	Δ_ρ	Δ_ρ	U_ρ	U_ρ	U_w	∇	∇	U	U	U_w	U_w	-	-	-

Keys for resultant benefit-risk metric

- U Utilities
- ψ Scores
- Δ Rates
- ∇ Visualisation of B-R threshold

Subscript keys

- w Weighted
- E Expected
- ρ Threshold

Example comparison for each class

	Level of complexity	Level of input data	Max options	Perspective for stakeholders
BRAT	Simple (intuitive and general organisation with basic knowledge of probabilities)	Population or individual	≤2	Simple decisions for health authorities and pharmaceutical companies
TURBO	Simple (intuitive but require some medical knowledge)	Population	>2	Simple decisions for patients, physicians, and pharmaceutical companies
MCDA	Complex (training needed to understand the concepts and software)	Population or individual	>2	More complicated decisions usually involve high stakes in pharmaceutical companies, healthcare providers, and regulatory agencies
QALY / DALY	Medium (statistical knowledge on treatment comparison or ANOVA)	Individual	>2	Decisions involving high stakes in pharmaceutical companies, healthcare providers, regulatory agencies, patients and healthcare providers
NNT / NNH	Simple (basic knowledge of probabilities)	Population	≤2	Simple decisions for patients and healthcare providers
BRC	Medium (basic knowledge on confidence inferences)	Population	≤2	Simple to medium level decisions by healthcare providers
SPM	Complex (heavy resources and understanding of experimental design)	Individual or population	n/a	More complicated decisions usually involve high stakes in pharmaceutical companies, healthcare providers, and regulatory agencies
MDP	Complex (require knowledge of Markov processes and simulation techniques)	Population	>2	More complicated decisions usually involve high stakes in pharmaceutical companies, healthcare providers, and regulatory agencies

PROTECT WP5: Achievements Year 1

- Charter completed (re-opened for inclusion of recommendations from EAB)
- Protocol for review of methodologies
- Selection Case studies wave 1 (Tysabri, Raptiva, Acomplia, Ketek)
- Framework for data collection (PrOACT-URL)
- Interaction with other initiatives
  - CHMP
  - OMOP
  - Sentinel
  - BRAT (22 June, 10 Nov 2010)
- Numerous presentations at congresses, conferences, meetings

PROTECT WP5: Ongoing Work Year 2

- Conduct review of B-R methodologies and visualisation methods (planned publication)
- Criteria for and selection of wave 2 case-studies
- Determine and gather data for case studies