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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT): Results and their impact on regulatory practice

5 September 2016

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Executive summary

Introduction

The purpose of this report is to review the key outputs of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project, which took place from 1st September 2009 to 30 June 2015, and evaluate how these outputs have been or will be implemented into regulatory practice.

PROTECT was developed by the European Medicines Agency as a response to a call published by the Innovative Medicines Initiative (IMI) to address limitations of current methods used in pharmacovigilance and pharmacoepidemiology and to significantly strengthen the monitoring of benefit-risk (B-R) of medicines marketed in Europe.

In order to achieve this overall goal, a comprehensive and integrated project was designed aiming to develop and validate a set of innovative tools and methods to:

- enhance data collection directly from consumers of medicines in their natural language in several EU countries, using modern tools of communication;
- improve early and proactive signal detection (SD) from spontaneous reports, electronic health records and clinical trials;
- develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological (PE) studies applicable to different safety issues and using different data sources;
- develop methods for continuous B-R 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 EU (e.g. clinical registries) in order to identify and help resolve operational difficulties linked to multi-site investigations.

PROTECT outputs

PROTECT has generated a significant amount of scientific research across the European Union. The project is behind a total of 74 original articles in peer-reviewed scientific journals, of which 26 were co-authored by EMA staff.In addition, projects from PROTECT were the subject of 14 doctoral theses and 3 master theses carried out in universities across the EU. Reports, publications, presentations and databases generated by PROTECT are available on the PROTECT website[1] and a specific PROTECT benefit-risk website[2] on case studies and recommendations for benefit-risk assessment.

The main results and recommendations include:

- A guidance for observational studies on medicines in several databases and several countries with common protocols; this guidance will support the use of real world evidence for regulatory purposes by increasing consistency in findings from safety studies and revealing causes of differential drug effects, and will lead to updates to the methods guide of the European Network of

[1] http://www.imi-protect.eu/
[2] http://protectbenefitrisk.eu/

Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP); details of this research can be found in a series of 16 articles published in a special issue of the journal Pharmacoepidemiology and Drug Safety;[3]

- A comprehensive review of good detection practices has identified significant improvements tosignal detection methods applied by national and international regulatory agencies and in pharmaceutical companies; this guidance was used to update methods for signal detection from EudraVigilance and will be integrated in revised regulatory guidance on signal management in 2016. Details about this review are published in an article in the journal Drug Safety;[4]
- Recommendations for benefit-risk assessment methodologies and visual representations based on real-world case examples to facilitate clear and transparent decision-making; this has already led to initiatives that explore practical application of harmonised methods and the involvement of patients and the wider public in the assessment of benefits and risks of medicines. More details are available in an article in the journal Pharmacoepidemiology and Drug Safety;[5]
- Exploring new methods to collect data directly from patients, including via the internet; this research included the collection of information from pregnant women via the web to better understand the safety of medicines during pregnancy. This project is described in an article in the journal JMIR Public Health and Surveillance.[6]

To optimise their positive impact, these outputs need to be translated into *outcomes* in terms of long-term improvement on regulatory practices leading to improved decision-making and surveillance on medicinal products (Figure 1). The actual or potential impact of PROTECT on innovation, benefit-risk evaluation of medicines and ultimately public health is therefore a question to be addressed. Several aspects may need to be considered in this process: do the outputs need further development and research work, e.g. in terms of validation and peer-review, before they form a basis to implement changes in regulatory or clinical practice, and should implementation be prioritised for some outputs, and based on which criteria?

A final list of 23 outputs were identified in 4 categories: Recommendations for pharmacoepidemiology (n=5), Methods for signal detection (n=8), Benefit-risk integration and representation (n=7) and Data collection directly from consumers (n=3).

Measurement of potential impact of PROTECT outputs

A panel was established within the European Medicines Agency to address the questions of whether PROTECT outputs were mature enough to form a basis to implement changes in regulatory or clinical practice or should first be further validated, scrutinised and peer reviewed in the scientific community before their implementation. The EMA panel developed a methodology to assess the potential impact of outputs of regulatory science projects and tested it with the outputs of the PROTECT project. The EMA panel first identified criteria that could be used to evaluate the potential regulatory impact of project outputs.

A survey on 20 outputs was carried-out in May 2015 with participants to the Final PROTECT Symposium (18-20 February 2016) and additional panels of EMA staff members. The objective of the survey was to rate the outputs as to their impact on public health and feasibility, based on a set of 6 criteria.

[3] http://onlinelibrary.wiley.com/doi/10.1002/pds.v25.S1/issuetoc
[4] http://rd.springer.com/article/10.1007%2Fs40264-016-0405-1
[5] http://onlinelibrary.wiley.com/doi/10.1002/pds.3958/abstract
[6] http://publichealth.jmir.org/2015/2/e22/

Based on a total of 230 evaluations, five goups of outputs were identified: 1) high impact and high feasibility, including the Inventory of drug utilisation databases, Recommendations for the sub-grouping and stratification in statistical signal detection and the Repository of training material for benefit –risk integration and representation; 2) high impact but moderate feasibility, including Final tools for graphical B:R representation, Recommendations on methodologies for B-R integration and representation and Development of accessible material to patients; 3) moderate impact and high feasibility, including Comparison of covariate adjustment methods and Grouping of existing adverse drug reaction terminologies; 4) moderate impact and low feasibility, including Statistical signal detection from clinical trials and Statistical signal detection from electronic health records; and 5) variable scores around moderate impact and feasibility. For each output, factors affecting feasibility were identified. Consequences for IT and human resources were the most frequently cited factors affecting feasibility.

PROTECT outcomes

A review of each of the 23 outputs is presented with a short description of their nature, how they have been used in the past and how they could be used in the future. Based on this review, PROTECT outcomes with impact on public health, resources and future research are identified.

A concrete implementation of outcomes is the use of the SmPC-ADR database to create on a monthly/bimonthly basis the electronic Reaction Monitoring Reports by EMA for national competent authorities for >1500 active substances. Other examples include the integration of the inventory of drug consumption databases into the inventory of real-world evidence data sources being created by the EMA, the integration of recommendations on signal detection into the Addendum of GVP Module IV (Signal Management) as well as in Revision 5 of the ENCePP Guide on Methodological standards in pharmacoepidemiology, use of the established network for pharmacoepidemiological studies in an EMA-funded study (following a tendering procedure), and inclusion of relevant recommendations on pharmacoepidemiologicals studies in Annex 1 of GVP Module VIII and in Revision 5 of the ENCePP Guide. It is noteworthy that those outcomes were also those considered as having the highest impact and feasibility of implementation in the survey of stakeholders.

In addition, the ground work performed on benefit-risk methodologies and visual representation is a leap forward towards the understanding of the values and usefulness of benefit-risk methods. Further work is also on-going to assess their implementation into regulatory decision-making. Research on direct-to-patient data collection in pregnant women has shown the added value of the internet for studies on medicines in vulnerable groups difficult to reach otherwise. Results are important in a very quickly changing environment where patients are actively sharing information.

Based on this review, it is concluded that PROTECT has achieved the objectives and deliverables of the Call Topic to which PROTECT applied. In addition, outcomes linked to signal detection and evaluation are being implemented into routine pharmacovigilance and regulatory practice and start to have a positive impact on public health and resources.

In the course of this evaluation of the impact of PROTECT outcomes, a survey tool to measure the balance of impact on public health and feasibility has been developed and piloted. Analysis of the results identified a number of characteristics that could be improved for evaluation of other projects.

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1. Introduction

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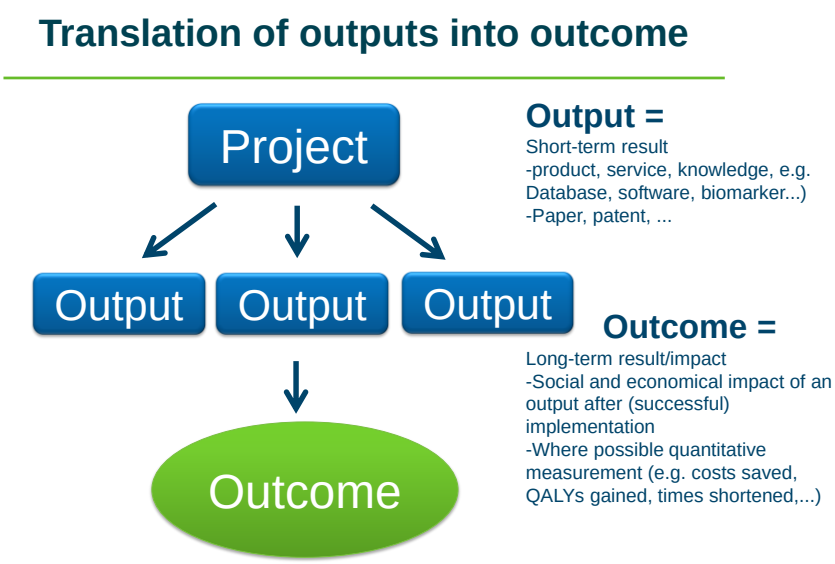
- test and validate various methods developed in PROTECT using a large variety of different sources in the EU (e.g. clinical registries) in order to identify and help resolve operational difficulties linked to multi-site investigations.

PROTECT generated many *outputs* in terms of reports, publications and training material. To optimise their positive impact, these outputs need to be translated into *outcomes* in terms of long-term improvement on regulatory practices leading to improved decision-making and surveillance on medicinal products (Figure 1). The actual or potential impact of PROTECT on innovation, benefit-risk evaluation of medicines and ultimately public health is therefore a question to be addressed. Several aspects may need to be considered in this process: do the outputs need further development and research work, e.g. in terms of validation and peer-review, before they form a basis to implement changes in regulatory or clinical practice, and should implementation be prioritised for some outputs, and based on which criteria?

Figure 1.



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

2. Objectives

The objective of this report is to describe the actual or potential impact of the PROTECT project on regulatory activities taking into account how its outputs have been implemented through regulatory guidance, training, research conduct or any other channels. It also identifies appropriate actions for the future implementation of several PROTECT results.

To achieve these objectives, the following aspects are covered:

- Description of work at initiation of PROTECT, which explains the initial objectives and work plan

- Process for selection of a short list of the main outputs of PROTECT

- Results of survey of stakeholders on PROTECT outputs in May 2015

- Description of the impact of outputs of PROTECT on different dimensions of regulatory impact

3. Description of work at initiation of PROTECT

The Description of the work submitted to IMI as part of the research application (Annex 1 of Grant Agreement N° 115004) included a description of the anticipated impact of PROTECT on the future drug development process and post-marketing surveillance activities. This proposal relied on two main assumptions: 1) the results of PROTECT would improve the monitoring and evaluation of the safety of medicinal products and lead to improvements in public health, and 2) PROTECT will increase regulators' confidence about the evaluation of benefit-risk profile and ongoing monitoring of medicinal products, that would ultimately facilitate earlier access of novel medicines to patients.

The description of the expected impact of PROTECT in the project submitted to IMI included the following elements:

i) New methods of data collection from consumers

- New methods will be increasingly important for medicines where numbers of patients in pre-authorisation studies are limited and close surveillance of treated patients post-marketing is needed, such as orphan drugs and advanced therapy medicinal products; in such cases, traceability over decades and evaluation of the long term effects of frequent changing between biosimilars are pharmacovigilance questions which will require new methodologies.
- They will help monitor the effects of drug use in pregnancy, as information from pre-clinical trials is not reliably predictive for teratogenic effects and pregnant women are usually excluded from clinical trials unless the medicine is for pregnancy related illnesses or essential to the wellbeing of the mother.
- They have the potential to be used to collect drug utilisation, outcome and other pharmacovigilance data on other target populations including those that are difficult to recruit and retain using conventional methods – for example older children, adolescents and people in full time work who may be unwilling or unable to attend clinics frequently.
- They will facilitate collection of data on long term follow up of safety, efficacy and outcomes can be collected and reduction of losses to follow up caused by patients moving away from study centres. This will therefore reduce bias and allow long term follow up which has either been prohibitively expensive or not feasible using more traditional methods, in particular for medication used in chronic diseases.
- They have the potential to provide a simpler method of confirming or refuting signals generated in the early post-marketing phase, or potential risks such as the long term effect of medications which alter the function of the immune system.

ii) Testing and development of methods for signal detection

- Optimisation of methods of signal detection from spontaneous reports and development of methods using electronic patient record data will impact on the use of a drug over its life-cycle and in the long-term improve the balance of benefits and risks.
- Use of the available drug safety data in an efficient and appropriate manner and earliest possible detection of emerging safety issues whilst avoiding unnecessary false safety signals.
- Better assessment of novel methods of signal detection which may arise in the future based on an assessment of both the positive and the negative aspects of using signal detection techniques and tools.

iii) Framework for pharmacoepidemiological studies

- Standard recommendations for essential methodological parameters and their related common operational definitions for the conduct of PE studies will improve overall study quality, decrease the discrepancies in results from different studies and increase the usefulness and reliability of these studies for benefit-risk assessment in the EU. They will eventually improve and strengthen the EU pharmacovigilance system.
- By defining the conditions for interoperability and sharing of datasets using a common protocol, the framework will lay the foundation to build an appropriate infrastructure and research tools to rapidly address any urgent safety issues in different population groups and countries and assess benefit-risk in a large number of data sources across Europe.

- These standards will also promote the development of new data resources and methodologies useful for benefit-risk assessment in other fields, such as advanced therapies, vaccines or paediatrics.
- Guidelines on how to identify and use national drug utilisation data will help in quicker assessment of the public health impact of safety signals.
- Guidelines on generating co-morbidity/risk factor profiles of indication populations may help prevent adverse drug reactions and/or prepare for safety signals in a proactive manner. Such profiles may also guide the drug development process.

iv) Benefit-risk integration and representation

- The clarity of thinking about benefits and risks has the potential to inform more efficient drug development programmes at an early stage.
- Methods to weigh benefits and risks of a medicine will be clarified, and the data and value judgements needed in this process will be highlighted.
- The development of a shared framework, especially in regard to communication of benefits and risks, has the potential to avoid unnecessary delays in decision-making about the licensing of medicines, to the benefit of patients, healthcare providers, pharmaceutical companies and regulators.
- The usefulness of the information on patient utilities available in the literature for regulatory benefit-risk assessment, and how this information could be put to use for the decision analysis models, will be better understood.

The dissemination of results and recommendations arising from PROTECT was discussed in the Description of work. It was expected that a number of reports providing standards and recommendations and the rationale underlying these would be expected and it was proposed to disseminate hem through:

- The PROTECT web portal, where relevant deliverables for public use and public consultation have been posted, including all publications available in open access.
- Publications, including presentations to conferences
- The ENCePP network, to which results of the PROTECT programme would be made available and introduced as an input to the activity of the relevant working parties, e.g. the one developing ENCePP research standards and guidance**.**
- Training programmes to which the EMA, PROTECT partners and other institutions are contributing, such as pharmacovigilance training within the EMA or the EU2P training programme.
- The EMA Scientific Committees, Working Parties and regulatory activities; tools and methodological standards developed in PROTECT are relevant for signal detection, risk management plans, pharmacoepidemiological studies studies and other relevant drug-related activities performed by the industry, regulatory agencies and other stakeholders; therefore PROTECT outputs would be introduced in regulatory guidance documents, especially the Good pharmacovigilance practices (these did not already exist at the inception of PROTECT in 2009).
- Pre-Standards and Standards Development Organisations: some components of the requirements (e.g. data collection formats) and interoperability standardised data formats developed in WP4 (New tools for data collection from consumers) may be relevant and be submitted to appropriate pre-standards and standards development organisations including Integrating the Healthcare

Enterprise (IHE), the Clinical Data Interchange Standards Consortium (CDISC), The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the International Organization for Organization (ISO), or the European Committee for Standardisation.

4. The PROTECT outputs and their dissemination

Annex 1 of Grant Agreement N° 115004 Rev. 8 presents the list of deliverables planned to be provided during the course of the project. This list includes 101 deliverables, many of them representing intermediate steps towards achievement of a final deliverable. From this list, were excluded deliverables that represented intermediate outputs or milestones (such as study protocols, progress reports, interim results or reports on results of specific case studies performed for testing purposes), that had been removed from the work programme or that were considered duplicate activities. Three deliverables related to Work Package 7 (Training and Communication) were also excluded as they were related to communication about PROTECT progress and results (i.e. they were enablers rather than being considered key outputs in their own right).

These exclusions resulted in a final list of 23 outputs in 4 categories: Recommendations for pharmacoepidemiology (n=5), Methods for signal detection (n=8), Benefit-risk integration and representation (n=7) and Data collection directly from consumers (n=3).

Table 1 provides the list of main PROTECT outputs and sources of information available for their assessment.

Output number	Output name
Recommendations for pharmacoepidemiology	
1	Inventory on drug utilisation data
2	Comparison of methods to control for confounding
3	Balance measures for propensity score models
4	Comparison of covariate adjustment methods
5	Recommendations for pharmacoepidemiological studies
Recommendations on methods for signal detection	
6	Evaluation of disproportionality analysis
7	Adverse Drug Reaction Repository
8	Lessons learnt from a characterisation of databases used for signal detection
9	Grouping of existing adverse drug reaction terminologies
10	Novel groupings for adverse drug reactions
11	Subgrouping and stratification in statistical signal detection
12	Statistical signal detection from clinical trials
13	Statistical signal detection from electronic health records
Recommendations for benefit-risk integration and representation	
14	Methodologies for benefit-risk evaluation
15	Methodologies for graphical representation
16	Final tools for graphical B:R representation
17	Recommendations on methodologies for B-R integration and representation
18	Development of material to patients
19	Repository of training material
20	Enhanced software for benefit-risk evaluation
Recommendations for data collection directly from consumers	
21	Results of prospective study on medication use and lifestyle factors
22	Comparison of ability and cost-effectiveness of advertising methods
23	Challenges related to data protection in direct-to-patient research

PROTECT outputs were disseminated through a number of channels.

4.1. Publications

A total of 75 original full articles published in peer-review journals had been identified by 5th Septemer 2016, including a special issue of the journal Pharmacoepidemiology and Drug Safety containing 16 articles. The list of these publications is posted on the PROTECT website in the "Results" section (http://www.imi-protect.eu/results.shtml). They relate to the work done regarding the Recommendations in Pharmacoepidemiology (including Replication Studies) (n=56), Methods for Signal Detection (n=12), Benefit-Risk Integration and Representation (n=4), and Data collection directly from consumers (n=3).

In the draft report of IMI Socio-economic impacts dated 29th March 2016 and written by Biggar Economics on behalf of an Evaluation Expert Group, an average citation rate of 1.36 is cited for PROTECT based on 61 articles (this is considered a good value), with 16.4% of articles "highly cited".

4.2. Presentations

It is estimated that more than 100 presentations have been given and 74 of which are listed on the PROTECT website. Two symposia on PROTECT were presented at the International Conference on Pharmacoepidemiology, one in 2014 and one in 2015.

4.3. Databases

PROTECT resulted in the development of three databases/software: the Adverse Drug Reaction databases, the Drug Consumption Database in Europe and an additional module of the Addis software for benefit-risk analyses. These outputs are further presented in Chapter 5.

4.4. Website

A specific website (http://protectbenefitrisk.eu/) has been specifically created as receptacle of results and recommendations of the Benefit-risk integration and representation work package. This website is presented in details in Chapter 5

4.5. Training and education

The regulatory impact of PROTECT will also depend on the dissemination and implementation of its outputs by trained personnel. In this respect, the fact that several public and private partners of PROTECT also participated to the IMI Eu2P project[7] had a very positive impact on the inclusion of PROTECT outputs in the EU2P training programme.

Important PROTECT outputs were also included as recommendations in the ENCePP Guide on Methodological Guide in Pharmacoepidemiology and Pharmacovigilance, which had monthly averages of 1782 downloads and 2780 hits in the first quarter of 2016.

Academic education is also an important step to promote dissemination and use of the PROTECT outputs. Research done in PROTECT led to the submission of 14 doctoral theses and 3 master theses, as presented in Table 2.

Of these, 7 theses concerned Recommendations for Pharmacoepidemiology, 6 concerned Benefit-risk integration and representation, 3 concerned Methods for signal detection and 1 concerned Data collection directly from consumers.

[7] The European programme in Pharmacovigilance and Pharmacoepidemiology (Eu2P) was launched by the Innovative Medicines Initiative and offers a web-based education & training offer in pharmacovigilance and pharmacoepidemiology (www.eu2p.org).

Table 2. List of doctoral and master theses based on PROTECT.

Number	Author	Title	University	Type	Date of submission /defence
1	Shahrul Mt-Isa	Improving Evidence-Based Risk-Benefit Decision-Making of Medicines for Children	Imperial College London	Phd	Dec-10
2	Ed Waddingham	Data Uncertainty in Benefit-Risk: A Bayesian Approach Using Multi-Criteria Decision Analysis	Imperial College London	Masters	Sep-12
3	Ji An	A Markov Model for Cost-Effectiveness Evaluation of Anti-hypertensive Pharmacological Intervention in the Very Elderly Population	Imperial College London	Masters	Sep-13
4	Kimberley Hockley	Patient and Public Involvement in Benefit-Risk Assessment and Regulatory Decision-Making	Imperial College London	Phd	Oct-13
5	Ruth Brauer	The self controlled case series applied to the investigation of two suspected adverse drug events	University of London	Phd	Oct-13
6	Gema Requena	Pharmacoepidemiology of Benzodiazepines and its association with hip/phemur fractures: a methodological evaluation (Mention of International Doctor).	Department of Biomedical Sciences (Pharmacology), UNIVERSITY OF ALCALA (SPAIN)	PhD Program in Health Sciences	Jul-14
7	M.S. Ali.	Improving propensity score methods in pharmacoepidemiology.	Utrecht University	Phd	01-Oct-14
8	M.J. Uddin	Performance of statistical methods to control for unmeasured confounding in pharmacoepidemiology. Focus on instrumental variables.	Utrecht University	Phd	15-Dec-14
9	Yuni Do	Benefit-Risk Assessment of Anti-Hypertensive Medication in the Very Elderly: Using the Structured Frameworks to Assist Clinical Decision-Making	Imperial College London	Masters	Sep-15
10	Adriana Mantilla	Evolución del consumo de macrólidos y amoxicilina/clavulánico en varios países europeos (2007-2010). Evaluación de algunos factores relacionados con su uso" ("Patterns of use of macrolides and	Universitat Autònoma de Barcelona	Phd	Dec-15
11	Victoria Abbing-Karahagopian	Understanding differences in findings from pharmacoepidemiological studies. The case of antidepressant and benzodiazepine use and hip fracture	Utrecht University	Phd	Jan-16
12	Priscilla Zetstra-van der Woude	Data collection on risk factors in pregnancy	Rijksuniversiteit Groningen	Phd	Jan-16
13	Ainhoa Gómez	Determinants of antidepressant use across several European countries. Population attributable risk of hip fractures in antidepressant users	Universitat Autònoma de Barcelona	Phd	Planned 2017
14	H.A. van den Ham.	Benefits and risks for the individual: anticoagulation for patients with atrial fibrillation.	Utrecht University	Phd	Planned date of defense 25 May 2016
15	Ed Waddingham	Bayesian statistics in the assessment of the benefit-risk balance of medicines using Multi-Criteria Decision Analysis	Imperial College London	Phd	Planned September 2018
16	Kevin Wing	Improving the measurement and detection of serious adverse drug reactions in databases of stored electronic health records	London School of Hygiene and Tropical Medicine	Phd	Submitted July 2015, defended October 2015
17	Michael Ranopa	Methodological issues in electronic healthcare database studies of drug cancer associations: identification of cancers, and drivers of discrepant results	London School of Hygiene and Tropical Medicine	Phd	September 2015, defended December 2015

5. Stakeholders' assessment of PROTECT outputs

5.1. Background

In order to address the questions of whether PROTECT outputs were mature enough to form a basis to implement changes in regulatory or clinical practice or should first be further validated, scrutinised and peer reviewed in the scientific community before their implementation, and which ones should be prioritised for implementation, a panel was established within the Agency to develop a methodology to assess the potential impact of outputs of regulatory science projects and test it with the outputs of the PROTECT project. The objectives of this panel were to develop a conceptual framework for the review of the regulatory impact of results of regulatory science projects, and to apply and test this conceptual framework to the outcomes of the PROTECT project

The EMA panel first identified criteria that could be used to evaluate the potential regulatory impact of project outputs.

Outputs of a project may be tangible (measurable) and intangible (unmeasurable). Unmeasurable outputs could include, for example, acquisition of knowledge and expertise by Agency. This evaluation focussed on tangible outputs.

A survey was carried-out in May 2015 with participants to the Final PROTECT Symposium that took place on 18-20 February 2016.

5.1.1. Dimensions of changes

Following Coglianese (2012),[8] three main dimensions of changes are generally described in the context of change management:

- Process: changes in process are reflected in changes in guidelines, procedures, work instructions, training courses, etc., for example use of the SmPC-ADR database to flag already listed adverse events the in electronic Reaction Monitoring Reports (eRMRs) used in signal detection, leading to a change in the process for the review of eRMRs ;

- Behaviour: the deliverable may modify the behaviour of individuals or targeted entities affected by the deliverable, for example more time allocated by reviewers to the evaluation of new adverse events reported for a drug; this dimension is sometimes difficult to differentiate from the Process dimension ;

- Outcome: the deliverable may provide benefits in terms of actions implemented and final results, e.g. gain in efficiency for the detection of new safety signals by decreasing the numbers of false positive signals.

These dimensions represent descriptors of the potential impact of outputs and not criteria for impact evaluation. Although a hierarchy exists in these dimensions (an impact on "outcome" may be considered more important than an impact on "process"), these three dimensions were not formally evaluated in the survey because they represent characteristics of the outputs and are therefore inherently descriptive. These dimensions should however be taken into account for the evaluation of the outputs.

[8] Coglianese C. Measuring Regulatory Performance-Evaluating the impact of regulation and regulatory policy, OECD, August 2012.

5.1.2. Criteria for evaluation

The following criteria were identified by the panel of experts convened by EMA and evaluated in the survey:

- Impact of change on public health: evaluation of the level of benefit brought by the change, considering its impact on the number of processes, behaviours and outcomes, and the number of concerned stakeholders (eg. patients) or an estimate of public health impact;

- Maturity*:* a deliverable is considered mature if it can be used without major further development for what it was purported to achieve; such further development may include the need for validation, confirmation, testing or peer review. Maturity is a categorical variable defined by the need (or not) for further development and the nature of such development:

  - Inadequate: the development has not reached such a level that it can be used in regulatory practice; additional ground work is needed
  - Incomplete: some further development is still needed, such as independent confirmation, re-testing in another setting or use in practice to better understand its usefulness and feasibility
  - Nearly complete: the output needs to undergo a peer review process or minor adjustments
  - Complete: no further development is needed.

- Feasibility of the implementation in terms of resources:

  - Potential impact on human resources
  - Potential impact on IT resources

- Acceptability by concerned stakeholders (yes/no)

- Speed of implementation: evaluation of the speed with which the deliverable can be implemented, i.e. within 1 year, in 1-2 years, after 2 years.

5.1.2.1. Scoring

Each indicator can be scored on a simple scale, i.e. 1-2, 1-3 or 1-4. In a first stage, equal distances are set between the categories of each criterion. In future evaluations, greater weight may be given to some categories that may significantly influence implementation of an output, e.g. if the level of development of an output is considered complete or not.

5.1.2.2. Perspective

Different perspectives may be taken when evaluating the impact of regulatory science projects: regulatory authority, industry, health care professional, patient. It is therefore important to record the affiliation and speciality of the persons conducting an impact assessment in order to identify priorities for different stakeholders.

5.1.2.3. Outcome of impact assessment

The objective of this mpact assessment is the prioritisation of outputs for implementation into regulatory practice. The main outcome of the assessment is therefore, for each output, a recommendation for an action in terms of its implementation based on criteria of anticipated public health impact, feasibility and need for further scientific development validation or confirmation.

Categories of action could include: introduction into guidance documents, introduction into work processes, future implementation by regulatory committees or other stakeholders, request for additional scientific input, validation or peer review (e.g. initiation of replication study), low level of prioritisation or decision not to implement the output.

Impact assessment can also lead to the evaluation and comparison of the overall impact of one or several projects or research programmes, allowing the identification of determinants of success.

5.2. The PROTECT survey

5.2.1. Objective

The objective of the survey was to test the conceptual framework on a number of outputs of PROTECT. As the survey was initiated in May 2015, not all outputs were already available at the time of the survey. However, many of them were available as publications, reports made public on the PROTECT website or slide presentations given during the Final PROTECT Symposium (19-20 February 2015).

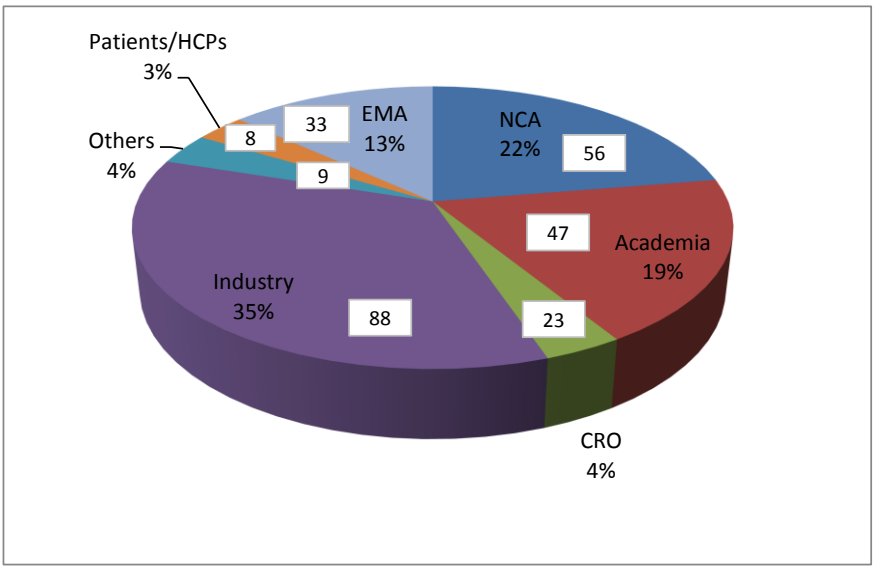
5.2.2. Methods

For the survey, the PROTECT outputs included the 20 first outputs listed in Table 1. Three outputs related to Recommendations on data collection directly from consumers were not available at the time of the survey.

Two populations were used to perform an impact assessment of the above PROTECT outputs. In a first stage, the survey included participants to the Final PROTECT Symposium organised at the European Medicine Agency on 18-20 February 2015 in order to present and discuss the main results of PROTECT to a large audience. The registration was voluntary, unrestricted and free of charge and a total of 264 participants were registered to the symposium, 132 of them (50.0%) being affiliated to an organisation that was a partner of the PROTECT consortium. The draft conceptual framework for impact assessment was presented at the end of the symposium and the survey was announced. On 28 May 2015, the 264 registered participants were contacted by email to ask for their collaboration to the survey.

The distribution of registered participants according to organisation is displayed in Figure 2.

Figure 2. Distribution of participants registered to the Final PROTECT Symposium, by origin (n=264)



In order to complement the survey, two panels of EMA staff members were convened to specifically assess the impact of outputs related to the recommendations for pharmacoepidemiology and for signal detection. These panels included respectively 4 and 10 persons selected according to their expertise. After a short presentation of each outputs, they were asked to assess their impact using the same questionnaire as the one used for the survey. The panel members had also participated to the PROTECT Symposium.

An electronic questionnaire was designed with the SurveyMonkey tool. The participants received by email an Excel file with the list of outputs and, for each output, one or several links to relevant reference documents and a link to the questionnaire. The same questionnaire was used for each output and had to be submitted online after completion. In the cover email, participants were asked to assess at least three outputs chosen according to their expertise. The survey was anonymous but the IP address is recorded by Survey Monkey in an Excel file together with the answers. The EMA panel members were asked to assess all outputs of either pharmacoepidemiology or signal detection using the same questionnaire as for the survey.

The questions of content and the scores assigned to each category of a response are presented in Tables 2a and 2b. Questions were divided into two dimensions: Impact and Feasibility.

Table 2a. Questions and scoring for the impact evaluation of PROTECT outputs

Criterion	Description	Score 1	Score 2	Score 3	Score 4
I1	Question 4 – If the change is implemented, how do you rate its potential impact on public health?	None	Small	Moderate	Important
I2	Question 6 – How do you rate the degree of acceptability by the group of stakeholders to which you belong?	N/A	Small	Moderate	Important

Table 2b. Questions and scoring for the feasibility evaluation of PROTECT outputs

Criterion	Description	Score 1	Score 2	Score 3	Score 4
F1	Question 1 – How do you rate the degree of scientific development of the output?	Inadequate	Incomplete	Nearly complete	Complete
F2	Question 7 – What is your estimate of the delay within which this output could be implemented in practice?	N/A	>2 years	1-2 years	<1 year
F3	Question 5 – How do you rate the feasibility of the implementation of the output in terms of IT resources?	N/A	Important	Moderate	Small
F4	Question 5 – How do you rate the feasibility of the implementation of the output in terms human resources?	N/A	Important	Moderate	Small

For each output, the scores were averaged separately for each criterion and the average scores were summed-up to provide two overall scores, one for Impact and one for Feasibility. The scores range from 3 to 8 for Impact outputs and from 7 to 16 for Feasibility outputs. A missing value for a criterion (response "I do not know" or no answer) was replaced by the mid-value for that criterion (score of 3 for I2, F2, F3 and F4, score of 2.5 for I1 and F1) as a neutral value that would not influence the mean score. An additional criterion was created by dichotomising answers to Question 1 (degree of scientific development) as follows: inadequate or incomplete; nearly complete or complete.

The two overall scores for all outputs were plotted on a same graph to provide a graphical representation of their overall assessment.

5.2.3. Participation

A total of 230 evaluations of outputs were received, 133 from the survey and 97 from the EMA panels. For the survey, responses were received from 40 different IP addresses with the following declared affiliations: pharmaceutical industry: 16 (40.0%), academia: 7 (17.5%), regulatory authorities: 6 (15.0%), patient representatives: 2 (5.0%), CRO: 2 (5.0%) and other or missing: 7 (17.5%). If each IP address corresponds to a different respondent, the response rate from the survey was 40/264 or 15.2% with an average of 6 outputs evaluated per respondent. Of the 133 evaluations received from these 40 respondents, 52 (39.1%) concerned outputs of pharmacoepidemiology, 32 (24.1%) concerned outputs of signal detection and 49 (36.8%) concerned outputs of benefit-risk integration and representation.

Of the 97 evaluations received from the internal EMA panels, 18 concerned recommendations for pharmacoepidemiology and 79 concerned methods for signal detection.

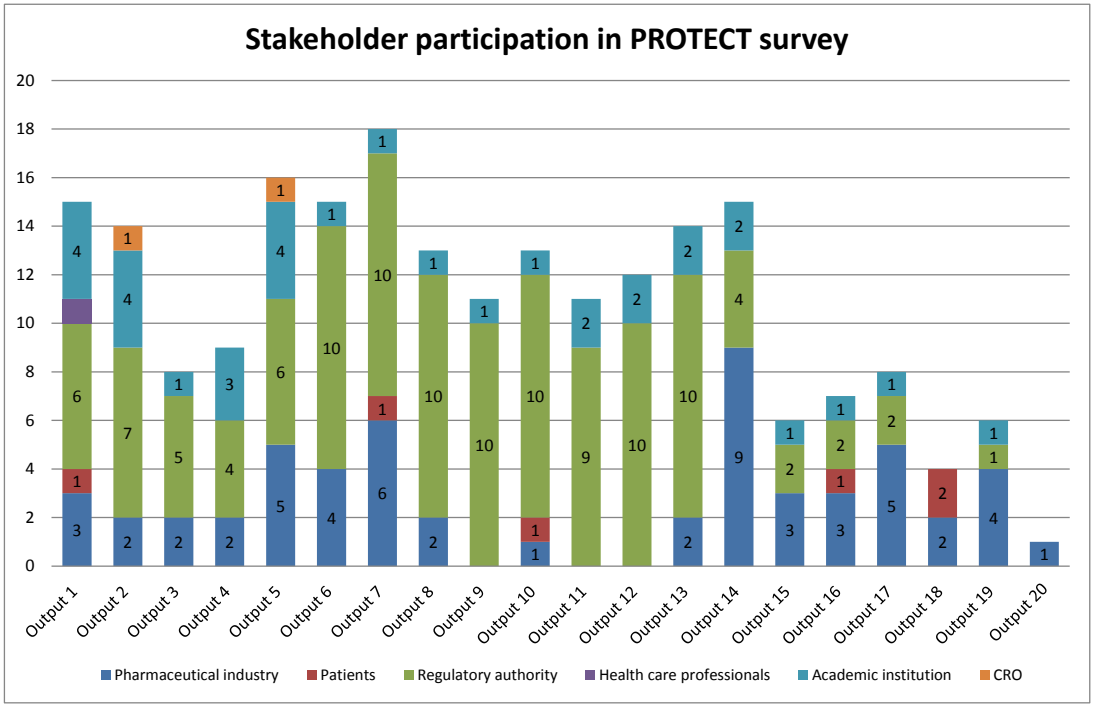
The number of responses from the survey and the EMA panels per output is provided in Table 3.

Table 3.

Output number	Survey n	EMA panels n	Total n
1	14	4	18
2	12	4	16
3	4	4	8
4	6	3	9
5	16	3	19
6	8	10	18
7	9	10	19
8	3	10	13
9	1	10	11
10	3	10	13
11	2	9	11
12	2	10	12
13	4	10	14
14	17	10	27
15	6		6
16	7		7
17	8		8
18	4		4
19	6		6
20	1		1

The distribution of all responses for each output according to affiliation is presented in Figure 3.

Figure 3.

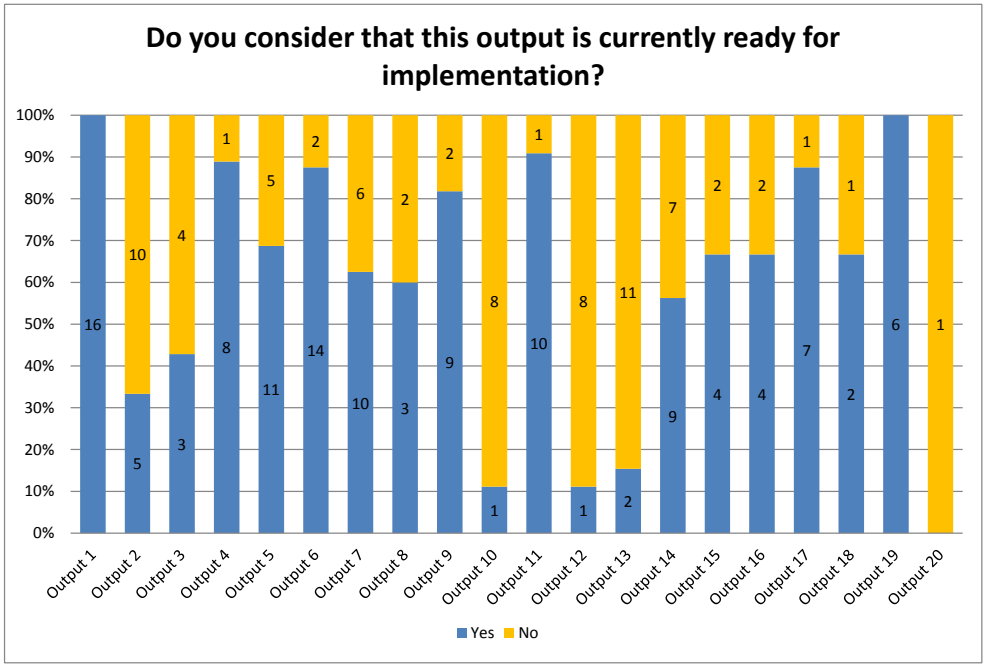


5.2.3.1. Results

a) Maturity

Figure 4 presents the views on whether the output was considered ready for implementation.

Figure 4.

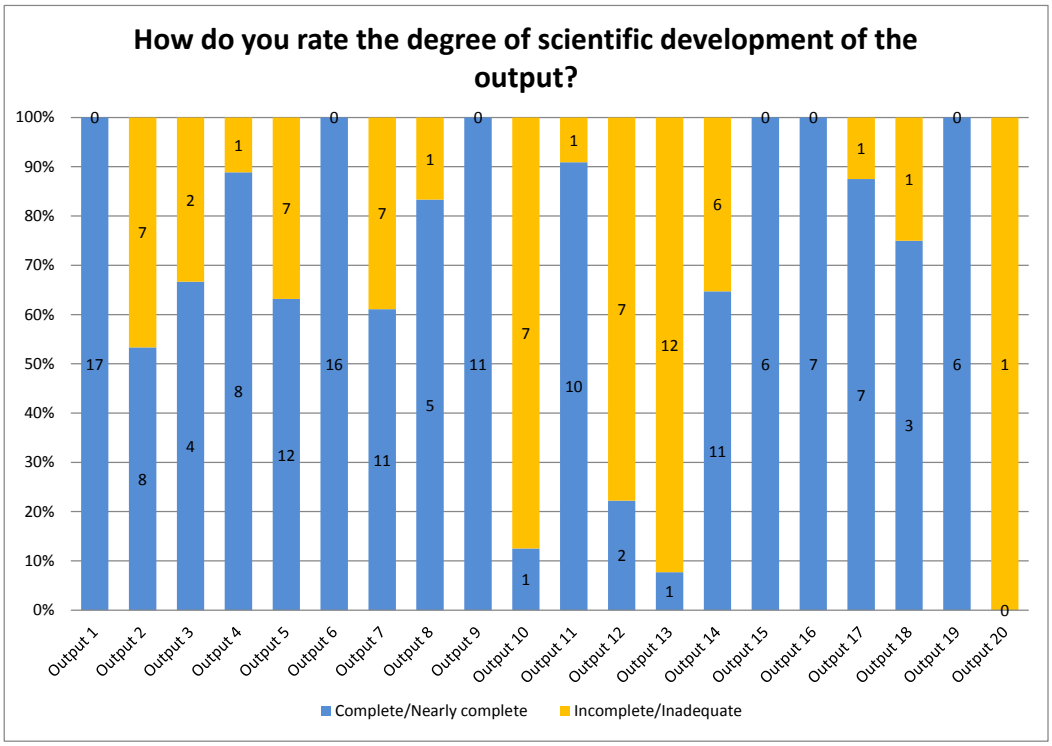


Outputs 1 (Inventory of drug utilisation data), 4 (Comparison of covariate adjustment methods), 6 (Evaluation of disproportionality analyses), 9 (Grouping of existing adverse drug reaction terminologies), 11 (Subgrouping and stratification of signal detection), 17 (Recommendations on methodologies for B-R integration and representation) and 19 (Repository of training material) are those that are clearly considered as being ready for implementation (>60% of positive answers).

Outputs that were generally not considered as being ready for implementation are outputs 2 (Comparisons of methods to control for confounding), 3 (Balance measures for propensity score models), 10 (Novel groupings for adverse drug reactions), 12 (Statistical signal detection from clinical trials), 13 (Statistical signal detection from electronic health records) and 20 (Enhanced ADDIS software, based on only one evaluation).

Figure 5 presents results on whether the scientific development of each output was considered complete/nearly complete vs. incomplete or inadequate. These data are in line with those of Figure 3, with the difference that several outputs have a 100% (nearly) completeness of data with <100% recommendation for implementation. This is explain by the fact that some respondents considered that nearly complete outputs are not yet ready for implementation.

Figure 5.



Figures 6 and 7 show the distribution of the responses regarding readiness for implementation separately for regulators and other respondents.

Figure 6.

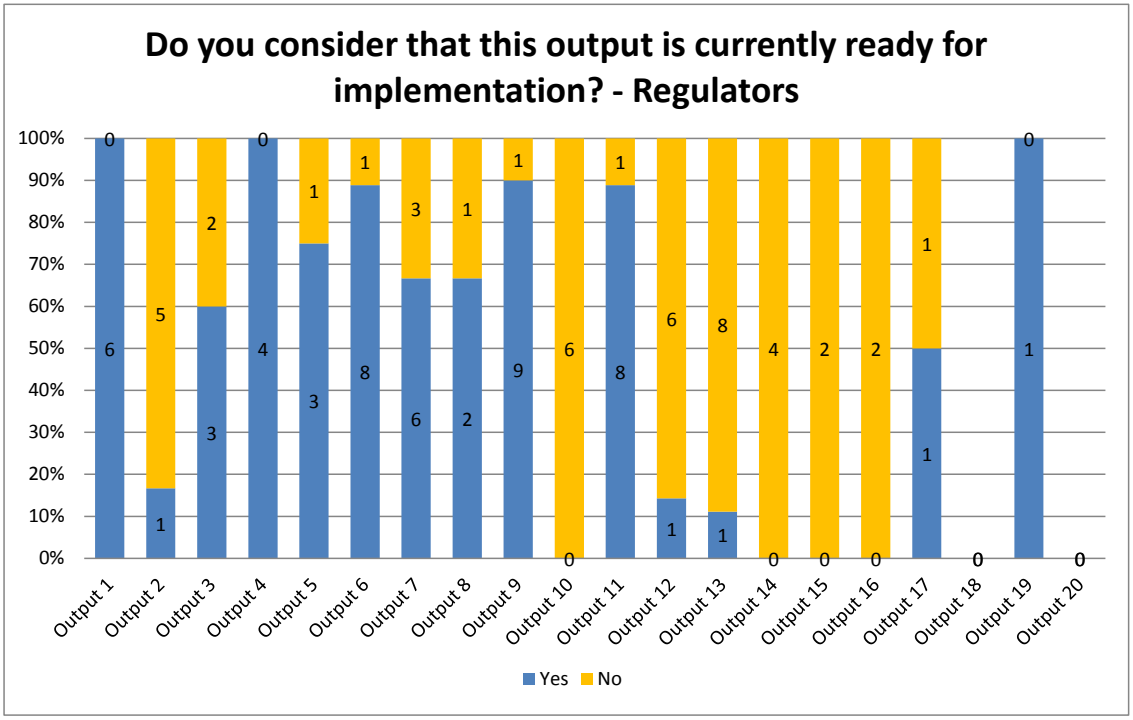
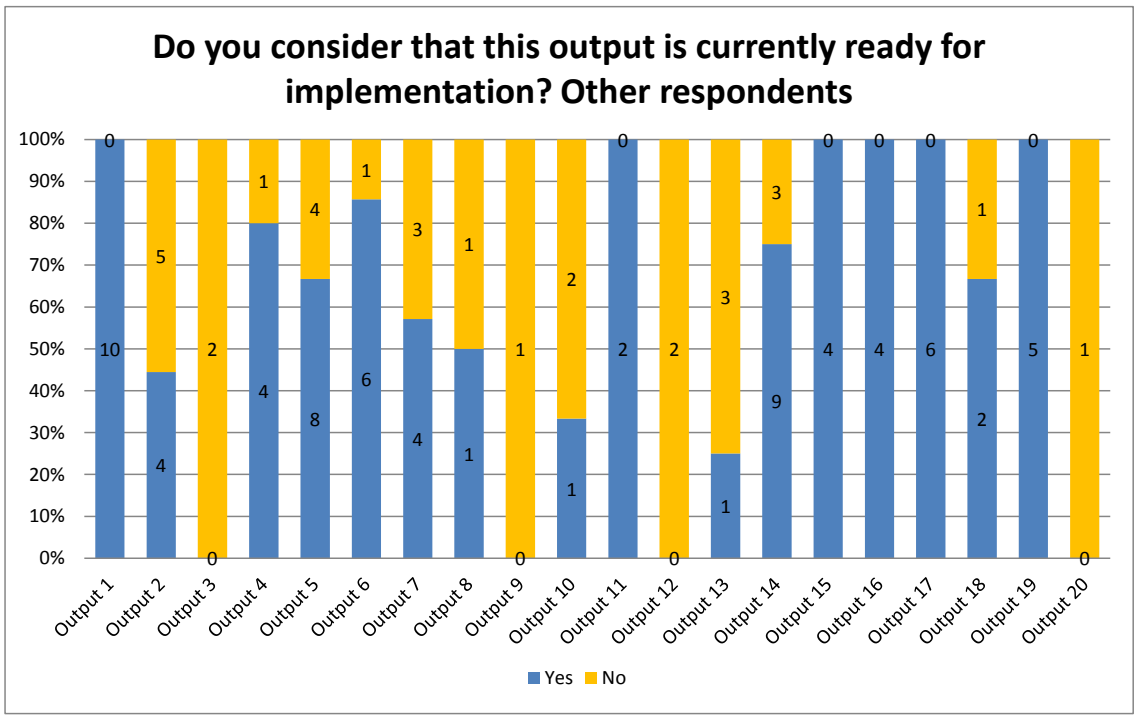


Figure 7.

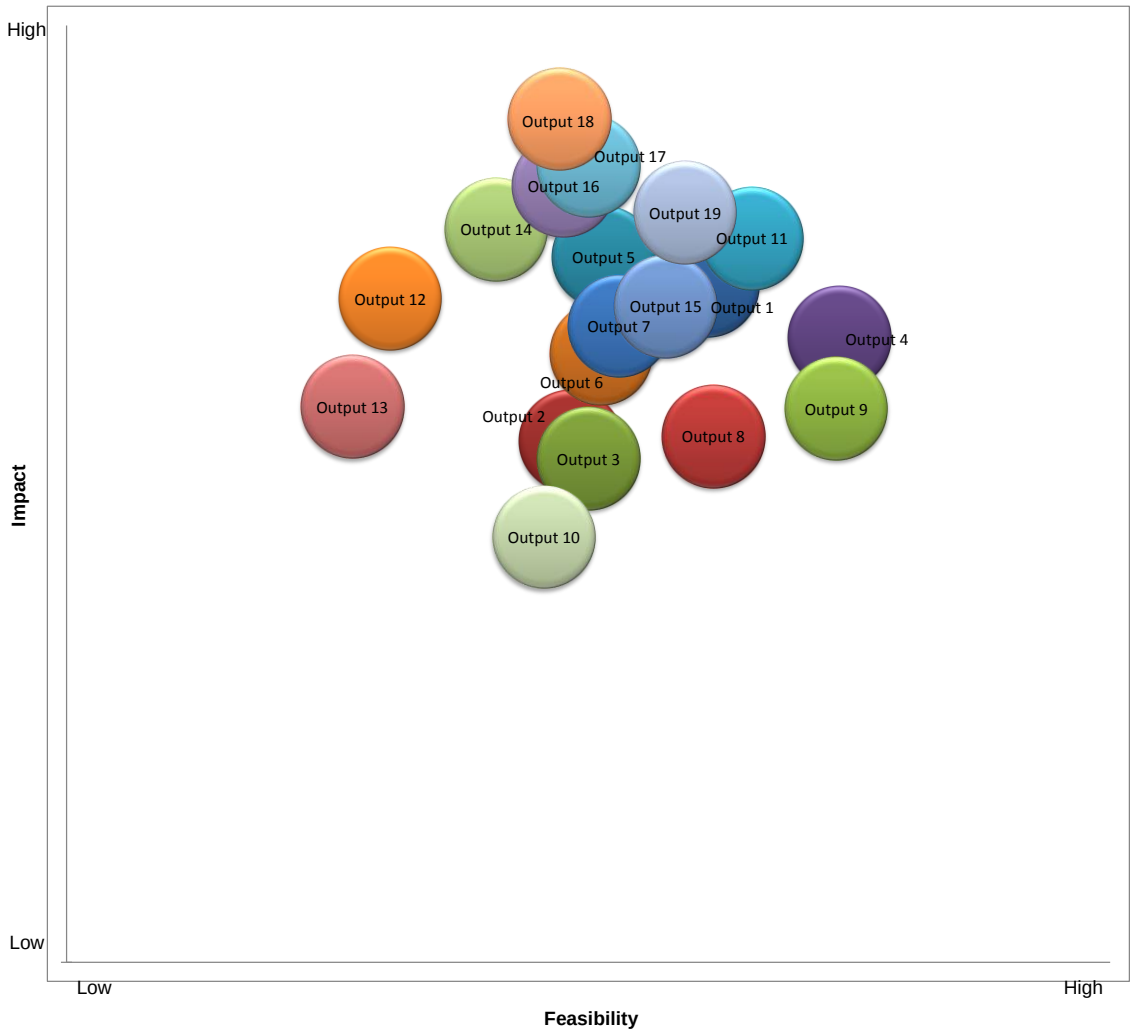


The numbers are small but based on the available responses, there were divergent evaluations between the two groups, especially for output 3 (Balance measures for propensity scores), which regulators considered more frequently ready for implementation and the four main outputs of the benefit-risk assessment (14, 15, 16, 17), which regulators did not consider ready for implementation in contrast to the other stakeholders.

b) Feasibility vs. Impact

Figure 8 displays the plot of outputs according to their feasibility and impact assessment scores. Output 20 was evaluated only once and was not plotted. Outputs with the most favourable profile (high impact and high feasibility) are located in the top right area of the plot, those with an unfavourable profile are in the bottom left area.

Figure 8.



Overall, the graph gives an image of a moderate to high impact of most outputs, but with a moderate feasibility.

Different groups of outputs can be identified:

1- High impact and high feasibility

Output 1	Inventory on drug utilisation data
Output 11	Subgrouping and stratification in statistical signal detection
Output 19	Repository of training material

3- High impact and moderate feasibility

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

3- Moderate impact and high feasibility

Output 4 Comparison of covariate adjustment methods

Output 9 Grouping of existing adverse drug reaction terminologies

4- Moderate impact and low feasibility

Output 12 Statistical signal detection from clinical trials

Output 13 Statistical signal detection from electronic health records

5- Other outputs with variable scores around moderate impact and feasibility.

c) Factors associated with low impact

Two aspects were considered in impact assessment: impact on public health and acceptability by the stakeholders' group. For outputs 2 (Methods to control for confounding) and 3 (Balance measures for propensity scores), the moderate impact was mainly affected with a low impact on public health. For outputs 8 (Characterisation of databases of adverse reactions) and 10 (Novel groupings for adverse reactions), both criteria were affected.

d) Factors associated with low feasibility

Feasibility was assessed according to five aspects: degree of scientific development, time for implementation, impact on human resources, impact on IT resources, and impact on other resources. Table 4 indicates which of these five aspects contributed more frequently to a low feasibility.

Table 4.

Output	Name	Factor(s) affecting feasibility
1	Inventory on drug utilisation data	Impact on resources
2	Methods to control for confounding	Maturity, timelines, resources
3	Balance measures for propensity score models	Maturity, timelines, resources
4	Comparison of covariate adjustment methods	n/a
5	Recommendations for PE studies	Impact on resources
6	Evaluation of disproportionality analysis	Delay for implementation
7	Adverse Drug Reaction Repository	Maturity, timelines, resources
8	Databases for signal detection	n/a
9	Grouping of existing ADR terminologies	n/a
10	Novel groupings for adverse drug reactions	Maturity
11	Subgrouping and stratification in statistical SD	Impact on IT resources
12	Statistical SD from clinical trials	Maturity, timelines, resources
13	Statistical SD from electronic health records	Maturity, timelines, resources
14	Methodologies for benefit-risk evaluation	Impact on IT and human resources
15	Methodologies for graphical representation	Timelines, impact on resources
16	Final tools for graphical B:R representation	Timelines, impact on resources
17	Recommendations on methodologies for B-R	Impact on IT and human resources
18	Development of accessible material to patients	Impact on IT and human resources
19	Repository of training material	Impact on IT and human resources

Impact on IT and human resources was clearly the major concern affecting the feasibility of output implementation. The level of scientific development is the unique concern only for Output 10. Delay for implementation is most frequently associated with concerns about resources.

e) Perspectives

Since the primary focus of this document is on the impact of PROTECT on regulatory activities, Figures 9 and 10 provide a plot of impact and feasibility scores are plotted according to two perspectives: the Regulators' perspective (Figure 9) and the perspective from other respondents (Figure 10). The perspective of other stakeholders has not been further divided and therefore represent the views of industry and academic representatives.

Figure 9. Regulators' perspective

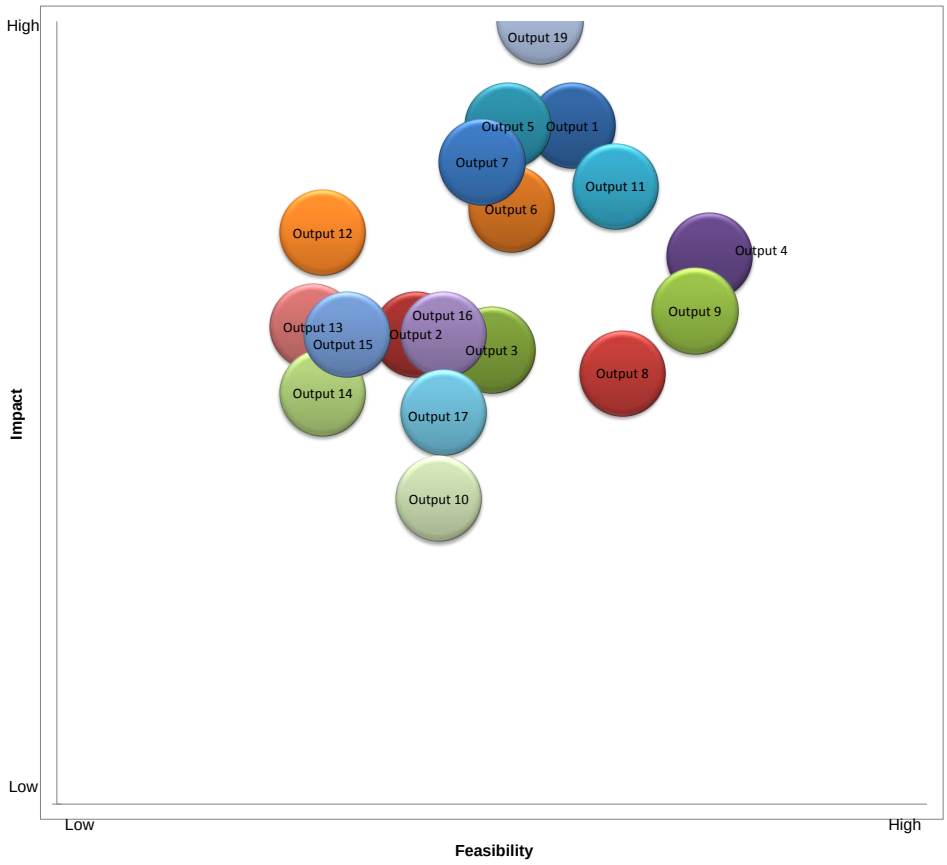
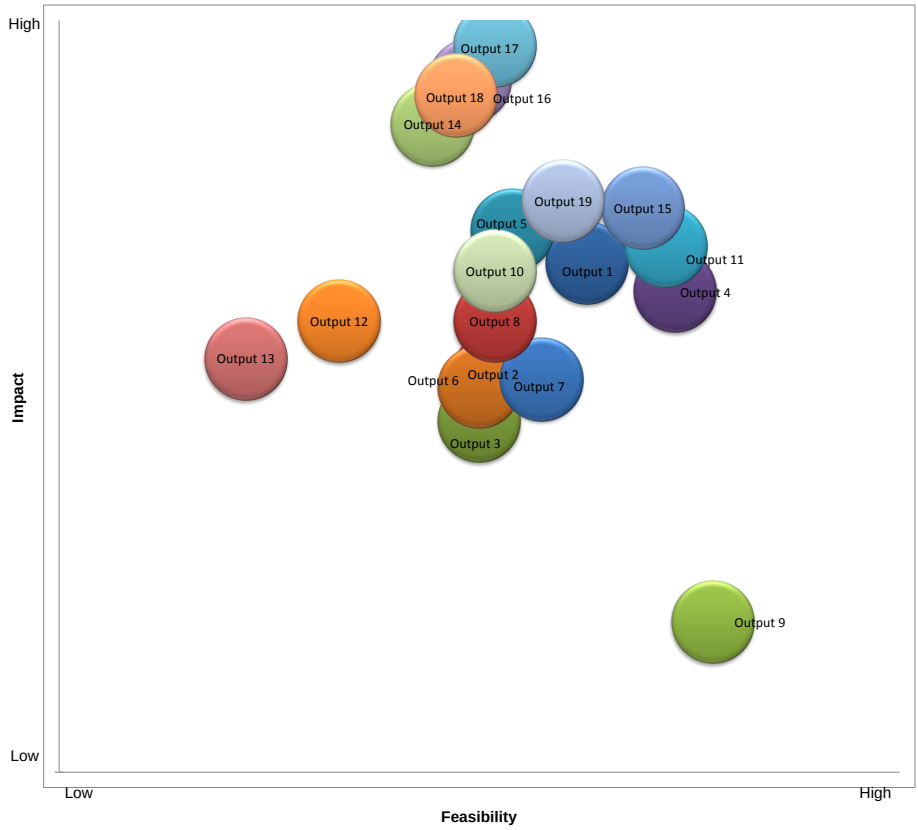


Figure 10. Perspective from other respondents



Figures 9 and 10 illustrate a clear difference between regulators and other stakeholders: while regulators gave a preference to outputs related to methods in pharmacoepidemiology (outputs 1, 5, 6, 7), other stakeholders gave the highest score for impact on outputs related to recommendations for benefit-risk integration and representation (outputs 14, 16, 17, 18), even if feasibility was scored similarly. It should be noted that Outputs with a high impact included a high proportion of responders from industry with percentages of 82% for Output 14, 60% for Output 16, 83% for Output 17 and 50% for Output 18 (however, the percentage for Output 15 was 75%, although this Output was rated lower on Impact). Other differences existed for outputs 9 (Grouping of existing ADR terminologies) and 19 (Repository of training material).

5.2.4. Discussion

5.2.4.1. Methodology

An evaluation of the potential impact of outputs of regulatory science projects if they were implemented is inherently subjective. However, by applying criteria in a methodical way this subjectivity is structured and transparent. In addition, it is not known at the stage of evaluation how all the outputs will be implemented and used. The framework developed and tested in this survey aimed to help identify the project outputs that could be prioritised for implementation. Therefore, it did not specifically aim to retrospectively evaluate the impact on regulatory practice of implemented measures.

The indicators covered two main dimensions: the impact on public health, based on an overall evaluation of impact and the level of acceptability by the stakeholder group, and the feasibility of the implementation, based on an evaluation of the degree of scientific development, the impact on IT and human resources and the timelines for implementation. These two dimensions were plotted one

against the other to represent graphically the relative importance of each output in terms of impact and feasibility.

This simple approach may need to be refined. The classification of the criteria into two main dimensions (Impact and Feasibility) is useful to visualise the balance between the potential impact of an output and the feasibility of its implementation, which would help prioritisation of resource allocation. This classification may however need to be revised. Question I2 (degree of acceptability) could be viewed as related to Feasibility as well as to Impact, although it was considered that a method would have no impact if it is not accepted. On the other hand, questions F1 and F2 could be seen related more to Impact than to Feasibility.

A revised classification could be as follows:

Table 5a. Questions and scoring for the impact evaluation of PROTECT outputs (Revised)

Criterion	Description	Score 1	Score 2	Score 3	Score 4
I1	If the change is implemented, how do you rate its potential impact on public health?	None	Small	Moderate	Important
I2	How do you rate the degree of scientific development of the output?	Inadequate	Incomplete	Nearly complete	Complete
I3	What is your estimate of the delay within which this output could be implemented in practice?	N/A	>2 years	1-2 years	<1 year

Table 5b. Questions and scoring for the feasibility evaluation of PROTECT outputs (Revised)

Criterion	Description	Score 1	Score 2	Score 3	Score 4
F1	How do you rate the degree of acceptability by the group of stakeholders to which you belong?	N/A	Small	Moderate	Important
F2	How do you rate the feasibility of the implementation of the output in terms of IT resources?	N/A	Important	Moderate	Small
F3	How do you rate the feasibility of the implementation of the output in terms human resources?	N/A	Important	Moderate	Small

Further refinement may concern the scoring matrix (i.e. score allocation for each category of a response) and the possible relative weighing of some indicators, but the effect of various scores and weighting on overall results would need to be assessed. In addition, an additive model has been used, i.e. scores have been summed-up over each dimension. Whether a multiplicative model would have been more appropriate could be examined but at this stage of development it was considered that a simple approach was preferable.

The survey was based on a selection of outputs from the PROTECT project. Although attempts have been made to select final outputs, some of them had not been published yet and reference documents consisted in presentations or long reports. This differences does not seem to have influenced the results For testing purpose, 20 outputs have been selected and survey participants were asked to select at least three of them. It should be noted that such number is not necessary and the framework could be applied to only 1 or 2 outputs as at a time.

The testing was done with a survey of participants to the PROTECT symposium. An alternative method for evaluation could be discussions organised with focus groups or in meetings. The advantage of the

survey is however two-fold: it allows to quickly contact a large number of persons with different affiliations and different profiles; and it allows an independent and anonymous evaluation of the potential impact of a project, which would be more difficult in meetings.

5.2.4.2. Participation

There was a low participation to the survey as only 15.6% of the participants to the PROTECT Symposium are assumed to have responded to the survey. Different factors may explain this low participation rate:

- due to the time needed to finalise and present some outputs, three months had elapsed between the Final PROTECT Symposium and the mailing of the survey; many participants may have lost interest in the impact assessment.

- the survey was presented as a test of a framework for impact assessment using the PROTECT outputs as example; it is possible that this presentation attracted less participants than in a real-life situation where opinions would have direct effect on the decision to implement.

- many participants attended the PROTECT Symposium to learn about methods in pharmacovigilance and pharmacoepidemiology; they may have not felt able to assess whether outputs are ready for implementation and what would be their impact.

- 76% of participants to the symposium were not regulators and many of them may have not felt able to assess the potential regulatory impact of PROTECT outputs.

The survey used a convenience sample and participants to the survey could choose which of the outputs they would evaluate. The number of responses per output therefore indicates the interest of the respondents. The large number of responses were received for outputs 1 (Inventory of drug utilisation data), 5 (recommendations for pharmacoepidemiology), 6 (Evaluation of disproportionality analyses), 7 (ADR repository) and 14 (Methodologies for benefit-risk evaluation). These frequencies are not correlated with the Impact-feasibility profile of outputs.

There is no doubt that, were this framework to be implemented in real-life practice, careful consideration should be given to the selected stakeholders and the presentation, which would be the case for any survey. Alternative methods such as focus groups would also be considered.

5.2.4.3. Impact and feasibility of output implementation

Plots of impact vs. feasibility provide a visual representation of the relative importance of outputs as regards future implementation. Three of the outputs that are considered to have a high impact are tangible outputs that are already available and do not require resources for implementation (Inventory of drug utilisation, Development of accessible material to patients and Repository of training material). However, under this framework, the fact that they are established would not necessarily entail a high acceptability and impact on public health. On the other hand, it may be surprising that the ADR repository (output), which is already implemented by regulators, has overall average scores. Examination of the different components of the score showed that three factors of low feasibility (maturity, timelines and resources) were associated with this relatively low scoring.

5.2.4.4. Differences between regulators and other respondents

A clear difference between regulators and other respondants (most of them being from industry) is the evaluation of the degree of scientific development of three outputs related to methodologies for benefit-risk assessment: Outputs 14 (Methodologies for benefit-risk evaluation), 15 (Methodologies for

graphical representation) and 16 (Final tools for graphical B:R representation). There was a consensus for regulators to state that the degree of development of these outputs was inadequate for their implementation (Figure 5), whith a consenus to the opposite direction for other respondants. This difference is interpreted by the differing perspective taken for this evaluation: regulators may have considered the implementation of the outputs in their daily regulatory practice where use of B/R quantitative tools is not currently foreseen, while other responsants may have considered the readiness of the outputs for future implementation.

6. Impact of individual PROTECT outputs

In this section, each individual PROTECT output is examined in order to describe its:

- Characteristics, potential use or impact in regulatory activities
- Past use: whether and where (if applicable) it has been already been included in regulatory or guidance document
- Future use: whether and where (if applicable) it could be included in regulatory or guidance documents.

6.1. Inventory of drug utilisation databases

6.1.1. Description

The inventory of **Drug Consumption Databases in Europe** (http://www.imi-protect.eu/drugConsumption.shtml) 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 summarises the main results by country and provides extensive information for each country. This database was last updated in February 2015 at the end of the 6-mont extension of the PROTECT project. It includes information on 29 countries (from Europe and including Turkey) related to the available data, accessibility and conditions of access, bibliographic references, points of contact for future information.

This data source is unique in that it provides an inventory of resources available in nearly all member states including member states' statistics on reimbursement, dispensing, prescription or sales data on medicinal products. While this is potentially very useful to support safety and benefit-risk assessments, these data sources have limitations, as most of them provide aggregated data on medicinal products at Member State (MS) level.

6.1.2. Past use

There has been anecdotal information that the inventory was used by assessors to check information related to drug exposure at the time of PSUR assessment, and by members of the EURODurg project.

Download statistics had shown reasonably good usage, mainly from the United-States.

The inventory is referenced in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology as a source of information on drug exposure.

In the survey, this output was found to be have a high level of maturity and high impact and feasibility.

6.1.3. Future use

Information from the Inventory has been extracted to be included in the inventory of real world evidence being established by EMA as a support to regulatory decision-making by EMA Committees. For a number of such data sources however, there is no link provided but only a contact point available (with email address and telephone number). For some Member States, the links provided give direct access to the statistics of consumptions of medicinal products. Language aspects also limit the use of some websites.

In the final recommendations of PROTECT WP2, it is recommended that the inventory should be kept updated and that free access should be given to the data for researchers. It is also considered useful to organise a permanent contact and communication between the major providers of drug utilisation, to exchange ideas and compare disparities between data. It can also be useful to produce a complete picture of all aspects of drug utilisation in the country, if possible in a longitudinal way over extended periods of time. Information at European level would however require a time-consuming compilation of heterogeneous product-specific data from various MS with heterogeneity at the level of the naming of products, nature of data and data source. In some cases, data owners would need to be contacted. Although detailed information could be obtained by country, the workload involved for regulatory authorities should be balanced with the validity and precision of sales data that can be obtained from companies upon request. In addition, PRAC or CHMP members may have better access to data sources from their own countries. The inventory seems therefore of limited use for routine benefit-risk evaluation and would be most useful for specific studies. For this purpose, it is well placed in the ENCePP Guide. Reference in other documents about drug exposure should be considered.

As an additional action, the data sources have been considered for inclusion into the inventory of data sources relevant for the real-world evidence strategy developed by the EMA's Surveillance & Epidemiology service.

6.2. Comparison of methods to control for confounding

- **Comparison of methods to control for confounding (Output 2)**
- **Balance measures for propensity score models (Output 3)**
- **Comparison of covariate adjustment methods (Output 4)**

6.2.1. Description

These three outputs include several components related to the testing of different methods to control for confounding for various types of confounding factors, assess the validity of these methods and compare them with more traditional methods such as multivariate statistical analyses and stratification. Methods tested included propensity scores, instrumental variables and marginal structural models. Their validation included simulations and analyses based on real life adverse event-drug data from electronic health records used by PROTECT. These outputs led to a large number of publications in prominent journals in pharmacoepidemiology (these publications are listed in the PROTECT website), including in the special issue of Pharmacoepidemiology and Drug Safety.

6.2.2. Past use

As it was based on simulations, these outputs led to the first publications of PROTECT and they were included in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology at an early stage, already in Revision 3. They were also presented in several conferences of ICPE.

In the survey, they were found to have a moderate impact and feasibility and moderate degree of scientific development. Outputs 2 and 3 were found to have lower levels of scientific degrees of development.

6.2.3. Future use

As these outputs provide methodological recommendations for the design and analyses of the pharmacoepidemiology studies, they do not have a direct impact on the decision-making but they contribute to better planning, analyses and interpretation of drug safety studies, and therefore to better and faster decision-making.They may also influence the review and approval of protocols by the regulators.

It should however be considered that methods evolve with research and in the future this work may be superseded. The fact that these outputs were not considered as fully ready for implementation in the survey may reflect their level of complexity, the ability of some survey responders to understand and judge the outputs. For example, for instrumental variables the research concluded that their usefulness was limited except in case of residual confounding, and this conclusion may have been used for the evaluation of the output.

6.3. Recommendations for pharmacoepidemiological studies

6.3.1. Description

This output (Output 5) is a major output of the PROTECT project and was aimed to significantly improve the design, conduct and analysis of studies, especially in the context of multi-centre studies. This output is the topic of the last chapter of the special PDS issue on PROTECT. Methodological issues that are examined include: consistency of findings across study designs and databases, outcome definition, exposure definition, control of confounding and choice of study population. It further discusses the implications of common study protocols for scientific and operationnal practice and strategies in choosing between multiple study designs.

6.3.2. Past use

The final recommendations were developed after finalisation of all specific studies, therefore at a late stage of the PROTECT project. This might explain that this output was considered ready for implementation by 60% of the respondants and that it obtaind average scores for Impact and Feasibility. Negative impact on resources was the main element evoked for a decrease in feasibility. However, this topic was presented in a specific symposium of several presentations presented at the International Conference of Pharmacoepidemiology in August 2014 (Taiwan). They were also presented in the Final PROTECT Symposium in February 2015. Some of these aspects were included in Revision 4 of the ENCePP Guide in 2015, but not systematically.

6.3.3. Future use

This output may play a major role in defining regulatory strategies for multicentre studies and joint studies. The current publication as a special issue of PDS will already have made a large impact but it is proposed to supplement it with the following activities:

- Inclusion of main messages into ENCePP Guide Revision 5

- Inclusion into Appendix 1 of the GVP Module VIII, or addition of an Appendix 2. Appendix 1 currently provides descriptive information on designs for PASS; it could be reorganised or supplemented to provide more guidance to industry and regulators regarding important aspects linked to PASS such as joint studies, multicentre studies with common protocols or with federated data approach, ….
- Information session to risk management specialists and other relevant EMA staff members.

In addition to its impact on scientific knowledge, this output may have an important impact on regulatory practice by establishing good practice in terms of planning, designing, conducting and analysing studies.

Systematic inclusion into trainings should also be considered.

6.4. Application of methods for disproportionate analysis

- **Evaluation of disproportionality analysis (Output 6)**
- **Lessons learnt from a characterisation of databases used for signal detection (Output 8)**

6.4.1. Description

These two outputs can be addressed together as they were the topics of a publication by Candore et al. in Drug Safety in June 2015 (Comparison of statistical signal detection methods within and across spontaneous reporting databases), and they are also addressed together in the final publication on Signal Detection Practices, also reflected in the Addendum of GVP Module IX Revision 1. The main recommendation from this paper is that the choice of a disproportionality statistic for signal detection should be primarily based on ease of implementation, interpretation and optimisation of resources. As all tested signal detection methods can achieve similar performance by choice of an appropriate signal detection algorithm, the choice should be based on criteria other than signal detection performance.

6.4.2. Past use

The mains conclusions of the publications available at that time have been included in Revision 4 of the ENCePP Guide. They have also been presented in the training session organised in the margins of the Final PROTECT Symposium in February 2015.

A major use of the output of signal detection was the update in 2016 of the electronic Reaction Monitoring Report (eRMR) developed by the Agency for use in EudraVigilance for more than 1500 substances authorised in the EU for which there is a PRAC Rapporteur or Lead Member State. The eRMR is the main tool for signal detection based on individual case safety reports. eRMRs are produced on a monthly or bimonthly basis and provided to the concerned Rapporteurs or Lead Member States. Major changes took place in the eRMR based on the PROTECT results, especially the use of the Relative Odds Ratio (ROR) in place of the Proportional Reporting Ratio (PRR), and the computation of more detailed statistics separately for paediatrics and adults. The recommendations regarding the choice of thresholds for the identification of signals of disproportionate reporting has also been based on the PROTECT results.

6.4.3. Future use

In addition to continuous updates in the ENCePP Guide and the eRMR, the PROTECT recommendations have been used as the backbone to GVP Module IX Addendum I – Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions, which will be finalised and published in 2016 after a public consultation.

6.5. Adverse Drug Reaction Repository

6.5.1. Description

This output (Output 7), also frequently called "SmPC-ADR database", is publicly available on the PROTECT website. It 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. While the first version was established in the context of the research project, it is being used to build the eRMR and it was agreed to have it maintained by the Signal and Incident Management service of the EMA. The datalock point of the version of the database currently available is 30 June 2015.

6.5.2. Past use

The database has been introduced in the eRMR to indicate drug-event combinations that are already listed in section 4.8 of the SmPC. It provides a large amount of time saving by reducing the number of times a signal validator needs to search, open and consult a SmPC to identify whether an ADR is already listed. Although no recent statistics have been generated, the ADR Repository have been frequently downloaded in the past, which may indicate it is also used elsewhere than in the Agency. The database has also been used in research to identify reference list of adverse events-drug pairs to test the performance of signal detection methods or algorithms. The database is also mentioned as a reference in the ENCePP Guide on Methodological standards.

6.5.3. Future use

While the database is the PROTECT output that probably has the highest economic impact, it proves difficult to ensure its maintenance due to the significant resource demand for maintenance and the database has now a delay of more than two years. The process for the maintenance is in place but the time limiting factor is the identification of variations to section 4.8 of the SmPC. Furthermore, the database is becoming a major resource for the translation of lay terms or non-MedDRA terms into the MedDRA classification, which could be used for nationally authorised products. It should also be noted that comments received suggest that additional formats for the database would increase its use, e.g. formats facilitating its use in electronic applications to general practitioners. The Good Signal Detection Practices paper also states that the database provides a useful template to establish a standard minimum structure for all SPC ADR database.

At this stage, there is a risk that this database will become obsolete, with a loss of an important resource-saving tool for the EMA and its stakeholders. All options should be considered to maintain it.

6.6. Groupings of adverse drug reactions

- Grouping of existing adverse drug reaction terminologies (output 9)

- Novel groupings for adverse drug reactions (output 10)

6.6.1. Description

These two outputs can be considered together as, besides separate publications, they are included in the Good Signal Detection Practices article. Interestingly, output 10 provides "negative results", in that they conclude that no advantage has been found in conducting signal detection at levels of MedDRA above the PT level, with recommendations for further research. For output 10, it is concluded that knowledge engineering techniques may be considered as an adjunct to the creation of custom groupings and SMQs designed for the selection and extraction of case reports, but additional research would be necessary. These conclusions were reflected in the evaluation of the maturity of these outputs in the survey. Output 10 received low scores as regards maturity, in line with its innovative nature.

6.6.2. Past use

Output 9 has had an important impact on signal detection and is sparing time and resources that would be spent otherwise in performing signal detection at other levels of the MedDRA classification than the PT level. It is included in the recommendations of the Addendum of GVP Module IX.

6.6.3. Future use

Output 9 will continue to be implemented and recommended. Its prominence in the Addendum of GVP Module IX will support its implementation by others.

Output 10 has been a useful piece of research, but it is not completed. The investigators of this part of the project (INSERM, France) are participating in other research projects and may be able in a positon to continue their research.

6.7. Subgrouping and stratification in statistical signal detection

6.7.1. Description

This output (Output 11) includes a set of recommendations regarding subgroup analyses of spontaneous report databases. The main conclusion is that subgroup analyses may be beneficial in routine first-pass signal detection and should be considered. Stratified/adjusted analyses are unlikely to provide added value.

6.7.2. Past use

This output already had an impact for signal detection with a subgrouping of cases of EudraVigilance by age category in the electronic Reaction Monitoring Report. It is discussed in the Good Signal detection Practices Document and the GVP IX Addendum.

6.7.3. Future use

This output is likely to have impact on signal detection practices and consideration should be given on how to best train pharmacovigilance specialists for such output, as especially on how to decide when to subgroup and when not to subgroup ICSRs. Detailed recommendations will be provided by specific guidance expanding on the GVP Module IX addendum.

6.8. Statistical signal detection from clinical trials

6.8.1. Description

This output (Output 12) is mainly based on one publication by a single author regarding ximelagatran (Southworth et al. Stat Med 2014) and an overview of the methods and approaches presented in the training session of the PROTECT symposium. This information has been integrated in the Good Signal Detection Practices article and supplemented with a literature review and further discussion of the issue. This has led to a set of eight fully elaborated recommendations. Even if they are not all based on original results and they need to be further tested, the Good Signal Detection Practices recommendations on extreme value modelling, multiplicity adjustement as a tool in signal detection and use of the Bayesian Hierarchical model provide original thinking on better use of clinical trials for early signal detection and identifiying of possible safety issues to be further explored in the course of drug development.

6.8.2. Past use

The recommendations offer areas for further investigation. Therefore, it is not surprising that few respondents in the survey considered it not to be ready for implementation, although the Impact dimension was higher than average (Figure 7).

6.8.3. Future use

Signal detection from clinical trials can benefit from the randomisation of treatment groups, which addresses the issue of known and unknown confounding and facilitates ascertainement of imbalances in incidence of adverse events. The study on ximelagatran also showed that results from phase II trials were predictive of the phase III results (which led to refusal of approval in the US) and could therefore lead to economic savings and avoidance of drug testing in humans. Much work is however needed to further test these findings to other data and situations. It is not known at this stage if the method would be applicable to phase IV clinical trials.

6.9. Statistical signal detection from electronic health records

6.9.1. Description

This output (Output 13) is based on three studies which led to two publications.These results and accompanying recommendations are also presented in the Good Signal detction Practices publication. They show that longitudinal observational data are useful to detect increased rates of multifactorial

ADRs but evidence is lacking regarding their usefulness for signal detection for all drugs and medical events. Therefore, at this stage, longitudinal observational data cannot replace spontaneous ICSRs for signal detection and further explorations are needed. In addition, signal detection in longitudinal onservational data should include clinical, pharmacological and epidemiological review of identified temporal associations. It should also take into account for the limitations of the underlying data, and the selection of the data set should take into account the size and scope of the dataset.

Although it is acknowledged that the body of evidence is currently insufficient to provide robust recommendations on the merits of signal detection in longitudinal observational data, these results and recommendations have examined several situations where this was done in the past and may trigger further research.

6.9.2. Past use

This work has led to two scientific publications in PDS and Drug Safety. As for signal detection from clinical trials, the survey's results show that respondants consider this output not ready for implementation. This evaluation reflects the recommendations (published after the survey was performed) that further research is needed.

6.9.3. Future use

Whilst this research provided a very good basis for the further evaluation of the performance of longitudinal observational data in signal detection, there is still a long way to go before using them in routine signal detection, especially for specific medicinal products. Further research would be needed about situations where these data would detect signals at a reasonable cost in terms of false positives, given that, without a clinical review, the majority of highlighted associations would have been false positives. It will be necessary to examine what is needed to improve on the situation: better statistical techniques, better algorithms, better data or other elements.

6.10. Methodologies for benefit-risk evaluation

- **Methodologies for benefit-risk evaluation (Output 14)**
- **Recommendations on methodologies for B-R integration and representation (Output 17)**

6.10.1. Description

These outputs have been the topic of a publication in PDS (Sharul Mt-Isa et al., PDS 2014;23:667-678) presenting a systematic review and classification of available methodologies. A total of 49 methodologies were reviewed in depth, classified and appraised to inform future use. The authors recommended 13 of them for further appraisal for use in the real life benefit-risk assessment of medicines. The 49 methodologies are also described and explained in a specific website (http://protectbenefitrisk.eu/methods.html). These 13 methodologies were further used in 8 case studies fully described on the website and summarised in another publication (Hughes et al. PDS 2016; DOI: 10.1002/pds.3958). It provides a practical guidance for stuctured approaches to benefit-risk assessment as tested in real-world problems, taking the scientific community closer to a harmonised approach to benefit-risk assessment from multiple perspectives. The aticle provides recommendations not only on use of specific methods but also on the approach and different stages of benefit-risk assessment.

6.10.2. Past use

Whilst the first publication already changed the landscape of benefit-risk assessment through a comprehensive identification and assessment of benefit-risk assessment, with numerous applications, this work culminated in the second publication and its description in a public website. It changed the landscape of research in this field. The methods and approaches were recommended as a starting point to continue work in several IMI-funded research projects, such as ADVANCE, GetReal or PREFER. They were also used in the CHMP Benefit-risk methodological project.

It is noteworthy that a search on Google for the terms "Benefit-risk assessment" returns the PROTECT description of methods as one of the first non-advertised references.

6.10.3. Future use

This work has "cleaned" this field and is a cornerstone for future research. There will be a "before" and an "after" PROTECT, even if it is difficult to state at this stage what will be the practical applications in regulatory practices. PROTECT has shown that they can be used in practice. It is noteworthy that in the survey these two outputs were found to have a high level of readiness for implementation and were reported to have a high impact. There is however a sharp difference between regulators and other participants. This difference may reflect some of the respondents' *willingness* for these outputs to have an impact.

6.11. Methodologies for graphical representations

- **Methodologies for graphical representation (Output 15)**
- **Final tools for graphical representation (Output 16)**

6.11.1. Description

As there was a lack of consensus on which visual representations are most suitable to display benefit-risk profiles, PROTECT has reviewed, described and illustrated 16 ways in which benefits and risks are presented and communicated. This work is presented on the specific website, which is best suited for the representation of the methods. (http://protectbenefitrisk.eu/visualisations.html). The review of visual representations of benefits and risks has been conducted in two stages. The first stage evaluated the suitability of visuals for the benefit-risk approaches included in the reviewed methodologes. The second stage explored and identified suitable visuals to communicate benefits and risks to different stakeholders in different situations. This second stage included the use of dynamic and interactive visualisation methods. Interactive visual displays available for free on the GapMinder website were also tested and presented.

6.11.2. Past use

Visual displays are available in many electronic tools (such as Excel) but PROTECT provides in addition a guide on their use for benefit-risk representations. This guide has a much wider application than benefit-risk assessment.

6.11.3. Future use

The PROTECT benefit-risk website provides a link to the Gap Minder website where visual representations may be built, including interactive representations that allow to see how a graph

changes by changing numbers. PROTECT has not developed a software or an application that would provide a "ready to use" solution. There are three reasons for this. First of all, such software or application would have required resources beyond those available to PROTECT, secondly the temporary nature of the PROTECT project would have made such tool difficult to maintain and update and thirdly other software (e.g. those to perform MCDA analyses) already exist (e.g.HighView). It was therefore considered more important to provide recommendations on how to interpret and correctly use different visual representations than to provide a technical tool to create them. As regards the evaluation of the potential impact, the same difference as the one described in 6.10.3. was found in the survey.

6.12. Training material on benefit-risk evauation

- **Development of accessible material to patients (Output 18)**
- **Repository of training material (Output 19)**

6.12.1. Description

The PROTECT Benefit-risk website (http://protectbenefitrisk.eu) was created to provide training material. It includes a specific section providing a guide for patients and interested members of the public who are new to the benefit-risk assessment of medicines or would like to know more about the topic. This section was created by the Patient and Public Involvement project of PROTECT WP5 which involved patients' associations.

6.12.2. Past use

From anecdotal evidence, the PROTECT benefit-risk website is being used in training programmes, but the extent of this use is not known. Similarly the extent to which patients and other persons interested are using the website is not well known. However, a search for "benefit risk" in Google on 18th May 2016 identified the PROTECT Benefit-Risk website at the top of the list and the terms "Benefit-risk website" refers almost exclusively to the PROTECT benefit-risk website, which indicates it is probably the most frequently uploaded one or the main one publicly available.

6.12.3. Future use

The direct impact of these outputs (Outputs 19 and 20) are difficult to quantify. However, there is some evidence that it is useful and that it being used a ground work for further research and benefit-risk evaluations.

6.13. Enhanced software for benefit-risk evaluation

6.13.1. Description

The Aggregate Data Drug Information System (ADDIS) is an evidence-based decision support system for health care policy decision making that concerns alternative treatment options. ADDIS 2 is under development in order to provide a platform on which researchers can collaborate to perform systematic reviews, data extraction, evidence synthesis and decision analysis. This interface is freely available on the website at https://mcda.drugis.org (only registration is needed). It is a user interface for preference elicitation in MCDA models. It was initially funded by TI Pharma project Escher and integrated in ADDIS 2 with funding from IMI GetReal. Further development and the creation of training materials was supported by IMI PROTECT in the context of the 6-month extension of the project. The website mentions that the MCDA tool is relatively mature, but lacks solid documentation.

6.13.2. Past use

The MCDA plateform on the ADDIS website is new and has therefore not been used previously.

6.13.3. Future use

The MCDA plateform is connected to the ADDIS and therefore allows to use clinical trial data to build effect tables and perform MCDA analysis by incorporating patient preference information. At this stage, the extent of its use and its usefulness in practice is not known.

6.14. Results of prospective study with data collection directly from consumers

- **Results of prospective study on medication use and lifestyle factors (Output 21)**

6.14.1. Description

This output (Output 21) is the main output of WP4 of PROTECT, which has been published in December 2015 (Dreyer et al. Direct-to-Patient Research: Piloting a New Approach to Understanding Drug Safety During Pregnancy, JMIR Public Health and Surveill 2015;1(2), e22). Based on an internet feasibility study in 2,065 pregnant women, it concludes that self-reported information on medication use as well as other potential teratogenic factors can be collected via the Internet, although recruitement costs are not insubstantial and maintaining follow-up is challenging. However, clinical input may be needed to fully understand patients‘ medical histories and capture birth outcomes.

6.14.2. Past use

Given its publication in December 2015, these results have not been evaluated in the survey of participants to the PROTECT Final Symposium.

6.14.3. Future use

This study was a feasibility study done to assess the extent to which women recruited without the intervention of health care professionals will provide information useful for pharmacovigilance through direct-to-patient data collection. It was therefore not designed to be immediately applicable. It concluded that direct to patient is a useful method for learning about use of prescription and non-prescription medication use, including medications that may be administered in hospitals, emergency room or as outpatients, or used on an as-needed basis, and in some cases these data are more complete than data from prescription registers and electronic health records. These are useful results which may encourage further research on use of new technologies for pharmacovigilance as use of internet through smartphones would not be currently the main communication channel with pregnant women.

6.15. Comparison of advertising methods for data collection directly from consumers

- **Comparison of ability and cost-effectiveness of advertising methods (Output 22)**

6.15.1. Description

The authors of a publication derived from this output (Output 22) [Richarson et al. An International Study of the Ability and Cost-Effectiveness of Advertising Methods to Facilitate Participant Self-Entolment Into a Pilot Pharmacovigilance Study During Early Pregnancy. JMIR Public Health Surv 2016;2(1), e13] compared several direct-to-patient advertisement methods (websites, emails, leaflets, television and social media plateforms) and found large differences between countries.

6.15.2. Past use

These results have just been published and could therefore not be evaluated in the past. They were not included in the survey of the PROTECT symposium.

6.15.3. Future use

In practice, it is unclear how the data could be used in the future, but they serve as a warning for future researchers that methods of advertising have different effectiveness and their costs and feasibility may greatly vary according to country. The absolute costs are most probably not generalisable due to local factors and the rapid advances in this field that could influence them.

6.16. Challenges related to data protection in direct-to-patient research

6.16.1. Description

This output (Output 23) was the earliest one published by WP4 (Dreyer et al. Balancing the Interests of Patient Data Protection and Medication Safety Monitoring in a Public-Private Partnership. JMIR Med Inform 2015;3(2):e18). Its value lies in the practical illustration of practical aspects of studies: application of legal requirements for data protection in this primary data collection study greatly varies from country to country (1 day to 9 months in 4 countries) and is a limiting factor for researchers. While it is not clear whether the times indicated are truly generalisable to other types of studies, it raises questions about barriers that might apply to direct-to-consumers surveys.

6.16.2. Past use

None, besides a publication and presentations.

6.16.3. Future use

This publication represents a warning to researchers regarding the national implementation of the data protection legislation. In view of the future implementation of the General Data Protection Regulation, it also raises the question about the need to collect information of how it will be applied at the Member State level.

7. Discussion

Impacts on public health and feasibility of outputs in terms of resources were identified as two main criteria to judge the impact of PROTECT outputs. While the impact on resources referred to costs linked to the implementation of outputs, a number of PROTECT recommendations will also lead to savings due to improved efficiency of the system. Based on the review of the PROTECT outputs, the overall impacts of PROTECT on public health and resources are listed below. Possible topics for future research are also listed.

7.1. Overall impact on public health

- ***Faster and better detection of safety signals from spontaneous report databases***
  - The SmPC-ADR database supports the targeting of signal detection activities to new adverse events by providing a tool to flag ADRs listed in the SmPC and facilitating assessment of the masking effect of well-known ADRs.
  - Methodological recommendations will improve the timeliness and validity of signal detection.
  - Methods for sub-grouping in signal detection will facilitate signal detection for vulnerable groups such as paediatrics and geriatrics.
  - Recommendations will facilitate assessment of novel methods for signal detection and evaluation of their added value for public health
- ***Improved and faster evaluation of safety signals supporting robust decision-making***
  - The Inventory of drug consumption databases allows rapid identification of reliable and validated data sources on drug consumption (at the aggregated level) and support estimations of incidence rates of ADRs at population level and population attributable risks (PAR) of ADRs
  - Methodological recommendations on pharmacoepidemiological studies will support better and faster benefit-risk assessment on medicines by increasing overall study quality, increasing consistency in findings from drug safety studies across multiple designs, analyses, databases and countries, and by increasing confidence in results of observational studies using robust methods.
- ***Ground work for for future development of methods for benefit-risk assessment applied to regulatory decision-making.***
  - Shared framework for B/R assessment will support communication on benefits and risks and, in the long term, support decision-making.
  - Recommendations will facilitate better understanding of use of patient preferences (available from literature or survey) for decision-making.
- ***Improvement in data collection from pregnant women and other vulnerable groups***
  - Results have shown that it is possible to collect data directly from pregnant women on drug exposure and lifestyle factors early during pregnancy via the internet.
  - Results suggest that data collection may also be possible in target populations that are difficult to recruit and retain using conventional methods (e.g. adolescents, people in full time work).

7.2. Overall impact on resources

Positive impact on Agency's, national and industry's resources may arise from the following outcomes:

- The SmPC-ADR database decreases the need to consult SmPC to evaluate prior knowledge of ADRs when reviewing the electronic reaction monitoring report (eRMR) and therefore saves reviewers' time.
- By allowing inclusion of a field « LISTED » in the eRMR for reactions included in section 4.8 of the SmPC, the SmPC-ADR database leads to efficiency gain in the auditing of the eRMRs reviewed for every signal validator (at least one eRMR per signal validator is audited each year) ; time gain for the auditor is around 20-30' per eRMR depending on the number of suspected ADRs.

- The Inventory of drug consumption databases allows time saving by providing a resource to identify reliable and valid source of data and how to retrieve this information (with contact points).
- Several recommendations on methods for signal detection will support resource saving by:
  - Supporting the use of available safety data from spontaneous reports in a more efficient and appropriate manner at the levels of regulatory authorities and pharmaceutical companies
  - Recommending that the choice of statistical measure for signal detection should be based on ease of implementation, interpretation and optimisation of resources, as there are no fundamental differences between them for a same signal detection algorithm (e.g. threshold used); therefore, it may not be necessary to invest into expensive software if simple methods are adequate.
  - Providing clear guidance on the choice of terminology used for signal detection, i.e. that there is no added value in performing signal detection at a MedDRA level higher than the Preferred Term.
  - Increasing the efficiency of signal detection for targeted groups, by recommending, based on case studies, that sub-grouping performs better than stratification for such analyses.
  - Stating that electronic health records may not be more effective than spontaneous data for signal detection and require clinical review of detected signals. Therefore, resources should not be allocated to such activity if there is no specific objective.
- The recommendations on methodologies of pharmacoepidemiological studies may increase the efficiency and speed of multi-database studies by providing an efficient approach based on common-protocol study approach and an EU network including data sources and applying common methodologies.
- The recommendations for benefit-risk integration and representation provided the most comprehensive review and evaluation of methods and visualisation techniques up to date, and this review will not need to be repeated by other researchers. Moreover, it clarified the concepts on benefits and risks and will support efficient B/R evaluations.
- The work performed on data collection directly from consumers showed that the internet and direct-from-patient data collection on medical treatments and lifestyle variables is possible and adds value for drug safety evaluation. It may therefore give access to additional data sources and methodologies.

7.3. Impact on future research

PROTECT has led to results that are amenable to further research. Further research may include the following topics:

- General practitioners-based electronic health records or claims data are the main data source for drug monitoring and signal evaluation, and this scope may not be adequate for all situations. Mechanisms to gain access to and analyse other data sources are needed, e.g. in-hospital data, pharmacogenomics, specialists' registries.
- As regards signal detection, the following aspects could be further investigated:
  - Comparison of the performance on the positive predictive value of various sources of safety signals and different algorithms
  - Further research on the added value of electronic health records for signal detection

- Further research on methods for signal detection from clinical trials
- Signal detection for fixed-dose combinations.

- As regards recommendations for benefit-risk integration and representation, PROTECT has been cited in other IMI calls (such as ADVANCE, GetReal, ADAPT-SMART, PREFER…) as the starting point for further research. This research could cover:
  - methods for benefit-risk assessment during the life-cycle of the product using different sources of data and handling of bias and uncertainties,
  - benefit-risk assessment in population sub-groups: children, the elderly, pregnant women,..
  - testing the implementation and measuring the added value of quantitative methods for benefit-risk evaluation in the regulatory decision-making process.
- In terms of innovative methods to collect pharmacovigilance data directly from for consumers, PROTECT has shown that this approach may help provide data not available from other sources. Further development in this field can include best use of new technologies like smartphones. Research in this field has now started with the IMI WEB-RADR project. Given the speed of the development of such technologies, new approaches to study their validity and usefulness should be investigated.

8. Conclusion

Based on the review of the PROTECT outcomes, PROTECT has achieved the objectives and deliverables of the Call Topic to which PROTECT applied. In addition, outcomes linked to signal detection and evaluation are being implemented into routine pharmacovigilance and regulatory practice and start to have a positive impact on public health and resources.

In the course of this evaluation of the impact of PROTECT outcomes, a survey tool to measure the balance of Impact on public health and Feasibility has been developed and piloted. Analysis of the results identified a number of characteristics that could be improved for evaluation of other projects.

A very concrete implementation of outcomes is the use of the SmPC-ADR database to create on a monthly/bimonthly basis the electronic Reaction Monitoring Reports by EMA for national competent authorities for >1500 active substances. Other examples include the integration of the inventory of drug consumption databases into the inventory of real-world evidence data sources being created by the EMA, the integration of recommendations on signal detection into the Addendum of GVP Module IV (Signal Management) as well as in Revision 5 of the ENCePP Guide on Methodological standards in pharmacoepidemiology, use of the established network for pharmacoepidemiological studies in an EMA-funded study (following a tendering procedure), inclusion of relevant recommendations on pharmacoepidemiologicals studies in Annex 1 of GVP Module VIII and in Revision 5 of the ENCePP Guide. It is noteworthy that those outcomes were also those considered as having the highest impact and feasibility of implementation in the survey of stakeholders.

The groundwork done on benefit-risk methodologies and visual representation is a leap forward towards the understanding of the values and usefulness of benefit-risk methods. Further work is on-going to assess their implementation into regulatory decision-making.

Research on direct-to-patient data collection in pregnant women has shown the added value of the internet for studies on medicines. Results are important in a very quickly changing environment where patients are actively sharing information.