Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

Summary of PROJECT PERIODIC REPORT N° 1

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

Project acronym: **PROTECT**

Reporting Period: **1 September 2009 - 31 August 2010**

Work Package co-Leaders

Work Package	Co-Leaders	Partner
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	Robert Reynolds	Pfizer Limited
WP3 *Methods of Signal Detection*	Niklas Norén	Stiftelsen WHO Collaborating Centre for International Drug Monitoring
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WP4 *New Tools for Data Collection*	Stella Blackburn	European Medicines Agency
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WP5 *B/R Integration and Representation*	Deborah Ashby	Imperial College London
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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° 1 addresses the achievements of the 1st project year, starting on 1 September 2009 and ending on 31 August 2010. 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 29 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:

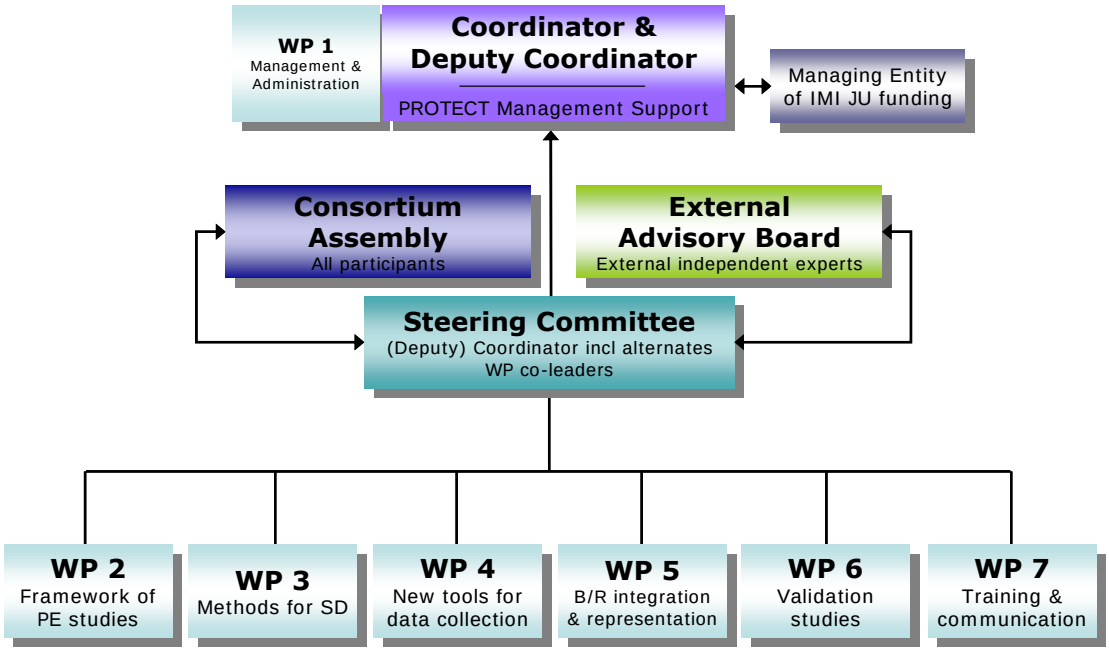

Figure 1: Organisational structure of PROTECT

Description of the work performed since the beginning of the project

Overall, PROTECT progressed well during the first project year. Much time was devoted to the refinement of objectives and the development of detailed work plans and study protocols.

During the first project year **Work Package 2 (Framework for Pharmacoepidemiological studies**) has established three working groups. Working group 1 has selected five key adverse events and drugs to be evaluated in different European databases. Furthermore, the basic characteristics of the seven available databases have been described. These results have been included in a scientific paper describing the background and rationale of Work Package 2 and will be submitted to an international peer-reviewed journal. Draft protocols have been written to study the association between 5 adverse events and 6 selected drugs in different European databases. Feasibility studies on incidence and prevalence of the 5 adverse events and drugs in the different databases is ongoing.

Working group 2 has developed a protocol for conducting simulation studies and a draft scientific paper on evaluation of several measures of balance for propensity score adjustment has been written that will be submitted to an international peer-reviewed journal. A simulation model for evaluation of the prior event rate ratio (PERR)/self-controlled case series has been developed and a protocol for hazard pattern analyses as an alternative for confounder adjustment has been approved by the scientific committee of the general practitioners' research database (GPRD) of the United-Kingdom.

Working group 3 has developed a draft inventory of public national drug utilisation resources. The possibility of using IMS data for drug utilisation studies is being explored and one of the EFPIA partners has started a pilot study comparing IMS data across five EU countries for two groups of drugs. Furthermore, this working group has made agreements with the EuroDURG group on exchanging information and expertise and is now exploring collaboration between this working group and EuroDURG.

Work Package 3 (Signal Detection) has focussed efforts on securing project coordination and effective collaboration within the 12 different sub-packages. The construction of a structured database of Summary of Product Characteristics 4.8 is the most advanced sub-package activity having been operational for most of the first year. A total of 348 substances (out of 375 in the pilot data set) have been extracted and mapped to standard MedDRA terms. The use of free text extraction methods to save manual resources has been explored and shown some promise. A first version of the database has been developed, and will be shared internally within the work package for review.

Most of the other sub-packages are still in their late planning phase, with some now entering an early execution phase. Study protocols have been agreed for the bench-mark study of different measures of disproportionality analysis in different data sets and for the analysis of optimal use of MedDRA. The execution of these two studies is scheduled for the next project year.

A draft survey for the characteristics of major data sets of individual case safety reports has been piloted and agreed. The full survey is to be completed during project year 2.

Work Package 4 (Data collection from consumers) is seeking to collect data directly from pregnant women throughout their pregnancy and to compare that collected with data in existing data sources where possible. This is not intended to be a definitive study to identify drugs with foetotoxic potential but a trial of the of data collection. It is expected to provide useful information which is currently not possible using existing methodologies.

Because this WP involves direct patient contact, the requirements for ethical, informed consent and research approvals needed to be clarified for three countries. Negotiations have started with two other websites to include a link from their sites to the study website. Domain names and URL of *pregnancystudy4.eu* have been registered. This website will be the public view of WP4 and a portal to the secure part of the website for recruitment of pregnant women and to enable data entry.

Significant progress has been made on developing the study protocol along with the web questionnaires and recruitment leaflet. The development of the data collection platform is on-going and the final development phase will start when the questionnaires and instructions are completed.

The overall objective of **Work Package 5 (Benefit-risk integration and representation)** 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. A framework for B-R analysis has been developed. It consists of the following major points:

- Review of methodologies, technologies and graphical representation,
- Selection of a tool kit of B-R methodologies,
- Establishment of criteria and process for selection of case-studies,
- Choice and implementation of case studies,
- Visualisation and Communication.

Development of a protocol for the conduct of reviews has been initiated and a comprehensive literature review has been undertaken. The following approach has been adopted: 1) to review methodologies used to model effects of medicines, elucidation of preferences and integrating effects and preferences; 2) to review methodologies for graphical representation, and 3) to deliver recommendation for methodology and visualisation techniques for case studies.

The definition of criteria for choice of cases studies has been completed.

The following activities have been planned: definition of data to be gathered from case studies in the required format, development of software to support application of methodology and graphical

representation, and application of methodology and graphical representation to next wave of case studies.

The overall objective of **Work Package 6 (Validation studies)** is 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 or members of the Extended Audience. There may also be the need to use data sources not currently defined within the Extended Audience list. Based on these tests, WP6 will propose amendments to recommendations and methodological standards presented in the WP programme.

WP6 was planned to start its work programme in year 2, once WP2 and WP5 have been well established. During the first year, WP6 has contacted the extended group of data partners and defined outcomes of interest and provisionally based on the primary adverse event – drug pair groups defined in WP2. This provides a systematic approach to evaluating some of the relevant methodologies in WP2 using alternative data sources. A detailed inventory describing the data sources in the Extended Audience is part of the deliverable for this WP and will inform the most appropriate data sources. Additional adverse event – drug pairs may also be chosen in the course of the evaluation phase of WP6.

In line with the work plan of **Work Package 7**, one of the main efforts in year 1 focused on the development of a platform of training opportunities. As a first step, a paper-based questionnaire was circulated and information on training opportunities within the Consortium were collected and compiled. By the end of project year 1, a first mock-up of an electronic platform was available, which is currently further developed in close collaboration with the PROTECT Coordinators.

Regular interaction with the Eu2P Consortium has been established and a mechanism was put into place to ensure a timely input from the PROTECT WPs 2-5 on potential outcomes that would suit themselves for being included in the Eu2P training programme.

A draft list of conferences and other international forums suitable for the presentation of the results of PROTECT is available. In addition to the identification of target journals, it will form the basis for the development of the communication plan.

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.

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