Innovative Medicines Initiative

Summary of PROJECT PERIODIC REPORT N° 3

Project title	**Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium**
Project Acronym	**PROTECT**
Period covered	**1 September 2011 – 31 August 2012**
Project website	**http://www.imi-protect.eu**

Work Package co-Leaders

Work Package	Co-Leaders	Partner
WP1 *Management and Administration*	Xavier Kurz	European Medicines Agency
	Elizabeth Swain	GlaxoSmithKline Research and Development Ltd.
WP2 *Framework of PE Studies*	Olaf Klungel	Utrecht University
	Robert Reynolds	Pfizer Limited
WP3 *Methods of Signal Detection*	Niklas Norén	Stiftelsen WHO Collaborating Centre for International Drug Monitoring
	Michael Kayser	Bayer Schering Pharma AG
WP4 *New Tools for Data Collection*	Stella Blackburn	European Medicines Agency
	Omer de Mol	Genzyme Europe B.V.
WP5 *B/R Integration and Representation*	Deborah Ashby	Imperial College London
	Alain Micaleff	Merck KGaA
WP6 *Validation Studies*	Lucien Abenhaim	L.A. Santé Épidémiologie Evaluation Recherche
	Laurent Auclert	Sanofi-Aventis Research and Development
WP7 *Training & Communication*	Joan-Ramon Laporte	Fundació Institut Català de Farmacologia

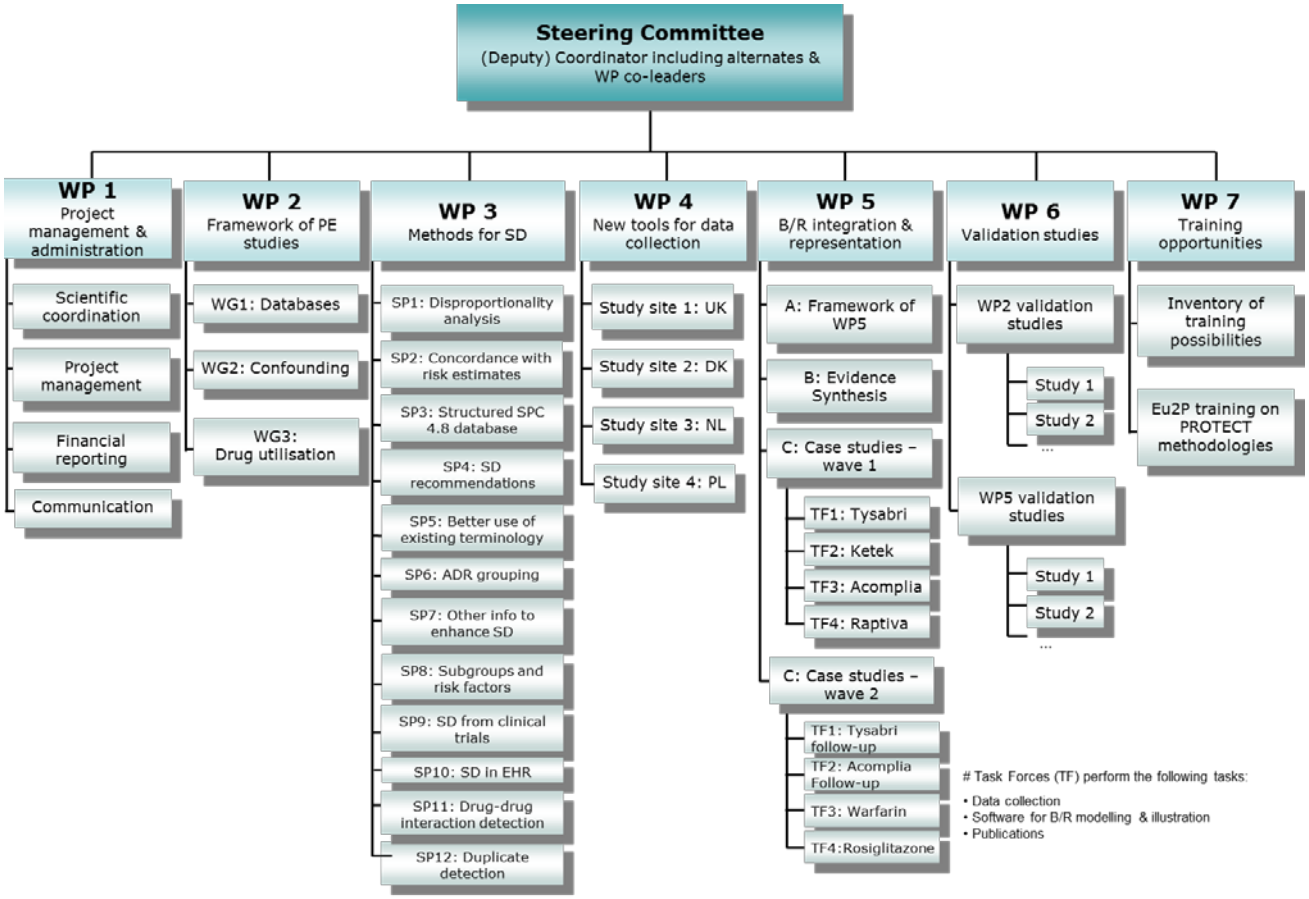
Executive summary

Project rationale and overall objectives of the project

The goal of PROTECT is to strengthen the monitoring of benefit and risk of medicines in Europe. Its objectives are: to enhance data collection directly from consumers in their native language in several countries using modern tools of communication; to improve early signal detection from spontaneous reports, electronic health records and clinical trials; to develop and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies applicable to different safety issues and different data sources; to develop methods for continuous benefit-risk monitoring of medicines, by integrating and presenting data on benefits and risks from clinical trials, observational studies and spontaneous reports; and to validate various methods developed in PROTECT using different data sources in order to identify and help resolve operational difficulties linked to multi-site investigations.

Work packages and sub-groups

Each Work Package consists of sub-groups which is illustrated in the organigram below:



Overall deliverables of the project

PROTECT will deliver a set of tools and methods to improve: detection and evaluation of drug safety signals, conduct, analysis and interpretation of pharmacoepidemiological studies, integration and representation of data for the benefit-risk assessment of medicines and collection of data directly from consumers. These tools and methods will be communicated as publications, reports, training modules, methodological standards and

electronic applications that will be actively disseminated to all relevant stakeholders, including scientists, regulatory authorities, pharmaceutical companies, international organisations, patients and health care professionals.

Summary of progress versus plan since last period

Pharmacoepidemiological studies to evaluate 6 selected drug-adverse event pairs in several European databases using various study designs have started. Specific studies were also conducted on propensity scores balance measures, time dependent confounding and instrumental variable analysis resulting in several publications. Eight new countries were identified for the updated version of the published inventory of drug utilisation databases in Europe. A common protocol for the systematic literature review of clinical trials and observational studies on the selected drug-adverse event pairs was developed, and a protocol to calculate the exposed population to drugs was finalised. There are no major deviations in the work plan for this programme. A separate work programme has been developed to independently test the reproducibility of the methods developed for pharmacoepidemiological studies. Six distinct objectives have been identified, involving 13 protocols, among which 9 have been completed, 6 data sources and 2 new PROTECT partners. The analyses have started and most of them will be completed by December 2012.

As regards the implementation and analysis of methods for signal detection, the challenges of diverse IT environments among the partner organisations and adapting programmes to data sets were overcome. Three sub-projects were prioritised, addressing signal detection methods from clinical trials and electronic health records and the review and evaluation of statistical methods for signal detection. Unforeseen legal difficulties to get access to some spontaneous report databases delayed the progress of the work programme relying on such databases.

The study to explore the feasibility and usefulness of modern communication methods to collect data directly from pregnant women was prepared, including the study questionnaires and material, submissions to ethics committees in the four countries involved, the recruitment plan and the web-based platform. Delays accumulated in previous years led to shorten timelines and all study phases.

The work on the relevance of various methodologies for benefit-risk assessment is progressing according to planned timelines. The first wave of 4 case studies was completed using methodologies recommended by the prior review. A second wave of 4 case studies to further explore benefit-risk methodology and visualisation is close to completion. A report related to novel visualisation methods has been drafted alongside details of available software packages for use in this area. Dissemination plans have been put in place. Due to some more time-consuming tasks than expected, the final recommendations are scheduled for February 2013. A programme was discussed to further test the visualisation tools with patients, using an outline platform for the capture and visualisation of benefit-risk by patients, evaluating the inter-patients group variability and account for time-dependency of outcomes using more advanced modelling.

Regarding the training programme, the platform for training opportunities was launched in August 2011 and linked to the IMI-funded Eu2P training programme. Some PROTECT results were introduced in training modules.

Significant achievement since last report

The work on methods for pharmacoepidemiological studies finalised study protocols applicable in several European databases, integrating various study designs for each of the drug-adverse event pairs and data specifications. Results of descriptive studies were delivered, while those of cohort studies are close to completion. Several articles were published or submitted on methods to control for confounding including on the performance of those methods. An inventory of drug utilisation resources in European countries is publicly

accessible on the PROTECT website, with an assessment of their comparability and graphical outputs. Use of such data to assess the public health impact of benzodiazepines and other drugs was published. An extensive programme for independent pharmacoepidemiological replicability studies was agreed and started, covering replication studies, negative control studies, use of alternative outcome definition, validation of outcomes and additional assessment of confounders. This required the development of a procedure ensuring the mutual blinding of investigators working on a same topic.

As regards signal detection, datasets with standardised results were set up from several databases, allowing direct comparison between sites and providing a valuable point of reference in subsequent analyses. A structured database of adverse drug reactions included in products' information was completed, published on the PROTECT website and is used by EU regulatory authorities in their routine pharmacovigilance activities. A project on better use of existing terminologies was completed and communicated, showing that contrary to expectations, grouping medically related adverse reaction terms for the purpose of analysis may not expedite signal detection. An algorithm was validated to address the masking effect associated with measures of disproportionality.

The programme on methods for benefit-risk assessment reached important milestones by finalising wave 1 and wave 2 case studies, preparing the ground for key reports and scientific publications that are highly likely to influence practice. This work generated a large external interest.

A draft document describing the strategy and work flow for knowledge transfer to the EU2P training programmes has been produced.

Key dissemination activities

The dissemination activities of the 3rd project year were mainly focused on presenting first results of PROTECT work to a wider audience. The following two publications were published in peer-reviewed journals:

- Groenwold, R. H. H., de Vries, F., de Boer, A., Pestman, W. R., Rutten, F. H., Hoes, A. W. and Klungel, O. H. (2011), Balance measures for propensity score methods: a clinical example on beta-agonist use and the risk of myocardial infarction. Pharmacoepidemiology and Drug Safety, 20: 1130–1137. doi: 10.1002/pds.2251
- Khong T.P., de Vries F, Goldenberg J.S.B., Klungel O.H., Robinson N.J., Ibanez L., Petri H. Potential Impact of Benzodiazepine Use on the Rate of Hip Fractures in Five Large European Countries and the United States. Calcified Tissue International: Volume 91, Issue 1 (2012), Page 24-31 DOI 10.1007/s00223-012-9603-8

In addition, a number of presentations and abstracts were presented at different venues (among others at the 28th International Conference on Pharmacoepidemiology & Therapeutic Risk Management) to increase the awareness of PROTECT in the scientific community and with other stakeholders.

A dedicated section for dissemination activities has been created on the PROTECT website (http://www.imi-protect.eu/results.shtml).