Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

Summary of PROJECT PERIODIC REPORT N° 2

Full project title: **Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium**

Project acronym: **PROTECT**

Reporting Period: **1 September 2010 - 31 August 2011**

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 Pharma AG
WP4 *New Tools for Data Collection*	Stella Blackburn	European Medicines Agency
	Jens Peter Balling	H. Lundbeck A/S
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
	Elena Rivero	Novartis Pharma AG

Project website address: **http://www.imi-protect.eu**

PROTECT Project Support
7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone: +44 (0)20 7418 7200 **Facsimile:** +44 (0)20 7418 8668
E-mail: PROTECT_Support@ema.europa.eu **Website:** http://www.imi-protect.eu

Purpose and scope of the periodic report

PROTECT is a project receiving funding from the European Union's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicines Initiative (www.imi.europa.eu) under Grant Agreement n° 115004. To monitor the project progress and the use of resources the project produces annual reports covering the respective past project year. Periodic Report n° 2 addresses the achievements of the 2nd project year, starting on 1 September 2010 and ending on 31 August 2011. The project will continue producing regular reports until its termination in 2014.

The following report is a joint effort of the PROTECT Consortium and reflects the progress and main results achieved by the project so far.

PROTECT Objectives

The goal of PROTECT is to strengthen the monitoring of benefit and risk of medicines in Europe. In order to achieve this overall goal, PROTECT has been designed as a comprehensive and integrated project aiming to develop and validate a set of innovative tools and methods that will:

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

The PROTECT project started on 1st September 2009. It is carried-out by a consortium of 31 public and private partners under the coordination of the European Medicines Agency. GSK is the deputy co-ordinator of PROTECT. The organisational structure is as follows:

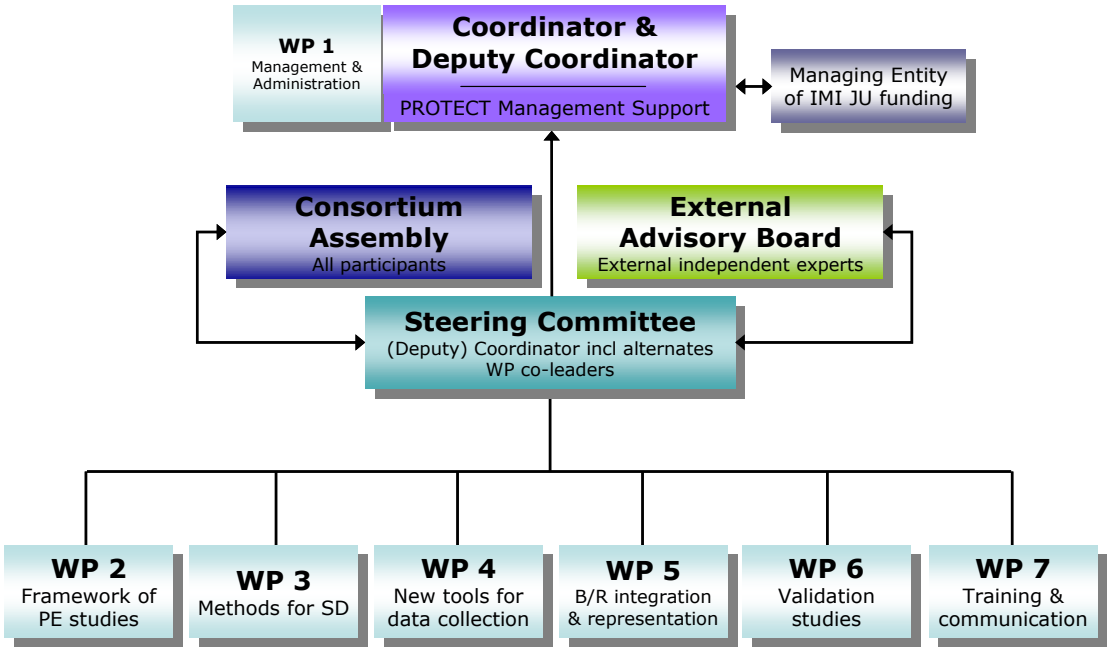

Figure 1: Organisational structure of PROTECT

Description of the work performed since the beginning of the project

Overall, PROTECT progressed well during the second project year. Much time was devoted in this period to the finalisation of study protocols and the development of technical and operational aspects of studies.

During the second project year, **Work Package 2** Working Group 1 ("Databases") has finalised the protocols for studying the selected 6 Drug-adverse event pairs to be evaluated in different European databases using various study designs for comparative purposes. Processes for requesting and preparing the data from the different databases have been put in place. In parallel, the data specifications for the descriptive studies of the individual databases, as well as for the cohort study designs within the databases, are being finalized in order to harmonise the methodology used within the same adverse event-drug pair. Working group 2 ("Confounding") has performed simulation studies. Investigations on propensity score balance measures and time dependent confounding have been published or are under review in scientific journals. Further research on instrumental variable methods is ongoing. Working Group 3 ("Drug utilisation") has completed a first version of the Inventory on Drug Utilisation databases in Europe (available on the PROTECT website at http://www.imi-protect.eu/results.html). DU data from different sources in Europe has been collected and will be used to study the estimated exposed population to selected Drugs of interest. This Inventory will be completed as the project evolves and be made publicly available for use by the external scientific community and contribution from other sources. IMS health data sources have been used to estimate potential population impact of the use of benzodiazepines and antidepressants on fracture risk in selected European countries (under review in scientific journals).

The focus of the second year of PROTECT in **Work Package 3** has been on the transition from setting up and refining project planning processes to the practicalities of realising programme implementation. Most of the 12 subprojects are at the stage of addressing the complexities of real data. Specific results have been achieved in most subpackages. Signal detection methods based on disproportionality analyses (EBGM, IC, PRR and the Urn method) have been set up and tested in SAS. The protocol for analysing the concordance of disproportionality analyses with risk estimates has been reviewed and accepted by the

group. The structured database for adverse reactions included in section 4.8 of the Summary of Product Characteristics has been finalised and the remaining refractory MedDRA coding difficulties have been addressed through expert clinical review. The survey of spontaneous report databases has been completed and will be used as a basis for signal detection recommendations. The technical report which investigates the effect of using different currently available levels of MedDRA and WHOART coding for signal detection has been finalised. All analyses were done in the Vigibase dataset to ensure a direct comparison. No grouping level emerged as clearly superior and this reinforces the need for development of grouping levels specifically aimed at earlier detection of signals. Novel tools for grouping adverse drug reactions have been addressed in a first stage by evaluating terminological reasoning for six safety topics. Results are encouraging for "Upper gastrointestinal bleeding" (Recall 94,4 % and precision 77,3 %). In addition, protocols and research papers have been developed for the investigation of masking in signal detection, stratification with spontaneous report data and clinical trial signal detection. Signal detection in electronic health records will be addressed by studying the timeliness and coherence for exploratory analyses with traditional approaches and developing an effective approach of refining potential signals.

To explore the feasibility and usefulness of modern communication methods to collect data related to health and medicines, **Work Package 4** will conduct a study with pregnant women who will provide information about their medication consumption, certain lifestyle factors and other risk factors on a periodic basis throughout their pregnancy using web-based screens, text messaging and computerised telephone interviews. During the second project year, WP4 finalised the study protocol taking into account country specific requirements and submitted the protocol to the Ethics Committees of the countries where the study will be conducted [Denmark (DK), The Netherlands (NL), Poland (PL) and United Kingdom (UK)]. Confirmation has been received from the relevant authorities that no ethical approval is required in DK, NL and PL and both ethical and research reviews are ongoing in the UK. A pilot testing of the data collection forms took place and let to improvements of the readability and user friendliness of the questionnaires. The recruitment strategy was finalised and content and design of the website and recruitment leaflets were agreed. The development of the data collection platform has started and is progressing well. A memorandum of understanding between the participants of WP4 about their roles and responsibilities with regards to data protection as been prepared and agreed in August 2011.

The overall objective of **Work Package 5** is to assess the relevance of various methodologies for Benefit-Risk (B-R) assessment including the provision of usable data and information, the underpinning modelling and the presentation of the results, with a particular emphasis on visualisation methods. During the second reporting period, The review of benefit risk methodologies resulted in recommendations of those to be used in the wave 1 case studies. It is envisaged that a revised version will be released once the case studies are complete in order to take account of any additional methodologies, comments and experience gained via the case study process. The case studies to be used for wave 1 have been chosen and are progressing well. They include Tysabri (natalizumab), Ketek (telithromycine), Acomplia (rimonabant) and Raptiva (efalizumab). First reports from the wave 1 case studies have been delayed a little and are due in December 2011. Alongside this, the first of the wave 2 case studies (warfarin) has been selected and has started.

Work Package 6 aims to test the transferability/feasibility of methods developed in WP2 to 5 (in particular WP2 and WP5) in a range of data sources owned or managed by Consortium Partners, by participants in the Extended Audience (EAp) or by other centres not identified in the original EAp list. WP6 will then propose amendments to recommendations and methodological standards presented in the WP programme. During the second reporting period, the EAp were contacted on behalf of the PROTECT programme to gauge interest and explore the availability and suitability of data sources for WP6 purposes. Validation studies with specific objectives have been identified in relation to WP2 drug-adverse

event studies, protocols have been developed and data sources have been identified, leading to a revised list for the Extended Audience. The objectives of these studies are to assess the availability of data on confounders; to measure associations with alternative outcome definitions and confounders, and assess their impact on the study results; to conduct negative control studies; to perform studies on diagnostic specificity; to study different forms of the event; for cancers, to investigate different types of cancer registers and to assess their suitability for conducting pharmacoepidemiology studies. The following relevant data sources have been identified : LabRx/Premier Perspective PCD, General Practice Research Database (GPRD), PGRx, The Danish Psychiatric Central Research Registry (PCRR), the Utrecht Patient Oriented Database (UPOD), the Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N), the Thomson Reuters MarketScan Commercial and Medicare databases.

The general objective of **Work Package 7** is to identify training opportunities and support training programmes in the fields addressed by PROTECT. A major achievement in the current reporting period was the launch of the public platform of training opportunities (https://w3.icf.uab.es/trainingopp/). A link to the platform is provided from the PROTECT website. The platform will be used in collaboration with the *European Programme in Pharmacovigilance and Pharmacoepidemiology* (Eu2P, the project funded under IMI_Call_2008_1_06) and will offer positions for training of PhD and postgraduate students in the field of the expertise and areas of research of both projects. So far, the platform was populated by PROTECT participants; however it is also advertised for use by organisations outside the consortium. To this end, the platform will be presented to the *European Network of Centres for Pharmacoepidemiology and Pharmacovigilance* (ENCePP) and selected organisations have been contacted directly.

Expected final results and their potential impact and use

PROTECT has been designed as a comprehensive and integrated Project aiming to develop and validate a set of innovative tools and methods that will:

- enhance data collection directly from consumers of medicines in their natural language in several EU countries, using modern tools of communication; thereby facilitating early detection of potential drug safety issues;
- improve early and proactive signal detection (SD) from spontaneous reports, electronic health records and clinical trials, thereby contributing to expedite implementation of risk minimisation measures and protecting public health;
- 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, thereby providing robust evidence for regulatory decision-making and choice of prescription in clinical practice;
- develop methods for continuous benefit-risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports, including the presentation of the results with 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;
- contribute to disseminate recommendations for methodological research standards and tools for the understanding of the benefit-risk profile of medicines.

Publications

All publications to date in relation to the project are listed at http://www.imi-protect.eu/documents.html. During the 2nd year two papers were published in peer-reviewed journals:

- Belitser, S. V., Martens, E. P., Pestman, W. R., Groenwold, R. H., de Boer, A. and Klungel, O. H. (2011), Measuring balance and model selection in propensity score methods. Pharmacoepidemiology and Drug Safety. doi: 10.1002/pds.2188
- Groenwold R, Klungel O, Grobbee D, Hoes A. Selection of confounding variables should not be based on observed associations with exposure, Eur J Epidemiol, Volume 26, Number 8, 589-93

Address of the public website: http://www.imi-protect.eu.