UPDATE ON PROTECT

(FROM FINAL SYMPOSIUM, 19-20 FEBRUARY)

Xavier Kurz

PROTECT: Goals

EUROPEAN MEDICINES AGENCY

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

PROTECT: Objectives

Data collection

- ✓ efficient and simple methods for early data collection directly from patients
- ✓ non-prescribed medicines
- ✓ linkage to health event databases

Signal detection

- ✓ spontaneous reports: in-depth analysis of methods and good practice recommendations
- ✓ better use of electronic health records and clinical trials

Risk assessment

- ✓ understanding the variability in results of studies of a same safety issue in different data sources, supporting decision-making
- ✓ detailed guidance and standards regarding design, conduct and analysis of pharmacoepidemiological studies for evaluation of safety concerns

Benefit-risk assessment

- ✓ analysis , testing and recommendations of methods for integrating and communicating data on benefits and risks from clinical trials, observational studies and drug reaction reports
- ✓ benefit-risk assessment based on patients and prescribers' perspectives

PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Visualizing Uncertainty among laypersons and experts

PROTECT SYMPOSIUM
20 February 2015

Andrea Beyer Phd

Research questions

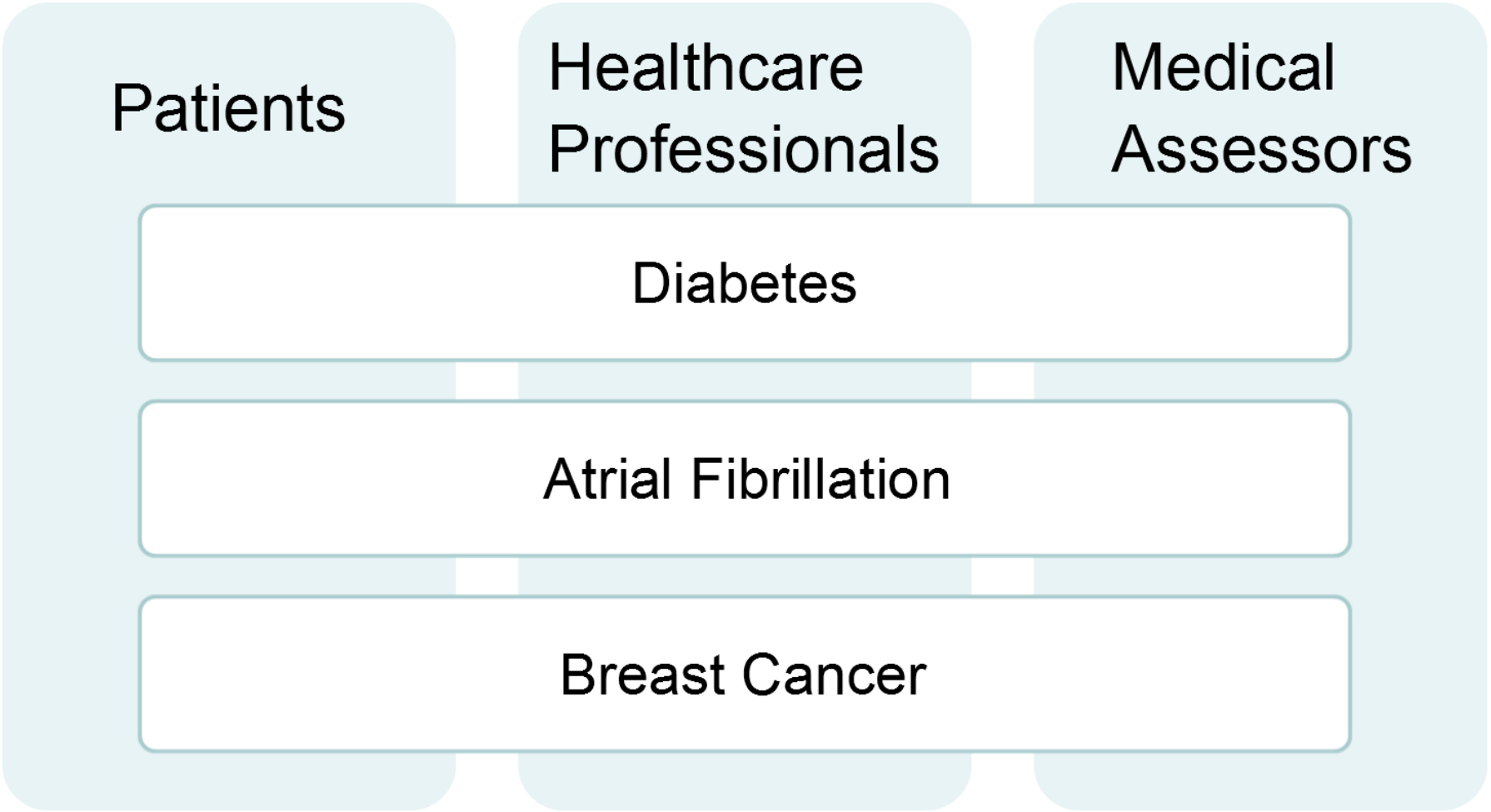
Validation of Methods for Presentation of BR data

- 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 helping patients to understand benefits and risks of medicines?

Extension of Methodology to Elicit Patient Preferences

- Research Questions:
  - How comparable are the methods used in WP5 for eliciting preferences?
  - What are the differences in preferences for treatment outcomes among 3 stakeholders (patients, healthcare professionals, medical assessors)?

Study design – Study Popualtion



Study design – Countries

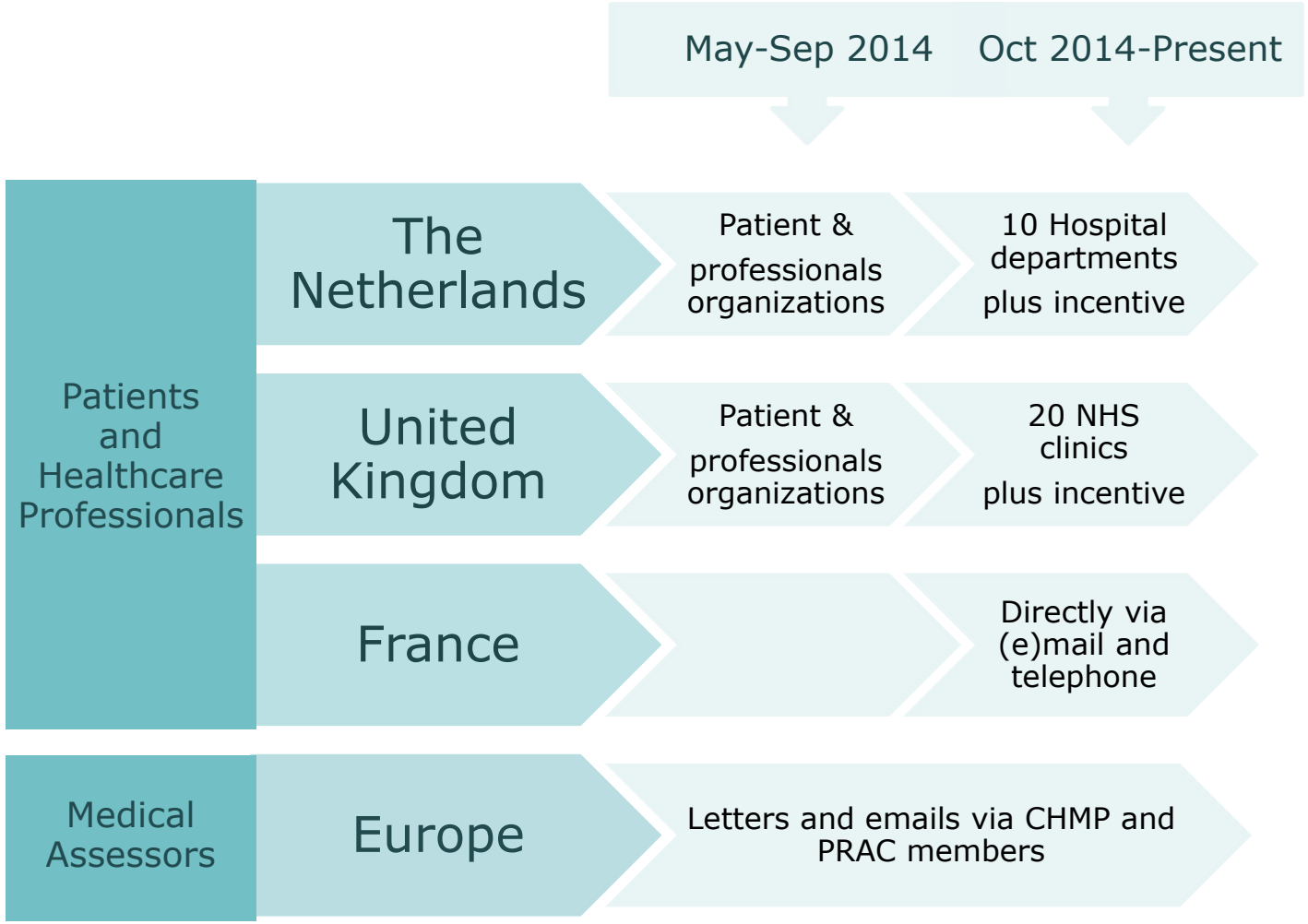
Patients and Healthcare Professionals

- United Kingdom
- The Netherlands
- France

Medical Assessors

- All European countries invited to participate via CHMP and PRAC

Study design - Recruitment methods



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Study design – Focus groups (150 pts per disease area)

Disease Area	Benefits	Risks
Diabetes	Reduction HbA1c levels	Hospitalization for heart failure
	Change in fasting plasma glucose levels	Pancreatitis
		Weight gain
Atrial fibrillation	Reduction ischemic stroke	Fatal bleeding
	Reduction myocardial infarction	Major bleeding
	Reduction pulmonary embolism	Minor bleeding
Breast cancer	Overall survival	Gastrointestinal symptoms
	Progression free survival	Cardiac disorders
		Peripheral neuropathy

Examples of presentation formats

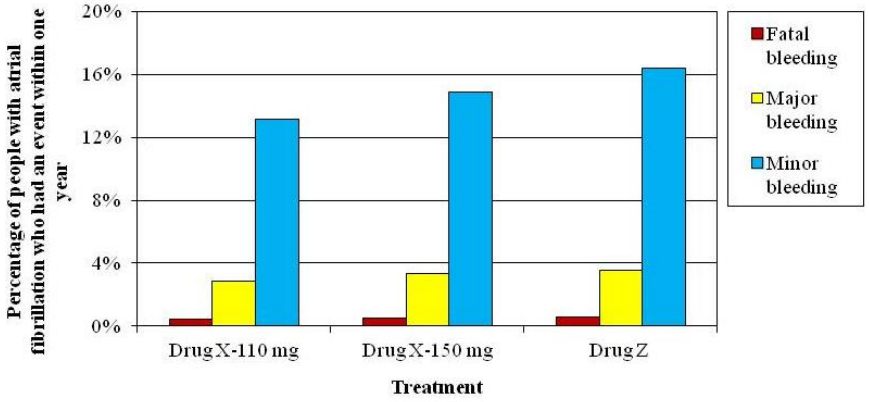
Drug Vignette (similar to EPAR):

A study for the treatment of diabetes showed that HbA1c levels in patients who took Drug X, fell by 0.5% after 2 years, compared with a decrease of 0.2% in patients taking placebo. Furthermore, fasting plasma glucose levels decreased 3.1 mg/dl in the patients who took Drug X, whereas it increased 1.6 mg/dl in the patients taking placebo.

Abbreviated Effects Table

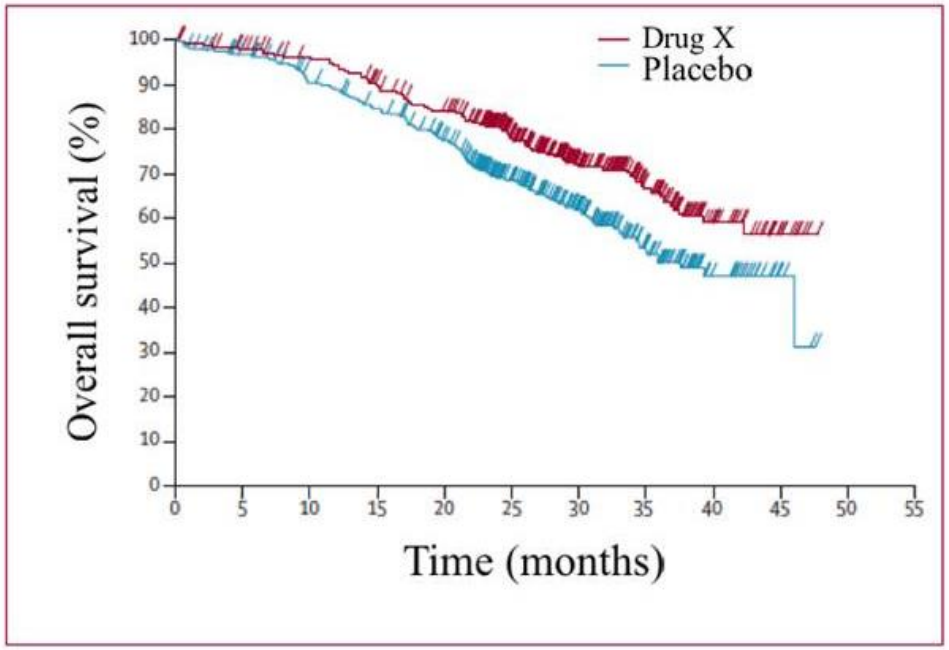
	Description	Drug X	Placebo
Benefits	Reduction in HbA1c levels	0.5%	0.2%
Benefits	Change in fasting plasma glucose levels (mean)	3.1 mg/dl reduction	1.6 mg/dl increase
Risks	Hospitalization for heart failure	3.5%	2.8%
Risks	Pancreatitis	0.3%	0.3%
Risks	Weight gain (mean)	0.6 kg	1.0 kg

Bar graphs

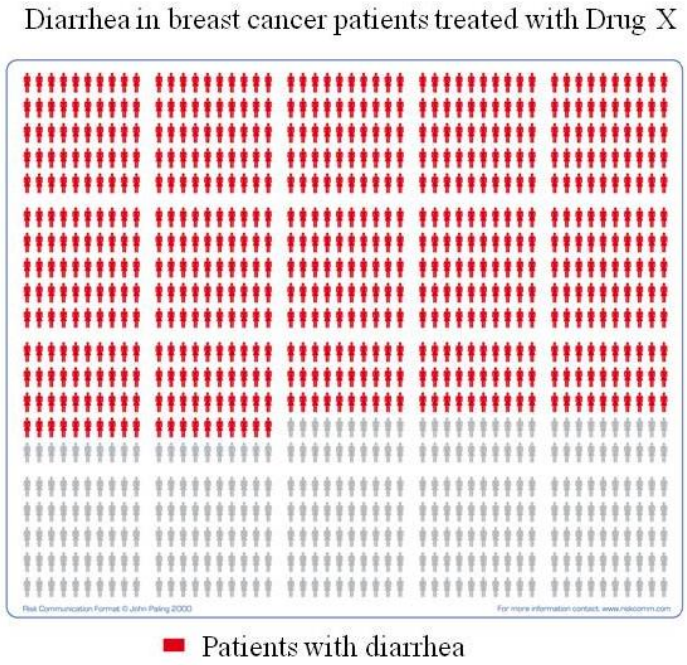


Examples of presentation formats

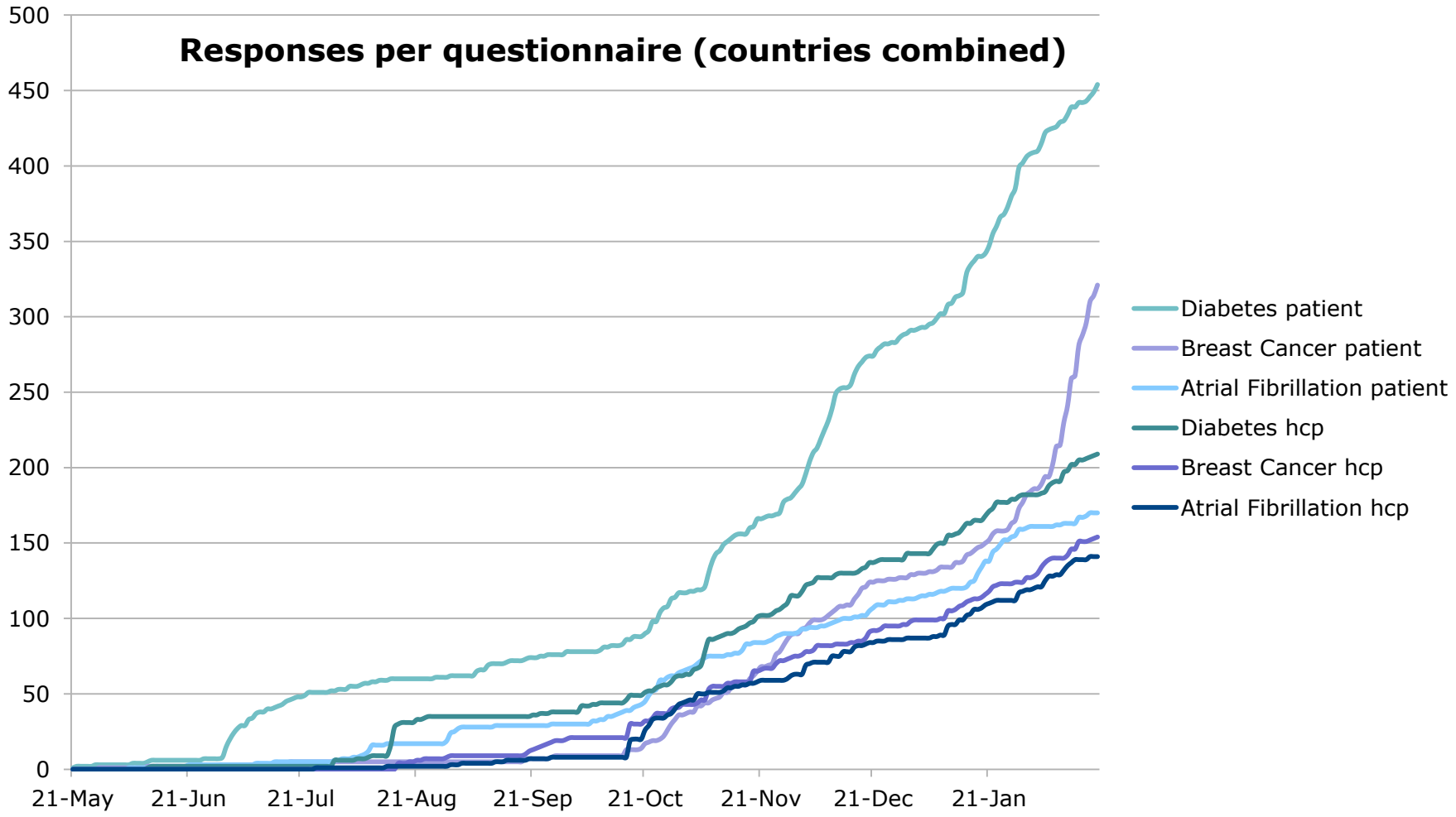
Survival curve



Pictograms



Recruitment efforts – Progress



Preliminary results (cut off Jan 30)

Demographics (countries combined)

	Diabetes	Atrial fibrillation	Breast cancer
	N= 419 Patients	N= 161 Patients	N= 190 Patients
Gender (male)	59%	69%	0%
Age (mean ± sd)	60 ± 12	64 ± 9.9	57 ± 11
Education			
< Associate degree	64%	62%	57%
≥ Associate degree	36%	38%	43%
Numeracy level (mean ± sd)	1.9 ± 1.0	2.1 ± 1.0	1.8 ± 1.1
- 0 questions correct	12%	9%	16%
- 1 question correct	21%	21%	20%
- 2 questions correct	30%	23%	32%
- 3 questions correct	37%	47%	32%

Comprehension – Benefit and Risks (DB)

	Percentage of patients with correct answers			
	0 questions correct	1 question correct	2 questions correct	3 questions correct
Drug vignette – Benefits	3%	6%	48%	43%
Drug vignette – Risks	9%	6%	18%	67%
Table – Benefits	4%	8%	34%	54%
Table – Risks	6%	4%	10%	80%
Bar graph – Benefits	4%	7%	41%	48%
Bar graph – Risks	5%	8%	14%	73%

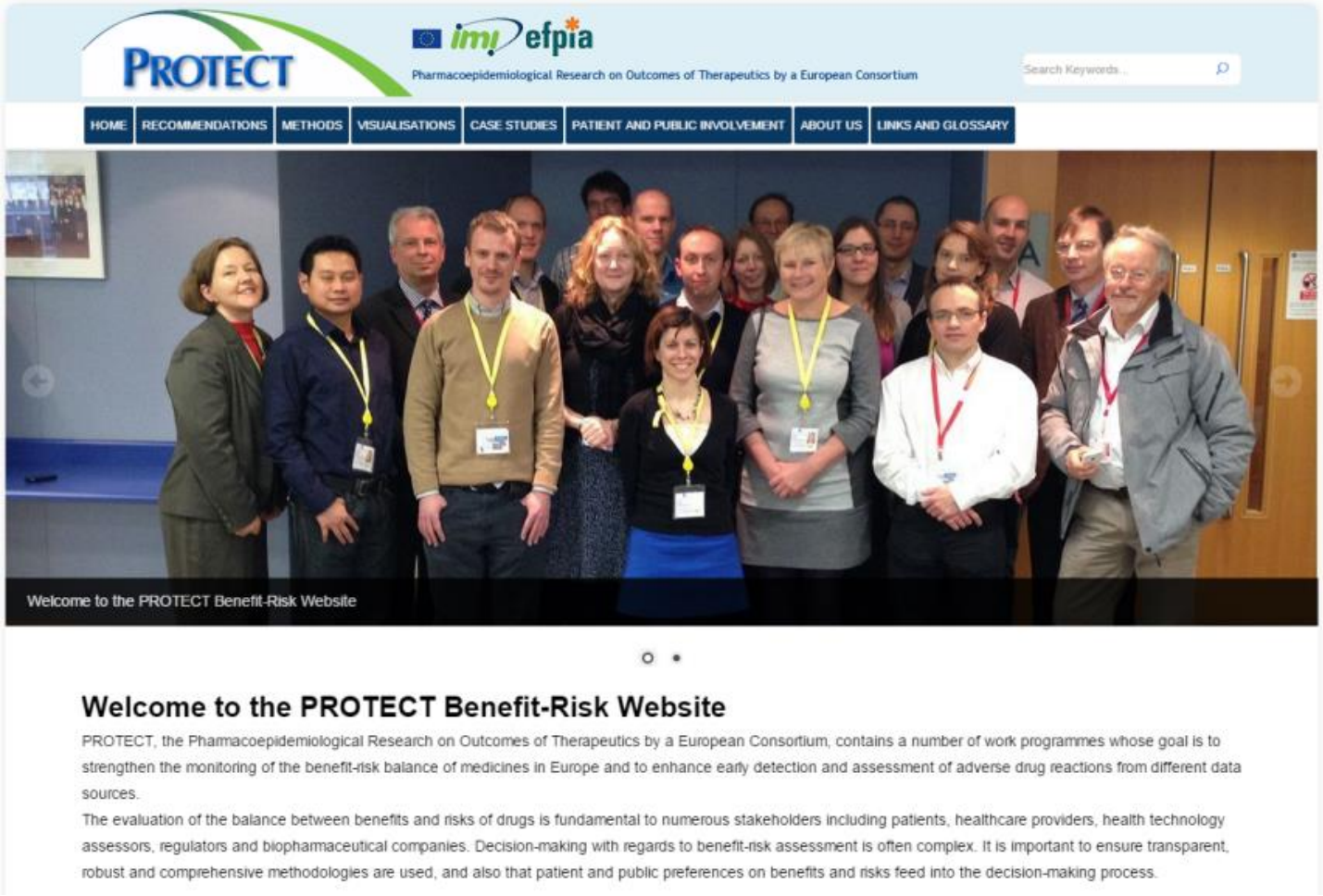
Comprehension – Benefit and Risks (AF)

	Percentage of patients with correct answers			
	0 questions correct	1 question correct	2 questions correct	3 questions correct
Drug vignette – Benefits	7%	10%	18%	65%
Drug vignette – Risks	11%	7%	17%	65%
Table – Benefits	5%	6%	18%	71%
Table – Risks	4%	13%	12%	71%
Bar graph – Benefits	5%	9%	53%	33%
Bar graph – Risks	5%	7%	41%	47%

Comprehension – Benefit and Risks (BC)

	Percentage of patients with correct answers			
	0 questions correct	1 question correct	2 questions correct	3 questions correct
Drug vignette – Benefits	4%	7%	12%	77%
Drug vignette – Risks	5%	4%	15%	76%
Table – Benefits	2%	9%	19%	70%
Table – Risks	2%	4%	12%	82%
Survival curve – Benefits	6%	7%	18%	69%
Pictogram – Risks	4%	7%	24%	65%

Dissemination and recommendations arising from PROTECT



http://PROTECTBenefitRisk.eu/

PROTECT

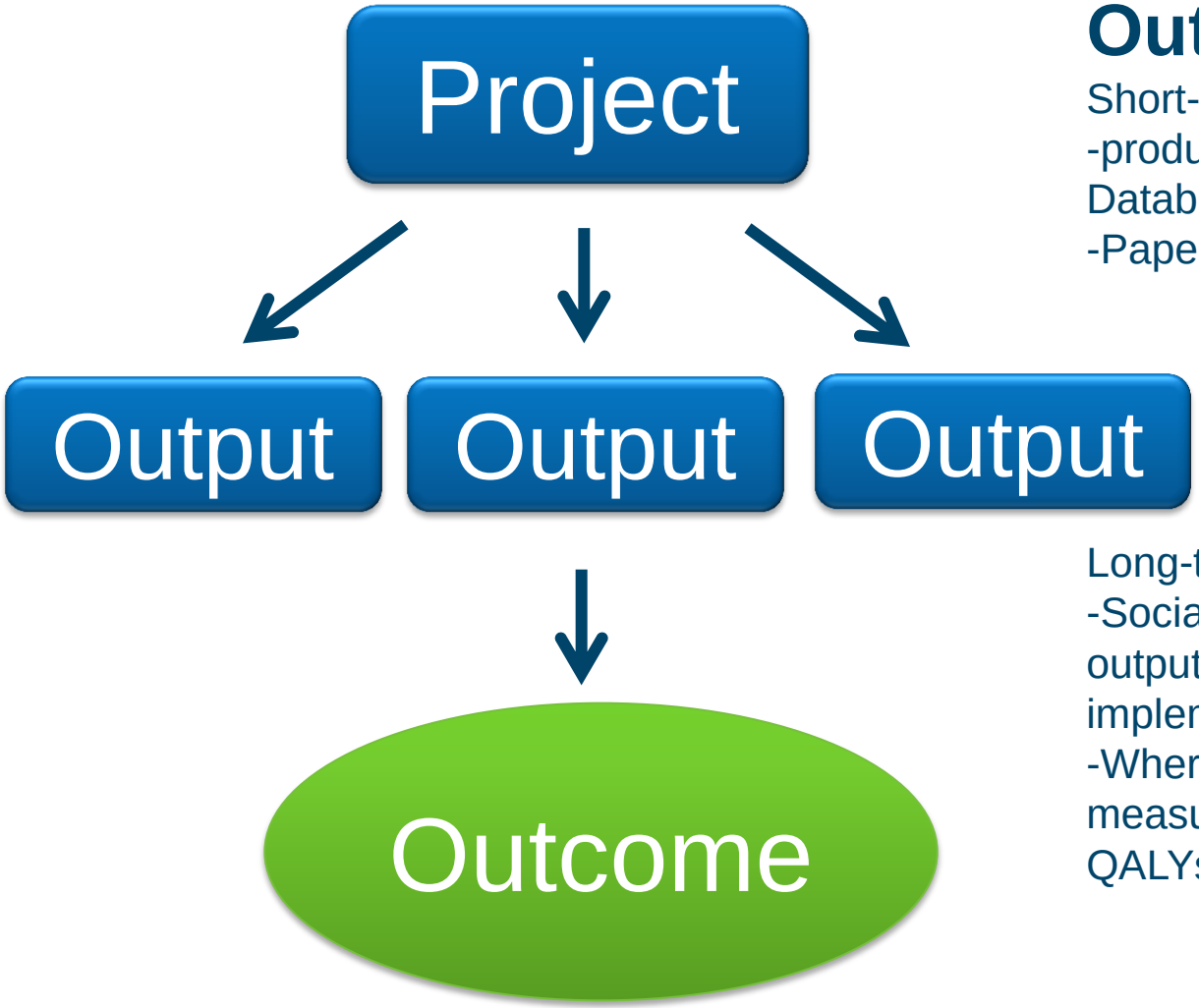
Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Contribution from PROTECT to regulatory practice: from science to process improvement

PCWP/HCPWP joint meeting
4 March 2015

Xavier Kurz

Translation of outputs into outcome



Output =

Short-term result
-product, service, knowledge, e.g. Database, software, biomarker...)
-Paper, patent, ...

Outcome =

Long-term result/impact
-Social and economical impact of an output after (successful) implementation
-Where possible quantitative measurement (e.g. costs saved, QALYs gained, times shortened,...)

Source: Angela Wittelsberger. ADVANCE 3rd General Assembly meeting, 18-19 September 2014

ULTIMATE JUDGE OF SUCCESS IS WHETHER THE EXCELLENT RESEARCH RESULTS (OUTPUTS) ARE CONVERTED INTO OUTCOMES FOR INNOVATION AND PUBLIC HEALTH

PROTECT Impact assessment Objectives

1. To develop a conceptual framework for the review of the potential impact of outputs of regulatory science projects and the prioritisation of their implementation into regulatory practice

Using the PROTECT project as an example:

2. To test this conceptual framework to the outputs of PROTECT.
3. To make recommendations to EMA and its committees for an appropriate action on PROTECT results.

Scope: Regulatory science

EMA definition: Range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that **inform regulatory decision-making throughout the lifecycle of a medicine**. It encompasses basic and applied medicinal science and social sciences, and contributes to the **development of regulatory standards and tools**.

European Medicines Agency process for engaging in external regulatory sciences and process improvement research activities for public and animal health EMA/14946/2013.
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/03/WC500139888.pdf

FDA definition: Science of developing **new tools, standards, and approaches** to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

Advancing Regulatory Science. -Moving Regulatory Science into the 21st Century.
http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm?utm_campaign=Goo

Questions to be addressed

- When are results matured enough to form a basis to implement changes in regulatory or clinical practice?
- To what extent should results/recommendations from regulatory science projects be systematically validated, scrutinised and peer reviewed in the scientific community before their implementation?
- Should there be a trade-off between timing of implementation and scientific replication/validation?
- Which outputs should be prioritised for implementation?

Proposed criteria

Domain	Indicator	Description
Description	Process	Changes in process to be reflected in guidelines or procedures
	Behaviour	Impact on behaviour of individuals or targeted entities
	Outcome	Positive or negative impact reflected in actions
Evaluation	Impact of change	Evaluation of the level of benefits brought by the change in each dimension
	Maturity	Need for further development or verification before use
	Feasibility	
	- Resources	Amount of resources needed for implementation
	- Acceptability	Acceptability by stakeholders
	- Compliance	Alignment with the legislation
	Timing of implementation	Timing with which the deliverable can be implemented

Scoring

- Semi-quantitative: zero, low, medium, high
- Weighting possible according to stakeholders' perspective
- Criteria divided in two categories:

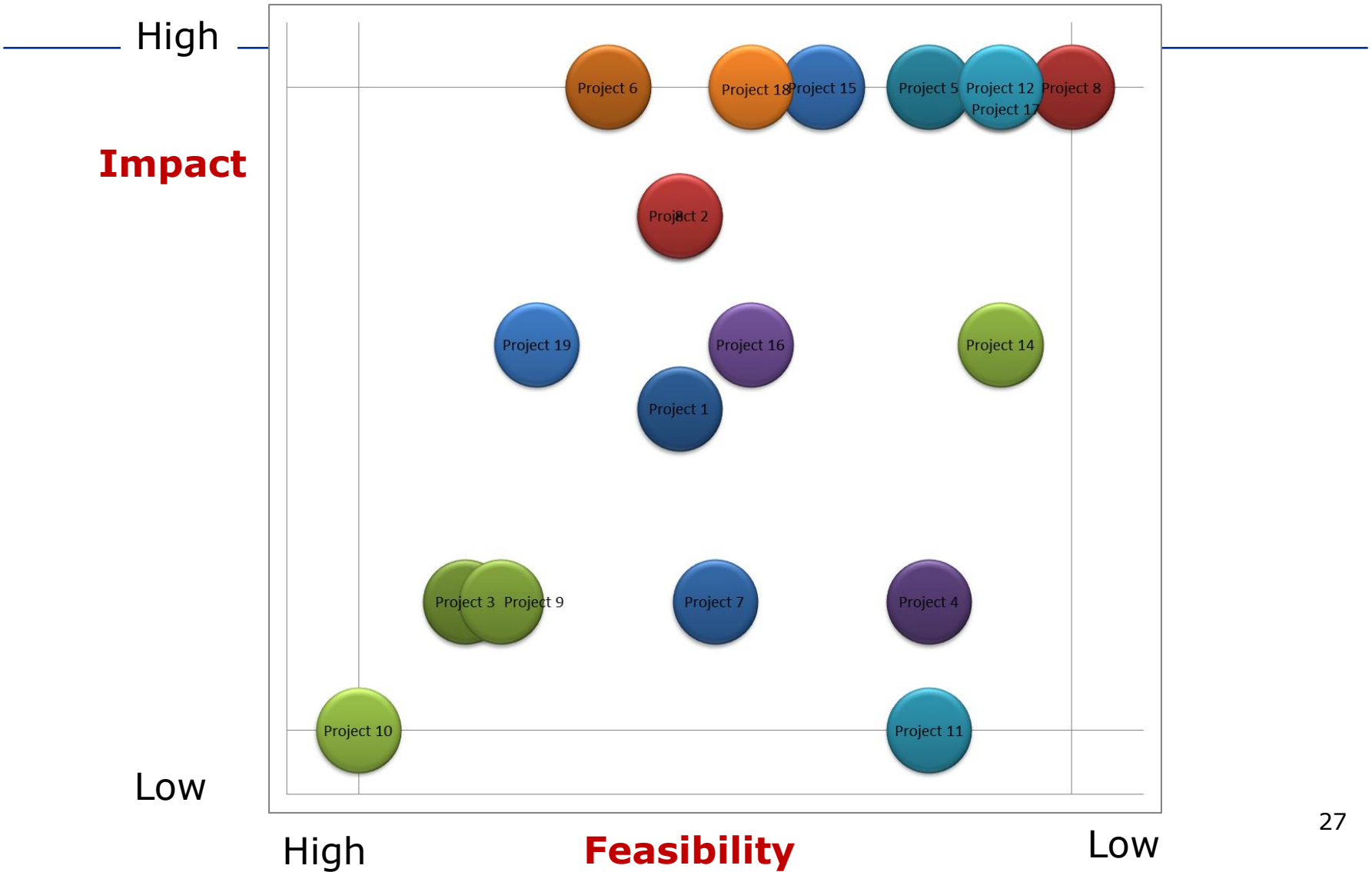
Feasibility category

- Impact of the implementation of the output in terms of resources (human, financial, infrastructure, IT or other resource needed)
- Acceptability by concerned stakeholders
- Compliance with the existing applicable legislation
- Evaluation of the timing for implementation (e.g. <6 m., 1 y., 2 y, >2 y.)

Impact category

- Evaluation of the level of benefit brought by the change in each indicator
- Deliverable maturity (inadequate, incomplete, nearly complete, complete)

Visual representation



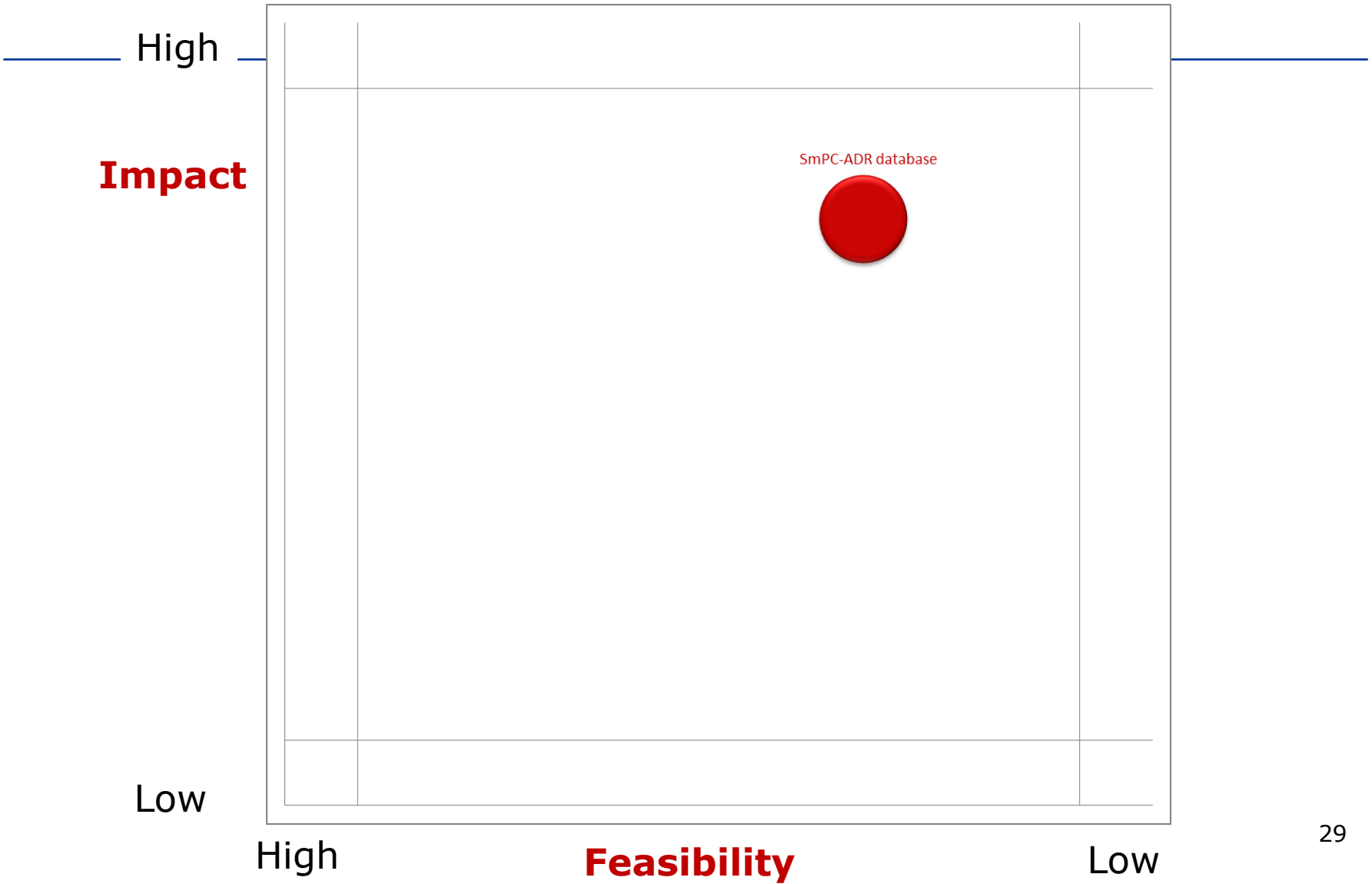
Example

PROTECT ADR database: Impact assessment

Indicators	
Intended target - Process - Behaviour - Outcome	 ++ - +++
Impact of change	+++
Maturity	++
Feasibility - impact on resources - acceptability - alignment with legislation	 + +++ +++
Timing	++

Last update: 30 June 2013

SmPC-ADR database



Planned PROTECT Deliverables

All planned deliverables:	101
"Final" deliverables:	42

WP2. Improving consistency between pharmacoepidemiological studies	7
WP3. Methods for signal detection	16
WP4. Direct-to-Patient Pharmacovigilance	7
WP5. Benefit-risk integration and representation	8
WP6. Replication studies	3
WP7. Training & Communication	1

Several outputs (reports, publications, databases, …) for each deliverable

Next steps

1. Confirm evaluation criteria and scoring options
2. Confirm relative weightings
3. Identify which outputs are to be assessed as part of the prioritisation exercise.
4. Select documentation for each output (e.g. published article, executive summary)
5. Evaluate outputs against scoring matrix
6. Prioritise implementation of outputs


Thank You
Mahalo
Kiitos
Tack
Toda
Grazie
Obrigado
Thanks
Takk
Merci
Gracias