

## PROTECT

### Pharmacoepidemiological research on outcomes of therapeutics by a European consortium

#### Summary

The PROTECT project will enhance the monitoring of the safety of medicinal products. It will also contribute to better evaluate and communicate their benefit-risk profile throughout their lifecycle. To this end, innovative tools and methodological standards will be developed. The European Medicines Agency coordinates PROTECT and manages a Consortium of 29 public and private participants.

PROTECT aims at explaining discrepancies between the reported outcomes from pharmacoepidemiology studies by studying combinations of drugs and adverse events in several databases. It will identify and further explore sources of variability that may currently affect drug safety studies. Modern ways of collecting data on medication, lifestyle and risk factors directly from consumers using internet and telephony will also be explored in 4 countries with 5600 pregnant women. The ability of these systems to collect regular, accurate and complete reporting without the intervention of health professionals will be tested. Good practice recommendations for the detection of safety signals are developed based on extensive testing of existing and new methods, creation of a database of known adverse drug reactions, and exploring the use of electronic health records and clinical trials data. In addition, PROTECT will use new modeling approaches to integrate existing information from various data sources to facilitate and enhance the continuous monitoring of the benefit-risk of medicines. Particular emphasis will be given on a graphical representation of benefit-risk profiles for use by patients, healthcare professionals, regulatory agencies, and drug manufacturers.

#### Achievements & News

**Article highlights PROTECT's impact on regulatory science and practice** The impacts of IMI's [PROTECT project](#) on **regulatory science and practice** are spelt out in a new paper by project coordinator Xavier Kurz of the [European Medicines Agency](#) (EMA), published in the journal [Pharmacoepidemiology and Drug Safety](#). One area where the project made an important difference in regulatory practice is in signal detection, through which medicines regulators gather information on suspected adverse drug reactions (ADRs). **Based on PROTECT work, changes were made** in the tools and processes used for signal detection in the EU database of reports of suspected ADRs. These changes have **improved** the signal detection process, with fewer false positives and more validated signals. Another area where the project has had an impact is in pharmacoepidemiology, which is the study of the use and effects of medicines in large numbers of people. According to Xavier Kurz, **PROTECT's recommendations** in this area will help to **improve the quality and consistency of studies**, increase confidence in the results of observational studies, and strengthen regulatory decision-making. **Benefit-risk assessment** was another area where PROTECT delivered results, including a framework for benefit-risk assessment, greater understanding of the use of patient preferences for decision-making, and a [website](#) with training material on the subject. These deliverables also provide foundations for further methodological developments in this field. Finally, PROTECT carried out preliminary research on using the internet as a data collection tool. (March 2017)

#### PROTECT project's legacy on assessing benefits and risks of medicines

One of IMI's first projects, [PROTECT](#) was set up to develop innovative methods for monitoring the benefits and risks of medicines. Although the project is over, its legacy lives on in the knowledge and tools generated by the project, many of which are presented in a [special issue](#) of the journal *Pharmacoepidemiology and Drug Safety* and a [short report](#) published by the European Medicines Agency (EMA), which coordinated the project. 'PROTECT has made a significant contribution to the body of scientific knowledge of benefit-risk monitoring methodologies', said Peter Arlett, Head of the EMA's Pharmacovigilance department. 'Results are being implemented into routine pharmacovigilance and regulatory practice. They have already started to improve day-to-day medicines monitoring operations of regulators and pharmaceutical companies, for better safety of

European patients.’ Highlights from the project include: - Good Signal Detection Practice was integrated into tools and regulatory guidance for national authorities and companies. - Recommendations for observational studies on medicines were integrated into scientific guidance and will be integrated into regulatory practice. - Recommendations for benefit-risk assessment methodologies and visual representations have 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. - Exploring new methods to collect data directly from patients, including via the internet. - A specific PROTECT benefit-risk [website](#). - 72 articles in peer-reviewed scientific journals, 14 doctoral theses and 3 master theses.

### **PROTECT project’s benefit risk assessment advice published**

The [PROTECT project’s](#) overarching recommendations on the assessment and visualisation of the benefits and risks of medicines have been [published](#) in the journal *Pharmacoepidemiology and Drug Safety*. Evaluating the balance between the benefits and risks of drugs is challenging. The assessment methodologies and visual representation tools may facilitate benefit-risk assessments. The newly-published paper explains how the project’s recommendations are based on a number of case studies using real medicines. ‘Adopting formal, structured approaches to benefit–risk assessment was feasible in real-world problems and facilitated clear, transparent decision-making,’ the researchers write. ‘Prior to this work, no extensive practical application and appraisal of methodologies had been conducted using real-world case examples, leaving users with limited knowledge of their usefulness in the real world. The practical guidance provided here takes us one step closer to a harmonised approach to benefit–risk assessment from multiple perspectives.’ Details of the PROTECT project’s output can be found on the [project’s website](#).

**Presentations and video recordings from the [Final Symposium Training of the PROTECT](#) are now available online.** The material covers: - the main concepts of **benefit-risk assessment**, - a range of methodologies used in connection with benefit-risk assessment, - key methodologies via worked examples, - a range of visual representations to accompany benefit-risk assessment and - a selection of visual displays via worked examples, and the role of patient and public involvement in benefit-risk assessment (April 2015)

**PROTECT benefit / risk website goes live** IMI’s [PROTECT](#) project has launched a [new website](#) showcasing its work on ways of assessing and visualising the benefits and risks of medicines. The evaluation of the balance between the benefits and risks of drugs is fundamental to numerous stakeholders including patients, healthcare providers, health technology assessors, regulators and pharmaceutical companies. Decision-making with regards to benefit-risk assessment is often complex. It is important to ensure transparent, robust and comprehensive methodologies are used, and also that patient and public preferences on benefits and risks feed into the decision-making process. To achieve these goals, the PROTECT Benefit-Risk group has developed a clear set of practical recommendations for benefit-risk decision processes and supporting tools, which the project hopes will serve as a valuable guide for people who are new to the world of benefit-risk assessment. These recommendations highlight key issues and considerations that are common to many approaches and benefit-risk decision problems.

**PROTECT survey to improve communication of benefits & risks** IMI’s [PROTECT project](#) is running a [survey](#) that will feed into efforts to improve the way the benefits and risks of medicines are communicated to patients and health professionals alike. All medicines come with both benefits and risks, and understanding the balance between these is essential when making treatment decisions. Benefits and risks can be communicated in diverse ways, including written texts and different kinds of graphics. The PROTECT survey sets out different ways of presenting benefits and risks and asks which are best for making treatment decisions. The project has designed different surveys for patients, healthcare professionals, and those responsible for assessing medicines in three areas: breast cancer, diabetes, and atrial fibrillation. It takes 30-65 minutes to complete, depending on the disease area. No personal identifying information is collected and all answers are kept confidential. (June 2014)

**Updates of the Drug Consumption Databases published** IMI’s [PROTECT project](#) has published an updated version of the [Drug Consumption Databases](#) – a comprehensive and structured source of information on drug consumption in the out- and inpatient healthcare sector in Europe. The databases consist of two documents: a master document containing a detailed account of the information already available and methods to retrieve it and

a country profile document summarising by country information on national health systems, reimbursement characteristics and a list of websites of interest. The databases contain information for the following countries: Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Slovenia, Spain, Sweden, the Netherlands, and the United Kingdom. All interested readers are encouraged to review and comment on the two documents as they are a shared source among researchers, regulatory agencies, and pharmaceutical companies. - Inventory on Drug Consumption - [Master Document](#) - Inventory on Drug Consumption - [Countries Summary](#) (February 2014)

**PROTECT releases reviews of benefit - risk methods and their visualisation** IMI project [PROTECT](#) has published reviews of the available methodologies for the assessment, integration and visualisation of the risks and benefits of medicines. The project team analysed a wide range of methodologies for assessing the benefits and risks of medicines; the report on this shows the links between different methods and groups them. Finally, the report sets out recommendations on the methods that merit further consideration for decision-making on medicines in different contexts. These methods will be explored further in the next stage of the PROTECT project. PROTECT also analysed different ways of visualising benefits and risks. The report presents visual representations that could be associated with the 13 benefit-risk methodologies recommended in the benefit-risk methodology review, assesses their suitability and offers recommendations for suitable visuals for each benefit-risk assessment approach. - Both reports, along with a number of case studies, can be found [online](#) (July 2013)

**PROTECT project releases major pharmacovigilance databases** IMI's [PROTECT project](#) has published two key databases for pharmacovigilance on its website. The [inventory of Drug Consumption Databases in Europe](#) provides a comprehensive and structured source of information on drug consumption in Europe, while the [PROTECT ADR database](#) is a downloadable Excel file listing all adverse drug reactions (ADRs) listed in the Summary of Product Characteristics (SPC) of medicinal products authorised in the EU. 'We hope that these databases will represent useful resources for the scientific community and for regulatory and public health authorities,' said PROTECT project coordinator Xavier Kurz of the European Medicines Agency (EMA). (February 2013)

**Pregnant women needed for PROTECT survey on medicines use in pregnancy** Elsewhere, the [PROTECT](#) team has launched a major, four-country [survey](#) on drug use by pregnant women. Although automated systems can find out what medicines have been prescribed for pregnant women, they do not provide information on whether or not the patient actually took the drugs, and they do not cover medicines bought over the counter or herbal and homeopathic remedies. By gathering detailed data on pregnant women's actual medicine intake, as well as information on lifestyle factors, the PROTECT project hopes to be able to improve the advice given to pregnant women and so make pregnancies safer. (February 2013)

## Participants

### EFPIA member companies

- GlaxoSmithKline Research and Development LTD, Brentford, UK
- Amgen NV, Brussels, Belgium
- Bayer Schering Pharma AG, Berlin, Germany
- AstraZeneca AB, Södertälje, Sweden
- Genzyme Europe B.V., Naarden, The Netherlands
- H. Lundbeck A/S, Valby, Denmark
- Merck KGaA, Darmstadt, Germany
- Novartis Pharma AG, Basel, Switzerland
- Novo Nordisk A/S, Bagsvaerd, Denmark
- Pfizer Limited, Sandwich, United Kingdom
- F. Hoffmann-La Roche AG, Basel, Switzerland
- Sanofi-Aventis Research and Development, Chilly-Mazarin, France

### Universities, Research Organisations, Public Bodies & Non-Profit

- European Medicines Agency
- Lægemiddelstyrelsen (Danish Medicines Agency, Copenhagen, Denmark)
- Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain
- Fundación Centro Español de Investigación
- Farmacoepidemiológica, Madrid, Spain
- Fundació Institut Català de Farmacologia, Barcelona, Spain
- International Alliance of Patients' Organizations, London, UK
- Imperial College of Science, Technology & Medicine, London, UK
- Institut National de la Santé et de la Recherche Médicale, Paris, France
- Ludwig-Maximilians-Universität München, München, Germany
- Mario Negri Institute for Pharmacological Research, Milan, Italy
- Medicines and Healthcare products Regulatory Agency, London, UK
- Rijksuniversiteit Groningen, Groningen, The Netherlands
- Stiftelsen WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
- University of Newcastle upon Tyne, Newcastle upon Tyne, UK
- Universiteit Utrecht, Utrecht, The Netherlands

## **SMEs**

- LA Santé Épidémiologie Evaluation Recherche, Paris, France
- Outcome Europe Sarl, St. Prex, Switzerland

**Facts & Figures**

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**Links and Documents**

**Project Website:** [www.imi-protect.eu](http://www.imi-protect.eu)  
[IMI funding per project participant](#)

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