PROTECT – WP6

- Extension /Validation of Benefit-Risk Methods, Tools and Processes Evaluated in PROTECT- WP5

Presented by: Andrea Beyer, EMA

Outline

- Challenges in medical decision making
- About IMI-PROTECT
- PROTECT Work Package 5 methodology review
- Extension studies in Work Package 6

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Challenges in medical decision-making

- Should we formalize 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?

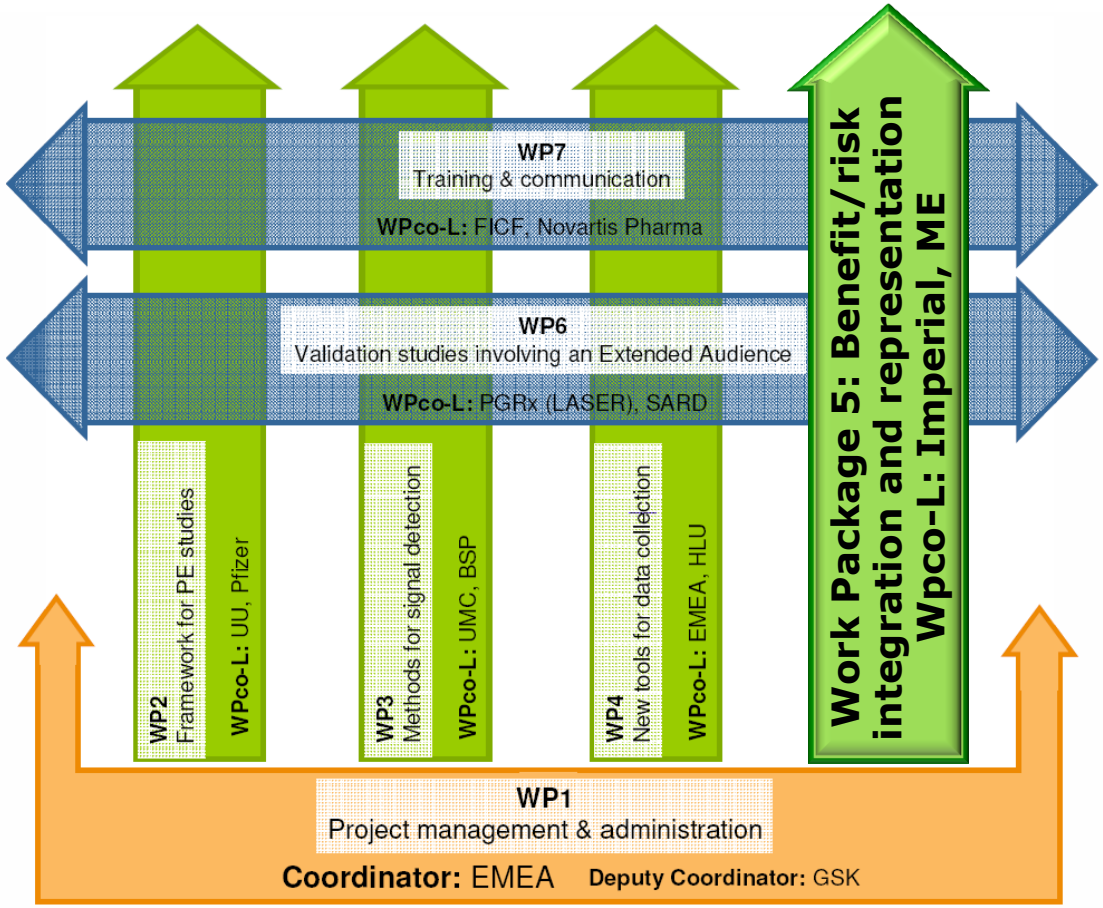
The IMI-PROTECT

- PROTECT[1] (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium)

- "Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU" including graphical representation of risk-benefit led by EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

[1] PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

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

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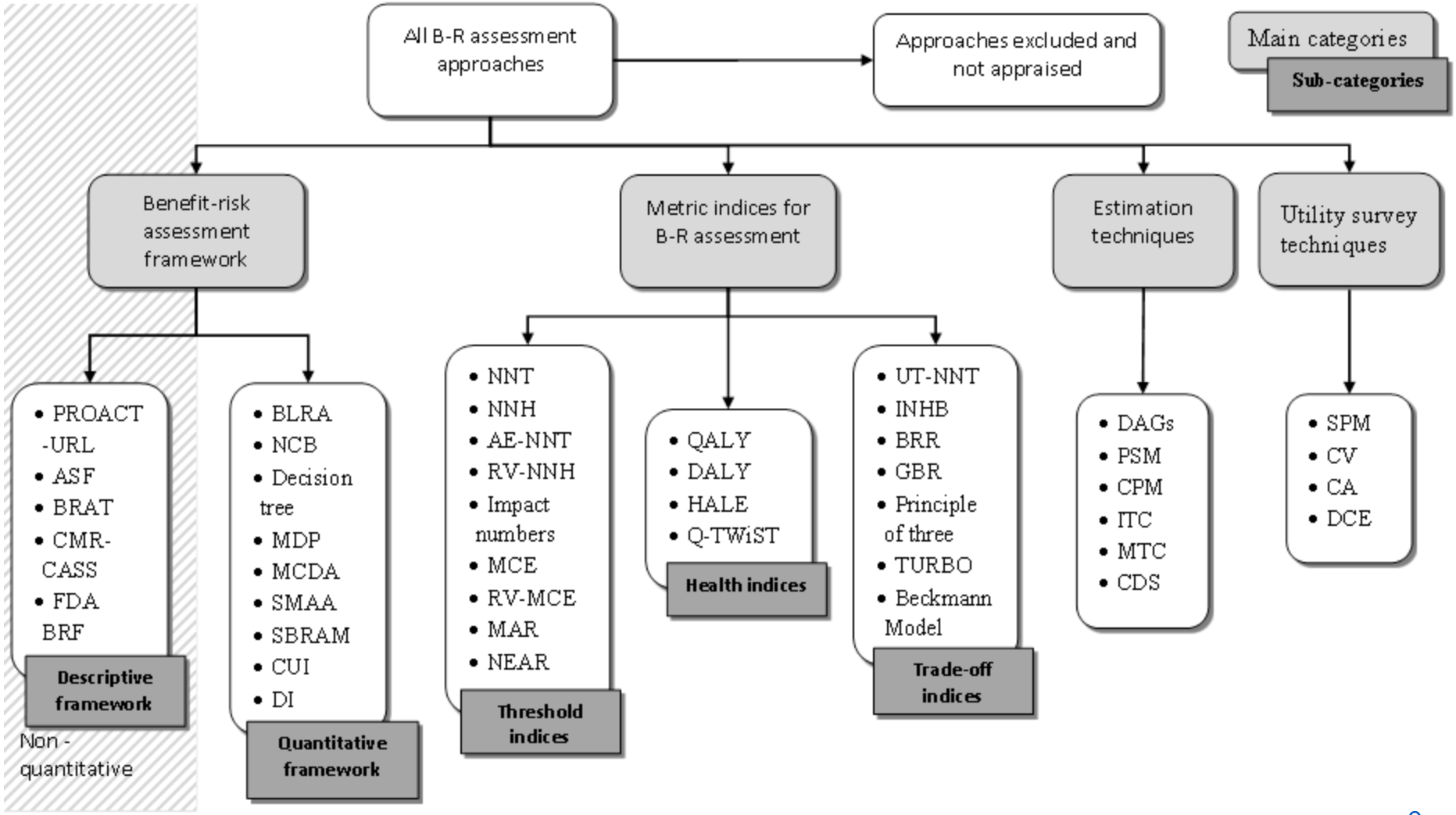
Work Package 5 of PROTECT (membership)

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)

Classifications of approaches



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

Raptiva example

Active drug	Efalizumab
Indication	Psoriasis
Severe side effects	Progressive Multifocal Leukoencephalopathy
Regulatory history	Approved 2004 License withdrawn 2009
Data source	EPAR SPC PSUR10
Methodologies tested	PrOACT-URL, BRAT, MCDA, BRR + Decision conferencing to elicit value preference using swing-weighting

Tysabri example

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-URL, BRAT, MCDA, NNT & NNH, BRR, PSM, MTC + Decision conferencing to elicit value preference directly

Acomplia

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

Raptiva: PrOACT-URL

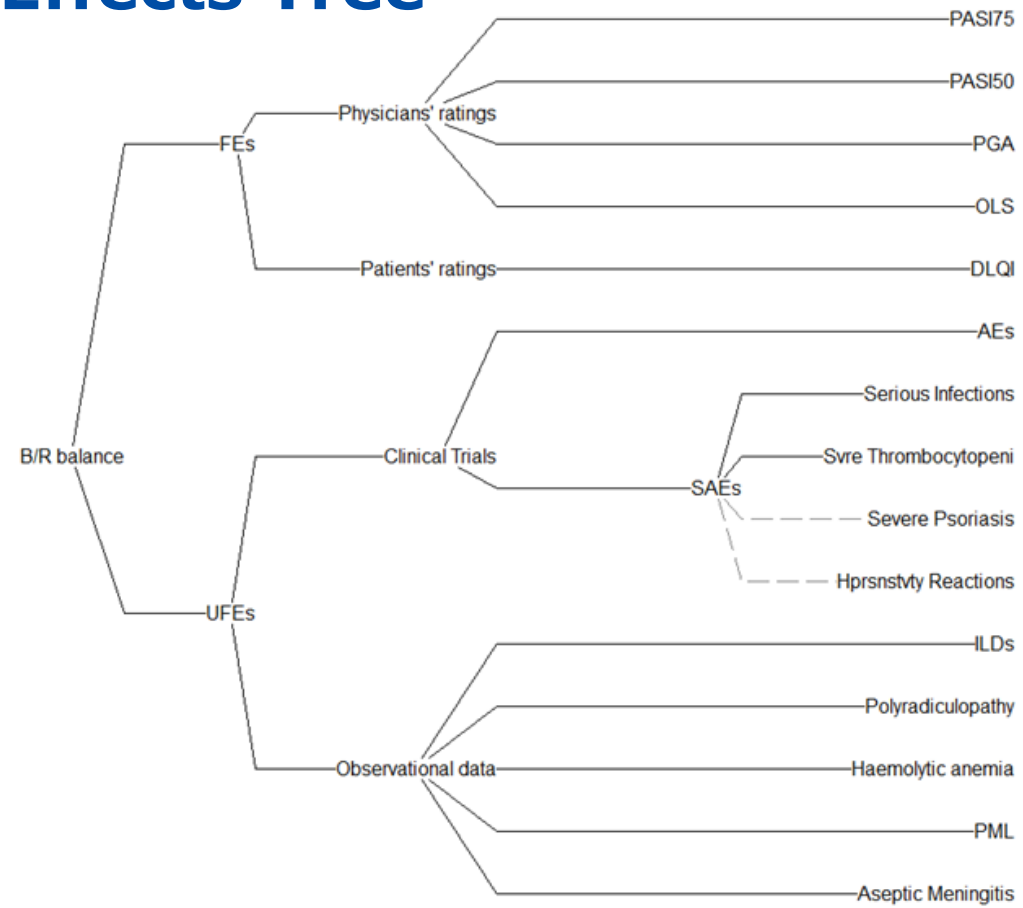
Options

- Raptiva
- Placebo

No data for vary, suspend or withdraw.

Add post-approval data; examine resulting benefit-risk balance.

Effects Tree



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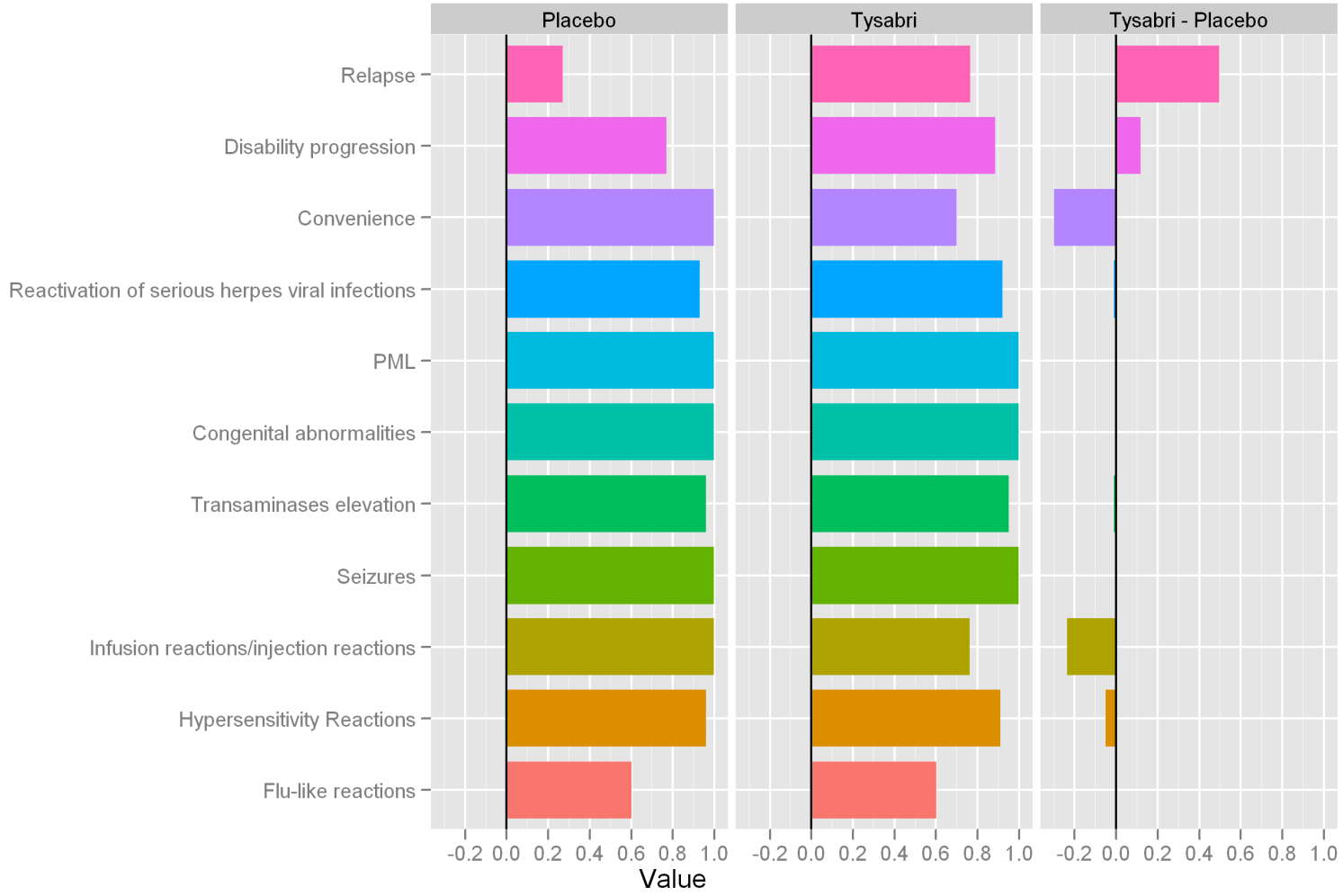
Raptiva: PrOACT-URL effects Table

	Name	Description	Fixed Upper	Fixed Lower	Units	Raptiva	Placebo
Favourable Effects	PASI75	Percentage of patients achieving 75% reduction in baseline PASI[1] at week 12.	60.0	0.0	%	29.5	2.7
	PASI50	Percentage of patients achieving 50% reduction in baseline PASI[1] at week 12.	60.0	0.0	%	54.9	16.7
	PGA	Percentage of patients achieving Physician's Global Assessment[2] clear/almost clear at week12.	40.0	0.0	%	295	5.1
	OLS	Percentage of patients with Overall Lesion Severity rating of minimal or clear at FT (day 84).	40.0	0.0	%	32.1	2.9
	DLQI	Dermatology Life Quality Index[3]. Mean percentage of patients showing an improvement.	10.0	0.0	Change score	5.8	2.1
Unfavourable Effects	AEs	Percentage of patients exhibiting injection site reactions, mild to moderate dose-related acute flu like symptoms.	50.0	20.0	%/100ptyrs	41.0	24.0
	Severe infections	Proportion of patients experiencing infections serious enough to require hospitalisation.	3.00	0.00	%/100ptyrs	2.83	1.4
	Severe Thrombocytopenia	Number of cases exhibiting severe (grade 3 and above) thrombocytopenia[4].	10	0	number	9	0
	Psoriasis Severe Forms	Percentage of patients developing severe forms of psoriasis (erythrodermic, pustular).	4.0	0.0	%	3.2	1.4
	Hypersensitivity Reactions	Percentage of patients exhibiting hypersensitivity reactions, arthralgia, psoriatic arthritis, flares, back pain asthenia, ALT and Ph. Alk increase.	10.0	0.0	%	5.0	0
	Interstitial Lung Disease	Number of cases of interstitial lung disease.	20	0	number	18	0
	Inflammatory Polyradiculopathy	Number of cases of inflammatory polyradiculopathy.	5	0	Data	4	0
	SAEs	Number of cases of haemolytic anemia.	25	0	number	24	0
	PML	Number of cases of progressive multifocal leukoencephalopathy.	5	0	number	3	0
	Aseptic Meningitis	Number of cases of aseptic meningitis.	30	0	number	29	0

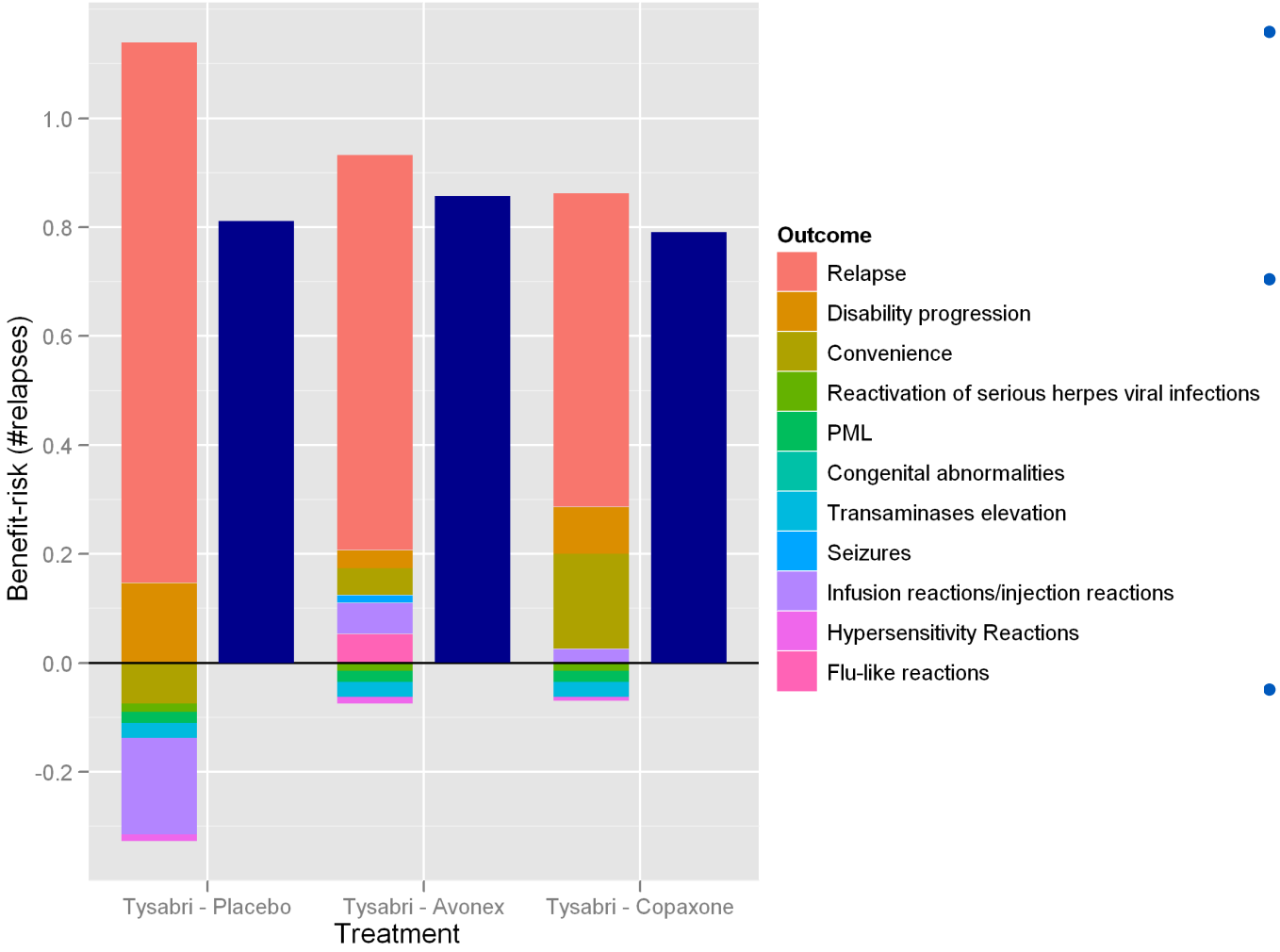
Tysabri: MCDA difference display

Incremental value scores for Tysabri compared to placebo



Tysabri: MCDA criteria contribution

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

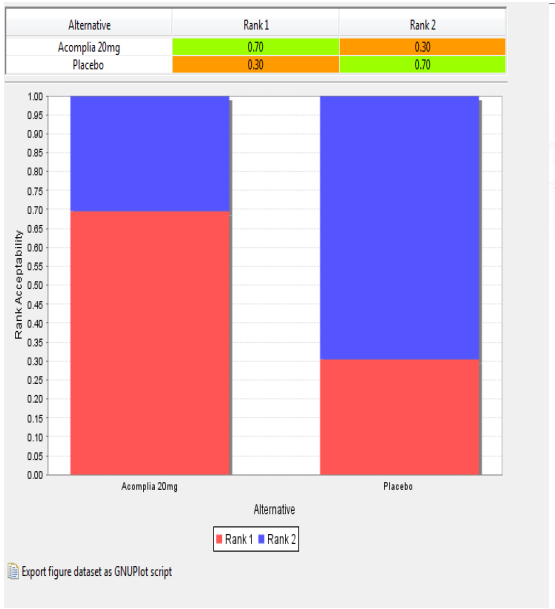


- Same information shown as a stacked bar chart.
- Positive incremental benefit-risk components above the x-axis and negative ones below.
- Total benefit-risk shown as the dark blue bar.

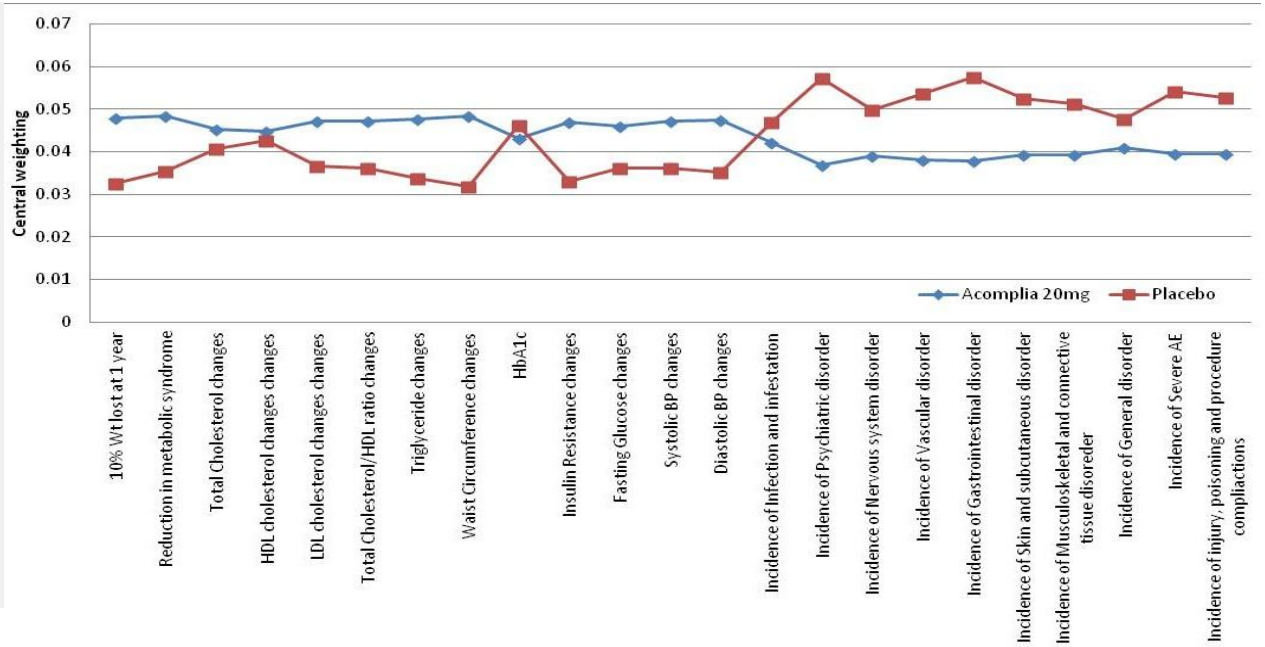
Acomplia: SMAA (preference-free)

Acceptability index

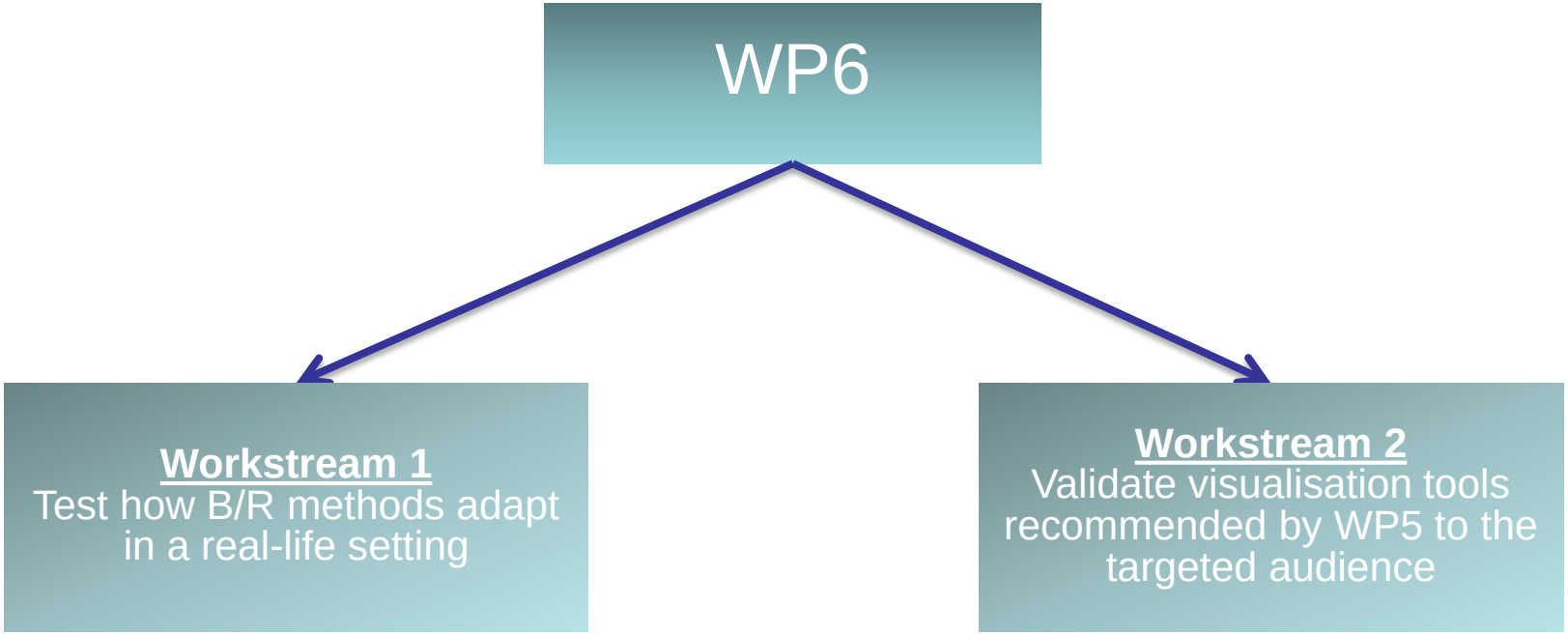
alternative *i* is ranked *r*



Preference values for an "average" decision-maker resulting in the preference on the left



WP6-WP5 activities



Lead Billy Amzal (LASER)

Lead Andrea Beyer (EMA)

Work Package 6 – WorkStream 2 of PROTECT (membership)

Public	Private
EMA (co-leader) University of Groningen (RUG/UMCG) DKMA University of Utrecht	Laser (co-leader) Sanofi-Aventis Merck KGaA Amgen

Workstream 2 – Web Survey

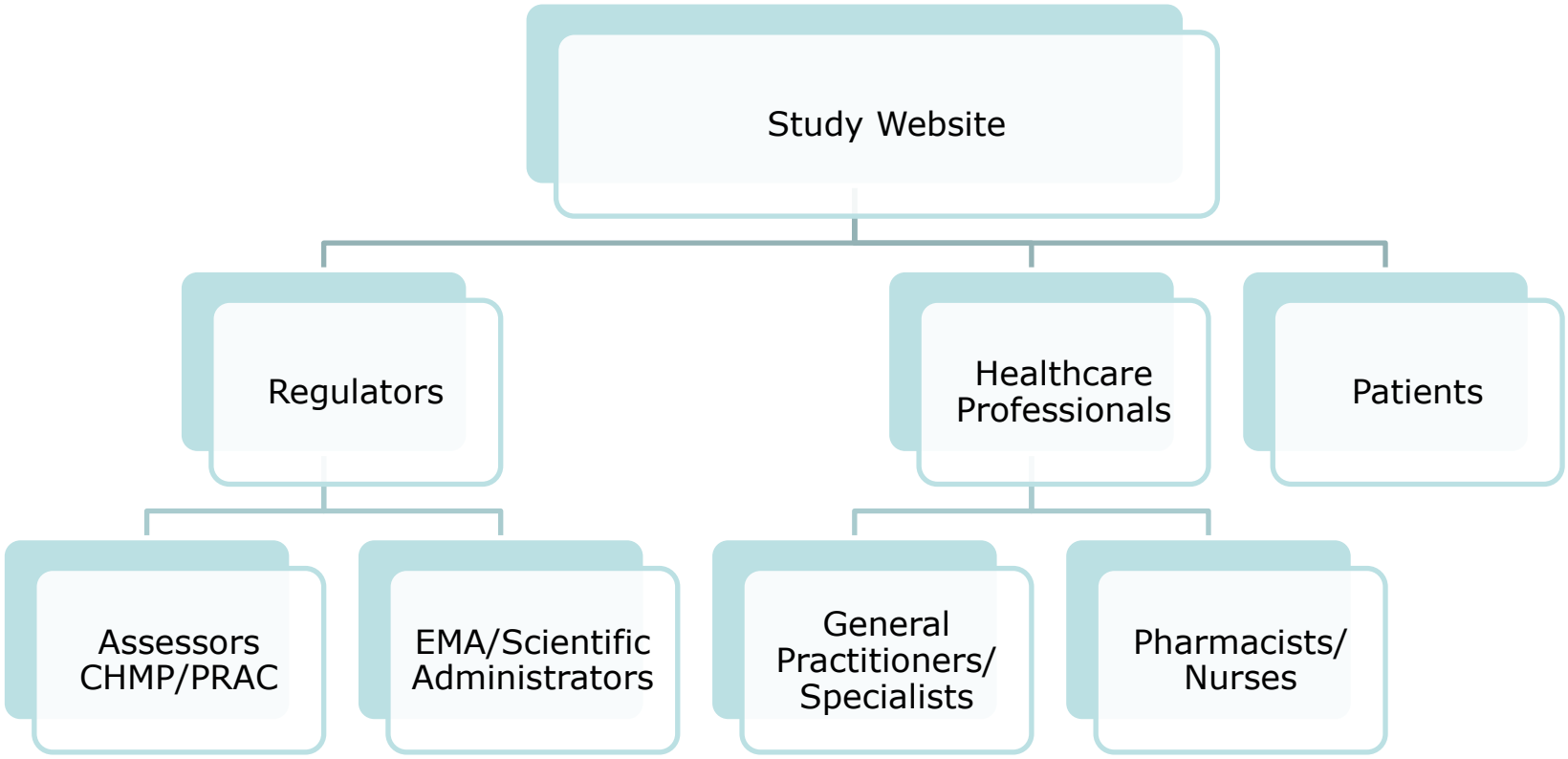
Validation of Methods to Present BR data

- Research Questions:
  - What graphical presentation methods are most useful for regulators/physicians in evaluating benefit-risk tradeoffs?
  - What graphical presentation methods are most useful for communicating benefit-risk tradeoffs to physicians/patients?
  - Does risk or benefit perception change depending on the mode of presentation?

Extension of Methodology to Elicit Patient Preferences

- Research Questions:
  - Do the 3 methods used in WP5 for eliciting preferences produce the same results?
  - What are the differences in preferences for treatment outcomes among 3 stakeholders?
- **Benefit and Risk Perception**
  - Differences in perception among stakeholders

Study Participants



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Therapeutic Areas

Atrial Fibrillation	• Warfarin
Diabetes	• Avandia
Breast Cancer	• Perjeta

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Patients/HCP/ Regulators

Perception

Measure dimensions of benefit and risk perception

Visual presentation of data

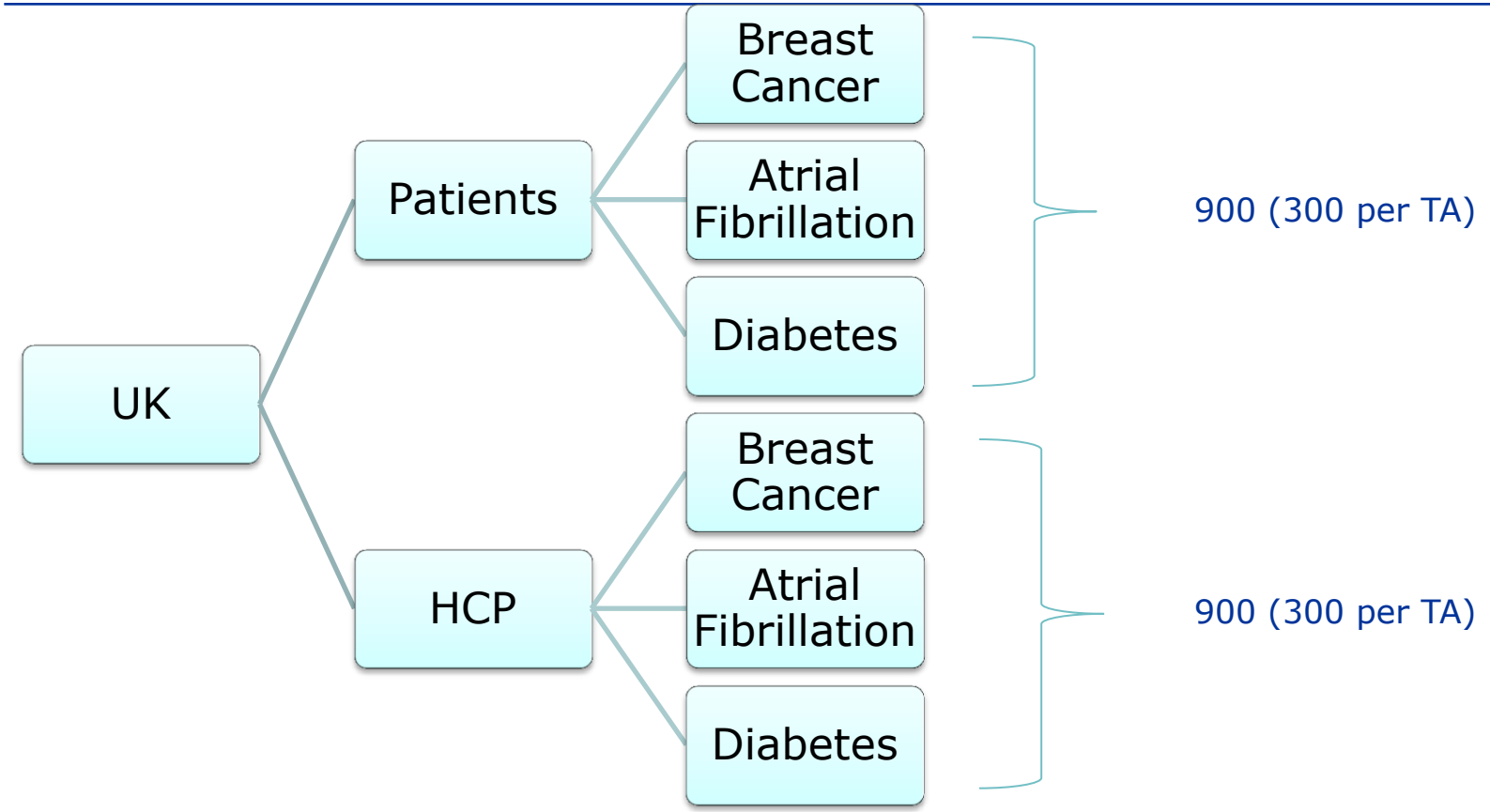
Visual presentation of benefit and risks using tabular and graphical formats

Elicitation of preferences for treatment outcomes

Discrete Choice Experiment

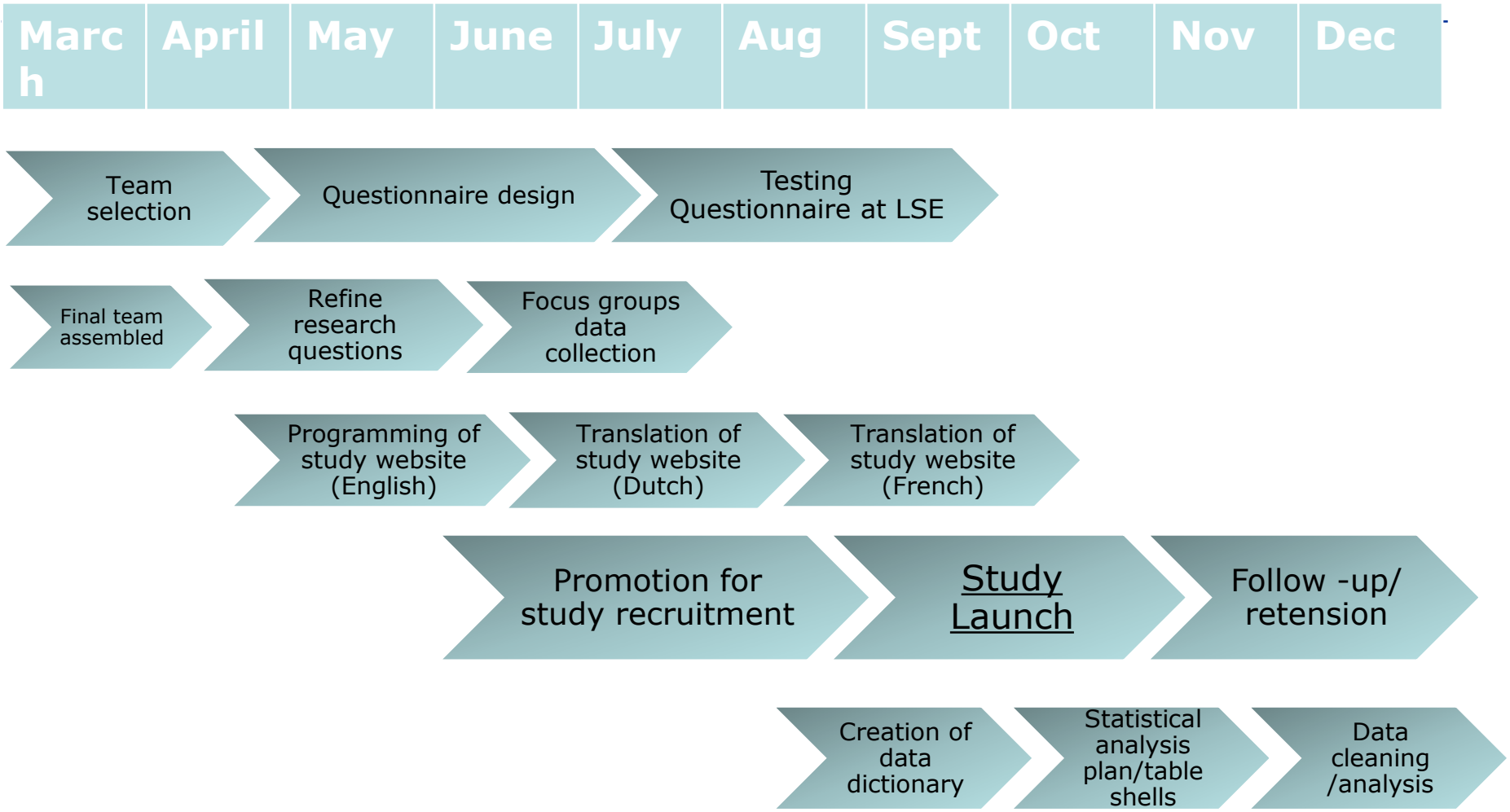
MCDA - MACBETH

Participant Disposition



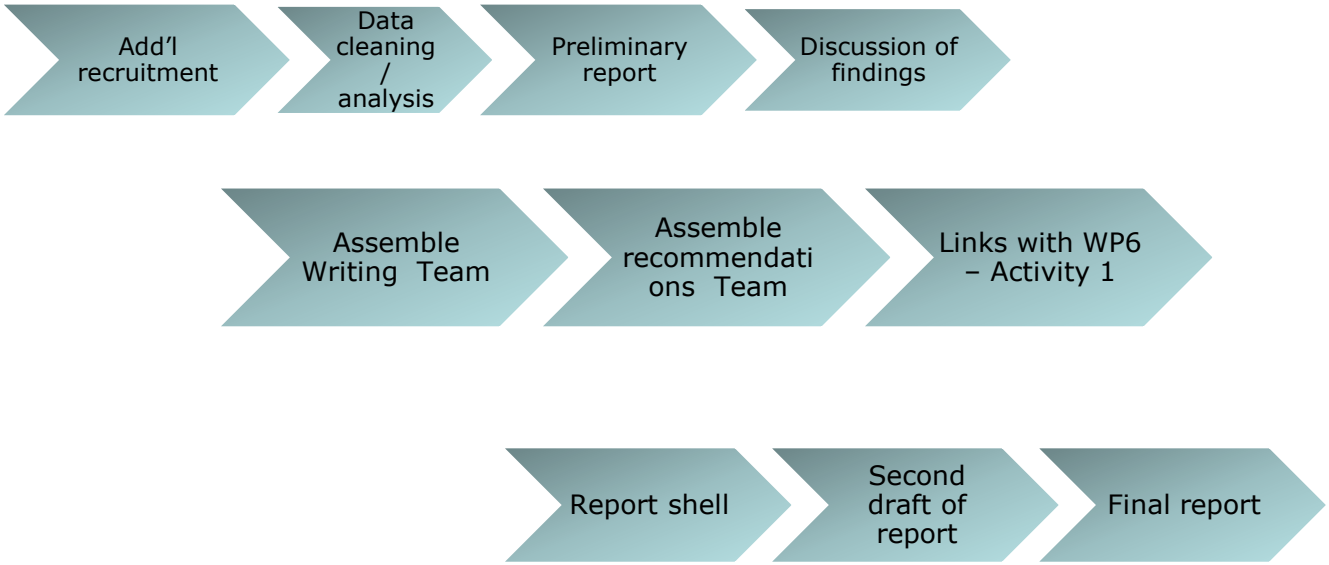
5400 Patients and Healthcare Professionals across 3 countries (plus Regulators)

Timeline/Deliverables 2013



Timeline/Deliverables 2014

Jan	Feb	March	April	May	June	July	Aug



What is needed from the PCWP/HCPWP?

- Participate in meeting to discuss the specifics of the project
- Announce upcoming study on website/seminars
- Identify contact person to liaise with PROTECT team
  - Create/maintain database of member email addresses
  - Provide a helpdesk for general questions after study launch
  - Forward technical questions (anonymously) to the PROTECT team

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Thank You for Your Support!