EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SYMPOSIUM

PROTECT: The Challenges and Successes

What difference will PROTECT make to regulatory practice?

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ICPE, 2015

Disclaimer

The views expressed in this presentation are my own views and may not be understood or quoted as being made on behalf of the European Medicines Agency or one of its Committees or working parties.

I have no conflicts of interest to declare.

In this presentation

- Best evidence in the context of regulatory decision-making
- PROTECT: some successes
- PROTECT: challenges
  - Impact of PROTECT on research
  - Impact of PROTECT on regulatory practice
- Conclusions

Best evidence in context

- EMA seeks to optimise the benefit/risk profile of medicines
- This involves many complementary initiatives to support knowledge management and decisions on benefit/risk
- Bottom line is ensuring we are effective in doing this and we are doing it as efficiently as possible

Best evidence in context

- The EU network manages or has direct or indirect access to potentially highly relevant data, information or knowledge e.g.:
  - Safety data from clinical trials (SUSARs in EudraVigilance)
  - Suspected adverse reaction reports from marketed use (EudraVigilance data)
  - Published literature
  - Electronic healthcare records (e.g. THIN, IMS, BIFAP, CPRD)
  - Access to networks that have data, and methodological expertise e.g. the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
  - Patient registries
  - Research projects

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PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by an European ConsorTium

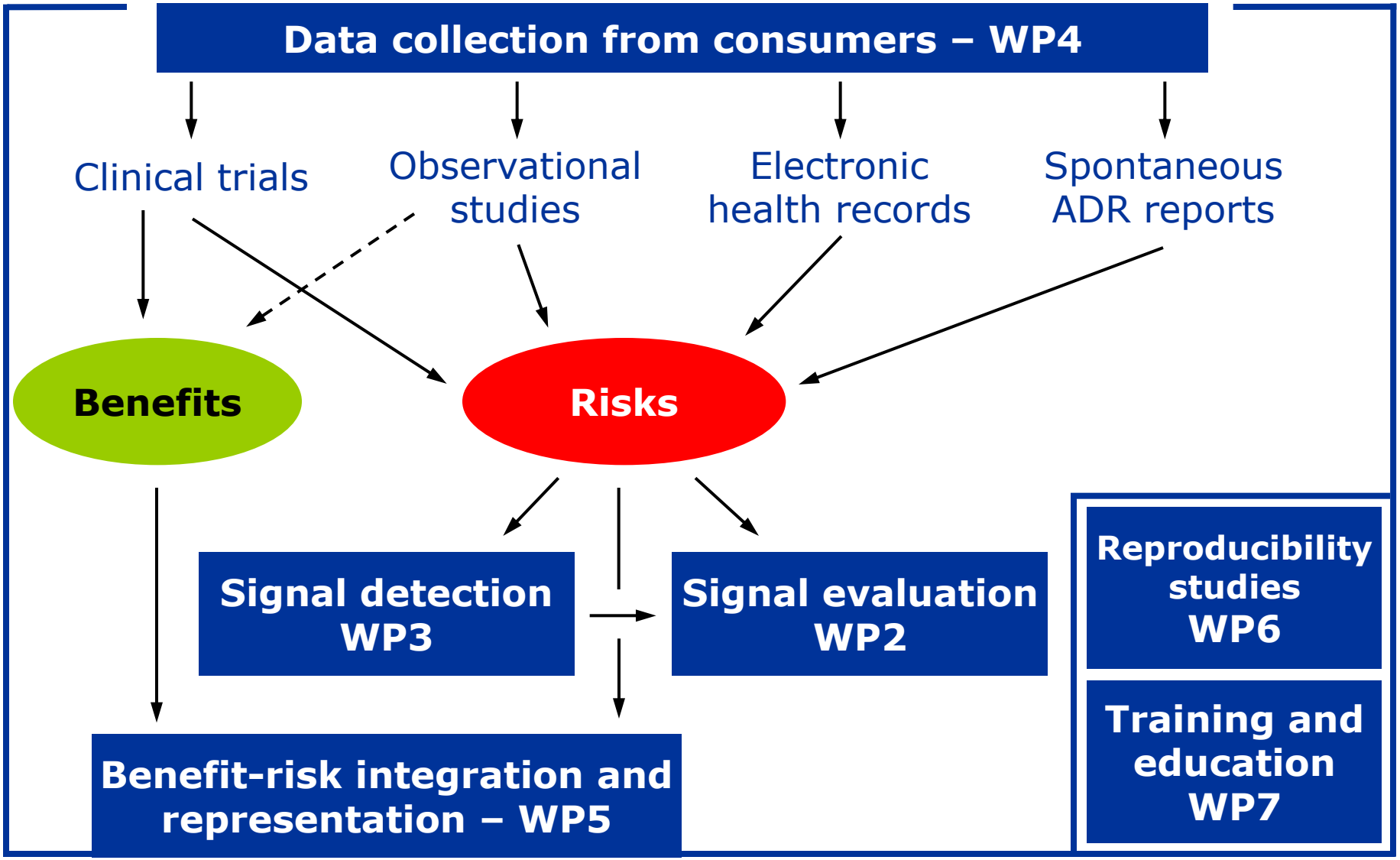
To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

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

Started 1st September 2009, finished 30 June 2015

PROTECT work programme



PROTECT: Successes

www.imi-protect.eu

By June 2015, 52 publications and many others in preparation

Benefit-risk integration and representation

www.PROTECTBenefitRisk.eu

PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Home | Contact Us | Search

PROJECT
About PROTECT
Objectives
Governance structure
Partners
Work programme

News

Results

PROTECT Symposium NEW

General Presentations

eRoom - partners only

Links
General Links
Collaborations
Training Opportunities
Pregnancy Study
Adverse Drug Reactions Database NEW
Drug Consumption Databases in Europe NEW
PROTECT Benefit-Risk Website NEW

Adverse Drug Reactions Database

The **PROTECT ADR database** is a downloadable Excel file listing of all MedDRA PT or LLT adverse drug reactions (ADRs). It is a structured Excel database of all adverse drug reactions (ADRs) listed in section 4.8 of the Summary of Product Characteristics (SPC) of medicinal products authorised in the EU according to the centralised procedure. It is based exclusively on MedDRA terminology. In principle, MedDRA Preferred Terms (PT) are used to map terms of the SPC. When they are used in the SPC to add precision in the description of the ADR, Low Level Terms (LLTs) are also coded. PTs and LLTs are linked to a primary System Organ Class (SOC). The database also includes information on gender, causality, frequency, class warning and source of information for ADRs for which additional information is provided in the SPC. Fields are described in the file Database structure.

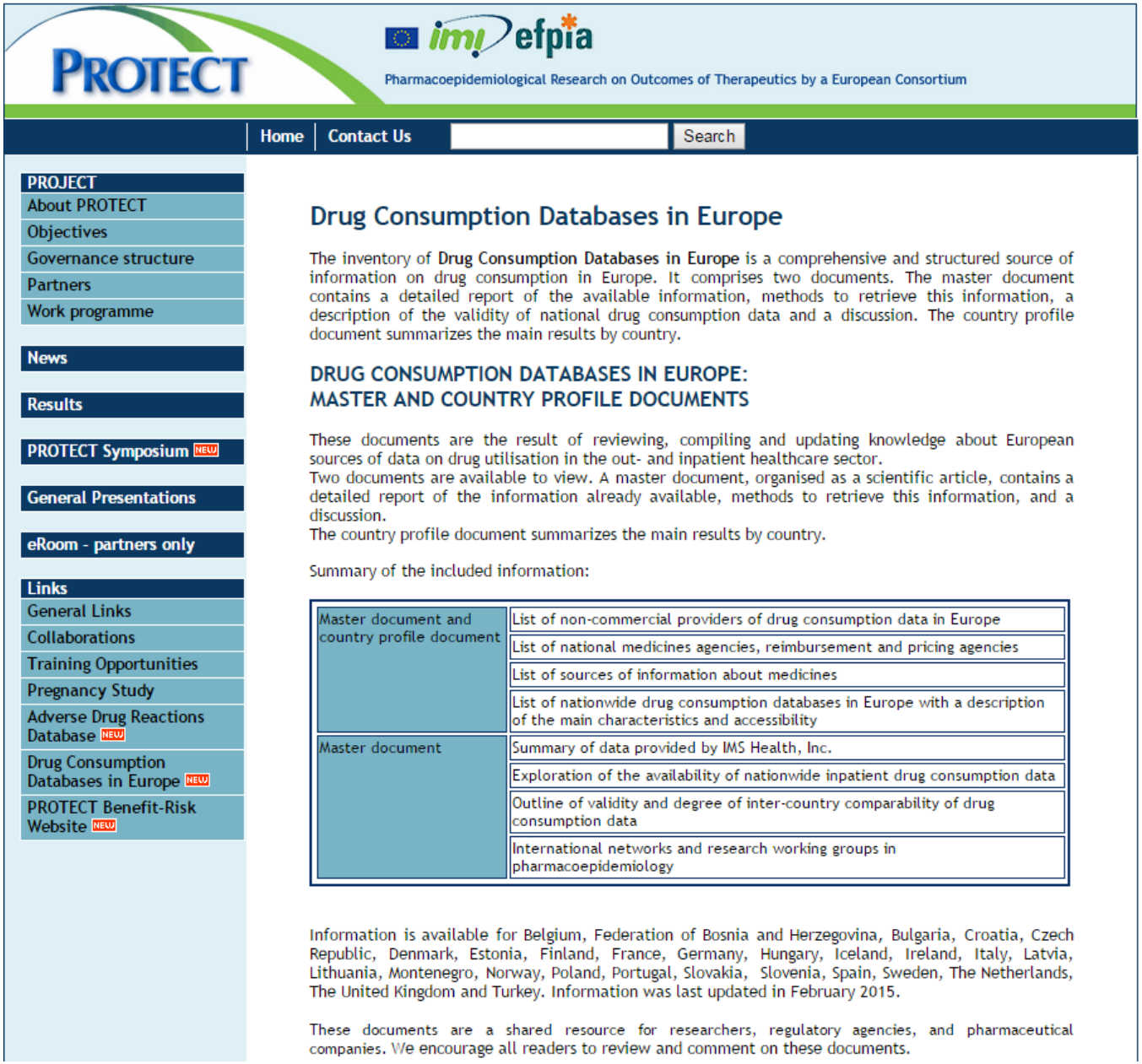
The current database has been updated up to 30 June 2013 based on latest available SPC which can be found on the European Commission website. The database includes for each product the date of the SPC which has been used to list ADRs.

The database has been created by EMA and partners in PROTECT Work Package 3 through a stepwise approach using automated mapping of ADR terms listed in section 4.8 of the SPC to the MedDRA terminology, fuzzy text matching (Bergvall et al. Pharmacoepidemiol Drug Saf. 2011;20(S1), S143) and expert review.
It is aimed to routinely update the database at least once a year based on amended SPCs. It can also be amended between routine updates to correct data entries.

Objectives

A time-consuming step in signal detection of adverse reactions is the determination of whether an effect is already recorded in the European Summary of Product Characteristics (SPC). Thus there is a need for a structured database which can be searched for this information. Such a database also allows filtering or flagging reaction monitoring reports for signals related to unlisted reactions only, thus improving considerably the efficiency of the signal detection process.

A data set of established ADRs also allows a comparison to coincidental or unidentified drug-adverse event combinations only, an adjustment of statistical signals for known ADRs, and an evaluation of the effect of background restriction on the performance of statistical signal detection.
The objective of the ADR database is not to provide a continuously updated list of ADRs to centrally-authorised products.



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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Home | Contact Us | Search

PROJECT
About PROTECT
Objectives
Governance structure
Partners
Work programme

News

Results

PROTECT Symposium NEW

General Presentations

eRoom - partners only

Links
General Links
Collaborations
Training Opportunities
Pregnancy Study
Adverse Drug Reactions Database NEW
Drug Consumption Databases in Europe NEW
PROTECT Benefit-Risk Website NEW

Drug Consumption Databases in Europe

The inventory of **Drug Consumption Databases in Europe** is a comprehensive and structured source of information on drug consumption in Europe. It comprises two documents. The master document contains a detailed report of the available information, methods to retrieve this information, a description of the validity of national drug consumption data and a discussion. The country profile document summarizes the main results by country.

DRUG CONSUMPTION DATABASES IN EUROPE: MASTER AND COUNTRY PROFILE DOCUMENTS

These documents are the result of reviewing, compiling and updating knowledge about European sources of data on drug utilisation in the out- and inpatient healthcare sector.
Two documents are available to view. A master document, organised as a scientific article, contains a detailed report of the information already available, methods to retrieve this information, and a discussion.
The country profile document summarizes the main results by country.

Summary of the included information:

Master document and country profile document	List of non-commercial providers of drug consumption data in Europe
	List of national medicines agencies, reimbursement and pricing agencies
	List of sources of information about medicines
	List of nationwide drug consumption databases in Europe with a description of the main characteristics and accessibility
Master document	Summary of data provided by IMS Health, Inc.
	Exploration of the availability of nationwide inpatient drug consumption data
	Outline of validity and degree of inter-country comparability of drug consumption data
	International networks and research working groups in pharmacoepidemiology

Information is available for Belgium, Federation of Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Montenegro, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, The Netherlands, The United Kingdom and Turkey. Information was last updated in February 2015.

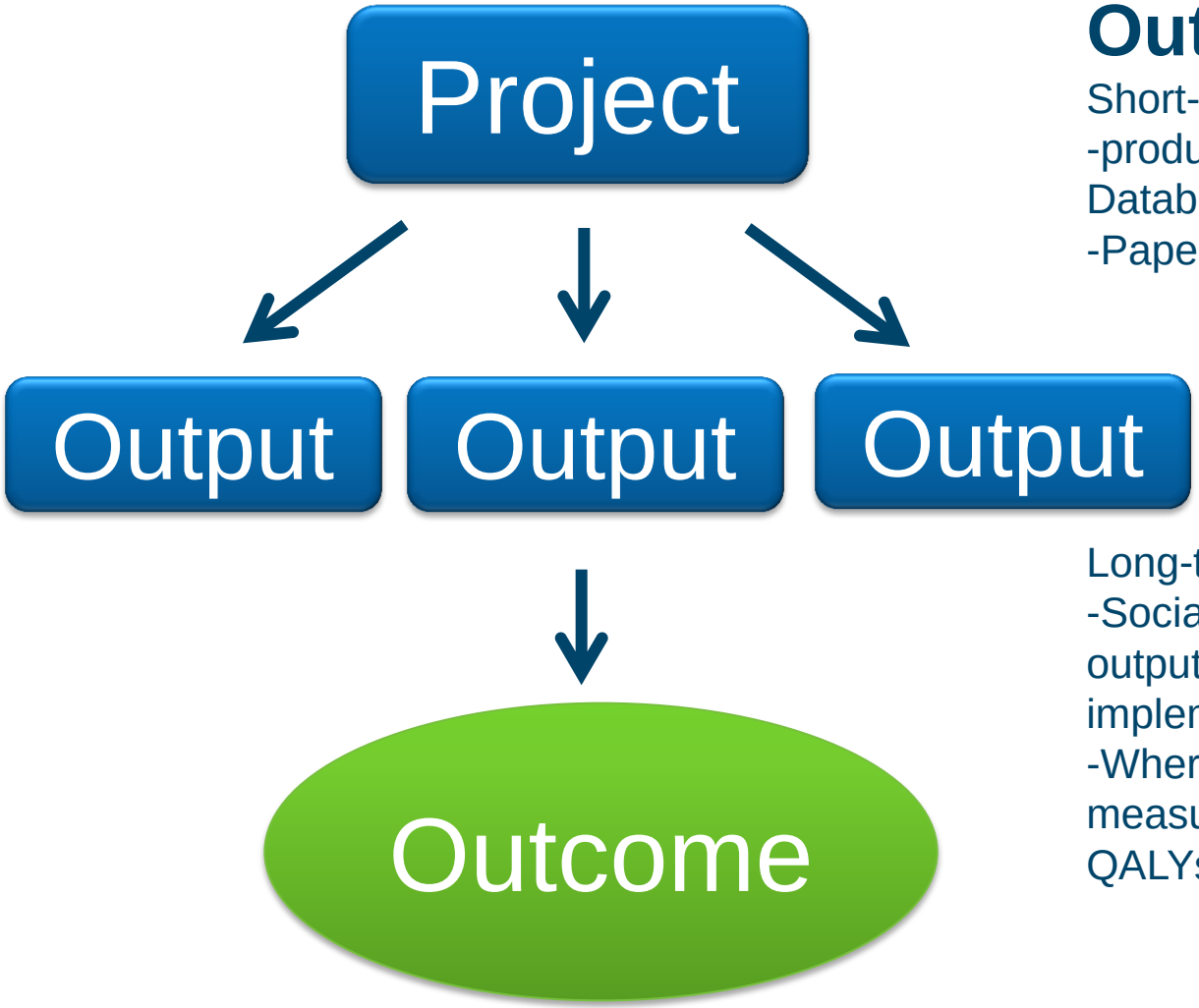
These documents are a shared resource for researchers, regulatory agencies, and pharmaceutical companies. We encourage all readers to review and comment on these documents.

GOOD JOB – WORKED WELL!

BUT…

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

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

PROTECT: Challenges

What will be the impact of PROTECT?

Potential impact on research

- IMI1 7th Call (2012) **Incorporating real-life clinical data into drug development (GetReal)**
  This work will draw on the experience gained in the IMI PROTECT project. The PROTECT project will deliver a standardized approach to the analyses of risk of events, in order to increase the consistency of observational studies of drug effects.
- IMI1 7th Call (2012) **Developing a framework for rapid assessment of vaccination benefits and risks in Europe (ADVANCE)**
  ADVANCE activities will capitalize on the benefit-risk appraisal, integration and representation for drugs as performed in the PROTECT project.

  Benefit-risk monitoring: In WP5 of the PROTECT project, benefit-risk methodologies for drugs have been appraised and tested - this knowledge will be utilized in ADVANCE and extended to the vaccine area.

Potential impact on research

- IMI1 9th Call (2013) **WEBAE – Leveraging emerging technology for pharmacovigilance**
  Relevant projects: WP4 of the PROTECT project is relevant to the proposed Call Topic.

- IMI2 5th Call (July 2015) - **Patient perspective elicitation on benefits and risks of medicinal products, from development through the entire life cycle, to inform the decision-making process by regulators and health technology assessment bodies**

  In particular the activities of this action would strongly build on the project started by IMI PROTECT WP5 (Benefit-risk integration and representation)/ WP6 (Replication studies) that finished in Q1 2015. http://www.imi-protect.eu/index.shtml).

Potential impact on regulatory practice

- When are results matured enough to form a basis to implement changes in regulatory or clinical practice?
- To what extent should results/recommendations 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?
- Are results acceptable to potential users? Will they actually use them?

→ Conceptual framework for impact and feasibility assessment

→ Survey and test of this framework with PROTECT outputs

Objectives of survey: To develop and test on the PROTECT results a conceptual framework for the review of the potential impact and feasibility of outputs of regulatory science projects and the prioritisation of their implementation into regulatory practice

- On 28 May 2015, survey of 264 participants of the Final PROTECT Symposium (18-20 February 2015)
- Two EMA panels convened on signal detection and pharmacoepidemiology

- Questionnaire developed to assess **potential impact and feasibility** of the implementation of the selected recommendations and outputs
- Links to reference documents, publications or presentations provided on each selected output.
- Survey participants asked to evaluate at least three outputs based on their expertise

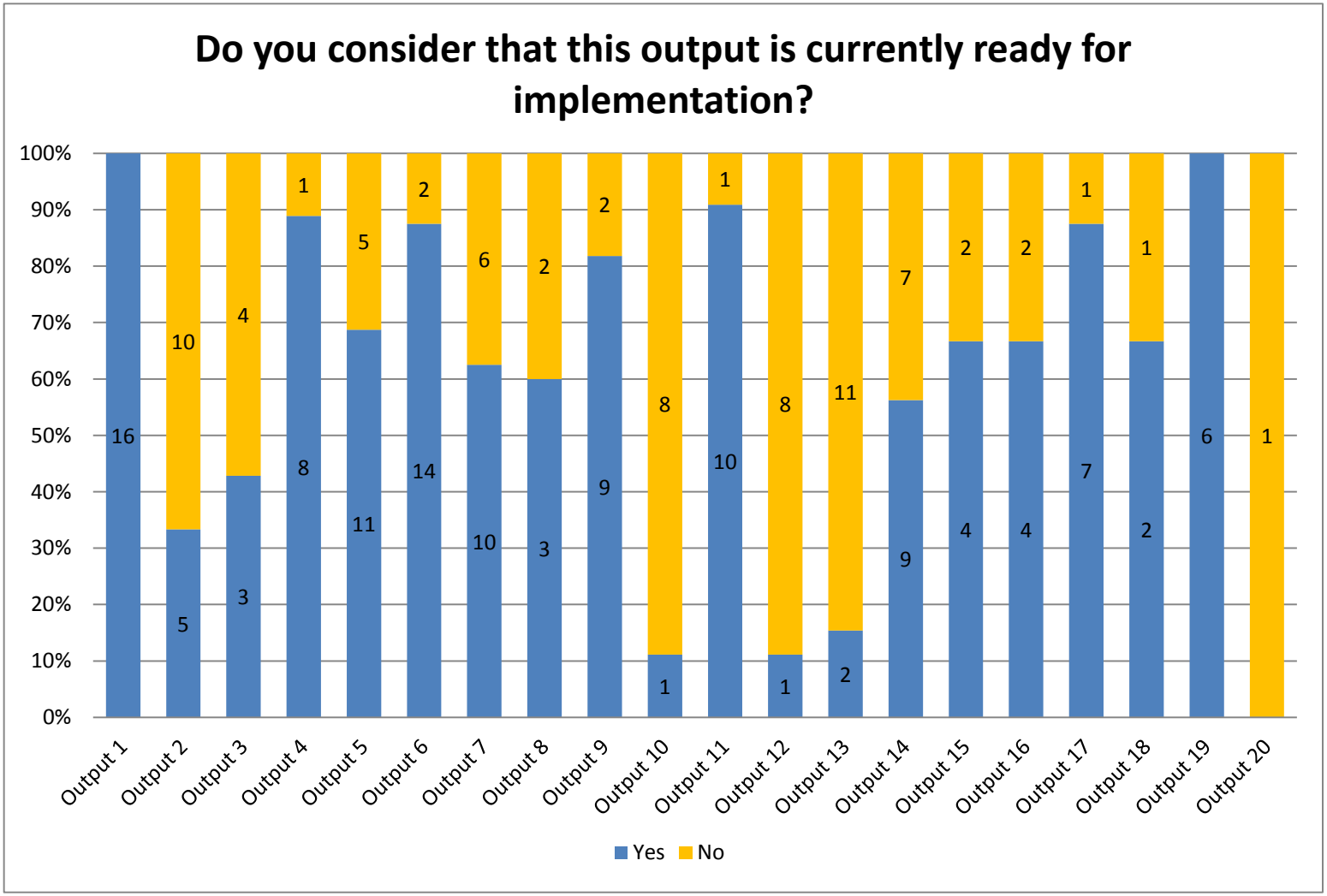
- Survey: 133 evaluations received from 40 participants
- EMA Panel: 97 evaluations received from 14 participants

Criteria for output evaluation

Scoring of outputs	
Dimension: Impact	
Potential impact on public health	None/small/moderate/ important
Acceptability by stakeholder's group	Small/moderate/important
Dimension: Feasibility	
Degree of scientific development	Inadequate/incomplete/ nearly complete/complete
Delay needed for implementation	>2y./1-2 y./<1 y.
Impact of implementation on IT	Small/moderate/important
Impact of implementation on human resources	Small/moderate/important

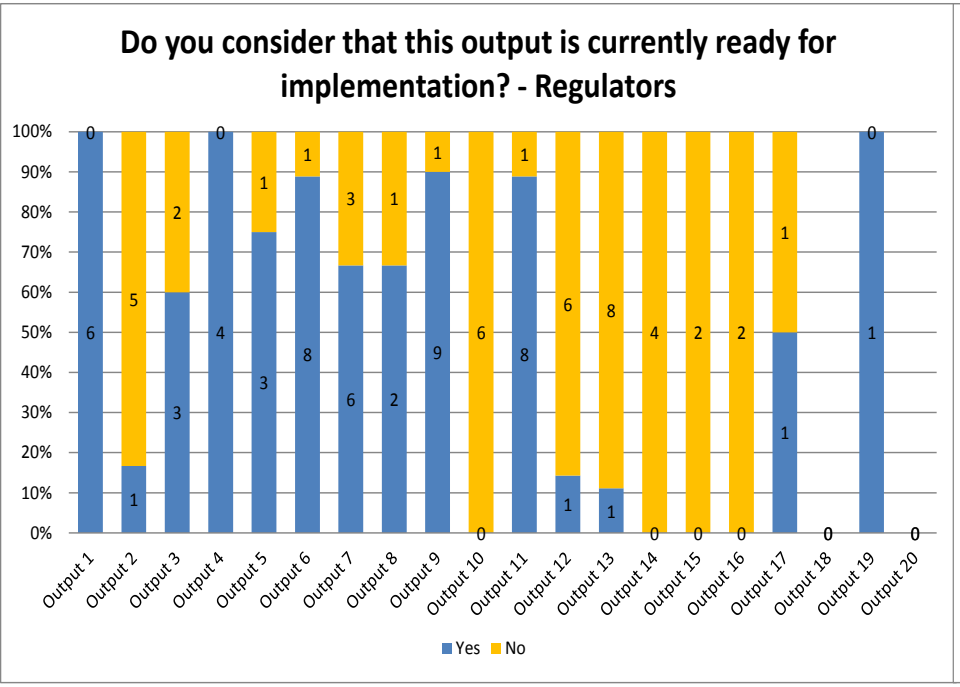
Final PROTECT outputs selected for evaluation

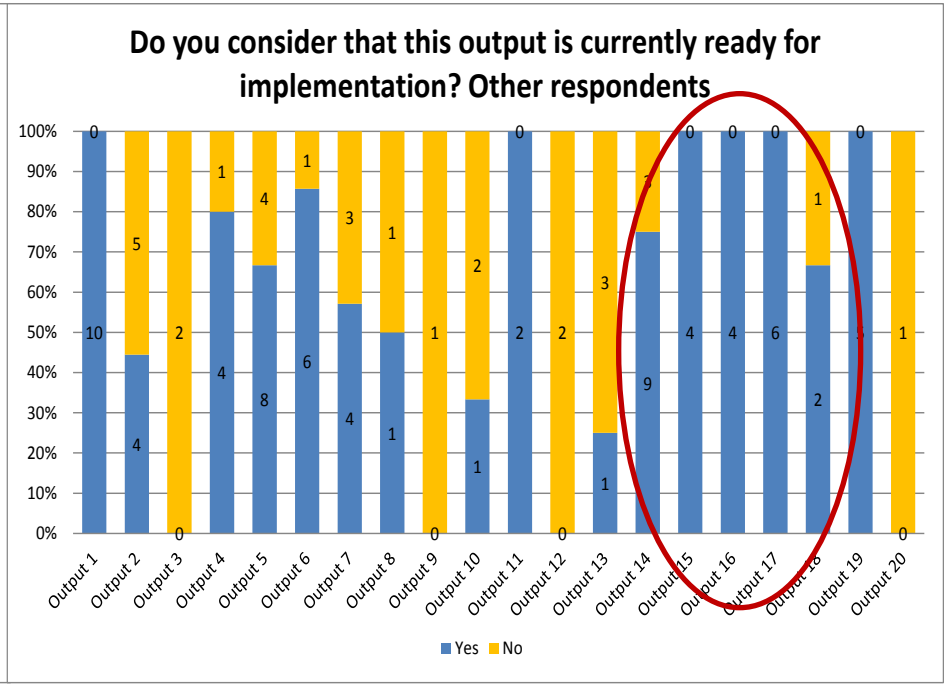
Selection of 20 outputs among 101 PROTECT deliverables	
Recommendations for pharmacoepidemiology	
Output 1	Inventory on drug utilisation data
Output 2	Comparison of methods to control for confounding
Output 3	Balance measures for propensity score models
Output 4	Comparison of covariate adjustment methods
Output 5	Recommendations for pharmacoepidemiological
Methods for signal detection	
Output 6	Evaluation of disproportionality analysis
Output 7	Adverse Drug Reaction Repository
Output 8	Lessons learnt from a characterisation of databases used for signal detection
Output 9	Grouping of existing adverse drug reaction terminologies
Output 10	Novel groupings for adverse drug reactions
Output 11	Subgrouping and stratification in statistical signal detection
Output 12	Statistical signal detection from clinical trials
Output 13	Statistical signal detection from electronic health records
Benefit risk integration and representation	
Output 14	Methodologies for benefit-risk evaluation
Output 15	Methodologies for graphical representation
Output 16	Final tools for graphical B:R representation
Output 17	Recommendations on methodologies for B-R integration and representation
Output 18	Development of accessible material to patients
Output 19	Repository of training material
Output 20	Enhanced ADDIS software

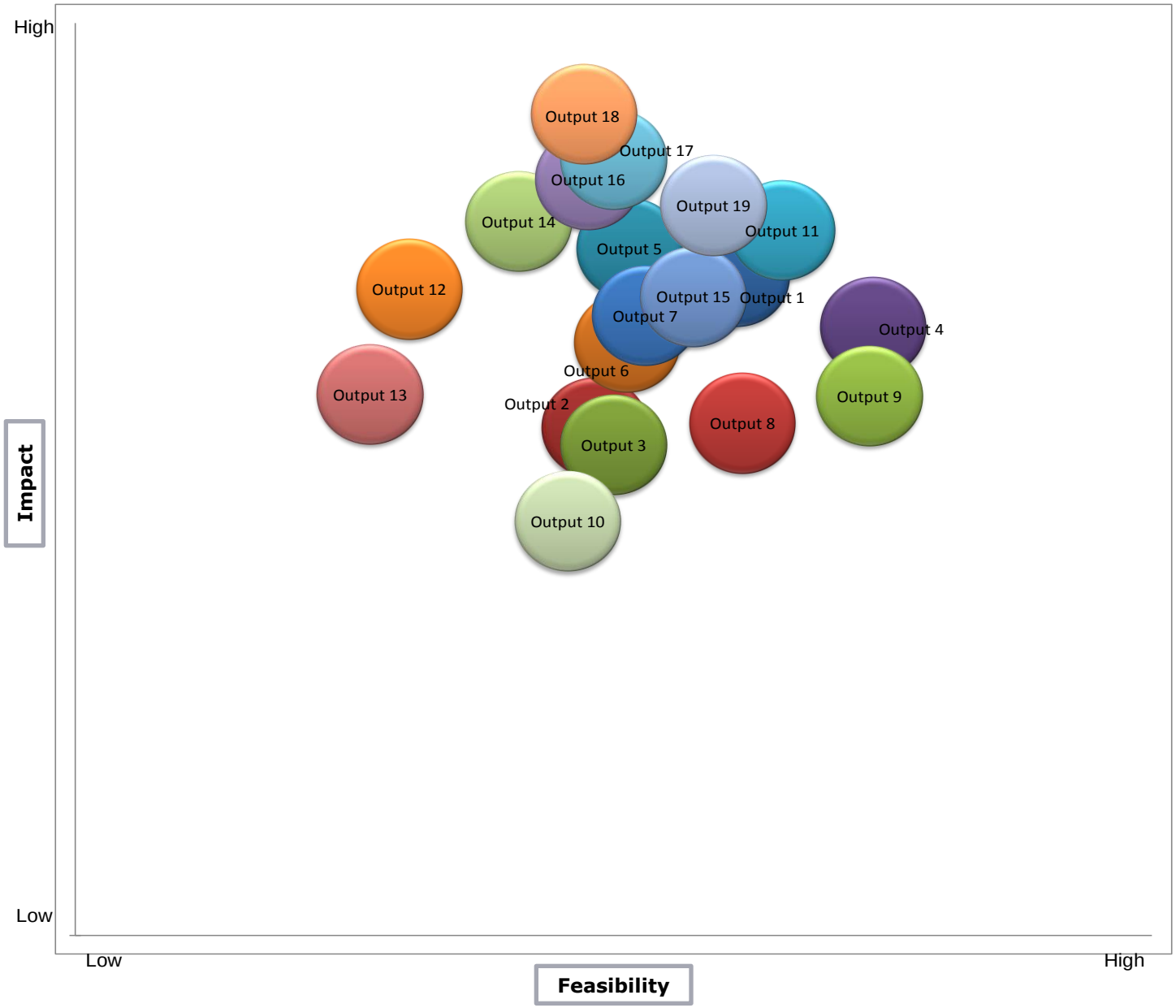


Outputs 1 (**Inventory of drug utilisation data**), 4 (**Comparison of covariate adjustment methods**), 6 (**Evaluation of disproportionality analyses**), 9 (**Grouping of existing adverse drug reaction terminologies**), 11 (**Subgrouping and stratification of signal detection**), 17 (**Recommendations on methodologies for B-R integration and representation**) and 19 (**Repository of training material**) are those that are clearly considered as being ready for implementation.

Main difference: other respondents (mostly industry) consider that methods for benefit-risk integration and representation are ready for implementation.



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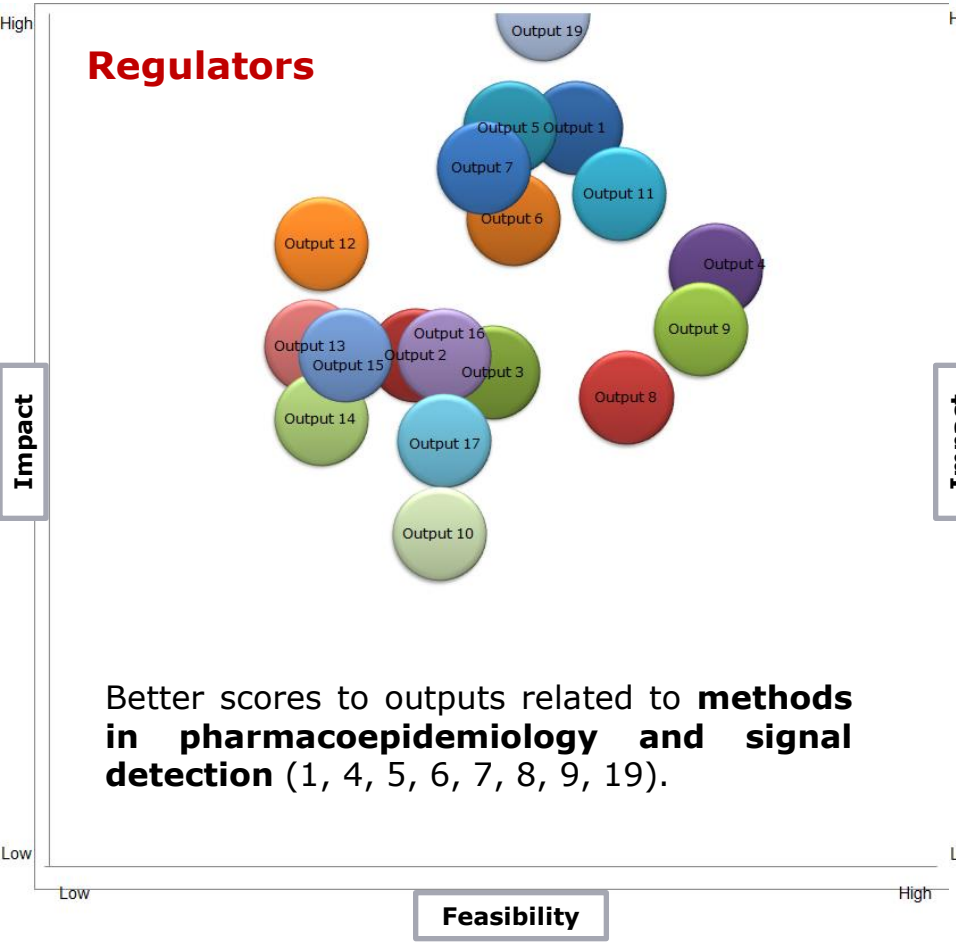
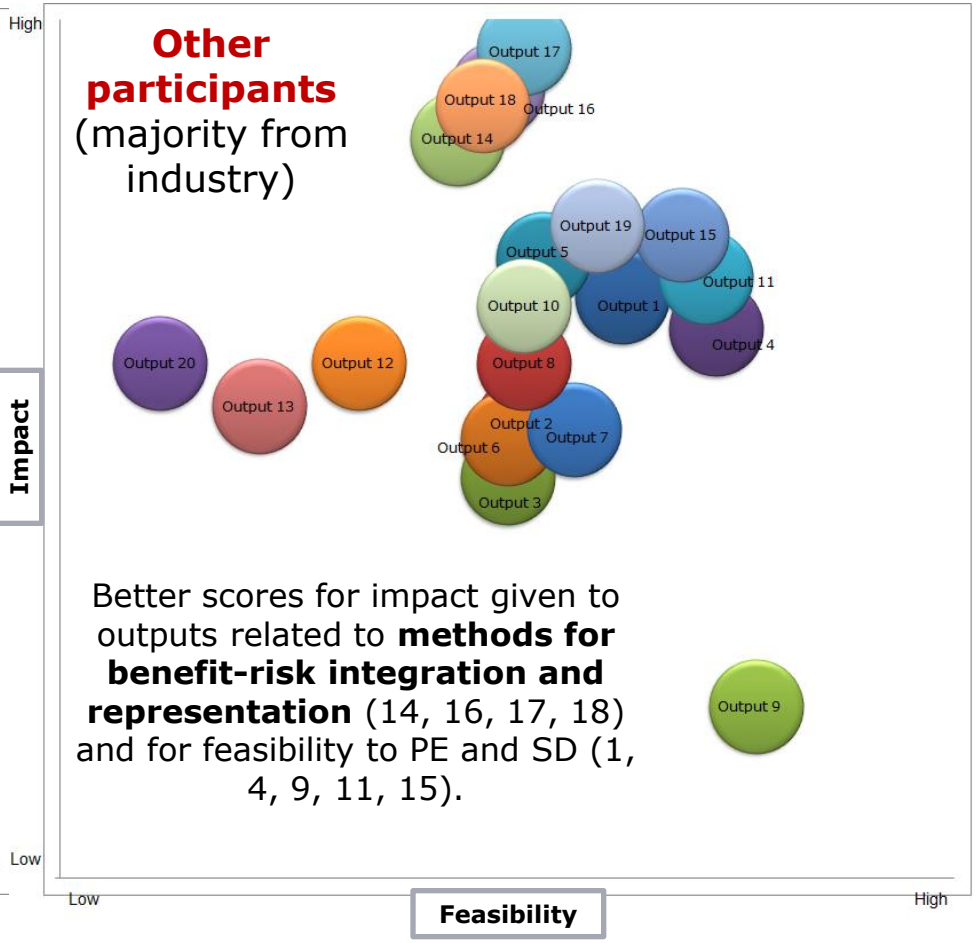


Better scores to outputs related to **methods in pharmacoepidemiology and signal detection** (1, 4, 5, 6, 7, 8, 9, 19).



Better scores for impact given to outputs related to **methods for benefit-risk integration and representation** (14, 16, 17, 18) and for feasibility to PE and SD (1, 4, 9, 11, 15).

Discussion of survey results

- Method tested with non-random sample of symposium participants
- Limited sample size
- Differences in scoring of outputs between regulators and other participants may reflecting expertise and work priorities
- Visual representation potentially useful for prioritisation
- Assessment criteria, survey methods and scoring matrix to be further developed.

Conclusions: Challenges and successes

Successes:

- Extensive work programme executed in full
- Many publications and outputs

  Some of them already implemented
- PROTECT results used as starting point for other research projects

Challenges:

- What will be the actual impact on regulatory practice? And on innovation and public health?
- How to identify and prioritise those results with the greatest potential impact?
- How to implement these results?
- How to measure the actual impact on

  Process – Behaviors - Outcome

Thank you for your attention

Further information

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