PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PROTECT : from outputs to outcomes

Turning regulatory science into better pharmacovigilance

Tenth stakeholder forum on the pharmacovigilance legislation

21 September 2016

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European Medicines Agency

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

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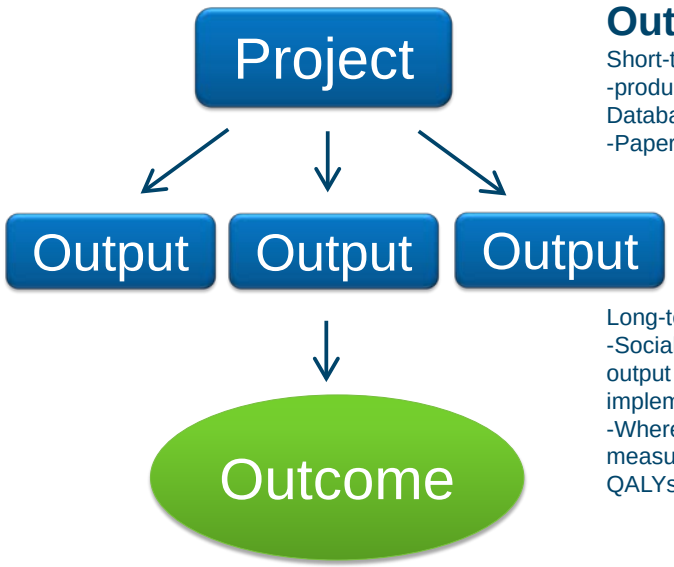
Objective of this presentation

To discuss outcomes of PROTECT in terms of impact on benefit-risk monitoring and decision-making of medicines and potential socio-economic impact.

Translation of outputs into outcome



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

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

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

In this presentation

- Goal and objectives of PROTECT
- Key outputs
- Main outcomes
- Conclusions

PROTECT Goal and objectives

First IMI call, 30 April 2008

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

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

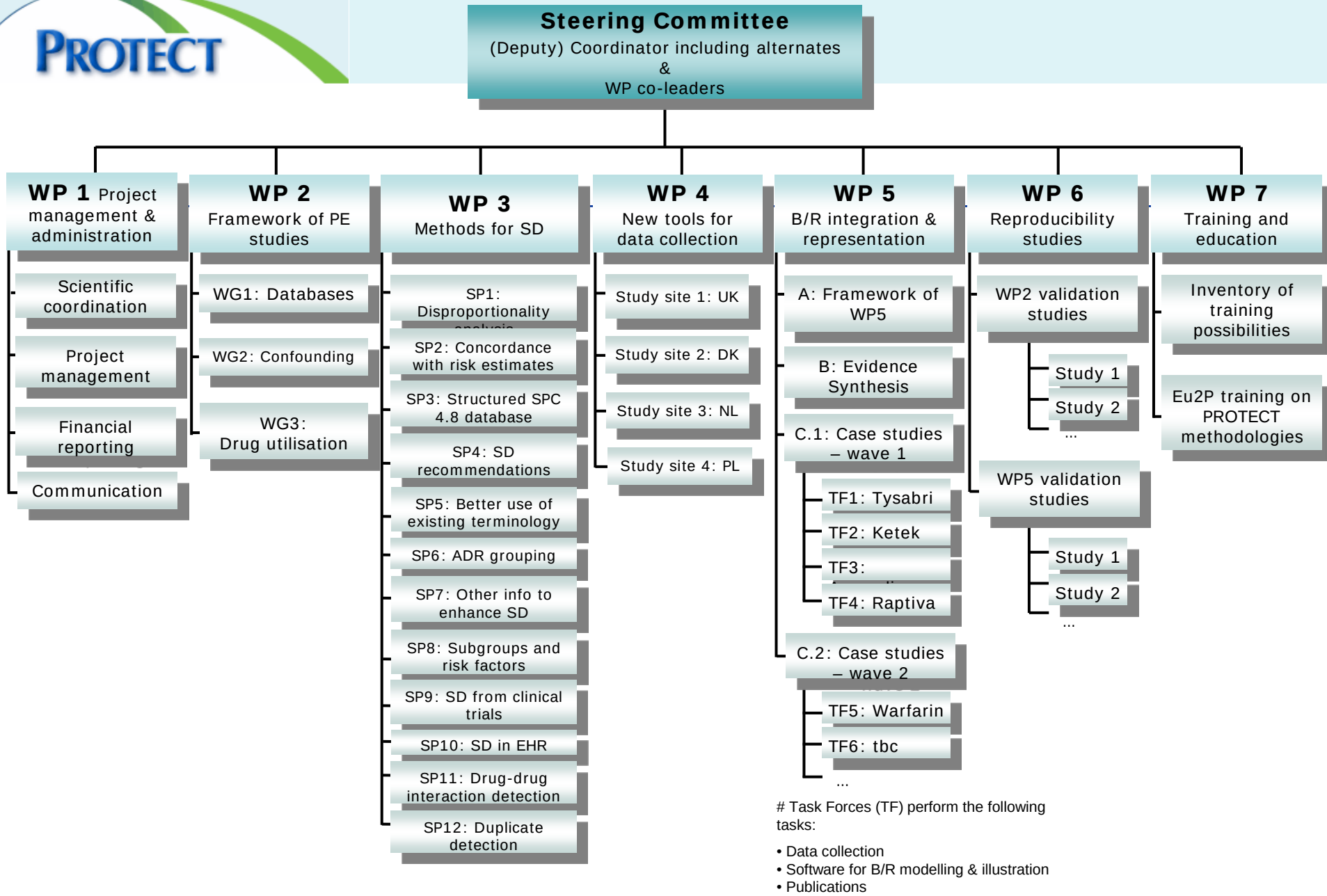
Key Deliverables from Call text

KD 1. New methods of data collection in pharmacovigilance including methods for collecting data in the natural language and research on how to simplify data collection from reporters whoever they are

KD 2a and 2b. Evaluation of methods for signal detection and signal evaluation. Determination of these methods' performance characteristics and capacity for early detection of AEs.

KD 2c. Establishment of methods for graphical expression of the benefit and risk of medicinal products using evidence from clinical trials, epidemiology studies and spontaneous reports.

KD 3. Investigation and development of standards and processes for interoperability and sharing of European epidemiology data sources to determine their capacity for pharmacovigilance, signal detection and large epidemiology studies for quantification of benefit and risk outcomes.



Task Forces (TF) perform the following tasks:

- Data collection
- Software for B/R modelling & illustration
- Publications

35 partners

01/09/2009 – 31/08/2014 + 6-month extension to 28/02/2015

Outputs – some numbers

- 75 original articles in peer-review journals to-date
- > 100 (published) presentations in conferences and meetings
- 2 specific symposia at the International Conference of Pharmacoepidemiology (ICPE)
- 2 databases
- 2 websites (http://www.imi-protect.eu - http://protectbenefitrisk.eu)
- Final Symposium (18-20 February 2015)

- 14 doctoral theses, 3 master theses

- Integration of results in educational programmes (e.g. Eu2P)
- Integration of results in annual revisions of EnCePP Guide on Methodological Standards in Pharmacoepidemiology and Pharmacovigilance

PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

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PROTECT Symposium NEW

General Presentations

eRoom - partners only

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

Key achievements of PROTECT

Framework for pharmacoepidemiology studies
- Presentations (33)
- Publications (38)
- Reports and Databases (1)

Methods for Signal Detection
- Presentations (15)
- Publications (12)
- Reports and Databases (2)

New Methods for data collection from consumers
- Presentations (6)
- Publications (3)
- Reports and Databases (1)

Benefit-Risk integration and representation
- Presentations (16)
- Publications (4)
- Reports and Databases (14)

Replication studies
- Presentations (2)
- Publications (2)
- Reports and Databases (1)

Training and Communication
- Presentations
- Publications
- Reports and Databases (1)

http://www.imi-protect.eu

Main Outcomes

- SmPC-ADR Database
- Inventory of drug consumption databases
- Good signal detection practices
- Recommendations for pharmacoepidemiological studies
- Recommendations for benefit-risk assessment methodologies and visual representation
- Recommendations for Direct-to-Patient Research

SmPC-ADR Database

- Publicly available structured Excel database of all ADRs listed in section 4.8 of the SmPC of CAPs;
- Based exclusively on MedDRA terminology;
- Provides characterisation of ADRs (frequency, age, gender, causality, class warning, source of information, date).

18 July 2016
EMA/494345/2016
Inspections and Human Medicines Pharmacovigilance

ADR repository
Data lock point 30 June 2015

PRODUCT	SUBSTANCE	DATE OF MOST RECENT SPC	ADR AS IT APPEARS IN THE SPC	MEDDRA PT	PT CODE	SOC CODE	AGE GROUP	GENDER	CAUSALITY	FREQUENCY	ASS WARNI	INICAL TRI	ST-MARKET
Abasaglar	GLARGINE	09/09/2014	ALLERGIC REACTIONS	HYPERSENSITIVITY	10020751	10021428	0	0	0	2	1	0	0
Abasaglar	GLARGINE	09/09/2014	ANGIOOEDEMA	ANGIOEDEMA	10002424	10040785	0	0	0	0	1	0	0
Abasaglar	GLARGINE	09/09/2014	BRONCHOSPASM	BRONCHOSPASM	10006482	10038738	0	0	0	0	1	0	0
Abasaglar	GLARGINE	09/09/2014	DYSGEUSIA	DYSGEUSIA	10013911	10029205	0	0	0	1	0	0	0
Abasaglar	GLARGINE	09/09/2014	HYPOGLYCAEMIA	HYPOGLYCAEMIA	10020993	10027433	0	0	0	5	0	0	0
Abasaglar	GLARGINE	09/09/2014	HYPOTENSION	HYPOTENSION	10021097	10047065	0	0	0	0	1	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE HIVES	INJECTION SITE URTICARIA	10022107	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE INFLAMMATION	INJECTION SITE INFLAMMATION	10022078	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE ITCHING	INJECTION SITE PRURITUS	10022093	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE PAIN	INJECTION SITE PAIN	10022086	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE REACTIONS	INJECTION SITE REACTION	10022095	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE REDNESS	INJECTION SITE ERYTHEMA	10022061	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	INJECTION SITE SWELLING	INJECTION SITE SWELLING	10053425	10018065	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	LIPOATROPHY	LIPOATROPHY	10024604	10040785	0	0	0	3	0	0	0
Abasaglar	GLARGINE	09/09/2014	LIPODYSTROPHY AT THE INJECTION SITE	LIPODYSTROPHY ACQUIRED	10049287	10040785	0	0	0	0	0	0	0
Abasaglar	GLARGINE	09/09/2014	LIPOHYPERTROPHY	LIPOHYPERTROPHY	10062315	10040785	0	0	0	4	0	0	0
Abasaglar	GLARGINE	09/09/2014	MYALGIA	MYALGIA	10028411	10028395	0	0	0	1	0	0	0
Abasaglar	GLARGINE	09/09/2014	OEDEMA	OEDEMA	10030095	10018065	0	0	0	2	0	0	0
Abasaglar	GLARGINE	09/09/2014	RETINOPATHY	RETINOPATHY	10038923	10015919	0	0	0	2	0	0	0
Abasaglar	GLARGINE	09/09/2014	SHOCK	SHOCK	10040560	10047065	0	0	0	0	1	0	0
Abasaglar	GLARGINE	09/09/2014	SKIN REACTIONS	SKIN REACTION	10040914	10040785	0	0	0	0	1	0	0
Abasaglar	GLARGINE	09/09/2014	SODIUM RETENTION	SODIUM RETENTION	10041277	10027433	0	0	0	0	0	0	0
Abasaglar	GLARGINE	09/09/2014	VISUAL IMPAIRMENT	VISUAL IMPAIRMENT	10047571	10015919	0	0	0	2	0	0	0
Abilify	ARIPIPRAZOLE	24/04/2015	ABDOMINAL DISCOMFORT	ABDOMINAL DISCOMFORT	10000059	10017947	0	0	0	0	0	0	1
Abilify	ARIPIPRAZOLE	24/04/2015	ABDOMINAL PAIN UPPER	ABDOMINAL PAIN UPPER	10000087	10017947	1	0	0	4	0	1	0
Abilify	ARIPIPRAZOLE	24/04/2015	AGITATION	AGITATION	10001497	10037175	0	0	0	0	0	0	1

SmPC-ADR Database

Used for the monthly/bimonthly creation of the electronic Reaction Monitoring Reports by EMA for national competent authorities for >1500 active substances.

Updated by EMA - last DLP: 30 June 2015
downloaded 150-200 x/month

Impact on public health:

- targeting of signal detection activities to adverse events not listed in SmPC
- facilitate assessment of masking effect of well known ADRs

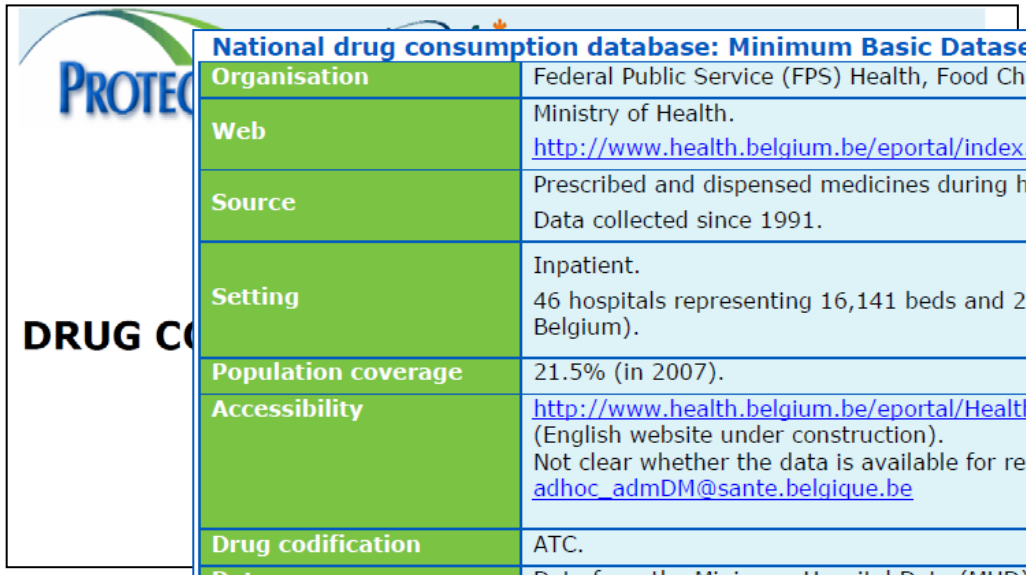
Impact on resources:

- faster evaluation of prior knowledge on ADRs

Inventory of drug consumption database

Publicly available and downloadable comprehensive and structured source of information on drug consumption in Europe.

- Master document + Country profile document
- Covers 28 countries – last updated February 2015



National drug consumption database: Minimum Basic Dataset (MBDS)

Organisation	Federal Public Service (FPS) Health, Food Chain Safety and Environment.
Web	Ministry of Health. http://www.health.belgium.be/eportal/index.htm?fodnlang=fr
Source	Prescribed and dispensed medicines during hospital stay. Data collected since 1991.
Setting	Inpatient. 46 hospitals representing 16,141 beds and 2,467,698 patient stays (21.5%; information on 214 hospitals in Belgium).
Population coverage	21.5% (in 2007).
Accessibility	http://www.health.belgium.be/eportal/Healthcare/Healthcarefacilities/Registrationsystems/index.htm?fodnlang=fr (English website under construction). Not clear whether the data is available for researchers outside Belgium. adhoc_admDM@sante.belgique.be
Drug codification	ATC.
Data	Data from the Minimum Hospital Data (MHD), Minimum Clinical Data (MCD), Minimum Nursing Data (MND), and Minimum Psychiatric Data (MPD).
Record period	Since 1991.
Language	French.
Record linkage	Yes, with other hospital statistics.

Inventory of drug consumption database

Impact on public health:

- Identification of reliable and validated data sources on drug consumption (aggregated level)
- Used to estimate incidence rates of ADRs at population level and population attributable risks (PAR) of ADRs

Impact on resources:

- Time gained in identifiying reliable and valid source of data and how to retrieve this information.

Good Signal Detection practices

Set of recommendations on signal detection from spontaneous reports, electronic health records and clinical trials that can be converted into meaningful and implementable outputs and for further research.

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 April 2016
EMA/282386/2016

Guideline on good pharmacovigilance practices (GVP)
Module IX Addendum I – Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions

Drug Saf (2016) 39:469–490
DOI 10.1007/s40264-016-0405-1

CrossMark

SPECIAL ARTICLE

Good Signal Detection Practices: Evidence from IMI PROTECT

Antoni F. Z. Wisniewski[1] · Andrew Bate[2] · Cedric Bousquet[3,4] · Andreas Brueckner[5] · Gianmario Candore[6] · Kristina Juhlin[7] · Miguel A. Macia-Martinez[8] · Katrin Manlik[9] · Naashika Quarcoo[10] · Suzie Seabroke[11] · Jim Slattery[6] · Harry Southworth[12] · Bharat Thakrar[13] · Phil Tregunno[11] · Lionel Van Holle[14] · Michael Kayser[15] · G. Niklas Norén[7]

Published online: 7 March 2016

Recommendations integrated in:

- electronic Reaction Monitoring Report
- GVP Signal Management (Module IX),
- users' guide for EudraVigilance
- Revision 5 of ENCePP Guide on Methodological Standards in Pharmacoepidemiology

Good Signal Detection practices

Impact on public health:

- Timeliness and validity of signal detection, impact on decision-making
- Targeted signal detection
- Better assessment of novel methods of signal detection

Impact on resources:

- Gain in efficiency
- Increased performance
- Choice of statistical measures for signal detection from spontaneous reports should be based on ease of implementation, interpretation and optimisation of resources.
- Choice of terminology
- EHRs may not be more effective than spontaneous data for signal detection

Recommendations for pharmacoepidemiology

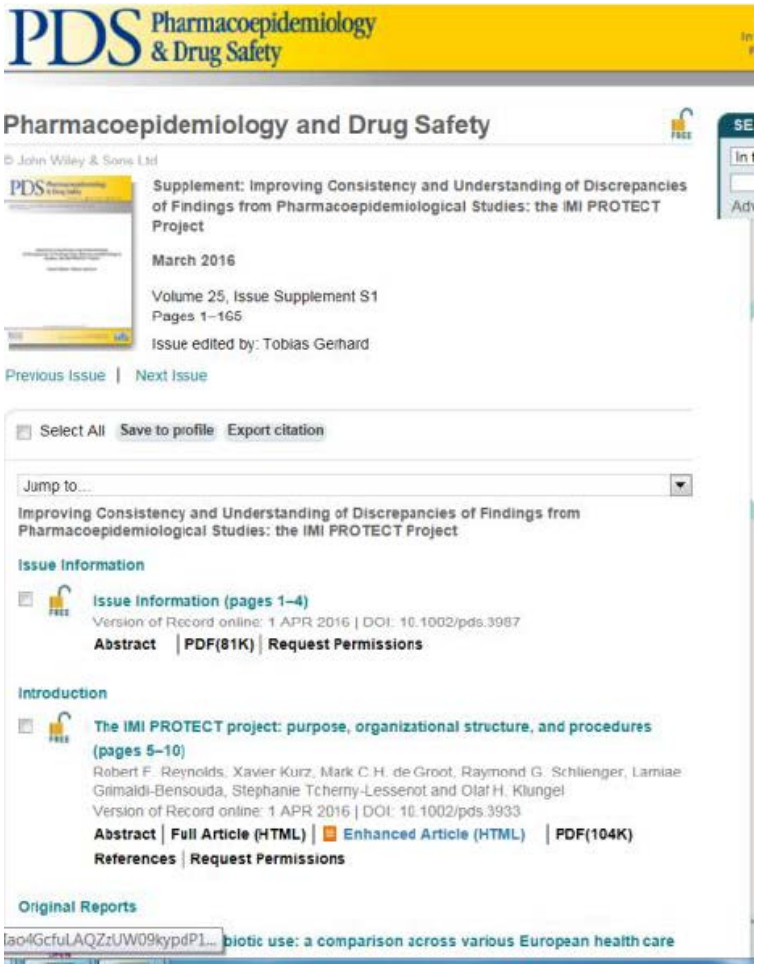
- Comprehensive review, analysis and testing of methods to control for confounding
- Methods for drug utilisation studies
- Recommendations for increasing consistency of findings of multi-centre database studies based on different designs and analytic methodologies
- Measurement of effects of differences in definitions, database characteristics and study designs on results of drug safety studies.
- European research network created for safety signal assessment and method development.

Recommendations for pharmacoepidemiology

Integrated in Annex 1 (Methods) of Rev.3 of GVP Module VIII (Post-authorisation safety studies)

Integrated in Rev.5 of ENCePP Guide on Methodological Research Standards

"Common study protocol model" for multicentre, multi-database studies



Recommendations for pharmacoepidemiology

Impact on public health

- Increased overall study quality
- Increased consistency in findings from drug safety studies across multiple designs, analyses and databases

Impact on resources

- Efficient approach for multi-database studies based on common-protocol
- Development of new infrastructure, data resources and methodologies
- Faster multi-country studies?

Recommendations for benefit-risk assessment methodologies and visual representation

- Comprehensive description, review, testing and selection of methods and graphical representations for benefit-risk assessment.

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2014; **23**: 667–678
Published online 13 May 2014 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3636

REVIEW

Balancing benefit and risk of medicines: a systematic review and classification of available methodologies†

Shahrul Mt-Isa[1], Christine E. Hallgreen[1], Nan Wang[1], Torbjörn Callréus[2], Georgy Genov[3], Ian Hirsch[4], Stephen F. Hobbiger[5], Kimberley S. Hockley[1], Davide Luciani[6], Lawrence D. Phillips[3], George Quartey[7], Sinan B. Sarac[2], Isabelle Stoeckert[8], Ioanna Tzoulaki[1]*, Alain Micaleff[9] and Deborah Ashby[1]
on behalf of the IMI-PROTECT benefit–risk participants

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**: 238–250
Published online 2 November 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3880

REVIEW

Literature review of visual representation of the results of benefit–risk assessments of medicinal products†

Christine E. Hallgreen[1]*, Shahrul Mt-Isa[1], Alfons Lieftucht[2], Lawrence D. Phillips[3], Diana Hughes[4], Susan Talbot[5], Alex Asiimwe[6], Gerald Downey[5], Georgy Genov[7], Richard Hermann[8], Rebecca Noel[9], Ruth Peters[1], Alain Micaleff[10], Ioanna Tzoulaki[1], Deborah Ashby[1] and On behalf of PROTECT Benefit–Risk group

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**: 251–262
Published online 22 January 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3958

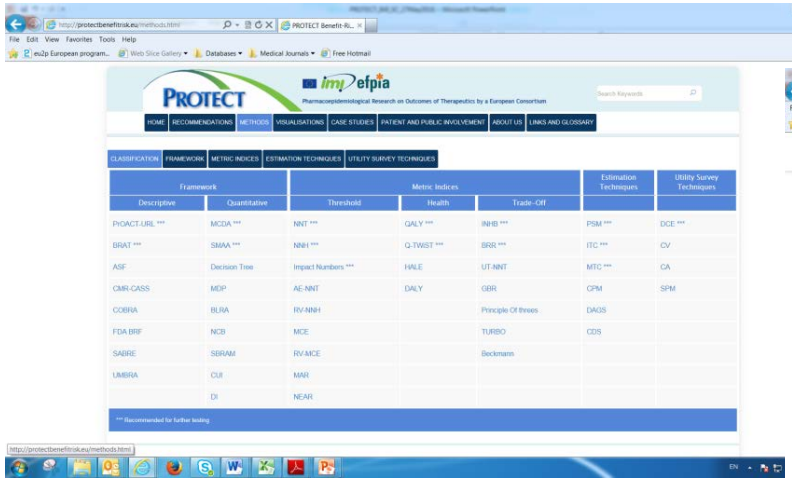
ORIGINAL REPORT

Recommendations for benefit–risk assessment methodologies and visual representations§

Diana Hughes[1†], Ed Waddingham[2*†], Shahrul Mt-Isa[2], Alesia Goginsky[3], Edmond Chan[4], Gerald F. Downey[5], Christine E. Hallgreen[2,6], Kimberley S. Hockley[2], Juhaeri Juhaeri[7], Alfons Lieftucht[8], Marilyn A. Metcalf[9], Rebecca A. Noel[10], Lawrence D. Phillips[11], Deborah Ashby[2‡], Alain Micaleff[12‡] and
PROTECT Benefit–Risk Group

Recommendations for benefit-risk assessment methodologies and visual representation

http://protectbenefitrisk.eu



- Used in CHMP Methodology project on Benefit-risk assessment and in EMA Add-Value project
- Ground work recommended to be used in other IMI research projects: ADVANCE, GetReal, ADAPT-SMART, PREFER…

Recommendations for benefit-risk assessment methodologies and visual representation

Impact on public health

- Ground work for future development of methods for benefit-risk assessment
- Shared framework for B/R assessment to support communication on benefits and risks
- Better understanding of use of patient preferences for decision-making

Impact on resources

- Comprehensive review and evaluation of methods and visualisation techniques
- Clarity of concepts on B and R for more efficient drug development programmes

Recommendations for Direct-to-Patient Research

Direct-to-patient method for learning about use of prescription and non-prescription medication use; more complete data than those from prescription registers and electronic health records.

Internet and direct-from-patient data collection on medical treatments and lifestyle variables is possible and adds value for drug safety evaluation.

JMIR PUBLIC HEALTH AND SURVEILLANCE Dreyer et al

Original Paper

Direct-to-Patient Research: Piloting a New Approach to Understanding Drug Safety During Pregnancy

Nancy A Dreyer[1], MPH, PhD; Stella CF Blackburn[2], MBBS, MA, MSc; Shahrul Mt-Isa[3], BSc, PhD; Jonathan L Richardson[4,5], BBSc (Hons); Simon Thomas[4,5], BSc, MD, FRCP; Maja Laursen[6], MSc, PhD; Priscilla Zetstra-van der Woude[7], MSc; Anna Jamry-Dziurla[8], MSc; Valerie Hliva[9], PhD; Alison Bourke[10], BSc, MSc; Lolkje de Jong-van den Berg[7], PharmD, PhD

Recommendations for Direct-to-Patient Research

Impact on public health

- Data collection on drug safety in pregnant women
- Data collection in target populations that are difficult to recruit and retain using conventional methods (e.g. adolescents, people in full time work)

Impact on resources

- Comparison of cost-effectiveness of advertising methods to recruit pregnant women.

Test of framework for impact assessment of regulatory science projects

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

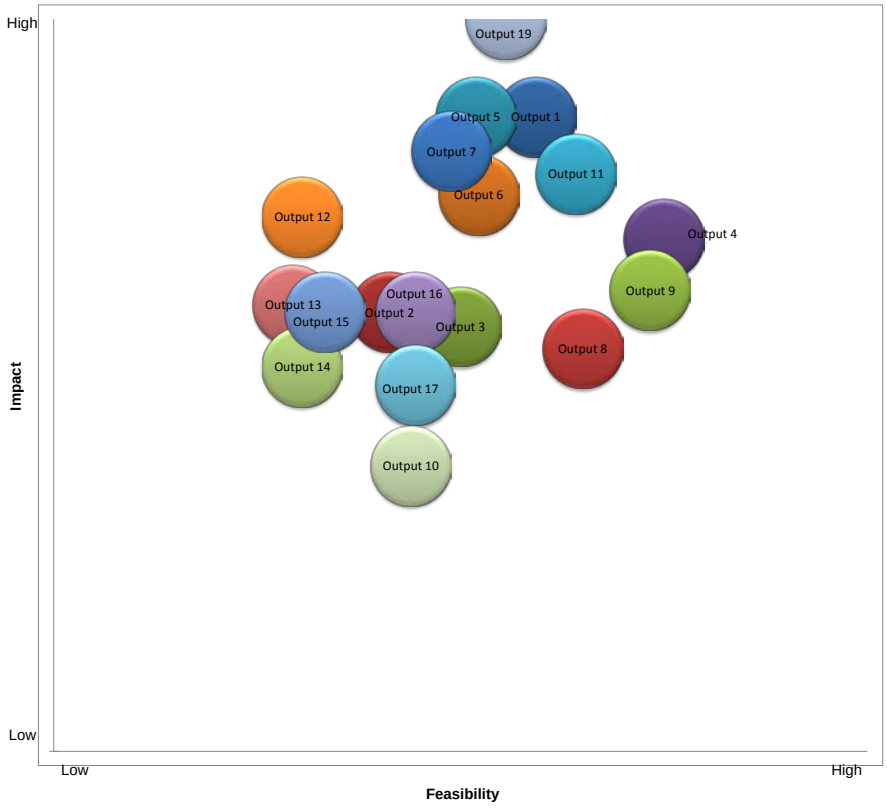
Criterion	Description	Score 1	Score 2	Score 3	Score 4
I1	If the change is implemented, how do you rate its potential impact on public health?	None	Small	Moderate	Important
I2	How do you rate the degree of scientific development of the output?	Inadequate	Incomplete	Nearly complete	Complete
I3	What is 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)

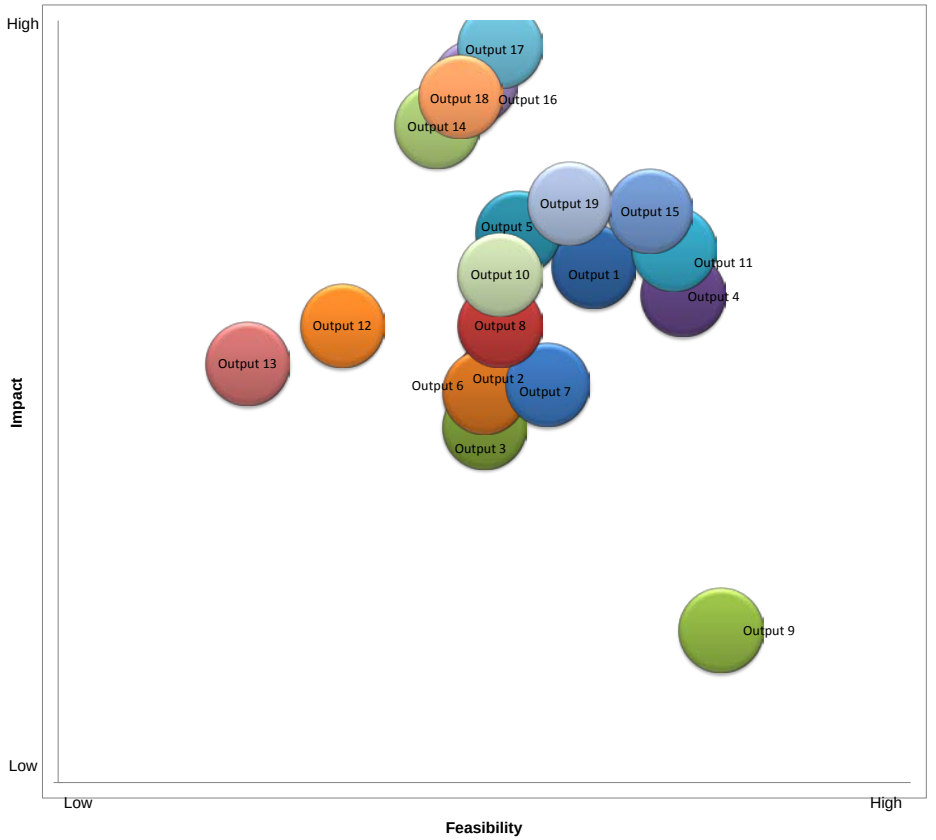
Criterion	Description	Score 1	Score 2	Score 3	Score 4
F1	How do you rate the degree of acceptability by the group of stakeholders to which you belong?	N/A	Small	Moderate	Important
F2	How do you rate the feasibility of the implementation of the output in terms of IT resources?	N/A	Important	Moderate	Small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

Test of framework for impact assessment of regulatory science projects

Regulators' perspective



Other respondants' perspective (mainly industry)



Conclusions

PROTECT has achieved its objectives.

Outcomes are being implemented into routine pharmacovigilance and regulatory practice with positive impact public health and resources.

Leap forward towards the understanding of the values and usefulness of benefit-risk methods.

Demonstrated potential added value of the internet for pharmacovigilance is important in very quickly changing environment where patients are actively sharing information.

Thank you!

Full report to be published on http://www.imi-protect.eu