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INTRODUCTION

The IMI PROTECT project: purpose, organizational structure, and procedures

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ABSTRACT

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) initiative was a collaborative European project that sought to address limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance. Initiated in 2009 and ending in 2015, PROTECT was part of the Innovative Medicines Initiative, a joint undertaking by the European Union and pharmaceutical industry. Thirty-five partners including academics, regulators, small and medium enterprises, and European Federation of Pharmaceuticals Industries and Associations companies contributed to PROTECT. Two work packages within PROTECT implemented research examining the extent to which differences in the study design, methodology, and choice of data source can contribute to producing discrepant results from observational studies on drug safety. To evaluate the effect of these differences, the project applied different designs and analytic methodology for six drug–adverse event pairs across several electronic healthcare databases and registries. This papers introduces the organizational structure and procedures of PROTECT, including how drug–adverse event and data sources were selected, study design and analyses documents were developed, and results managed centrally. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—pharmacoepidemiology; Innovative Medicines Initiative; PROTECT; observational studies; methodology; electronic healthcare databases; European Medicines Agency

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INTRODUCTION

Over the past two decades, the use of large-scale, electronic healthcare databases and registries for medicine safety evaluation has increased significantly.[1] In part this is because of the limitations of pivotal and post-

marketing randomized clinical trials which are often characterized by small numbers of participants, highly selected populations, and short duration of exposure and follow-up. These trials do not usually obtain data from the patient populations treated in clinical practice, which limits their usefulness in predicting the type and frequency of drug–adverse events likely to be observed in usual care situations.[2] The increase also reflects a growing demand by stakeholders for the safety assessment of medicines as they are actually prescribed and taken. Observational studies have become routine as post approval commitments that are part of Risk Management Plans proposed by pharmaceutical sponsors and approved by medicines regulators in the European Union and the USA.[3] The growth in the number and type of available large electronic health record databases has also made the conduct of drug safety studies in these data sources more feasible and, in some cases, less costly. Importantly, they are more rapid than large primary data collection epidemiologic cohorts and also, because of their large size and breath of data collection, better equipped for studying less frequent, and less severe adverse events than randomized clinical trials. An example is the risk of deep venous thrombosis in users of third generation oral contraceptives.[4] Concerns about the bias inherent to observational designs have been addressed in recent years by new methods for the control of confounding (e.g., propensity score methods), and the ability to compare drug–adverse event pairs with low absolute and relative risks has improved with the application of rapid cycle analyses in large data networks.[5–9]

Even with these advances, however, there is continued scepticism about the reliability of observational study findings to guide policy decisions, whether at the population or individual level.[10,11] This situation poses difficulties for different decision-makers, including regulatory agencies, the pharmaceutical industry, healthcare professionals, and patients. Difficulties in interpreting individual and/or groups of observational studies limit their usefulness for decision-making about the benefit–risk balance of a particular medicine or drug class. Some have suggested that methodological developments may have pushed pharmacoepidemiology to the borders of what can reliably be detected beyond the level of background rates in the indicated population.[12] Furthermore, efforts focusing on evaluation of type A adverse events (those with dose-dependent and predictably augmented pharmacological effects) and intended effects of drugs have increased the potential for bias.[13]

Study conduct and design choices are two of the main factors contributing to the diversity and discrepancy of study results.[14–27] In order to interpret differences in associations between drugs and adverse events that arise between types of data sources and healthcare systems in different countries, the influence of methodological variation will ideally be minimized and quantified. Further, clear interpretation of differences in results between studies performed in the same database, and between different databases, will increase understanding of the implications of different methodological choices by investigators, including differences inherent to choice of data source. To evaluate the effect of these differences, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project applied different designs and analytic methodology for six drug–adverse event pairs across several electronic healthcare databases and registries.

PROTECT'S ORGANIZATIONAL STRUCTURE AND GOALS

The PROTECT initiative was a collaborative European project that sought to address limitations of current methods in the field of pharmacoepidemiology and pharmacovigilance.[28] Initiated in 2009 and ending in 2015, PROTECT was part of the Innovative Medicines Initiative, a joint undertaking by the European Union and pharmaceutical industry.[29] Thirty-five partners including academics, regulators, small and medium enterprises, and European Federation of Pharmaceuticals Industries and Associations companies contributed to PROTECT.

The project was structured into seven work packages to achieve its goal of developing and testing methods for improving benefit–risk assessment of medicines in the European Union. It was governed by a Scientific Steering Committee charged with overseeing the performance of the work packages, allocating budget to specific activities, and making decisions regarding communication and dissemination of the project deliverables. The Scientific Steering Committee was composed of the coordinating group (European Medicines Agency), the deputy coordinating group (GlaxoSmithKline), and the private and public institutional co-chairs of each Work Package. Additional governance was provided by an External Advisory Board, made up of drug safety experts from universities, regulatory agencies, and patient organizations. External Advisory Board members were assigned to specific Work Packages to provide scientific advice and operational guidance. More detailed information about the structure, governance, and objectives of PROTECT and each Work Package is available online at the PROTECT website.[28]

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Two of the seven work packages focused on issues relevant to pharmacoepidemiology. Work Package 2 and Work Package 6 implemented research examining the extent to which differences in the study design, methodology, and choice of data source can contribute to producing discrepant results from observational studies on drug safety. Work Package 2 participants were organized into three Working Groups. Working Group 1 addressed the methodological challenges of using electronic medical records, transactional claims data, and registries to study medicine safety in Europe for consistent and transparent results. Working Group 2 evaluated the optimal methods for control of confounding, including propensity scores and instrumental variables. Working Group 3 assessed data sources and methods for drug utilization studies. Work Package 6 independently tested the replicability of Work Package 2 results in the same or different data sources as well as investigated the added value of specific aspects of study designs such as the use of an alternative outcome definition, validation of outcomes, and assessment of additional confounders. Each Work Package was co-led by representatives of the public and private sectors (Work Package 2: OK and RR/Work Package 6: LGB, XK, and STL).

Drug–adverse event association studies using different designs across multiple data sources are the primary focus of this supplement. However, the supplement also includes descriptive and outcome validation studies and two assessments of the use of instrumental variables as a method for control of confounding. Several manuscripts from the PROTECT project were published prior to the development of this supplement.[30–62]

PROTECT WORK PACKAGE 2 AND WORK PACKAGE 6 PROCEDURES

Selection of drug–adverse event pairs and data sources

Adverse events of interest were selected in three steps. In the first step, each partner in Work Package 2 was asked to nominate 10 drug–adverse event pairs to create a pool of adverse events and drugs that could be prioritized for study by Work Package 2. Partners were asked to rank adverse events and drugs based on four criteria. Criterion one was an important regulatory action resulting from the adverse event such as a drug withdrawal or major changes to the summary of product characteristics (e.g., approved label). Criterion two was the public health impact of the adverse event, e.g., the seriousness of the adverse event, with priority given to more serious events, and the frequency of the adverse event, with a priority to include both rare and common adverse events. Criterion three was the feasibility to ascertain the adverse event in an electronic healthcare database; partners were asked to include adverse events that are easy or difficult to ascertain. Finally, in order to facilitate comparison with other international initiatives, criterion four mandated inclusion of at least one drug–adverse event pair studied by the Observational Medical Outcomes Partnership (OMOP),[5–7] the US Food and Drug Administration's Sentinel Initiative,[8] and the EU-ADR project.[9]This resulted in a list of 55 adverse events and more than 55 drugs. The second step, a face to face consensus meeting, resulted in the selection of five adverse events and about two to three drugs potentially associated with each adverse event.

The final step was therefore to narrow the selection of drugs to study in Work Package 2. We selected six drugs based on the prevalence of drug exposure (commonly used drugs and infrequently used drugs) and the possibility to investigate a broad range of relevant methodological issues including) hazard functions (acute and long-term effects, delayed/transient effects), setting of drug use (in-/outpatient use), type of use (short-/long-term, as needed), and different indications of use.

The six drug–adverse event pairs fulfilling these a priori criteria and selected by the Work Package 2 partners for the project are as follows: (i) inhaled long-acting beta-2 agonists and acute myocardial infarction; (ii) antimicrobials and acute liver injury; (iii) antidepressants and hip fracture; (iv) benzodiazepines and hip fracture; (v) anticonvulsants and suicide/suicide attempts; and (vi) calcium channel blockers and cancer. A detailed description of each drug–adverse event pair with regard to public health impact, drug utilization, the level of evidence to support a causal association, the proposed pharmacological mechanism(s), and methodological challenges specific for the drug–adverse event association has been published previously.[63] In addition to replicating studies with the drug–adverse event pairs selected by Work Package 2, Work Package 6 chose antibiotics and acute myocardial infarction as a "negative control" drug–adverse event pair, i.e., a pair thought to not represent a true causal relationship (results not presented in the supplement).

Detailed features of the databases that participated in Work Package 2 drug–adverse event association studies are described by Abbing-Karahagopian et al.[63] Briefly, Work Package 2 used five databases containing data from patients from six different European nations: the Danish national registries, the Dutch Mondriaan databases, the UK CPRD and THIN databases, and the Spanish BIFAP database. Work Package 6 also used the PGRx case referent system

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(Pharmacoepidemiologic General Research eXtension), the Utrecht Patient Oriented Database (UPOD), and Clinformatics Datamart, a US health insurance claims database. The Danish registries have national coverage, while most other databases contain regional data or a representative sample of a total population. Most of the databases were established more than 10 years ago with regular and expanding data collection. Routine checks on quality are performed in all databases. The majority of databases include general practitioner data and two (Danish and CPRD) include registries for and linkages to mortality, cancer, and secondary care data. The PGRx system and UPOD, a hospital database, include more selected patient populations.

Study document process, analytic approach, and management of results

A common study protocol was developed for each drug–adverse event study and followed the ENCePP methodological standards (including the ENCePP checklist).[64] Operational definitions of exposures and outcomes were harmonized and only varied if an available database had additional variables (e.g., socio-economic or lifestyle factors). For transparency, these protocols were also submitted to the ENCePP registry of studies.[65] Studies used different designs including cohort, nested case–control, case–control, case-crossover, and self-controlled case series. All studies are retrospective, based on existing data from the databases described in the preceding texts. Table 1 lists the designs and databases for each drug–adverse event pair by Work Package. Each study used data from the period 2001–2009 except for the PGRx case–control analyses (2007–2010 and 2007–2012 for myocardial infarction and suicide attempts analyses respectively) and the Clinformatics Datamart case control analyses (2004–2009). Exposure was analyzed time-dependently in all studies, and some confounders were classified time-dependently if appropriate. Different methods for the selection of and control for confounding variables were applied. As not all databases have the same level of detail with regard to confounders, each drug–adverse event pair analysis included a minimum set of confounders that all databases have available (e.g., age, sex, prior medical history, outcome risk factors, concomitant medications). In subsequent sensitivity analyses, based on data availability, impact of further adjustment for confounders was assessed. For all databases, we described the pattern of exposure to the drugs of interest. For those databases with sufficient information on diagnoses, we have described the prevalence and incidence of the outcomes of interest.[57–62] For the drug–adverse event association studies we implemented a blinding procedure with central results management. Results for each design were un-blinded only after project teams submitted adjusted association measures to the coordinating center at Utrecht University.

Table 1. Design and data sources for drug–adverse event association studies completed by Work Packages 2 and 6

Drug-adverse event pair	Cohort	Case–control	Nested case–control	Case-crossover	Self-controlled case series
Antibiotics –Acute liver injury	*CPRD* *BIFAP*	*Clinformatics** *UPOD** *CPRD**	*CPRD* *BIFAP*	*CPRD*	*CPRD*
Antiepileptics – Suicide (completed, attempts, ideation)	*CPRD* *Danish registries**	*PGRx**			
Antidepressants – Hip fractures	*THIN* *Mondriaan* *BIFAP*		*THIN* *Mondriaan* *BIFAP*	*THIN* *Mondriaan*	*THIN* *Mondriaan*
Benzodiazepines – Hip fractures	*CPRD* *BIFAP* *Mondriaan*		*CPRD* *BIFAP* *Mondriaan*	*CPRD* *BIFAP*	*CPRD* *BIFAP*
B_2Agonists –Acute myocardial infarction	*CPRD*† *Mondriaan* † *Clinformatics**†	*PGRx**†			
Calcium channel blockers – Cancer (all, cause-specific)	*CPRD*				
Antibiotics – Myocardial infarction (negative control)		PGRx*† *Clinformatics**†			

BIFAP (Spain); Clinical Practice Research Database (CPRD, UK); LabRx (USA); Mondriaan (Netherlands); Pharmacoepidemiologic General Research eXtension case referent system (PGRx, France); The Heath Improvement Network database (THIN, United Kingdom).
*A WP6 replication study, all others completed by WP2.
†Results not published in PDS supplement.

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SUMMARY

We studied six drug–adverse event associations that are important to regulatory agencies, patients, and the pharmaceutical industry. The findings from our studies, conducted using different designs and methods in multiple electronic healthcare databases and registries, provide information relevant to making pharmacoepidemiologic studies more useful and reliable for benefit-risk decision-making. Furthermore, a pan-European research network structure with processes governing collaboration between public and private partners has been created for future pharmacoepidemiology studies.

CONFLICT OF INTEREST

RS is an employee and stockholder of Novartis Pharma AG. RF Reynolds is an employee and shareholder of Pfizer, Inc. The views expressed herein are his and do not necessarily reflect those of Pfizer, Inc.

KEY POINTS

- PROTECT evaluated the effect of study design and analytic choices for six drug–adverse event pairs in several electronic healthcare databases and registries.
- Common protocols and analytic specifications were used by research teams composed of public and private partners located throughout Europe and the United States.
- A blinding procedure with central result management was used to minimize the potential for bias.
- The findings, presented in this supplement, provide information relevant to making pharmacoepidemiologic studies more useful and reliable for benefit-risk decision-making.
- A pan-European research network with processes governing collaboration between public and private partners has been created for future pharmacoepidemiology studies.

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The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu), which was a public-private partnership coordinated by the European Medicines Agency.

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