



Innovative Medicines Initiative



IMI PROTECT PERIODIC REPORT N° 4

Project title	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium
Project Acronym	PROTECT
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Table of content

Table of content	2
Declaration of the coordinator	3
Abbreviations	4
1. Executive summary	6
1.1. Project rationale and overall objectives of the project.....	6
1.2. Overall deliverables of the project.....	6
1.3. Summary of progress versus plan since last period	6
1.4. Significant achievement since last report	7
2. Summary of progress against objectives	9
2.1. Summary of work progress by Work package and significant results	10
2.2. Deliverables and milestones in this period	18
2.3. Deviations from Description of Work.....	29
3. Summary of Major Achievements and key dissemination activities	33
3.1. Major achievements.....	33
3.2. Key dissemination activities	35
3.3. Use and dissemination of foreground.....	36
4. Management of Project and Consortium	37
4.1. Overall management of the project.....	37
4.1.1. Completed tasks in WP1 and other management activities	37
4.1.2. Verification of legal status of PROTECT public participants	38
4.1.3. Synergies with other IMI projects or any other programmes.....	38
4.1.4. Public private partnership	39
4.2. Project plan for the remaining reporting periods	41
4.2.1. Prospective changes to the original work plan	56
4.3. Risk assessment, when appropriate.....	58
5. Finance - Cost	67
5.1. Cost summary.....	67
5.2. Description of deviation from original budget.....	67
6. Form C and Summary Financial Report	70
7. Annexes	71
7.1. Financial reporting documents	71
7.2. PROTECT Global Work Plan Year 4	71
7.3. Other relevant documents	71

Declaration of the coordinator

I, the coordinator of this project, declare that,

The periodic report submitted is in line with the obligations as stated in Article II.2.3 of the Grant Agreement:

The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;

The project (*tick as appropriate*):

- ☐ has fully achieved its objectives and technical goals for the period;
- ☐ has achieved most of its objectives and technical goals for the period with relatively minor deviations;
- ☐ has failed to achieve critical objectives and/or is not at all on schedule.

The public project website www.imi-protect.eu is up to date, if applicable.

To my best knowledge, the financial statements which are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project (section 5) and if applicable with the certificate on financial statement.

All participants, in particular non-profit public bodies, secondary and higher education establishments, research organisations and SMEs, have declared to have verified their legal status. Any changes or deviations have been reported under section 4 (Project Management) in accordance with Article II.3.f of the Grant Agreement.

Name of the Coordinator: **Xavier Kurz**

Date: 29/10/2013

Signature of the Coordinator:

Abbreviations

ADR – Adverse Drug Reaction
 AE – Adverse Event
 AEMPS - Agencia Española de Medicamentos y Productos Sanitarios
 Amgen - Amgen NV
 AZ - AstraZeneca AB
 BRAT - PhRMA Benefit-Risk Action Team Initiative
 Bayer - Bayer Pharma AG
 CA – Consortium Assembly
 CEIFE - Fundación Centro Español de Investigación Farmacoepidemiológica
 CFS – Certificate on the Financial Statement
 D – Deliverable
 DKMA - Lægemiddelstyrelsen - Danish Medicines Agency (Managing Entity of the IMI JU Fund)
 DU – Drug utilisation
 EAB – External Advisory Board
 EAp – Extended Audience of participants
 EFPIA - European Federation of Pharmaceutical Industries and Associations
 EMA – European Medicines Agency
 Eu2P – European Programme in Pharmacovigilance and Pharmacoepidemiology
 FICF - Fundació Institut Català de Farmacologia
 FP7 – 7th Framework Programme
 GA – Grant Agreement
 Genzyme - Genzyme Europe B.V.
 GPRD - The General Practice Research Database
 GSK - GlaxoSmithKline Research and Development LTD (Deputy Coordinator)
 HLU - H. Lundbeck A/S
 IAPO - International Alliance of Patients' Organizations
 IMI JU – Innovative Medicines Initiative Joint Undertaking
 Imperial - Imperial College of Science, Technology and Medicine
 INSERM - Institut National de la Santé et de la Recherche Médicale
 IRFMN - Mario Negri Institute for Pharmacological Research
 IVRS – Interactive Voice Response System
 LMU-MUENCHEN - Ludwig-Maximilians-Universität München
 ME - Merck KGaA
 M – Milestone
 MHRA - Medicines and Healthcare products Regulatory Agency
 Novartis Pharma - Novartis Pharma AG
 Novo - Novo Nordisk A/S
 OMOP - Observational Medical Outcomes Partnership
 Outcome – Outcome Europe Sarl
 PA – Project Agreement
 PE – Pharmacoepidemiology
 Pfizer - Pfizer Limited
 PGRx (LASER) - L.A. Santé Epidémiologie Evaluation Recherche (LASER)
 PhRMA - Pharmaceutical Research and Manufacturers of America
 PhV - Pharmacovigilance
 PMP – Project Management Plan
 Roche - F. Hoffmann-La Roche AG
 RUG - Rijksuniversiteit Groningen
 SARD - Sanofi–Aventis Research and Development (EFPIA co-Leader)
 SC – Steering Committee
 SME – Small and medium-sized enterprises

SP – sub-package (substructure to Work Package 3)

UMC - Stiftelsen WHO Collaborating Centre for International Drug Monitoring

UMCG- University Medical Center Groningen

UNEW - University of Newcastle upon Tyne

UU – University Utrecht

WG – Work group (substructure to Work Package 2)

WHU- Witten/Herdecke University

WP – Work Package

WS – Work streams (substructure to Work Package 5)

1. Executive summary

1.1. 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.

1.2. 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.

1.3. 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 were conducted. 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 included 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 method 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. Most of the analyses were completed by April 2013.

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 but the recruitment is on-going and timelines have been adapted to produce significant results by August 2014.

The work on the relevance of various methodologies for benefit-risk assessment is progressing according to planned timelines. The two wave of case studies were completed and reported were published. Reports related to methods for benefit-risk integration and visualisation were also published and presented in several international conferences. The final recommendations initially scheduled for February 2013 were published before July 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. This extension programme has now started.

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.

1.4. Significant achievement since last report

1.4.1. The work on methods for pharmacoepidemiological studies finalised descriptive studies and cohort studies applicable in several European databases, integrating various study designs for each of the drug-adverse event pairs and data specifications. Results for three of these adverse event-drug pairs (antidepressants and hip fractures, antibiotics and liver injury, antiepileptics and suicidal ideation/attempt) were presented in collaboration with WP6. 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 has updated once. 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 completed, covering replication studies, negative control studies, use of alternative outcome definition, and 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.

1.4.2. 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. The project has shown that the choice of disproportionality measures has a lower impact than threshold used for signal detection. A probabilistic record linkage technique has been tested for the identification of duplicates from spontaneous reports databases and seems very promising results leading to a possible application in a wide range of databases. A published structured database of adverse drug reactions included in products' information was updated and is used by EU regulatory authorities in their routine pharmacovigilance activities. An algorithm was validated to address the masking effect associated with measures of disproportionality.

1.4.3. The data collection platform and a specific website have been launched for the study to collect data directly from pregnancy women, and the recruitment has started in Denmark, the Netherlands, the United-Kingdom and Poland. Recruitment is progressing well and preliminary data yield good results.

1.4.4. The programme on methods for benefit-risk assessment reached important milestones by finalising wave 1 and wave 2 case studies and the publications of methodological reviews for data integration and visualisation, as well as results from these case studies, on the PROTECT public website. These results are preparing the ground for key reports and scientific publications that are highly likely to influence practice. This work generated a large external interest.

The work on benefit-risk assessment has been extended by work package 6 and a work plan has been developed and started during the reporting period. It includes two main workstreams:

- To test/extend the B/R methodology in the real life setting, including three main activities: assessment of the effect of the choice of the time horizon and of the time dependency; use of prior expert judgement and use of observational/post-marketing data as well as data from clinical trials; three cases studies have been selected: efalizumab, rimonabant and rosiglitazone.
- To validate visualisation tools by practitioners, regulators and patients, and to test methods to elicit preferences from patients, looking at whether the three methods currently used produce the same results, and at differences of preferences for treatment outcomes between the main stakeholders (regulators, patients, health care professionals). Three disease areas have been selected: breast cancer, atrial fibrillation, diabetes.

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

2. Summary of progress against objectives

The following participants have taken part in the project during the 4th project year:

Table 2-1 List of participants

Participant No.	Participant (Name of Organisation)	Short name
1	European Medicines Agency (<i>Coordinator</i>)	EMA
2	Lægemiddelstyrelsen - Danish Medicines Agency (<i>Managing Entity of the IMI JU Fund</i>)	DKMA
3	GlaxoSmithKline Research and Development LTD (<i>Deputy Coordinator</i>)	GSK
4	International Alliance of Patients' Organizations	IAPO
5	Outcome Europe Sarl	Outcome
6	Ludwig-Maximilians-Universität München	LMU-Muenchen
7	Agencia Española de Medicamentos y Productos Sanitarios	AEMPS
8	Fundació Institut Català de Farmacologia	FICF
9	Fundación Centro Español de Investigación Farmacoepidemiológica	CEIFE
10	Institut National de la Santé et de la Recherche Médicale	INSERM
11	L.A. Santé Epidémiologie Evaluation Recherche (LASER)	PGRx (LASER)
12	Mario Negri Institute for Pharmacological Research	IRFMN
13	Rijksuniversiteit Groningen	RUG
14	Universiteit Utrecht	UU
15	Stiftelsen WHO Collaborating Centre for International Drug Monitoring	UMC
16	Medicines and Healthcare products Regulatory Agency	MHRA
16.1	The General Practice Research Database	GPRD
17	Imperial College of Science, Technology and Medicine	Imperial
18	University of Newcastle upon Tyne	UNEW
19	Sanofi–Aventis Research and Development (<i>EFPIA co-Leader</i>)	SARD
20	Pfizer Limited	Pfizer
21	F. Hoffmann-La Roche AG	Roche
22	Novartis Pharma AG	Novartis Pharma
23	Amgen NV	Amgen
24	Genzyme Europe B.V.	Genzyme
25	Merck KGaA	ME
26	Bayer Pharma AG	Bayer
27	AstraZeneca AB	AZ
28	H. Lundbeck A/S	HLU
29	Novo Nordisk A/S	Novo
30	Poznan University of Medical Sciences	PUMS
31	Takeda Global Research and Development Centre (Europe) Ltd	TGRD(Europe)
32	Aarhus Universitet	AU
33	Eli Lilly and Company Limited	Eli Lilly

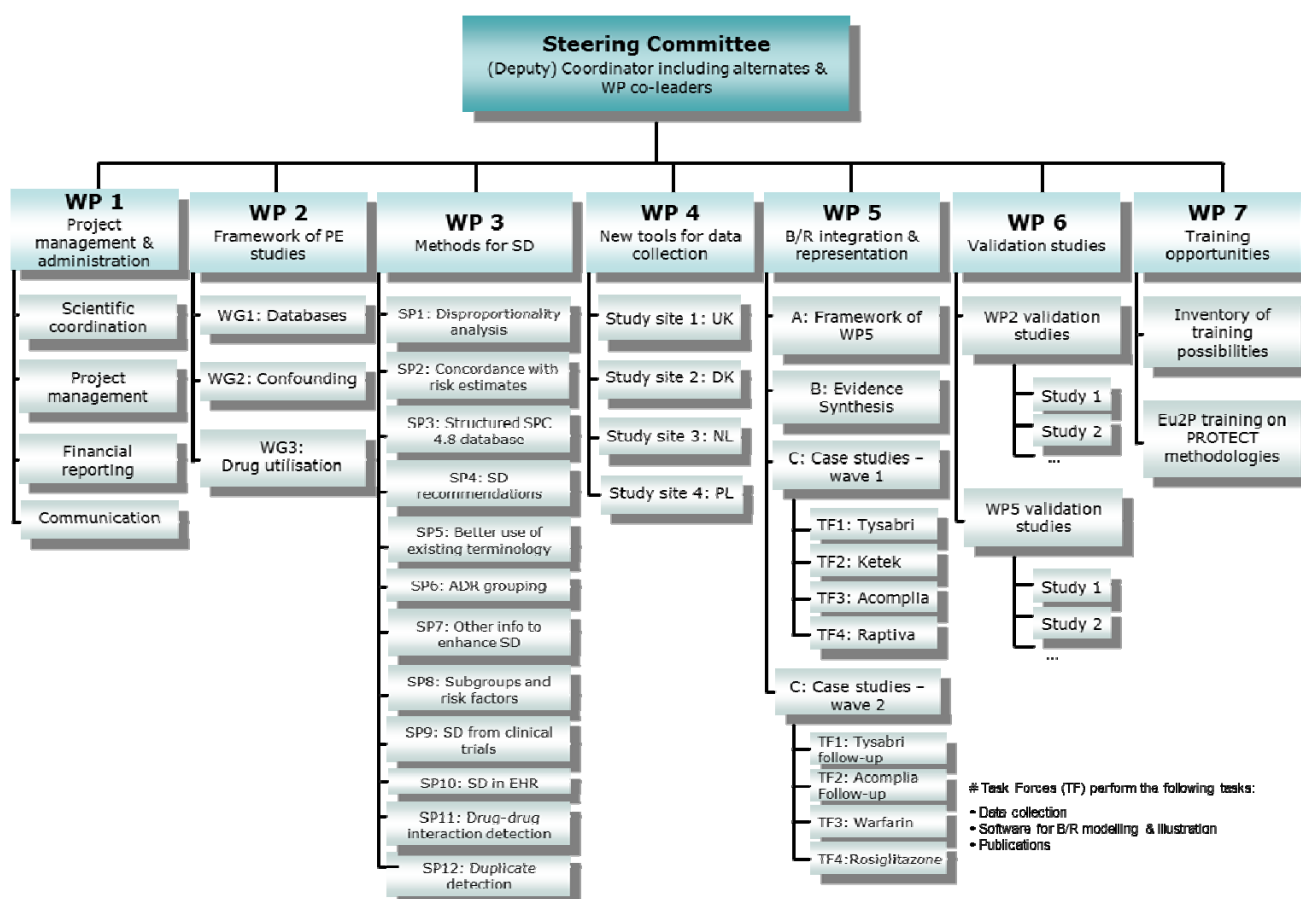
34*	Witten/Herdecke University	WHU
35*	University Medical Center Groningen	UMCG

* Partners 34 (Witten/Herdecke University) and 35 (University Medical Center Groningen) joined the PROTECT Consortium during the 4th project year by acceding to the Grant Agreement on 24 May 2013 and 8 July 2013, respectively.

Overall, the PROTECT project increased its momentum and continued progressing very well with number of publications on first results published (see Annex 7.3 – List of publication). The Work Packages (WP) further refined their work plans¹ and a review by the External Advisory Board in March 2013 of the work progress concluded that the project is mostly on track and has produced relevant results which is also reflected in the 4th half-year report (see Annex 7.3).

2.1. Summary of work progress by Work package and significant results

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



The progress of Work Packages WP2-7 during the reporting period is described below. Work Package 1 (Project Management & Administration) is addressed in chapter 4.

¹ The global project plan providing an overview of the completed, on-going and planned tasks is annexed to this report (Annex 7.3).

Work package 2

During the fourth project year WP2 has continued showing progress in accomplishing the tasks by its 3 working groups. WG1 (Databases) has conducted the descriptive and cohort studies on the selected 6 drug-AE pairs in the different European databases. Furthermore, the data specification documents for the studies using different study designs (nested case control, case crossover and self-controlled case series) were developed. One study on antiepileptic drugs and suicide has been delayed due to technical reasons and has been deprioritised in October 2013 to allow urgent finalisation of a more critical study (calcium channel blocker and cancer) by the same investigator. As mentioned in the 3rd periodic report, the registration of the six protocols in the ENCePP online registry was completed in September 2012. WG2 (Confounding) has performed further studies on propensity scores (PS) balance measures, time dependent confounding and instrumental variable (IV) analysis resulting in several manuscripts. WG3 (Drug Utilization) has identified 19 new European countries to be included in the inventory of drug utilization databases in Europe. Systematic literature reviews of clinical trials and observational studies on the selected drug-AE pairs have been completed. Furthermore, the protocol to calculate the exposed population to drugs has been further developed. During this period, the collaboration between the 3 WGs has been established. WG2 is supporting WG1 with the analysis of time-dependent confounding variables and WG2 will perform analyses on PS and IV using empirical data from WG1 databases. WG1 will provide data from the descriptive studies of prevalence of drug use to compare with those from drug consumption databases in WG3.

Significant results in the period:

Working Group 1 has drafted ten papers with results of the descriptive studies. Eight papers characterizing the patterns of drug use, i.e. for antibiotics, antiepileptics, antidepressants, benzodiazepines, long acting beta 2 agonists and calcium channel blockers and two papers comparing the incidence of two outcomes, i.e. acute liver injury and hip/femur fracture, across the databases participating in PROTECT WP2. Various results of WG1 descriptive studies were presented as posters at the International Conference on Pharmacoepidemiology (ICPE) 2013. Furthermore, the cohort analyses have been finalized for all drugAE pairs and manuscripts are under preparation. First results of the cohort studies on three associations (i.e. antibiotics/liver injury, antiepileptics/suicidality and antidepressant & benzodiazepines / hip/femur fracture) were presented at a symposium at ICPE 2013 and comparisons between WP2 and WP6 results were discussed.

Working Group 2 has submitted several papers to international peer-reviewed journals. These include a systematic review of the current measures of balance in propensity score analysis in the medical literature and a paper on the quantitative verification of instrumental variables assumptions using balance measures. In addition, a comment to the article 'Squeezing the Balloon: Propensity Scores and Unmeasured Covariate Balance' by JM Brooks and RL Ohsfeldt in Health Service Journal has been submitted. Furthermore, a manuscript on the application of instrumental variables analysis in pharmacoepidemiology using the Beta2-Agonist and Myocardial Infarction as an example is in preparation and two simulation studies were conducted, the first one to investigate the balance measures for determining optimal caliper width in propensity score matching and the second one to analyse the impact of censoring on estimates of adverse drug effects. WG2 was well represented at ICPE 2013 with four poster presentations and one slide presentation.

Working Group 3 has updated the inventory of drug utilisation resources in selected European countries (latest version released in October 2012). An assessment of the degree of comparability of the national databases in measuring drug exposure has also been explored. Graphical results related

to drug utilisation data for selected European countries are also available as part of the WG3 output. The inventory will be completed as the project evolves and has been made publicly available in the IMI-PROTECT website to facilitate contribution from external sources. Scientific papers based on the inventory have been submitted to scientific journals.

Having finalized the systematic literature reviews for the selected drugAE pairs, a paper on the review of studies on antiepileptics use and suicide has been submitted and another paper on the review of studies on the association between bronchodilator treatment and myocardial infarction in COPD patients is in preparation. In addition, the epidemiologic measures of drug use (i.e. antiepileptic, benzodiazepines, and antidepressants) in four European countries and the assessment of quality in systematic reviews of adverse effects have been investigated. Both systematic reviews and the two additional studies were presented as posters at ICPE 2013. The work published in 2012 on the “Potential impact of benzodiazepine use on the rate of hip fractures in five large European countries and The United States” based on drug utilisation data provided by IMS Health has been extended with the submission of another paper on the “Excess risk of hip fractures attributable to the use of antidepressants in 5 European countries and the US”.

Work package 3

During its fourth project year, PROTECT work package 3 has progressed from implementation and initial analysis to conclude several studies and begin to communicate their outcome to external stakeholders. Specifically, each of the three sub-packages of highest priority, as per the recommendation of the PROTECT External Advisory Board, have concluded their main analysis, presented these results at international scientific meetings, and drafted manuscripts to be submitted for scientific publication during project year 5: sub-package 3.01 has concluded its benchmark analysis of existing methods for screening spontaneous reports, sub-package 3.09 has evaluated two novel methods for signal detection in clinical trials, and sub-package 3.10 has studied the practical implications and effective processes for signal detection in longitudinal electronic patient records. Beyond that, sub-packages 3.7 (Strategies to reduce masking, or competition bias, in the analysis of spontaneous reports) and 3.12 (Duplicate detection) have concluded their analyses and submitted papers for peer reviewed scientific publication. Sub-package 3.06 which focuses on Novel tools to group ADRs have completed the analysis of their groupings within the protocol of, now completed, sub-package 5; they have also initiated a collaboration with MSSO (MedDRA management organization) to explore value of technology for support in designing new SMQs.

A number of projects are in the process of finalizing their analyses and will progress towards external communication and publication during project year 5. Sub-package 3.08 on subgroups and stratification is the only one not to have begun data analysis, as it awaited the finalization of the analysis of sub-package 3.01; resources will now be shifted from sub-package 3.01 to 3.08, and the completion and external communication of the latter is the greatest challenge of WP3 for the final year of PROTECT.

Significant results in the period:

The specific results for WP3 are briefly described for each of the sub-packages separately:

SP3.01 Merits of disproportionality analysis

- Analysis across all databases finalized
- Oral presentation at ICPE'13 in Montreal
- Manuscript drafted and to be finalized in the fall of 2013.

SP3.02 Concordance with risk estimates

- Scope clarified including an updated data set for analysis and a revised plan for the identification of formal studies
- Proposal for the identification of the best measure of association from published studies agreed

SP3.03 Structured database of SPC 4.8

- The database for Centrally Authorised Products is now completed and updated to 30 June 2012. It is available on the EMA website and maintenance is now a part of EMA routine business.
- Extended abstract published in Drug Safety

SP3.04 Signal detection recommendations

- Interim recommendations drafted

SP3.05 Better use of existing terminologies (Completed in project year 3)

- Extended abstract published in Drug Safety https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d9a20

SP3.06 Novel tools for grouping ADRs

- Terminological reasoning for seven additional safety topics completed
- Evaluation of impact on signal detection of novel groupings as per protocol of SP3.05 completed: no overall improvement but highlighted potential value of technology to identify smaller groups of clinically more closely related terms
- Data mining techniques were applied on the WHO database in order to evaluate if the provided novel groupings can expedite signal detection compared to preferred terms and custom groupings.
- Collaboration initiated with MSSO (MedDRA management organization) to explore value of technology for support in designing new SMQs
- Development of graphical user interface to design and execute queries using OntoADR, in order to create new groupings of ADRs using knowledge engineering methods

SP3.07 Other information to enhance signal detection

- Follow-up analysis of a mathematical framework to quantify the masking effect associated with the confidence intervals of measures of disproportionality completed
- Three manuscripts on masking effects in disproportionality analysis submitted for peer review

SP3.08 Subgroups and risk factors

- Project re-initiated following the completion of the analysis for SP3.01 in project year 4

SP3.09 Signal detection from clinical trials

- Analysis of Extreme Value Modeling for clinical trials completed
- Manuscript on the evaluation of Extreme Value Modeling under internal review

SP3.10 Signal detection in electronic health records

- Study of concordance between temporal pattern discovery method (signal detection) and published epidemiological studies completed: the former was more conservative than the latter highlighting a lower number of drug adverse event pairs, in total
- Poster presentation at ICPE'13 in Montreal
- The computational framework for exploratory screening of the THIN database has been finalised and made available to all sub-package participants for the study of strategies for evaluating potential signals in electronic health records
- Study of strategies for evaluating potential signals in electronic health records completed: manual review of highlighted associations crucial as a majority could be dismissed from further review; around 20% were classified as meriting further evaluation, which may involve review of individual patient histories or consideration of orthogonal information such as other drugs or adverse events, or complementary sources of information, including spontaneous reports and the literature

SP3.11 Drug-drug interaction detection

- Literature review of methods for drug-drug interaction detection finalized
- Study protocol for comparative evaluation of methods for drug-drug interaction in VigiBase and the US FDA's FOI database finalized
- Preliminary analysis in VigiBase completed

SP3.12 Duplicate detection

- Analysis of performance of probabilistic duplicate detection method in the WHO database, VigiBase, completed for all three national centres in the study: the probabilistic method achieves much better specificity than rule-based methods currently in use, and detects some duplicates missed by these methods
- Poster presentation at ICPE'13 in Montreal
- Manuscript submitted for peer review

Work package 4

Work package 4 (WP4) explores the feasibility and usefulness of modern communication methods to collect data related to health and medicines directly from consumers. WP4 is studying 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 current reporting period, WP4 reached a number of milestones, in particular the finalisation of the study recruitment website and data collection platform and the initiation of recruiting of participants to the study and data collection. The data collection platform was available from 01-October 2012 and recruitment began in Denmark on 12-October-2012, UK on 29-October-2012, and The Netherlands on 05-November-2012 and in Poland on 25-May-2013. As of early September 2013 there are 1348 participants enrolled into the study and a total of which 1118 have completed the baseline questionnaire. The study protocol and Informed Consent form were amended to detail that we will not follow-up on all participants until outcome is achieved.

The major issues encountered during the fourth project year and solutions are described below:

- Issues with recruiting participants. Per initial study assumptions we aimed to recruit 5600 participants to the study, 4800 via web and 800 via an interactive voice response system (IVRS). Recruitment strategies were customised to the healthcare systems and habits of each

country. Following the launch of recruitment it became evident that recruiting rates were much slower than expected. To targeting reach a wider audience budget was re-allocated to avail of paid advertising. Paid advertising proved effective demonstrated by an increase in enrolment figures.

- The option of collecting data via the interactive voice recognition system proved to be unpopular contrary to what had been expected. Only one participant chose this option to report data. To utilise resources more efficiently, recruitment via IVRS was stopped on 01-September 2013.
- Data Protection specificities in Poland led to a delay in recruitment initiation in Poland by almost 8 months. This delay has imposed a pressure to recruit the required amount of participants in a much shorter timeframe.

Significant results in the period:

During the fourth project year, the focus of WP4 was to:

- Finalise and launch the data collection platform.
- Finalise and launch of the public webpage: <https://www.pregnancystudy4.eu/> the webpage provides a public view of the project as well as being the entry portal to the data collection system.
- Roll out country specific recruitment strategies (distribution of leaflets, Facebook pages etc.)
- Recruitment of pregnant women to the study
- Monitor continuously recruitment figures and take action where possible to address any slowdown

Work package 5

The overall objective of WP5 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.

WP5 has continued to deliver during year 4.

Comprehensive reviews of benefit risk methodologies and of ways that these and their outcomes can be visualised have been completed and made available for download via the PROTECT website. The results of these reviews have informed case study work and both the first and second waves of case studies are now complete. The case studies have allowed the exploration and testing of benefit risk methodologies through increasing levels of complexity and with a focus on visual presentation and the reports of this work too is available on the PROTECT website. The drawing together of this knowledge and experience continues and an initial set of recommendations was distilled in spring 2013. This has been commented upon by the External advisory board and is being refined and finalised.

Patient/public involvement continues, work has been completed that has fed into the case study work and is linking into the final recommendations document. An interactive web based version of the recommendations work is also under construction.

Multiple presentations and academic publications are underway and work package 5 continues to hold face to face meetings for the whole work package on an approximately quarterly basis and Management Team meetings on a monthly basis.

Work package 6

The overall objective of WP6 is to evaluate the reproducibility of methods developed in WP2 to 5 . It has definitely focused on WP2 (pharmacoepidemiology methods) and WP5 (benefit-risk methods).. Based on this work, WP6 will complete recommendations and methodological standards developed in the WP2 and WP5 programmes.

Significant results in the period:

A-The plan to evaluate the reproducibility of the methods developed in WP2 has been well advanced:

- The plan, in relation to WP2 drug-adverse event studies, had been organised around 6 objectives:
 - Objective 1 - Replication study in same database: Is the study replicable when conducted independently in the same database?
 - Objective 2 - Replication study in different database: Do the results have external validity?
 - Objective 3 - Negative control study: Does a study using the same protocol provide absence of evidence of an association where the exposure is such that the expected result is one of no association?
 - Objective 4 - Use of alternative outcome definition: What is the impact of different levels of certainty of the outcome (e.g. definite, probable, and possible) on the effect estimate?
 - Objective 5 - Validation of outcome: Has the outcome of interest been validated through clinical record review? What is the impact of validation on the effect estimate?
 - Objective 6 - Assessment of confounders: Has confounding been adequately taken into consideration? Are there additional confounders that need to be assessed? How does better control for confounding impact the effect estimate?
- The data sources used have been the following:
 - PGRx (covering Several EU countries)
 - CPRD (ex-GPRD) (UK)
 - Danish Psychiatric, Somatic Hospital Discharge & Mortality Registers (DKMA) (DK)
 - the Utrecht Patient Orientated Database (UPOD) (NL)
 - Invision Damart (ex-LabRX) and Premier (US)
 - The use of E3N, a large prospective cohort study conducted in France on risk factors for female cancers, has been cancelled following evaluation of feasibility of access to this database.
- After the dropping-out of one industry partner (GSK) and the addition of one academic institution (Lundbeck), the partners contributing to the plan are:.
 - SME: LA-SER
 - Industry: Sanofi-aventis R&D, Takeda GRDC, Lundbeck
 - Academic institutions: Utrecht University and Aarhus University
- Twelve protocols have eventually been elaborated, and results have been obtained during the year for 10 of them. Four of these study results, covering two drug-AE pairs (antibiotics

and ALL, antiepileptics and suicidality) have been communicated together with the WP2 corresponding subjects at the International Congress of Pharmacoepidemiology (ICPE) in August 2013.

During the period, WP6 has defined a “replication” plan of WP5 methods, through numerous interactions with the WP5 researchers who have now completed their two waves of studies. The WP6-WP5 activities cannot actually be direct replication studies, due to the nature of Benefit/Risk (B/R) assessments, the plan’s overall objective is to ensure that the B/R methods and tools used and recommended by WP5 can be operationalized in the real-world setting of decision making.

Two groups of activities have been identified, with a working plan identifying resources, timelines and deliverables for each. The two activities are:

- **Activity 1: Testing/extending the B/R methodology in the real-life setting**
The objective of this activity is to extend the Benefit/Risk approaches from WP5 activities to the real-life conditions of B/R evaluations and re-evaluations over time. This activity is deemed to provide a closer focus to the real-world clinical and decision making practice, take the perspectives of both regulators’ and payers’ decision making, with a focus of a re-evaluation or a post-marketing assessment of B/R, and include patients’ utility. The framework and methods benchmarked within WP5 will be tested and possibly extended to this context. This development will consider including:
 - The assessment of the effect of time horizon choice on the B/R
 - Time-dependency modelling
 - Real-world modelling
 - The use of observational/post marketing data as well as RCT.
 - Inclusion of prior expert judgement

Three case studies have been selected: Efalizumab, rimonabant, rosiglitazone. The definition of a working plan for each of them is on-going.

- **Activity 2: Validation of visualization tools.**
The objective of this activity is to validate or test the visualisation tools proposed by WP5 using direct feedback from practitioners, decision makers and patients, i.e. the end-users of these tools. B/R visualisation tools are used to both capture preferences and communicate B/R evaluation outputs to decision makers. Direct testing of visualization tools will be made with involvement of direct users e.g. patients or patients representatives, decision makers, scientific evaluators. Methods to elicit preferences from patients will be tested, looking at whether the three methods currently used produce the same results, and at the differences of preferences for treatment outcomes that may exist between the main stakeholders (regulators, patients, health care professionals). Three disease areas have been selected: breast cancer, atrial fibrillation, diabetes. Three therapeutic areas have been defined (breast cancer, atrial fibrillation, and diabetes). An additional population (obese population) is in feasibility phase.

Work package 7

During the fourth year there have been between 9 and 12 positions offered at the Platform. Four of the positions offered in September 2012 were removed because the corresponding research project was completed and closed. Four new positions have been added, and the mechanisms for trainees recruitment have been improved at the two institutions offering these positions. In total, 27 inquiries for additional information were received (of which 10 from EU2P students), and 5 applications have been submitted by potential candidates. The backgrounds were Pharmacy (19), Medicine (4), Biosciences or Biology (3), and Veterinary (1). The countries of origin were mostly European (4 UK, 3

Germany, 2 Italy, 3 Spain, 2 The Netherlands, 1 Sweden, 1 Switzerland), and three were also inquiries from Colombia, Afghanistan, India, Australia, and Nepal. The main fields of interest were pharmacovigilance and case-population research (15), drug utilization (5), and “collaboration with an on-going study” (4).

A document describing the operational process and activities related to the identification of training programme deliverables and their transfer to the EU2P was produced. It describes the process of training topics identification from each WP, the proposed EU2P domain or training module, liaising with each potential EU2P WP leader and agreeing their inclusion in training programmes, and outcome tracking in the training programme.

Following the advice of the External Advisory Board (EAB) at their meeting in March 2013 (see eRoom at https://eroombayer.de/eRoomReg/Files/PH-GDC-PI-SID/IMI-PROTECT/0_d3459/EAB%20Recommendations%20Feb%202011.pdf) the development of a communication strategy was transferred from Work Package 7 to Work Package 1.

2.2. Deliverables and milestones in this period

Table 2-2 presents the overview of tasks (deliverables and milestones) completed during the 4th project year by PROTECT participants.

Table 2-2 List of completed deliverables and milestones in this period

WP	Milestone Deliverable	Due date	Related documents
1.4.3	Progress Report project year 3	Oct-12	3rd periodic report (including progress report and financial report) is available on eRoom at: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_e6ba9
1.5.3	Financial Report project year 3	Oct-12	
1.6.3	Publication Report project year 3	Oct-12	Publication Report https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5be8
2.2.1.5	Data specifications for other designs (nested case control, case crossover and self-controlled case series) analysis 'Antibiotics and liver injury'	Dec-12	Dataspecification document https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_ff5bf
2.2.3.5	Data specifications for other designs (nested case control, and case crossover and self controlled case series) analysis 'Antidepressants and hip fracture '	Jul-03	Dataspecification document https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_1077d9
2.2.4.5	Data specifications for other designs (nested case control and case crossover, self-controlled case series) analysis 'Benzodiazepines and hip fracture'	May-13	Dataspecification document https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d55bc

2.3.1.2.1	Data analysis (including create dataset) DESCRIPTIVE Antibiotic use	Oct-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.1.2.2	Data analysis (including create dataset) DESCRIPTIVE Liver injury incidence	Jan-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.1.2.3.	Data analysis (including create dataset) COHORT 'Antibiotics and liver injury'	Jan-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.1.2.4	Data analysis (including create dataset) NESTED CASE CONTROL 'Antibiotics and liver injury'	May-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.1.2.5	Data analysis (including create dataset SELF CONTROLLED CASE SERIES) 'Antibiotics and liver injury'	Mar-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3. 2	Conduct pilot PE studies 'Anticonvulsants and suicide attempt'	Mar-13	See 2.3.2.2.1. See 2.3.2.2.2 See 2.3.2.2.3.
2.3.2.2	Data analysis (including create dataset) 'Anticonvulsants and suicide attempt'	Mar-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.2.2.1	Data analysis (including create dataset) DESCRIPTIVE Anticonvulsants use	Dec-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.2.2.2	Data analysis (including create dataset) DESCRIPTIVE suicidality incidence	Dec-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.2.2.3	Data analysis (including create dataset COHORT) 'Anticonvulsants and suicide attempt'	May-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.3.2.1	Data analysis (including create dataset) DESCRIPTIVE Antidepressants use	Oct-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.3.2.2	Data analysis (including create dataset) DESCRIPTIVE Hip fracture incidence	Dec-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.3.2.3	Data analysis (including create dataset) COHORT 'Antidepressants and hip fracture'	May-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.4.2.1.	Data analysis (including create dataset) DESCRIPTIVE Benzodiazepines use	Oct-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.4.2.2	Data analysis (including create	Oct-12	WG1 results delivery tracking table, in the eRoom:

	dataset) DESCRIPTIVE Hip fracture incidence		https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.4.2.3	Data analysis (including create dataset) COHORT 'Benzodiazepines and hip fracture'	Mar-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.4.3	Study results 'Benzodiazepines and hip fracture'	Feb-13	See 2.7.2 Comparison and analysis of discrepancies in results from different databases
2.3.5	Conduct pilot PE studies 'Beta2agonist and myocardial infarction'	Mar-13	See 2.3.5.2.1 See 2.3.5.2.2 see 2.3.5.2.3
2.3.5.2	Data analysis (including create dataset) 'Beta2agonist and myocardial infarction'	Feb-13	See 2.3.5.2.1 See 2.3.5.2.2 see 2.3.5.2.3
2.3.5.2.1	Data analysis (including create dataset) DESCRIPTIVE Beta2agonist use	Dec-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.5.2.2	Data analysis (including create dataset) DESCRIPTIVE Myocardial infarction incidence	Mar-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.5.2.3	Data analysis (including create dataset) COHORT 'Beta2agonist and myocardial infarction'	Mar-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.6	Conduct pilot PE studies 'Calcium channel blockers and cancer'	Jun-13	See 2.3.6.2.1 See 2.3.6.2.2 see 2.3.6.2.3
2.3.6.2	Data analysis (including create dataset) 'Calcium channel blockers and cancer'	Jun-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.6.2.1	Data analysis (including create dataset) DESCRIPTIVE Calcium channel blockers use	Oct-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.6.2.2	Data analysis (including create dataset) DESCRIPTIVE Cancer incidence	Oct-12	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.3.6.2.3	Data analysis (including create dataset) COHORT 'Calcium channel blockers and cancer'	Jun-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc
2.5.4	Propensity scores/time-dependent	Aug-13	See 2.5.4.1 to 2.5.4.4
2.5.4.4	Report on application of time-dependent PS	Aug-13	Manual for time-dependent analysis in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d58d4
2.5.5.4	Perform IV analysis in Dutch databases	Aug-13	See 2.5.5.5 Paper "Uddin et al. Instrumental Variables: A Methodological Review for Epidemiologists" See publication tracking table on eRoom at https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c58 Manual for IV analysis in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d58d7
2.5.5.7	Perform IV analysis in partner databases	Aug-13	See 2.5.5.8
2.5.5.8	Results from IV analysis	Aug-13	Abstract Uddin et al. "Application of instrumental variable analysis in pharmacoepidemiology: an example of beta2-agonist use and myocardial infarction"

			See presentation tracking table on the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c4f
2.7.1	Literature search on RCT/OS and selection of RR/OR to calculate PAR with selected key ADRs	Dec-12	See 2.7.1.1.3 See 2.7.1.2.3 See 2.7.1.3.3 See 2.7.1.4.3 See 2.7.1.5.3 See 2.7.1.6.3
2.7.1.1.1	Protocol for literature search Antibiotics and liver injury	Jul-13	Protocol https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_ce5f4
2.7.1.2	Literature search and selection of RR/OR to calculate PAR on RCT / OS Anticonvulsants and suicide attempt	Dec-12	see 2.7.1.2.3
2.7.1.2.3	Final report on Literature search Anticonvulsants and suicide attempt	Dec-12	Report available in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_101b1c
2.7.1.3	Literature search and selection of RR/OR to calculate PAR on RCT Antidepressants and hip fracture	Dec-12	see 2.7.1.3.3
2.7.1.3.2	Results of literature search Antidepressants and hip fracture	Dec-12	Description of the literature search strategy is available in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_fa89a
2.7.1.3.3	Final report on Literature search Antidepressants and hip fracture	Dec-12	Paper Pietro-Alhambra et al. "Excess risk of hip fractures attributable to the use of antidepressants in 5 European countries and the US" See publication tracking table in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c58 ;
2.7.1.4	Literature search and selection of RR/OR to calculate PAR on RCT/ OS Benzodiazepines and hip fracture	Dec-12	see 2.7.1.4.3
2.7.1.4.2	Results of literature search Benzodiazepines and hip fracture	Dec-12	Description of the literature search strategy is available in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_fa89a
2.7.1.4.3	Final report on Literature search Benzodiazepines and hip fracture	Dec-12	Paper Khong et al. "Potential Impact of Benzodiazepine Use on the Rate of Hip Fractures in Five Large European Countries and the United States" https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_f31d2 https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c64
2.7.1.5	Literature search and selection of RR/OR to calculate PAR on RCT and OS Beta2agonists and myocardial infarction	Dec-12	See 2.7.1.5.3
2.7.1.5.3	Final report on Literature search Beta2agonists and myocardial infarction	Dec-12	Report in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_ff788 Draft paper is in preparation: Rottenkolber et al. "Inhaled

			beta-2-agonists/inhaled muscarinic antagonists and myocardial infarction: a systematic review”
2.7.1.6	Literature search and selection of RR/OR to calculate PAR on RCT / OS Calcium channel blockers and cancer	Dec-12	See 2.7.1.6.3
2.7.1.6.3	Final report on Literature search Calcium channel blockers and cancer	Dec-12	Report in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_ff788
2.7.2.1.1	Comparison and analysis of discrepancies across databases DESCRIPTIVE Antibiotics use	Dec-12	Paper Brauer et al. “Prevalence of antibiotic use: A methodological comparison across various European health care data sources” https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118
2.7.2.1.2	Comparison and analysis of discrepancies across databases DESCRIPTIVE Liver injury	Mar-13	Draft paper is in preparation Ruigomez et al. “Identification of acute liver injury (ALI) in two different European primary care databases”
2.7.2.2.1	Comparison and analysis of discrepancies across databases DESCRIPTIVE Anticonvulsants use	Dec-12	Paper de Groot et al. Antiepileptic drug use in seven electronic health record databases in Europe: A methodological comparison https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118
2.7.2.3.1	Comparison and analysis of discrepancies across databases DESCRIPTIVE Antidepressants use	Dec-12	Abbing et al. Antidepressant prescribing in five European countries: application of common definitions to assess prevalence of use. https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118
2.7.2.3.2	Comparison and analysis of discrepancies across databases DESCRIPTIVE hip fracture incidence	Dec-12	See 2.7.2.4.2
2.7.2.4.1	Comparison and analysis of discrepancies across databases DESCRIPTIVE Benzodiazepines use	Dec-12	Paper Huerta et al. Prevalence of use of benzodiazepine and related drugs in seven European databases: A cross-national descriptive study from the PROTECT-EU Project https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118
2.7.2.4.2	Comparison and analysis of discrepancies across databases DESCRIPTIVE hip fracture incidence	Dec-12	Paper Huerta et al. Prevalence of use of benzodiazepine and related drugs in seven European databases: A cross-national descriptive study from the PROTECT-EU Project https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118
2.7.2.5.1	Comparison and analysis of discrepancies across databases DESCRIPTIVE Beta2agonists use	Dec-12	Paper Rottenkolber et al. Prevalence of inhaled long-acting beta-2-agonists - a European comparative database study https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118

2.7.2.6.1	Comparison and analysis of discrepancies across databases DESCRIPTIVE Calcium channel blockers use	Feb-13	Paper de Groot et al. Comparison of seven electronic healthcare databases in EU countries using a standardized methodology; a descriptive study on the exposure to calcium-channel blockers (CCBs) https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_cf118
2.7.2.6.2	Comparison and analysis of discrepancies across databases DESCRIPTIVE Cancer incidence	Apr-13	Abstract Afonso et al. Comparison of five electronic healthcare databases in Europe using standardized protocols: a descriptive study on the incidence of cancer. https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d11df
2.8.2	Evaluation of absolute risks and patterns of risks	Apr-13	Draft paper is in preparation Ng et al. “Risk patterns in drug safety studies using relative times: an illustrative study of cancer risk of patients on diabetic therapies” Under WP2 internal review. Soon in the eRoom.
2.8.4	Review and evaluation of statistical methods	Jun-13	Abstract Groenwold et al. Impact of censoring on estimates of adverse drug effects: a simulation study https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d11df A white paper on methods to control for confounding has been completed.
3.1.3	Analysis complete	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.6.3	Analysis complete	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.7.3	Analysis complete	Dec-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.8.1	Protocol for investigating SDR effectiveness within subgroup	Feb-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.8.2	Dataset for analysis fixed	Nov-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.9.3	Develop company specific detailed analysis plan	Feb-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.9.4	Analysis complete	Jul-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.10.3	Analysis complete	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.10.3.1	Analysis complete sub study a: Comparing epidemiological methods with temporal pattern discovery method	Feb-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.10.3.2	Analysis complete sub study b: Strategies for evaluating potential signals in electronic health records	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.11.1	Summary of literature review & set of DDIs	Feb-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.11.2	Protocol for study evaluating different methods of DDIs	Feb-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69

3.12	Duplicate detection	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.12.3	Analysis complete	May-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
3.12.4	External communication	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b69
4.4	Development of data collection platform	Oct-12	At release, will be accessed through www.pregnancystudy4.eu for web platform or by phone at the following numbers: DK: 80801286 PL: 800020249 UK:08000121156 NL:08008786006
4.4.1	User Acceptance Testing of data collection platform	Sep-12	Comments will be placed on eRoom Many comments were provided to Outcome during the system build and these will be uploaded to the following place in the e-room: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_102689
4.4.2	Data collection platform operational	Oct-12	https://www.pregnancystudy4.eu/
4.6	Enrolment and collection of data from women	Oct-12	Enrollment status can be provided upon request and weekly ones will be placed on the e-room
4.6.1	Distribution of recruitment leaflets	Oct-12	Emails looking for confirmation of distribution of leaflets could be added to the e-room.
4.6.2	Establish linkage from established website	Oct-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b6c
4.6.3	Enrolment of women	Oct-12	
4.6.3.1	First pregnant woman enrolled	Oct-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_fdd64
4.6.3.2	Last pregnant woman enrolled	Aug-13	
4.6.4	Data collection from women	Oct-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b6c
4.6.4.1	First pregnant woman completes survey	Dec-12	
4.7	Interim analysis of functioning of system and completeness of data collection after 9 months operation	Mar-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b6c
5.3	Review of and reporting on methodologies for graphical representation	Dec-12	Part 1 and 2 available in the eroom https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.3.1	Review of methodologies for graphical representation	Dec-12	Parts 1 and 2 available in the eroom https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.3.2	Report on methods of graphical expression of benefit:risk	Dec-12	Part 2 is complete and is in final draft in the PROTECT WP5 study template https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.3.3	Deliver recommendation of methods of graphical representation	Dec-12	Part 2 of the graphical review is complete and is in final draft in the PROTECT WP5 study template https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.3.4	Publication of manuscript on	Jun-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-

	outcomes of reviews		PROTECT/0_f4af7>
5.6	Make adaptations to existing software packages if relevant or recommendations to use existing software packages	Nov-12	Case studies wave 1 and 2 and parts 1 and 2 of the graphical review (including software review) are complete. Final recommendations for BR are in draft form and will result in a 2D paper based version with links alongside an interactive web version. The latter is under construction.
5.6.2	Refine recommendations for graphics and software based on outcome of case studies in wave 1	Oct-12	Part 1 and part 2 available: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.6.3	Refine recommendations for graphics and software based on outcome of case studies in wave 2	Oct-12	Part 1 and part 2 available https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.6.4	Final tools for graphical B:R representation	Mar-13	All reports from which the final recommendations are being drawn are available https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94 Final recommendations for BR are in draft form and will result in a 2D paper based version with links alongside an interactive web version. The latter is under construction.
5.8	Further methodological development as necessary to finalise tools for benefit-risk integration and representation	Mar-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.9	Deliver recommendations on methodologies for B-R integration and representation	Mar-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.10	Develop protocol for validation studies	Nov-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_ff7f0
5.11	Writing of reports and academic publications	Jun-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
6.7	Study protocols, work plan and budget proposals a) Replication of WP2 b) Replication of WP5	Nov-12	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_eeef6
6.9	Conduct of studies a) Replication of WP2 b) Replication of WP5	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b72
7.4.2	Preliminary list of deliverables for training programme, Revision 1 (project months 0-42)	Feb-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75
7.5.2	List of deliverables agreed with Eu2P Consortium - Revision 1	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75
7.6.1	Training Modules covering project years 1 to 3	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75
7.6.2	Training Modules covering project years 1 to 4	Aug-13	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75

Table 2-3 lists the tasks (deliverables and milestones) that were planned to be completed during the 4th project year by PROTECT participants, however were delayed. Reason for the delay is explained in the table.

Table 2-3 List of delayed deliverables/milestones due for this period

WP-Id	Milestone/ Deliverable	Original due date	Revised due date	Related document	Justification for delay (as described below)
1.8.4	Communication plan for project year 5	Aug-13	Nov-13	Communication plan approved by the Steering Committee on the basis of proposals made by WP1. This plan will be updated on a yearly basis.	
2.3.1.2.4	Data analysis (including create dataset) NESTED CASE CONTROL 'Antibiotics and liver injury'	Mar-13	May-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc	The analyses took more time than originally planned.
2.3.1.2.5	Data analysis (including create dataset SELF CONTROLLED CASE SERIES) 'Antibiotics and liver injury'	Mar-13	April-13	WG1 results delivery tracking table, in the eRoom: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_d29bc	The analyses took more time than originally planned.
2.3.1.2.6	Data analysis (including create dataset) CASE CROSSOVER 'Antibiotics and liver injury'	May-13	Sep-13	WG1 results delivery tracking table	The analyses are taking more time than originally planned.
2.3.3.2.4	Data analysis (including create dataset) NESTED CASE CONTROL 'Antidepressants and hip fracture'	Aug-13	Sep-13	WG1 results delivery tracking table	The analyses are taking more time than originally planned .
2.7.2.1.4	Comparison and analysis of discrepancies across databases NESTED CASE CONTROL and SELF-CONTROLLED CASE SERIES Antibiotics and liver injury	Jul-13	Dec-13	Publication on discrepancies in results between databases	The completion of this task depends on the finalization of tasks 2.3.1.2.4 to 2.3.1.2.6 which are delayed (see above)
2.7.2.2.2	Comparison and analysis of discrepancies across databases DESCRIPTIVE Suicidality incidence	Apr-13	Feb-14	Publication	The analysis on suicidality in the DHMA-SSI database has been deprioritized due to technical reasons to allow urgent finalization of the CCB/cancer study.
2.7.2.2.3	Comparison and analysis of discrepancies across databases COHORT Anticonvulsants and suicidality	Apr-13	Feb-14	Publication	This task is delayed. The COHORT study was planned in 2 databases (CPRD and SSI-DHMA). Results from CPRD were delivered in June 2013. Results from SSI-DHMA are delayed. See also Risk section of this report

2.7.2.3.3	Comparison and analysis of discrepancies across databases COHORT Antidepressants and hip fracture	Apr-14	Dec-13	Publication on discrepancies in results between databases	Data analyses have been finalized in the 3 selected databases and the writing up of the manuscript is ongoing.
2.7.2.4.3	Comparison and analysis of discrepancies COHORT across databases Benzodiazepines and hip fracture	Apr-13	Dec-13	Publication on discrepancies in results between databases	Data analyses have been finalized in the 3 selected databases and the writing up of the manuscript is ongoing.
2.7.2.6.3	Comparison and analysis of discrepancies across databases COHORT Calcium channel blockers and cancer	Aug-13	Oct-13	Publication	This task is delayed. The COHORT study was planned in 2 databases (CPRD and SSI-DHMA). Results from CPRD were delivered in June 2013. Results from SSI-DHMA are delayed. See also Risk section of this report.
2.8.3	Workable data sharing models for EHR databases	Aug 13	Dec-13		One protocol for effects of design choices on results and another for getting IMS data were submitted in April 2013. Decisions from ISAC are pending.
3.2.4	External communication	Aug-13	Jun-14	Report on whether absolute values of disproportionality measures applied to spontaneous reporting databases give useful information concerning public health impact of adverse drug reactions.	
3.12.4	External communication	May-13	Aug-13	Report on duplicate detection	eRoom
5.6.4	Final tools for graphical B:R representation	Nov-12	Mar-13	Final recommendation for graphical methods, software choices for graphical expression of the benefits and risks of the medicinal products for use by patients, healthcare providers, the pharmaceutical industry and regulators.	All reports from which the final recommendations are being drawn are available https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94 Final recommendations for BR are in draft form and will result in a 2D paper based version with links alongside an interactive web version. The latter is under construction.
5.9	Deliver recommendations on methodologies for B-R integration and representation	Dec-12	Mar-13	Recommendations for benefit-risk integration and representation. These recommendations will be translated into scientific publications in the medical and statistical literature.	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
5.11	Writing of reports and academic publications	Feb-12	Jun-13	Reports and publications	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94

5.11.2	Framework of B-R analyses	Jun-13	Dec-13	Report on modelling approaches that would allow continuous benefit-risk risk-modelling along the lifecycle of the product, and support decision-making, including an assessment of strengths and weaknesses, and worked examples of their application	https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_100c94
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2.3. Deviations from Description of Work

In general, the work of PROTECT and its work packages has progressed as planned. A noteworthy delay was encountered only in WP4 (see explanation below).

Work Package 2

Task 2.6.7. The Bavaria claims database was found not suitable for the associations studies planned in WP2/WG1. The availability of prescriptions and diagnoses in quarters in this database is a severe limitation for a study on short-term/acute effects. The information regarding the inventory of characteristics of databases was provided by the Bavarian Insurer who maintains the database and LMU has provided this information to WP2 at the beginning of the project. However, the fact of quarterly availability of data and non-availability of exact dates of prescribing/diagnoses was only recently given to WP2. This was due to problems with getting access to the Bavarian database. After consultation with the EAB advisors Samy Suissa and Michael Lewis, it was agreed that partners LMU/Witten will not perform such studies using this database. The Bavaria claims database will still be used for descriptive studies in WP2/WG1 and was considered a good resource to perform drug utilization studies in WP2/WG3. It was agreed that LMU/Witten will perform 3 drug utilization studies in important, but infrequently studied patient populations (e.g. pediatric, off label use). Hence, new task 2.6.7. Conduct 3 drug-utilization studies using the Bavaria Claims Database was added to WP2/WG3 work plan.

Possible impact: The scientific scope of the comparison and analysis of discrepancies between EU databases is slightly reduced.

Tasks originally allocated to LMU that will be shared with Witten University are the co-leadership of the Beta2agonist/AMI group in WP2/WG1 and the development of protocols and interpretation of results of the 3 drug utilization studies in WP2/WG3.

Possible compact: Improve clinical expertise for the development of protocols and interpretation of results.

In addition, minor changes are explained in the table 2-4 below. Changes in the timelines resulting in a delay of the delivery of some tasks are not considered to have an impact on the overall delivery of the Work Package.

Work Package 3

A number of changes to the timelines have been made and these are shown in the PROTECT Global Work Plan (Annex 7.3).

Substantive changes to the work programme include:

- Minor delay in time frame of SP 3.1 for external communication of the project, resulting in no significantly extended dates. This will have impact on the delivery of 3.8, which also has been delayed.
 - Delay in the time frames of SP 3.2 due to the identified need for an amended strategy for selecting the best risk estimates, which were adopted recently (in May 2013).
 - Delay in time frames of SP 3.8 due to dependence on SP 3.1.
 - Delay of 5 months in time frame of SP 3.11 due to overseas assignment of sub-package leader.
- The project progresses but more slowly than planned

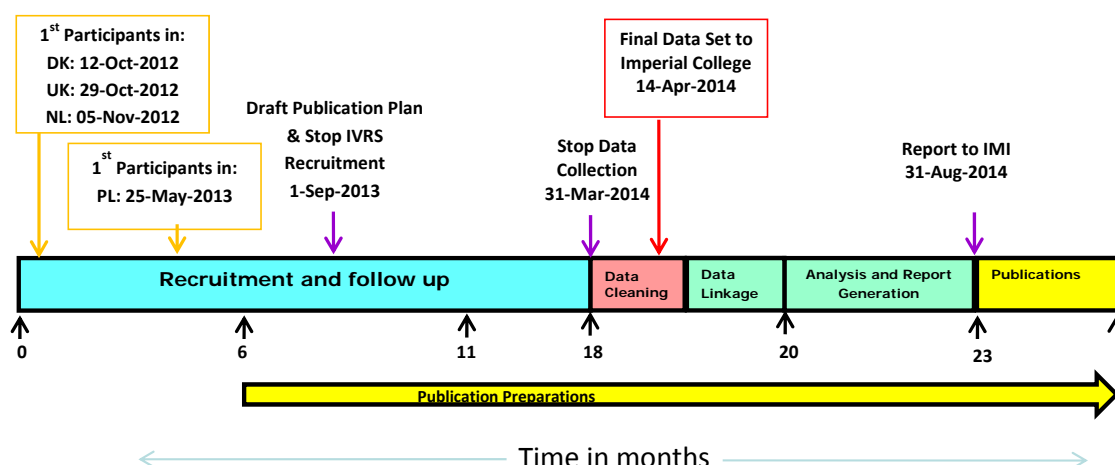
Work Package 4

The scope of the WP for the most part remains unchanged. One slight tweak comes with the utilisation of mid-wives to provide leaflets to pregnant women booking into pregnancy clinics in the UK. Originally we did not want to involve HCPs in any aspect of recruitment for the study, however due to poor recruitment and following feedback from the external advisory board (EAB), it was decided that asking midwives to hand over a study leaflet amongst the other papers presented to the women would not violate the aims of the study and would allow us to see if this affected recruitment.

A recommendation of the EAB was to conduct qualitative interviews with pregnant woman to get feedback on reasons as to why they would or would not want to participate in such a study and then use the results to provide guidance for how future studies should be conducted. This addition to the scope of work does not impact on study timelines but does require additional budget which will be provided by Amgen.

These changes do not materially affect the scientific potential of the study.

The only change to the study timeline is with regard to the extension of the recruitment period. Due to delays in the study start as a result of the delay in completion of the data collection platform, the unforeseen data protection approval issues in Poland and the slow recruitment rate, the data recruitment period has been extended from 31-August-2013 to 31-January 2014 in order to get as many participants recruited as possible without necessitating a complete study extension. This change means that not all participants can be followed until pregnancy outcome. Both the study protocol, ICF and the data collection platform have been amended to reflect this change. The timelines as per the revised protocol are:



Work Package 5

No major deviations from work plan. Minor deviations: The final recommendations document was presented to the External Advisory board in spring 2013 for comment. Subsequent to this work has continued to refine and streamline the huge amounts of information into a final public document. It is important to get this right and the time is being taken to do this. It is expected that the final complete version will be available in autumn 2013. An interactive web based version is also being built and this too is likely to be complete towards the end of 2013 with some initial delays due to logistical issues including needing a hosting site, a sub contract with a web developer etc.

Work Package 6

The overall scope of the “replication studies” of WP6 has not changed drastically since inception. Most of the replication studies targeted at the methods developed in WP2 have reached completion with first results communicated association with the WP2 authors at the ICPE in August 2013.

A new working plan has been developed to replicate the benefit-risk methods developed in WP5. No other Work Package in PROTECT will be subject to the replicability work of WP6.

The replication of the study on antiepileptic drugs and suicide in the Danish registries will not be possible given the fact that the WP2 study has been deprioritised in October 2013 due to technical problems. Part of the objectives of WP6 will however be kept (validation of outcomes).

Work Package 7

The overall scope and work plan of the training part of WP7 has not changed. In the initial work plan of WP7 it was expected that training topics would already be identified during the second year. However, few project results were identified that were not mature enough to be included in the Eu2P training program. In the 4th year a number of potential training topics, their corresponding competency area, and their possible placement in the general EU2P program framework have been identified.

During Year 4 an increasing number of publications, reports and other materials have been produced by PROTECT. Two working sessions of WP7 on topics identification have been held. In particular, since June 2013, the number of publications has substantially increased, and it is expected that by large the majority of training topics transferred to EU2P will occur during Year 5.

Due to the change in the work plan the following deliverables and milestones have been deleted.

Table 2-4 List of deleted deliverables and milestones

WP-Id	Milestone/ Deliverable	Due Date	Justification for deletion
2.8.1	Collection of minimal dataset	Mar-12	<p>This task has been deleted from WP2 work plan. An assessment of ongoing work with multidatabase studies indicated scepticism about the underlying assumption of statistical multidatabase analyses (i.e., semantic interoperability - the idea that one can map discrepant databases to a common database model). Semantic interoperability is unlikely given the differences in healthcare systems and reasons for data collection. Rather, the current approach is to view different database studies as discrete studies and we are working on the possibility of one study determining the hypothesis for the next study (and the statistics around that approach). The foundation of any multidatabase work is access to data and protocols and work is ongoing on these.</p> <p>This approach will be compared to several approaches that are currently explored in multidatabase studies such as individual patient data meta-analyses, conventional meta-analyses, high-dimensional propensity score analyses to accommodate for variation in available information on confounders in the different databases.</p> <p>No impact on WP2 overall objectives or the budget is foreseen.</p>
2.9	Evaluation of signals from WP 3	Feb-14	<p>This task has been deprioritized and deleted from WP2 work plan. WP2 and WP3 coleads have agreed to cancel the WP2 evaluation of a WP3 signal from patient records in response to the unanticipated preliminary results of WP3 subpackage 3.10 with no strong safety signals identified.</p> <p>No impact on WP2 overall objectives or the budget is foreseen.</p>

Due to the change in the work plan the following deliverables and milestones have been added to the work plan.

Table 2-5 **List of new deliverables and milestones**

WP-Id	Milestone/ Deliverable	Due Date	Justification for addition
2.8.1	Comparison of different approaches to multi-database analyses	Mar-13	New sub-task due to deletion of former task 2.8.1. - Collection of minimal dataset
2.8.2	Evaluation of absolute risks and patterns of risks	Dec-12	New sub-task due to deletion of former task 2.8.1. - Collection of minimal dataset
2.8.3	Workable data sharing models for EHR databases	Mar-13	New sub-task due to deletion of former task 2.8.1. - Collection of minimal dataset

3. Summary of Major Achievements and key dissemination activities

3.1. Major achievements

Work package 2

Major achievements include wide representation of WP2 work at 29th ICPE in Montreal from 25 to 28 August 2013. It included the organization by WP2 of the Symposium entitled “Improving Consistency in Findings from Pharmacoepidemiological Studies” - where the first results from WP2 and WP6 studies were presented jointly and comparisons between results were discussed,. WP2 presented 17 posters in total including results from its 3 WGs and one slide presentation from WG2 on the application on instrumental variable analysis in pharmacoepidemiology (https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_f74b7).

WP2 participated also at the International Society of Pharmacoepidemiology (ISPE) midyear meeting held in Munich from 11 to 13 April 2013. The main results from the 3 WGs were presented during a session dedicated entirely to PROTECT.

Furthermore, the online inventory of drug utilisation resources publicly accessible through the PROTECT website (<http://www.imi-protect.eu/frameworkRep.shtml>) is kept updated. A new version of the inventory's master document was published in the website in October 2012 and a shorter document with summarized information per country is also available online since January 2013. The 2013 inventory contains information from 25 European countries and 11 more have been contacted. From January to August 2013, the total number of downloads of both the short and the master documents of the inventory was approximately 1300. The majority of visits were from the United States of America. Other countries from where a high number of visits were registered were the United Kingdom, Ukraine, France, Germany and Japan.

Finally, several scientific papers on the descriptive studies of prevalence of use of the drugs of interest and incidence of the selected outcomes, as well as papers on various methodological issues such as propensity scores and instrumental variable analysis have been submitted. (https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c64).

Work package 3

Three major achievements for work-package 3 in the fourth project year are that:

1. We have shown that the choice of disproportionality measures has limited impact on performance in screening large collections of spontaneous reports, but that the operating characteristics for each measure depends to a large extent on the thresholds used in screening (statistical significance levels and requirements on a minimal total number of reports).
2. We have shown that probabilistic record linkage techniques can outperform rule-based methods in the identification of suspected duplicates in large collections of spontaneous reports. The probabilistic method in question significantly reduced manual workload which allowed true duplicates to be identified that had previously been overlooked. A characterization of all suspected duplicates in a global database highlighted that a disproportionate number relate to reports from the literature.

Work package 4

The finalisation and launch of the data collection platform and the project specific website (<https://www.pregnancystudy4.eu/>) at the start of the periodic year allowed us to launch the country specific recruitment strategies in Denmark, the NL and the UK. An analysis of THIN practices in the UK provided the basis for choosing which areas to target with recruitment leaflets. Pharmacists were invited to display leaflets in their shops and there was a high level of interest shown. In contrast, letters to pharmacists in the NL had a much lower response rate. The country leads in each country also identified websites and forum where flyers, text and/or pictures advertising the study could be displayed. In Poland, the country lead gave a TV interview advertising the study.

Facebook pages have been generated in each country

The following table shows the status of participants enrolled and the number of questionnaires and outcomes complete as of the end of August 2013.

Country	Web enrolment	IVRS Enrolment	Web Baseline	IVRS Baseline	Total patients with follow up	Total follow-up forms	End of pregnancy	Discontinuation
DK	560	1	460	1	221	874	54	21
NL	153	0	133	0	64	182	4	3
PL	48	0	36	0	12	31	2	0
UK	566	0	473	0	198	727	73	9
Total	1327	1	1102	1	495	1814	133	33

Analysis of preliminary data is yielding good results meaning that many of the questions raised in this exploratory study will be answered.

Work package 5

Work package 5 has completed all reviews and case study work, has drawn this together into a recommendations document and is now refining this for external consumption and creating an interactive web version and drafting academic manuscripts. Reports of the work so far are now available on the PROTECT website <http://www.imi-protect.eu/benefitsRep.shtml>

Work package 6

a) Reproducibility of WP2:

Major achievements are mainly related to the unblinding and communication of results for WP2 replication studies; several results communicated by WP2 were reproduced in WP6.

As a result, another major achievement has been collaborating with WP2 in the preparation and delivery of the Symposium entitled "Improving Consistency in Findings from Pharmacoepidemiological Studies" at the ICPE 2013 in Montreal.

8 studies were completed and 3 are on-going. Others were cancelled:

- Antiepileptic and suicidality in CPRD - Descriptive study / Population-case control by GSK (not enough cases to allow meaningful analyses)
- CCB and cancer – Descriptive study (Cohort if possible) the US MedStat database by GSK
- Benzodiazepines and hip fracture in CPRD - Self-controlled case series by GSK CCB and cancer in the E3N cohort.

b) Reproducibility of WP5:

The reproducibility of WP5 has been defined and planned. Two activities have been launched:

- Activity 1: Testing/extending the methodology in the real-life setting
 - The comparator products have been identified
 - Protocol for the analysis is near completion

3 study cases were launched with preliminary analysis of WP5 achievements based on the draft report.

- Activity 2: Validation of visualization tools
 - Protocol is complete
 - Questionnaire is under construction
 - Three therapeutic areas have been defined (breast cancer, atrial fibrillation, diabetes)

3.2. Key dissemination activities

The dissemination activities of the 4th project year were mainly focused on presenting first results of PROTECT work to the wider audience. More concretely, the following manuscripts were published (see Annex 7.3):

- Julien Souvignet, Gunnar Declerck, Marie-Christine Jaulent and Cédric Bousquet, Evaluation of automated term groupings for detecting upper gastrointestinal bleeding signals for drugs, *Pharmacoepidemiology and Drug Safety*; *Pharmacoepidemiology and Drug Safety Journal*, Oct 2012.
- M. Sanni Ali, R.H.H. Groenwold, W.R. Pestman, S.V. Belitser, A.W. Hoes, A. de Boer, Olaf H. Klungel “Time-dependent propensity score and collider-stratification bias: an example of beta2-agonist use and the risk of coronary heart disease”; published in: *American Journal of Epidemiology* / *International Journal of Epidemiology* / *European journal of epidemiology*, Feb 2013.
- R.H.H. Groenwold, O.H. Klungel, D.G. Altman, Y van der Graaf, A.W. Hoes, K.G.M. Moons, “Adjustment for continuous confounders: how to prevent residual confounding”; *CMAJ*, Feb 2013

The following publication has been presented on the PROTECT website (within the 4th project year):

- Ferrer P, Ballarín E, Sabaté M, Rottenkolber M, Hasford J, Tatt I, Schoonen M, Fortuny J, Petri H, Goh KL, Yeboa S, Solari P and Ibáñez L., on behalf of the PROTECT project. *Drug Consumption Databases in Europe*. Barcelona, August 2012. 170 pages

Additionally, a number of presentations and abstracts were presented at different venues (among others at 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management) to increase the awareness of PROTECT in the scientific community and with other stakeholders.

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

Full list of presentations and publications are provided in Annex 7.3. The tables reflect the current status at the time of the submission of this report.

3.3. Use and dissemination of foreground

For the dissemination activities please see chapter 3.2. Key dissemination activities.

4. Management of Project and Consortium

This chapter provides an overview of activities of Work package 1 including any issues arising during the 4th project year relating to the project coordination.

There were no major changes to the coordination/management of the PROTECT project other than a replacement of the WP co-leadership which was carried out in line with the procedure detailed in Clause 5.39 of the project agreement.

4.1. Overall management of the project

4.1.1. Completed tasks in WP1 and other management activities

The following tasks have been completed during the project year 4:

- **submission of the periodic report** covering 3rd project year: Periodic report (covering period of 1 September 2011 - 31 August 2012) was submitted to the IMI JU on 29 October 2012. The report was accepted by IMI JU on 12 December 2012.
- submission of the financial report covering 3rd project year: Financial report was submitted together with the periodic report (see above).
- **accession of 2 new partners to the Consortium:** Two new partners have acceded to the PROTECT Consortium during 4th project year:
 - Witten/Herdecke University, WHU, (May 2013)
 - University Medical Center Groningen, UMCG, (July 2013)
- **Maintenance of the Grant Agreement** (including Annex I.) and revision thereof and advice to PROTECT partners on relevant provisions
 - Amendment no. 6 – amendment of IMI model grant agreement
 - Amendment no. 7 – accession of new partners to PROTECT Consortium
 - Amendment no. 4 – amendment of IMI model grant agreement
- **Maintenance of the Project Agreement and revision of thereof (revision no.4) and advice to PROTECT partners on relevant provisions**
- **Adoption of the 4th half-year report** covering months 37-42 of the project (see Annex 7.3).
- Changes to the composition of the EAB
- Reflecting the change of the legal name of the DKMA to Danish Health and Medicines Authority (DHMA)

Organisation of regular Steering Committee meetings and a meeting of External Advisory Board (an overview of all meetings is in Annex 7.3).

Additional tasks undertaken by WP1 during the period:

- **update of the PROTECT web portal to include results section:** PROTECT web portal was greatly reorganised to include a separate section on results. The results are divided by topic and then by form. Currently, over 40 documents are available to wider audience and this will increase with progress of the work in individual work packages.

- **keeping publication records up to date** (see Tables 3-1 and 3-2 above): A detailed publication record is kept by the PROTECT Management Support Team and is available on eRoom:
 - for presentations go to: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c4f
 - for publications go to: https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c5c58
- keeping work programme up-to-date: work package leaders are asked regularly (twice a year) to update overall PROTECT work programme.
- The PROTECT Communication strategy and plan was adopted by the PROTECT Steering Committee on 8 October 2012 (Annex 7.1)
- **maintenance of PROTECT eRoom** (restricted partner forum): this partner forum is being kept up-to-date with relevant documents and announcements (such as: minutes of the governance meetings, updated project documents, etc.)
- maintenance of the Partner database: a list of contact details of all people involved in PROTECT is kept by the PROTECT Management Support team. Number of WP distributors is also used for communication.

4.1.2. Verification of legal status of PROTECT public participants

All beneficiaries eligible to receive IMI JU funding confirmed that their legal status has not changed. One exception was Outcome Europe Sarl which was acquired by Quintiles. Outcome thus lost its official legal status of an SME. Further to the communication with IMI JU it was confirmed that Outcome is still eligible to receive IMI JU funding.

4.1.3. Synergies with other IMI projects or any other programmes

Cooperation with other IMI projects and other relevant programmes are described by WP.

Work package 2

During this period there has been interaction with the IMI EU2P programme by continuous monitoring of results from WP2 for potential inclusion as teaching material in EU2P. Furthermore, a plan for collaboration between WP2/WG3 and the EURODURG group has been defined including the development of guidelines for cross-national comparison (CNC) studies as part of the PROTECT deliverable, the participation of WP2/WG3 members as co-authors in a chapter of a new version of McGavock's "Handbook of drug use research methodology" and a cross-national comparison of drug utilization studies on antiepileptic drugs

Work package 3

Communication with the Observational Medical Outcomes Partnership (OMOP) has been maintained throughout the year, and contacts with the European Global Research in Paediatrics – Network of Excellence (GRIP) project funded under the European 7th Framework Program have been pursued to explore a potential synergy related to the evaluation of methods for signal detection in children.

Work package 5

The Patient Public Involvement lead for WP5 has been liaising with members of EUPATI <http://www.patientsacademy.eu/index.php/en/>.

Work package 6

WP6 interaction with another IMI project (GetReal – WP2) during this 4th year has occurred in the form of presentation of methodology and preliminary results.

Work package 7

PROTECT WP7 interacts with EU2P by attending the EU2P meetings.

4.1.4. Public private partnership

Overall, the Public private partnership allows to face various challenges to be met in a complex project such as PROTECT. Its strengths include:

- large number of partners with a high level of complementary expertise from members of both public and private consortia complements;
- mix of experiences in the field of drug safety (regulatory authorities, academic institutions, pharmaceutical companies, SMEs)
- increased impact and visibility by targeting deliverables to a large audience.

Some difficulties are inherent to a project involving a large number of partners over a five-year period:

- the large number of partners slows down the decision-making process e.g. on agreement of study protocols and technical documents;
- members are leaving the project due to professional mobility; in some cases, this has brought additional resources to the project when a company recruiting a PROTECT member asked for admission to allow this member to continue the work in PROTECT;
- due to the nature of the subject matter (drug safety and benefit-risk evaluation) and the current environment of resource and time constraints, some activities can be temporarily affected in case of urgent procedures being initiated in the routine work; moreover, procedures and disclaimers had to be established for situation where a new safety issue is detected or where result of B/R assessment in case studies are not in accordance with regulatory decisions.

Work package 2

PPP has been successfully established in WP2. Each of the 3 working groups has one co-lead from a public institution working closely with another co-lead from an EFPIA company. In particular in WG1 and WG3, private partners are contributing to the retrieval and analyses of data from the CPRD and IMS data sources.

Work package 3

While there are associated challenges related to differences in culture and infrastructure, we believe that the nature of the project as a public private partnership is a key success factor to ensure that our findings and conclusions are relevant to as many of the stakeholders of pharmacovigilance as possible.

Work package 4

A new member from Imperial College London joined the team in late July 2013. This team member will be a key player in the publication strategy for the study and will also assist with recruitment within Denmark. Genzyme provided a project manager who has enabled WP4 to achieve a huge amount in the last 9 months.

Lundbeck printed the leaflets for the study and shipped them to the countries. In the NL, the University of Groningen contacted pharmacists whilst in the UK this was done by medical representatives from Glaxo who had been fully briefed on the project and provided with a letter from PROTECT outlining the scientific importance of this study.

Following slow recruitment and subsequent advice from the EAB, it was decided to use focus groups to provide greater insight into factors influencing recruitment. Amgen were able to use their knowledge of this area to target potential providers.

The private leadership of the work package has changed. Jens-Pieter Balling (Lundbeck) has handed over co-lead of the project to Omer de Mol (Genzyme a Sanofi Company) with Bina Patel (Amgen) as his alternate.

Work package 5

Input from the different public/private stakeholders continues to be key in the WP5 work in terms of evaluating benefit risk techniques with regard to the different uses that these may be put to. I.e. it is crucial for WP5 to have active input from industry, regulators, academia and patient groups.

Work package 6

WP6 is now composed of 2 reproducibility evaluations:

WP2-WP6

8 protocols and statistical plan have been finalised yet related to the WP2. There are still 3 in evaluation. The timeline was delayed because of additional delays in WP2 especially, explaining that the end is delayed by 3 months for the moment. 4 studies were cancelled.

Concerning the reproducibility of WP5 studies, the activities had been defined in detail with 2 activities:

- Activity 1: Testing/extending the methodology in the real-life setting
- Activity 2: Validation of visualization tools

Main results were communicated at ICPE congress but 2 studies will continue:

- UPOD part 2 until November 2013
- E3N

WP6 team should evaluate the “reproducibility” work – what had been learned, how to define the next steps: communications, explanations of results.b) WP5-WP6

4.2. Project plan for the remaining reporting periods

Work package 1

The focus of WP 1 in the fifth period will be to keep the project running as it has so far, planning on the delivery and integration of the final deliverables into coherent project outputs, stimulating and helping with dissemination of results of the individual WPs; organising weinars; organising an end-of-project workshop; investigating possibilities of raising awareness of the project and its results on Facebook, Twitter and LinkedIn; update of Annex I to the Grant Agreement following adoption of this periodic report, etc. ; final projects report; since this will be the project last year a closing event in October 2014 is planned- the WP1 will be handling the logistical and administrative arrangements for the event.

Work package 2

WG1 will conduct the rest of planned studies using the nested case control, case crossover and self-controlled case series for the selected DrugAE pairs according to the agreed work plan. The results from the cohort studies and the other designs will be compared and discrepancies will be described and explained in manuscripts.

WG2 will finalize the work on the application of propensity score and instrumental variable methods to control for confounding in empirical data from EU databases (e.g. those used in WG1). This group will work in statistical methods for multi-database studies in collaboration with WG1. In addition, WG2 will continue supplying methodological help for time-dependent analyses conducted within WG1.

WG3 will deliver a new updated version of the inventory of drug consumption databases in Europe and explore in collaboration with WP1 ways to maintain the database and update it on a regulatory basis. WG3 will also finalise the work on the estimation of the population attributable risk, and discrepancies between results of drug exposure from DU data source and EU databases (WG1) will be analysed.

Finally the lessons learnt from the WGs will be adopted and WP2 will elaborate a document describing guidelines and standards for pharmacoepidemiological and drug utilisation studies.

Work package 3

The focus for the final project year will be on external communication of the sub-packages for which the analyses are already completed or nearly so. They include sub-packages 3.01 – Merits of disproportionality analysis, 3.06 – Novel tools to group ADRs, 3.07 - Other Information to enhance signal detection, 3.09 – Signal detection in clinical trials, and 3.10 – Signal detection in electronic health records. Some of these have manuscripts under peer review, which can be expected to come back for revision in the twelve months to come. Three sub-packages need to both complete their analyses and communicate their outcome externally. They are 3.02 – Concordance with risk estimates, 3.08 – Subgroups and stratification, and 3.11 – Drug-drug interaction detection. A top priority of the final project year will be the aggregation and formulation of recommendations for signal detection across stakeholders based on the results of the work-package. Given the highly favourable performance of probabilistic methods for duplicate detection, we are undertaking an implementation and evaluation of the vigiMatch methodology

directly on national centre data, which have access to additional information useful for record matching, such as patient initials and birthdates.

Work package 4

Continued active recruitment and development of new recruitment strategies will be paramount until the end of Q 4 2013. The questionnaires to be used in the qualitative interviews must be finalised by end of Q3 2013 and the interviews and analysis of the data collected from these interview will be performed by the end of Q4 2013. The report for this activity is expected at the end of January 2014. Parallel to this, continued data analysis will be performed and the algorithms for data linkage will be planned. Work has already begun in developing a strong publication plan for the study which will feed the final required IMI study report. To date lead authors have been assigned and initial publications have been discussed but this will obviously be an extremely large focus for us over the remaining period.

Work package 5

Work package 5 is currently at the stage of dissemination and final recommendation. The vast majority of the work has been completed and is publically available. The next year should see the delivery of a final BR recommendations document for external consumption, a linked interactive version and several academic publications and presentations.

Work package 6

WP6 is now composed of 2 reproducibility evaluations:

WP2-WP6

9 of 13 protocols and statistical plan have been finalised yet related to the WP2. There are still 4 in evaluation. The timeline was delayed because of additional delays in WP2 especially, explaining that the end is delayed by 3 months for the moment. 3 studies were cancelled and one study on CCB and cancer to be applied on E3N is in progress.

Concerning the reproducibility of WP5 studies, the activities had been defined in detail with 2 activities:

- Activity 1: Testing/extending the methodology in the real-life setting
- Activity 2: Validation of visualization tools

Main results were communicated at ICPE congress but 2 studies will continue:

- UPOD part 2 until November 2013
- E3N

WP6 team should evaluate the “reproducibility” work – what had been learned, how to define the next steps: communications, explanations of results for WP2-WP6 for WP5-WP6.

Work package 7

1. Consolidate the work-flow for WP7 and WP1 to integrate the strategy for transmission of knowledge from PROTECT.
2. Continue monitoring of PROTECT outputs which may have an interest as training materials, and prepare proposal(s) for training module(s).
3. managing the Platform of Training Opportunities

4. Work in collaboration WP1 to prepare the first proposal of training module.

Table 4-1 List of main upcoming deliverables and milestones

WP-Id	Milestone/Deliverable	Due date	Related document
1.4	Progress reports and deliverables	Oct-14	Progress reports and PROTECT deliverables
1.4.4	Progress Report project year 4	Oct-13	Progress reports and PROTECT deliverables
1.4.5	Final Progress Report (including project year 5)	Oct-14	Progress reports and PROTECT deliverables
1.5	Financial reports	Oct-14	Financial reports
1.5.4	Financial Report project year 4	Oct-13	Financial reports
1.5.5	Final Financial Report (including project year 5)	Oct-14	Financial reports
1.6	Publication Record	Oct-14	Publication plan: it will list and briefly describe publications foreseen to be submitted during the following year, as agreed with the Steering Committee; it will also provide a tentative list of authors
1.6.4	Publication Report project year 4	Oct-13	Publication plan: it will list and briefly describe publications foreseen to be submitted during the following year, as agreed with the Steering Committee; it will also provide a tentative list of authors
1.6.5	Post-project reporting of publications	Aug-15	Publication plan: it will provide a list of publications submitted during the PROTECT project and the year following its termination.
1.7	Draft communication plan	Jun-14	
1.7.4	Draft communication plan for project year 5	Nov-13	
1.7.5	Draft communication plan for post project phase	Jun-14	
1.8	Communication plan	Aug-14	Communication plan approved by the Steering Committee on the basis of proposals made by WP1. This plan will

WP-Id	Milestone/Deliverable	Due date	Related document
			be updated on a yearly basis.
1.8.4	Communication plan for project year 5	Nov-13	Communication plan approved by the Steering Committee on the basis of proposals made by WP1. This plan will be updated on a yearly basis.
1.8.5	Communication plan for post project phase	Aug-14	Communication plan approved by the Steering Committee on the basis of proposals made by WP1. This plan will be updated on a yearly basis.
2.3.1. 2.6	Data analysis (including create dataset) CASE CROSSOVER 'Antibiotics and liver injury'	Sep-13	
2.3.1. 3	Study results 'Antibiotics and liver injury'	Feb-14	Publications with comparison of results in different databases for each study design
2.3.2. 3	Study results 'Anticonvulsants and suicide attempt'	Feb-14	Publications with comparison of results in different databases for each study design
2.3.3. 2.4	Data analysis (including create dataset) NESTED CASE CONTROL 'Antidepressants and hip fracture'	Sep-13	
2.3.3. 2.5	Data analysis (including create dataset) CASE CROSSOVER 'Antidepressants and hip fracture'	Dec-13	
2.3.3. 3	Study results 'Antidepressants and hip fracture'	Feb-14	Publications with comparison of results in different databases for each study design
2.3.4. 2.4	Data analysis (including create dataset) NESTED CASE CONTROL 'Benzodiazepines and hip fracture'	Sep-13	
2.3.4. 2.5	Data analysis (including create dataset) CASE CROSSOVER 'Benzodiazepines and hip fracture'	Sep-13	
2.3.4. 2.6	Data analysis (including create dataset) SELF CONTROLLED CASE SERIES 'Benzodiazepines and hip fracture'	Sep-13	
2.3.5. 3	Study results 'Beta2agonist and myocardial infarction'	Feb-14	Publications with comparison of results in different databases for each study design

WP-Id	Milestone/Deliverable	Due date	Related document
2.3.6.3	Study results 'Calcium channel blockers and cancer'	Feb-14	Publications with comparison of results in different databases for each study design
2.4	Inventory on drug utilisation data	Aug-14	Report/publication with an updated inventory of data sources on the consumption of the medicines of interest in the EU (including validity of data).
2.5	Methods to control for confounding	Feb-14	Publications on evaluation and application of methods to control for confounding.
2.5.5	Instrumental variables (IV)	Feb-14	
2.5.5.5	Report on application of IV	Feb-14	
2.5.6	External adjustment/sensitivity analyses	Feb-14	
2.5.7	Apply PERR adjustment for ADRs in Dutch database	Feb-14	
2.6	Public health impact analysis of ADRs	Feb-14	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.2	Public health impact analysis of Antibiotics and liver injury	Feb-14	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.1.1	Evaluate validity of DU data Antibiotics	Nov-13	
2.6.1.2	Estimate exposed population Antibiotics and calculate PAR Antibiotics and liver injury	Feb-14	see 2.6.1
2.6.2	Public health impact analysis of Anticonvulsants and suicide attempt	Feb-14	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.2.1	Evaluate validity of DU data Anticonvulsants	Nov-13	

WP-Id	Milestone/Deliverable	Due date	Related document
2.6.2. 2	Estimate exposed population Anticonvulsants and calculate PAR Anticonvulsants and suicide attempt	Feb-14	see 2.6.2
2.6.3	Public health impact analysis of Antidepressants and hip fracture	Feb-14	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.3. 1	Evaluate validity of DU data Antidepressants	Nov-13	
2.6.3. 2	Estimate exposed population Antidepressants and calculate PAR Antidepressants and hip fracture	Feb-14	see 2.6.3
2.6.4	Public health impact analysis of Benzodiazepines and hip fracture	Nov-13	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.4. 1	Evaluate validity of DU data Benzodiazepines	Nov-13	
2.6.4. 2	Estimate exposed population Benzodiazepines and calculate PAR Benzodiazepines and hip fracture	Nov-13	see 2.6.4
2.6.5	Public health impact analysis of Beta2agonists and myocardial infarction	Nov-13	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.5. 1	Evaluate validity of DU data Beta2agonists	Nov-13	
2.6.5. 2	Estimate exposed population Beta2agonists and calculate PAR Beta2agonists and myocardial infarction	Nov-13	see 2.6.5
2.6.6	Public health impact analysis of Calcium channel blockers and cancer	Nov-13	Report/publication with examples of estimation of the exposed population related to the drug-AE pairs of interest, and patterns of use of the products of interest.
2.6.6. 1	Evaluate validity of DU data Calcium channel blockers	Nov-13	

WP-Id	Milestone/Deliverable	Due date	Related document
2.6.6. 2	Estimate exposed population Calcium channel blockers and calculate PAR Calcium channel blockers and cancer	Nov-13	see 2.6.6
2.6.7	Conduct 3 drug-utilization studies using the Bavaria Claims Database	Feb-14	Publication off label use; Publication inhaler devices ; Publication inhaled corticosteroids
2.7	Analysis of discrepancies between studies	Feb-14	Report/publications on analysis of discrepancies between studies using common protocols and definitions in several data sources.
2.7.1. 1	Literature search and selection of RR/OR to calculate PAR on RCT/OC Antibiotics and liver injury	Sep-13	
2.7.1. 1.2	Results of literature search Antibiotics and liver injury	Oct-13	
2.7.1. 1.3	Final report on Literature search Antibiotics and liver injury	Oct-13	Report/publication with review of RCTs and OS
2.7.2	Comparison and analysis of discrepancies in results from different databases	Feb-14	Publications on analysis of discrepancies between studies in several databases
2.7.2. 1	Comparison and analysis of discrepancies Antibiotics and liver injury	Feb-14	Publication on discrepancies in results between databases
2.7.2. 1.3	"Comparison and analysis of discrepancies across databases, COHORT Antibiotics and liver injury	Dec-13	Publication on discrepancies in results between databases
2.7.2. 1.4	"Comparison and analysis of discrepancies across databases; NESTED CASE CONTROL and SELF-CONTROLLED CASE SERIES Antibiotics and liver injury	Dec-13	Publication on discrepancies in results between databases
2.7.2. 1.5	"Comparison and analysis of discrepancies across databases / designs, Antibiotics and liver injury	Feb-14	Publication on discrepancies in results between databases
2.7.2. 2	Comparison and analysis of discrepancies Anticonvulsants and suicide attempt	Feb-14	Publication on discrepancies in results between databases
2.7.2. 3	Comparison and analysis of discrepancies Antidepressants and hip fracture	Feb-14	Publication on discrepancies in results between databases

WP-Id	Milestone/Deliverable	Due date	Related document
2.7.2. 3.3	"Comparison and analysis of discrepancies across databases; COHORT Antidepressants and hip fracture	Dec-13	Publication on discrepancies in results between databases
2.7.2. 3.4	"Comparison and analysis of discrepancies across databases; NESTED CASE CONTROL Antidepressants and hip fracture	Jan-14	Publication on discrepancies in results between databases
2.7.2. 3.5	"Comparison and analysis of discrepancies across databases; CASE CROSSOVER Antidepressants and hip fracture	Jan-14	Publication on discrepancies in results between databases
2.7.2. 3.6	"Comparison and analysis of discrepancies across databases/designs; Antidepressants and hip fracture	Feb-14	Publication on discrepancies in results between databases
2.7.2. 4	Comparison and analysis of discrepancies; Benzodiazepines and hip fracture	Feb-14	Publication on discrepancies in results between databases
2.7.2. 4.3	"Comparison and analysis of discrepancies COHORT across databases, Benzodiazepines and hip fracture	Dec-13	Publication on discrepancies in results between databases
2.7.2. 4.4	"Comparison and analysis of discrepancies NESTED CASE CONTROL across databases; Benzodiazepines and hip fracture	Dec-13	Publication on discrepancies in results between databases
2.7.2. 4.5	"Comparison and analysis of discrepancies across databases; CASE CROSSOVER Benzodiazepines and hip fracture	Dec-13	Publication on discrepancies in results between databases
2.7.2. 4.6	"Comparison and analysis of discrepancies across databases/designs; Benzodiazepines and hip fracture		
2.7.2. 5	Comparison and analysis of discrepancies; Beta2agonists and myocardial infarction	Feb-14	Publication on discrepancies in results between databases
2.7.2. 5.2	"Comparison and analysis of discrepancies across databases; COHORT Beta2agonists and myocardial infarction	Dec-13	

WP-Id	Milestone/Deliverable	Due date	Related document
2.7.2.6	Comparison and analysis of discrepancies Calcium channel blockers and cancer	Feb-14	Publication on discrepancies in results between databases
2.7.3	Comparison of database and RCT results	Feb-14	
2.7.3.1	Comparison of database and RCT results for Antibiotics and liver injury	Feb-14	
2.7.3.2	Comparison of database and RCT results for Anticonvulsants and suicide attempt	Feb-14	
2.7.3.3	Comparison of database and RCT results for Antidepressants and hip fracture	Feb-14	
2.7.3.4	Comparison of database and RCT results for Benzodiazepines and hip fracture	Feb-14	
2.7.3.5	Comparison of database and RCT results for Beta2agonists and myocardial infarction	Feb-14	
2.7.3.6	Comparison of database and RCT results for Calcium channel blockers and cancer	Feb-14	
2.7.4	Comparison of prevalence of use (selected drug classes) between databases and national drug utilisation (DU) sources	Nov-13	
2.7.4.1	Compare prevalence of Antibiotics use between national DU and databases	Nov-13	
2.7.4.2	Compare prevalence of Anticonvulsants use between national DU and databases	Nov-13	
2.7.4.3	Compare prevalence of Antidepressants use between national DU and databases	Nov-13	
2.7.4.4	Compare prevalence of Benzodiazepines use between national DU and databases	Nov-13	
2.7.4.5	Compare prevalence of Beta2agonists use between national DU and databases	Nov-13	
2.7.4.6	Compare prevalence of Calcium channel blockers use between national DU and databases	Nov-13	
2.8	Statistical methods for multi-database studies	Feb-14	Report/publications on statistical methods to analyse multi-database studies.

WP-Id	Milestone/Deliverable	Due date	Related document
2.8.1	Comparison of different approaches to multi-database analyses	Feb-14	
2.8.3	Workable data sharing models for EHR databases	Dec-13	
2.8.5	Results of combined analyses of multiple databases	Feb-14	
2.9	Guidelines for PE and drug utilisation studies	Aug-14	Guidelines and methodological standards to scientific community and industry for conceptualization of PE studies.
2.9.1	Concept guidelines and standards for PE and drug utilisation studies (based on pilot PE studies and simulation studies).	Apr-14	
2.9.2	Finalised guidelines and standards for PE and drug utilisation studies (based on milestone 'instrumental variables' and results from validation studies in WP6).	Aug-14	
3.1	Evaluation of disproportionality analysis	Oct-13	
3.1.4	External communication	Oct-13	Report comparing current quantitative SD methods.
3.2	Risk estimates compared with disproportionality statistics	Jun-14	
3.2.3	Analysis complete	Dec-13	
3.2.4	External communication	Jun-14	Report on whether absolute values of disproportionality measures applied to spontaneous reporting databases give useful information concerning public health impact of adverse drug reactions.
3.3.5	Update and maintenance until project end	Aug-14	
3.4	Recommendations	Aug-14	Report of analyses using signal detection methodologies in international, national and EFPIA databases. Variation in the performance of SD systems across datasets will be assessed and possible methods to ensure the best possible performance in different, clearly

WP-Id	Milestone/Deliverable	Due date	Related document
			defined scenarios will be presented
3.4.3	Formal SD recommendations discussed and agreed	Sep-13	List of interim recommendations arising from WPs 3.03, 3.05. 3.06 and 3.12
3.4.3.1	Final formal SD recommendations discussed and agreed	Jan-14	
3.4.4	Summary recommendations on new SD methods	Aug-14	Report proposing – in conjunction with other WPs –fair and informative evaluation of new signal detection methods which can reveal added value relative to current pharmacovigilance practice.
3.6	Novel groupings for ADRs	Feb-14	
3.6.3	Analysis complete	Oct-13	
3.6.4	External communication	Feb-14	Report on possibilities for improving SD effectiveness using novel methods of grouping of ADRs.
3.7	Other Information to enhance signal detection	Feb-14	
3.7.4	External communication	Feb-14	"Report assessing the value and efficiency of an unmasking strategy for disproportionality analysis in spontaneous reports. Paper entitled "Assessing the extent and impact of the masking effect of disproportionality analyses on two spontaneous reporting systems databases" accepted by Pharmacoepidemiology and Drug Safety. Two other manuscripts (1. And 3. In comments field) submitted to Pharmacoepidemiology and Drug Safety. "
3.8	Subgroups and risk factors	Feb-14	
3.8.3	Analysis complete	Dec-13	
3.8.4	External communication	Feb-14	Report on the use of sub-grouping data in SD methods. It will include a set of recommendations and algorithms for quantitative SD (including for defined drug classes,

WP-Id	Milestone/Deliverable	Due date	Related document
			populations or safety issues).
3.9	Signal detection based on SUSARs	Oct-13	
3.9.5	External communication	Oct-13	Report on the use of SUSAR data for signal detection and possible enhancements to the system of data collection of ICSRs (Individual Case Safety Reports) from clinical trials.
3.10	Signal detection in EHRs	Aug-14	
3.10.3 .1	Analysis complete sub study a: Comparing epidemiological methods with temporal pattern discovery method	Dec-13	
3.10.3 .3	Analysis complete sub study c: Comparing timeliness of detected signals in electronic health records with individual case safety reports	Dec-13	
3.10.4	External communication	Aug-14	Report on the use of signal detection methods applied to electronic health records.
3.10.4 .1	External communication sub study a: Comparing epidemiological methods with temporal pattern discovery method	Aug-14	Report on the use of signal detection methods applied to electronic health records.
3.10.4 .2	External communication sub study b: Strategies for evaluating potential signals in electronic health records	Aug-14	Report on the use of signal detection methods applied to electronic health records.
3.10.4 .3	External communication sub study c: Comparing timeliness of detected signals in electronic health records with individual case safety reports	Aug-14	Report on the use of signal detection methods applied to electronic health records.
3.11	Drug-drug interaction	Jul-14	
3.11.4	Analysis complete	Dec-13	
3.11.5	External communication	Feb-14	Report on methods for drug-drug interactions
4.6.4. 2	Last data collection	Mar-14	
4.9	Completion of data cleaning	Apr-14	
4.10	Preparation of datasets	Apr-14	

WP-Id	Milestone/Deliverable	Due date	Related document
4.10.1	Preparation of country specific datasets for comparison with reference data sources	Apr-14	
4.10.2	Preparation of reference datasets	Jan-14	
4.10.3	Preparation of files and datasets for individual linkage	Jan-14	
4.10.4	Preparation of linked datasets	Jun-14	
4.10.5	Preparation of whole study datasets	Jun-14	
4.11	Analysis as per statistical plan	Aug-14	
4.12	Report on results of data collected directly from pregnant women including comparative evaluation with data from other databases	Aug-14	Report on results of data of drug utilisation collected directly from pregnant women including comparative evaluation with data from other databases (i.e. health records, registries.)
4.13	Development of linkage algorithm	Jun-14	
4.13.1	Report on linkage algorithm	Aug-14	A report on the feasibility pilot for linkage of different data sources to evaluate pregnancy exposures and outcomes, including specifications for standardised formats.
4.14	Exploration of feasibility of linkage with malformation registries	Aug-14	
4.14.1	Report on feasibility of linkage with malformation registries	Aug-14	A report on the feasibility pilot for linkage of different data sources to evaluate pregnancy exposures and outcomes, including specifications for standardised formats.
4.15	Report describing 1) the user requirements and formats for consumer-based tools, 2) the assessment of the efficiency, usefulness of and satisfaction with these tools, 3) recommendations on future development to facilitate the collection of drug utilisatio	Aug-14	Report describing i) the user requirements and formats for consumer-based tools for collecting drug utilisation and health outcome data, ii) the assessment of the efficiency, usefulness of and satisfaction with these tools (including natural language collection) in assessing exposure to prescribed and non-prescribed medicines, iii) recommendations on future development to facilitate the

WP-Id	Milestone/Deliverable	Due date	Related document
			collection of drug utilisation and outcome data directly from consumers.
4.16	Report on transferability of methodology to other target populations and pharmacovigilance situations	Aug-14	Report on transferability of methodology to other target populations and pharmacovigilance situations.
5.4.3	Criteria for WP6 validation studies	Nov-13	document detailing potential forms of validation
5.11.1	Report on modelling approaches for continuous benefit-risk risk-modelling along the lifecycle of the product	Dec-13	Report on modelling approaches that would allow continuous benefit-risk risk-modelling along the lifecycle of the product, and support decision-making, including an assessment of strengths and weaknesses, and worked examples of their application.
5.11.2	Framework of B-R analyses	Dec-13	Report on modelling approaches that would allow continuous benefit-risk risk-modelling along the lifecycle of the product, and support decision-making, including an assessment of strengths and weaknesses, and worked examples of their application
6.10	"Results of replication studies, a) Replication of WP2, b) Replication of WP5	Feb-14	Results of replication studies as in WP2.
6.11	Revised recommendations and methodological standards	Aug-14	Revised recommendations and methodological standards.
7.4	Preliminary list of deliverables for training programme	Feb-14	
7.4.3	Preliminary list of deliverables for training programme Final version (project months 0-54)	Feb-14	
7.5	List of deliverables agreed with Eu2P Consortium	Aug-14	List of deliverables that have been agreed with the IMI Call 18 Consortium to be included in the pharmacovigilance training programmes, with work plan.
7.5.3	List of deliverables agreed with Eu2P Consortium - Final version	Aug-14	List of deliverables that have been agreed with the IMI Call 18 Consortium to be included in the

WP-Id	Milestone/Deliverable	Due date	Related document
			pharmacovigilance training programmes, with work plan. https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75
7.1	Training modules developed with Eu2P Consortium	Aug-14	Training module(s) (programme contents and structure, objectives, activities, timing and resources) developed with IMI Call 18 Consortium. https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75
7.6.3	Training Modules covering project years 1 to 5	Aug-14	Training module(s) (programme contents and structure, objectives, activities, timing and resources) developed with IMI Call 18 Consortium. https://eroombayer.de/eRoom/PH-GDC-PI-SID/IMI-PROTECT/0_c1b75

Consideration has been given to the maintenance of important deliverables after the study termination and integration of results into routine pharmacovigilance activities. For example, the SPC ADR database, which has been made public on the public website, is now routinely used by regulatory authorities in the EU for signal detection for centrally-authorised products, and a maintenance process has been integrated into the regular EMA pharmacovigilance activities. It has also been planned that results of the evaluation of methods for signal detection will be integrated into the signal management process described in the Commission Implementing Regulation 520/2012. Outcomes of the work programme on pharmacoepidemiological studies will be integrated on a yearly basis in each revision of the ENCePP Guide on standards in pharmacoepidemiology, which is a guidance to be used as a reference for the development of protocols of non-interventional post-authorisation safety studies, as specified in Module VIII of the Good pharmacovigilance practices. Interactions between members of the work package working on benefit-risk assessment and the Patient and Consumer working party and the Health Care Professional working party were initiated to discuss long-term application of the work to these stakeholders.

4.2.1. Prospective changes to the original work plan

Work package 2

Subject	EuroDURG collaboration in WP2/WG3 Change affects task: 2.9 Guidelines for PE and drug utilisation studies
Short Explanation	Recent contact between EuroDurg group and WP2 members suggest that collaboration might be feasible. The objective is to help develop recommendations on cross national comparison studies as part of the PROTECT guidelines on DU research to be developed by WP2. In addition a collaboration on a book on DU has been set up and is led by Xavier Kurz
Possible impact	Increase the scientific scope of the PROTECT guidelines for DU studies and potential wider dissemination.

Work package 3

Subject	WP3: Delay in comparison of risk estimates and disproportionality (3.2.3 & 4)
Short Explanation	Delay in the completion of the analysis for the comparison between risk estimates and measures of disproportionality in spontaneous reports due to the identified need for an amended literature search strategy to determine risk estimates. This amended search strategy has been agreed and will now be executed.
Possible impact	As no other sub-package depends on the outcome of this analysis, no major impact is foreseen.

Subject	WP3: Split of milestone for signal detection recommendations (3.4.3)
Short Explanation	Milestone 3.4.3 has been split in an interim (3.4.3.1) and final milestone (3.4.3.1) to reflect that the final output of some key work sub-packages would not be available by Aug-13. The scope of the interim milestone is restricted to those sub-packages for which results were available in due time.
Possible impact	The time for preparing external communication will be shortened

Subject	WP3: Delay in subgroups and stratification analysis (3.8.3)
Short Explanation	Delay in completion of the subgroups and stratification analysis for spontaneous reports on account of the delay in completing the general benchmark analysis of disproportionality analysis in spontaneous reports (3.1.3). The subgroups and stratification analysis relies on the generic benchmark and also on many of the same key contributors.
Possible impact	The time for preparing external communication will be shortened

Work package 4

The date of recruitment has been extended from August 2013 until the end of January 2014. This change and any other potential extension i.e. stop date of data collection, will not impact on the overall extension of the study and will not impact on the deliver of the study report to IMI by the end of August 2013.

Work package 5

Although the BR recommendations were discussed with the EAB in spring 2013 and valuable comment received, refining these in order to craft the best possible document for external use is taking time. The creation of an interactive version is also taking time and both are expected to be complete by the end of 2013.

Work package 6

The workplan was slightly modified related to the need of WP5-WP6 reproducibility:

- Inclusion of 2 activities (1 and 2) as described before,
- New organisation involved – UMCG as third party for activity 2.
- Subgroups defined in activity 1: rimonabant, efalizumab and rosiglitazone. The use of three case studies is proposed to address different specific issues of the real-world use of B/R evaluation methods:

1) Case study 1: Efalizumab. Handling long-term outcomes and different time horizons

One common issue induced by the necessary use of heterogeneous data sources is the difference in time horizon between outcomes, especially between benefits and risks. This is likely to critically impact all aspects of the B/R evaluations as both the outcomes definitions and the risk or benefit perceptions may be changed. This is illustrated by the WP5 efalizumab case study, where 12 weeks Benefit criteria have been traded off against long term (2 years) Risks (mainly spontaneous reports of PML and other long term effects of an immune-suppressant). The objective is to check the result of modeling the efficacy criteria over a longer period and document its impact on the evolving B-R balance of the drug over a long term exposure.

2) Case study 2: Rosiglitazone. Case of fast decision making

This case will illustrate whether rapid assessment may be conducted as a preliminary decision support in the case a more refined model-based analysis is feasible. The B/ R assessment of rosiglitazone made in WP5 according to complex probabilistic methods will be “replicated” with a more simple method readily accessible to a rapporteur. If this replication study shows a possibility to speed up an assessment without major bias and providing an initial support for a decision to be made, it would offer a pragmatic approach pending the availability or time for a more sophisticated assessment. This assessment can be discussed in light of what was actually done and decided at the time Rosiglitazone was evaluated by EMA.

3) Case study 3: Rimonabant. Handling data heterogeneity and the mix of RCT and observational information

- This case will re-evaluate a WP5 case study using all of available data but addressing properly heterogeneity issues: the rimonabant case study provides an opportunity, adding the spontaneous reports, the PMS, the epidemiological data, as well as any relevant additional efficacy evidence.

Work package 7

Following the advice of the External Advisory Board (EAB) at their meeting in March 2013 (see eRoom at https://eroombayer.de/eRoomReq/Files/PH-GDC-PI-SID/IMI-PROTECT/0_d3459/EAB%20Recommendations%20Feb%202011.pdf) the development of a communication strategy was transferred from Work Package 7 to Work Package 1. The EAB noted that the area of communication on the project and its results could be improved. While the training component has been well addressed by WP7, a communication plan and strategy is missing. The EAB pointed out that the plan should consider means beyond standard communication, i.e. via conferences, journal, etc., to ensure that the target population, in particular patients, is reached. To this end, it was recommended to involve communication experts from outside the consortium.

Rick Assessment, when appropriate

Table 4-2 List of risks for the upcoming periods

Id.	Project Risk	Probability VH/H/M/L	Impact VH/H/M/L	Status light	Possible impact	Corrective Actions	Due Date
2-03	IMS data is available for all drug pairs but not for all European countries. IMS data sets cover between 5-10 main EU countries.	H	M	Green	The deliverable on public health impact of ADRs (exposed population) may be negatively affected and may not include all European countries. However the exposed population will be estimated in all available countries, independently of the source of data.	A 3rd party agreement was concluded with Novartis (antibiotic drugs) and Roche (antidepressants, calcium channel blockers and beta2agonists) and IMS data was received.	Nov 2013
2-04	Access to public drug consumption data will not be available for all drugs and for all European countries. However, new information on National Drug Consumption Databases has been added in the DU inventory and new utilization data is available for several of them. Drug utilization data is available for 17 European countries by now.	H	M	Green	Access to public drug consumption data will not be available for all drugs and for all European countries. However, new information on National Drug Consumption Databases has been added in the DU inventory and new utilization data is available for several of them. Drug utilization data is available for 17 European countries by now.	The accessibility of public data in main European countries was checked and a referent person in each of them was contacted and is yearly updated. At present European countries of more than 30 million population, those participating in PROTECT and most of the remaining European countries have been contacted and consumption data from several of them have been received. However, data from Poland and Finland won't be available. The data relating to the whole national drug consumption are collected only by IMS Health. FIFC has access to IMS data so data from Poland via the national contact institution has not been requested. For Finland, the data is not available due to lack of answer of the approached organization and a long delay to deliver the data (up to 5 years). However, sales data from Finland are freely available. Once the methodology to study the public health impact of ADR is established based on the available data, it could be applied in other countries. Efforts are kept to achieve information on maximum number of countries in the yearly update.	Aug 2014

2-07	Item 2.8 Statistical methods for multi-database studies is delayed	H	L	Yellow	At least a 6 months delay for deliverables under this task. No impact on other WP2 tasks nor on budget is foreseen.	This task is a top-priority at the moment for Working group 2. New subtasks and timelines have been defined	New subtasks to be delivered in the defined timelines.
2-09	LMU Muenchen obtained the data from the Bavaria Claims database (Germany) end March 2012 and started the descriptive analysis with 6 months delay.	H	H	Green	It might cause delay in the finalization of manuscripts. To avoid delays the results from the Bavaria database might not be considered resulting in a decrease of the scientific scope of the comparison between EU databases..	The Bavaria team delivered all descriptive results with delays. Results from the Bavaria database were included in the descriptive manuscripts of the planned Drug-event pairs. In addition, it was decided that no association studies will be performed using this database because prescriptions and diagnoses are available in quarters (no exact date) which is a severe limitation for a study on short-term/acute effects (see explanation in Section II. Major prospective changes to current plan). Therefore the risk of delays in delivering results is not applicable anymore.	September 2013
2-10	SSI (DHMA) descriptive results have been delivered for all drugAE pairs for exposure and included in the papers with minor delays not affecting the overall objectives of WP2. However, the descriptive results of suicidality outcome and the cohort results of AED/Suicidality and CCB/Cancer pairs from SSI remain delayed due to technical reasons. For AED/Suicidality, WP2/WP6 results from other databases have been presented at the Symposium at ICPE 2013. For CCB/Cancer, no studies were performed in WP6 so there were no other results to compare with at ICPE 2013 and the presentation was	H	H	Red	For the AED/Suicidality pair, the comparison of results between 2 databases in WP2 (SSI and CPRD) is planned and one study has been conducted in WP6. If SSI results are not delivered, the manuscript will include results from 1 database in WP2 and another in WP6. The study planned to be done by SSI and the study done by Aarhus University in WP6 use the same database (Danish registries). If SSI is unable to deliver the results, it would still be possible to analyse the impact of using different databases, but one of the objectives of WP6 would be lost for this drug-AE pair, namely replication of a study protocol in the same database. For the CCB/Cancer pair, the comparison	PROTECT coordinators have been informed about the delays and risk. The DHMA investigator has been contacted and the following actions have been agreed with the WP co-leaders and the PROTECT coordinators: - The AED/Suicidality study by SSI (DHMA) is deprioritised - The results of the CCB/Cancer study will be delivered by 24 October 2013 - The DHMA investigator will keep WP2 co-leads informed about the progress.	October 2013

	cancelled.				of results between 2 databases in WP2 (SSI and CPRD) is planned and no studies have been conducted in WP6. If SSI results are not delivered, no comparison will be feasible and the corresponding deliverable (manuscript) might not be completed according to the work plan. The publication of results on this Drug-AE pair will also be delayed.		
2-11	The cohort results from CPRD-La-Ser for CCB/Cancer study were delivered in June 2013.	L	L	Green	The results were delivered in time before Aug 2013.	Close monitoring by WP2/WG1 co-leads.	
2-12	Systematic review of acute liver injury and antibiotic; the whole task has been delayed. The data extraction is expected in September 2013 and the report in October 2013. This task is jointly conducted by Amgen and FICF.	L	L	Yellow	It might cause delay in the calculation of Population Attributable Fraction, the finalization of a manuscript/report	Close monitoring by WP2/WG3 coleads.	
3-01	Further delays in the completion of sub-package 3.02	L	L	Yellow	Failure to complete the objectives of 3.02 in time	Restriction of scope of literature review in amended literature search strategy in process	
3-02	Spanish presidency of EC	L	L		Sub-package 3.2 is led by AEMPS and early goals may be delayed.	Temporary very high workloads (6 months) may delay package but overall timeframe still believed achievable.	
3-03	Delays in the completion of sub-package 3.08 – Subgroups and stratification			Yellow	Such delays would make it difficult to include recommendations related to sub-package 3.08 in sub-package 3.04.	Sub-package 3.01, which will serve as the basis for Sub-package 3.08, has been completed and resources will be shifted from 3.01 to 3.08 during fall of 2013. Beyond that, we shall prioritize the different covariates to be considered in sub-package 3.08 for incremental implementation so that the full analysis be completed for the most important variables before we undertake implementation and evaluation of covariates of lower priority.	
3-03	Sub-package 3.7 – Other parameters			Yellow	There will be a delay to the interim	Scope of sub-package 3.07 revised and	

	to enhance signal detection is not making progress as planned. This sub-package was loosely specified in the original project specification with the aim that the project participants would have a chance to influence its direction, but has struggled to identify a concrete topic of broad enough interest to engage the other project participants. Up to now, the sub-package leader has been isolated in his work on this project without much input from other project participants. The current sub-package leader has indicated a desire to give up this role, and there is no natural replacement at this point.				milestones of the sub-package as indicated above and possibly also to the final completion of the sub-package.	clarified in June 2011, with Steering Committee endorsement to change focus to the analysis of masking effects in disproportionality analysis. Sub-package leadership reconfirmed at the same time. Results have been circulated to the Consortium for review and manuscripts have been submitted for publication.	
4-01	Limited budget has been allocated to subcontract EPIC. However, while the work plan for WP4 developed it became clear that the subcontracting part for EPIC needs to be extended. Further resources/budget is needed to finance this	L	L	Green	If the subcontracting budget for EPIC cannot be increased, the finalisation of the study protocol and questionnaires will be delayed and the linkage aspect and data comparison will be jeopardised as input from EPIC to both is essential to ensure EHR data linkage later on. Start of all other tasks depends on the study protocol and questionnaire. Could have impact on optimal delivery of all study objectives.	Pfizer has been approached in order to allocate some of the remaining (not yet allocated) financial contribution to increase involvement of EPIC as a subcontractor.	
4-02	A suitable organisation has been identified to join the consortium to conduct the study at the 4th study site. Accession of this organisation has been endorsed by the SC. However, formal steps of the accession, approval by the IMI JU and issues related to the financing of the work to be done are outstanding.	L	L	Green	If the selected organisation cannot or does not accede to the project, it might be too late to identify a replacement within the predefined timelines. This might compromise the implementation of WP4 as planned in 4 countries.	Close contact with the new organisation and IMI JU by WP co-leaders, Coordinators and PROTECT Support will enable any issues to be resolved quickly. Provide for formal accession without delay. --> PUMS acceded on 26 November 2010. Issue resolved.	

	There is a risk associated with these outstanding issues as there is a level of uncertainty e.g. as regards acceptability of the new centre by IMI and/or the IMI rule and the allocated budget by the organisation.						
4-03	An analysis of the expected number of women who had linkable EHRs and who had a child with a congenital anomaly suggested this would apply to so few women that it was not viable from the scientific point of view and certainly not cost effective.	L	L	Green	This deliverable would involve a considerable amount of resource and it is probable that there will not be a sufficient number of women who fulfil the criteria to be feasible anyway. This was a very minor part of the project and employing resources towards the more fruitful areas of research is more cost effective.	Discussion with Work Package member as to whether to pursue a variant of this deliverable. The WP agreed to perform a feasibility analysis which is in line with the description of work. If the number of women with linkable EHR record for children with a malformation is indeed too small, the feasibility report will be negative.	
4-04	Following discussions with professional organisations, it became clear that it was unlikely that pharmacies would be prepared to display recruitment leaflets free of charge. It was decided that a token gesture – e.g. a textbook – would be provided for participating pharmacists.	L	L	Green	Provision of textbooks was not planned for in original costing. Being unable to place leaflets in pharmacies would mean that recruitment was solely via website which could “disenfranchise” women without internet access	Funding for textbooks is being sought from the unused part of the “Direct financial contribution.” --> Additional funding was allocated to Work Package 4. These funds became available as some tasks performed in year 1 were less expensive than initially estimated.	
4-05	Refusal of IMI to allow reimbursement of data collection platform software development which has to be done in the US has caused development of data collection platform to cease.	L	L	Green	Further delay or failure to get alternative private funding for this may cause failure of WP4. If there is no funding possibility, the work package will have to be abandoned. Much more delay will lead to shortage of time to recruit women as data collection cannot start until data collection platform is operational. This may lead to failure to recruit enough women to make results meaningful.	Agreement was sought and reached from IMI JU to permit subcontracting of Outcome Sciences by a private partner. Agreement has been reached with Utrecht and Pfizer to switch part of the DFC from Pfizer to subcontract Outcome with Utrecht’s deficit being made up by reducing Outcome Saar’s public funding and using this to reimburse public partner. The subcontract has been concluded and all necessary budget amendments were implemented. The issue is therefore resolved. However major delays in the timelines of WP4 were encountered and put at risk the	

						recruitment of the planned number of women (see new risk item #4-08). In addition constraints mean that further development of the website has not been possible	
4-06	Delay in finalising the questionnaires and the study protocol	L	L	Green	Delay will impact on the time for testing/piloting the data collection forms and the time for recruiting women.	WP4 is aware of the delay and working hard to finalise the questionnaires and the protocol. The timelines will be closely monitored and the feasibility of recruiting the envisaged number of women will be assessed on an on-going basis. If there is no further delay than currently scheduled for, the impact of the delay will be minor and the risk will be moved to green light status. --> The protocols are finalised and the questionnaires were piloted. Issue resolved. The delay in timelines has an impact on the recruitment period (see new issue #4-08)	
4-07	Identification of the 'data controller' in line with data privacy legislation has proven difficult. The European data Protection Officer has advised that the members of WP4 should be considered as 'joint controllers' with Outcome being the 'principle controller'. Data protection notification in the individual countries has been done but the notification to the EDPS was delayed because of the need to provide proof of Outcome's notification. EDPS has indicated that they have further questions related to the notification which could cause a delay to the recruitment start up	H	H	Green	The issue has been discussed with the European Data Protection Supervisor and Outcome. Data collection cannot start and the ethical approval cannot be finalised unless the issue is resolved to the satisfaction of all parties concerned. There are potentially legal implications for the PROTECT partners that would fall under 'joint controller'.	EMA has received advice from the European Data Protection Supervisor (EDPS) and informed all parties concerned about the legal implications. Following the advice of the EDPS, Outcome is considered 'principle data controller' while all other WP4 participants are 'joint controllers' under data protection legislation. A memorandum of understanding has been prepared and was agreed with all WP4 participants before proceeding. Of note, since participant GPRD found it impossible to agree with the content of the memorandum, they terminated their involvement in WP4. No impact is expected as validation based on EHR data will be conducted in the UK using EPIC/THIN data.	Ongoing. Decision to delay recruitment start will be taken during September
4-08	Shortened recruitment period due to delays encountered since the start of the project might affect the	M	M	Yellow	The involvement of fewer women could lead to a smaller amount of data collected which will reduce the power of	Initially a staggered study start was foreseen, with data collection being launched first in the UK and only later in the other countries. In	In place. Recruitment will be closely

	recruitment of the planned maximum number of women.				data analysis. As the study in WP4 is exploratory in nature, the impact is expected to be limited as even with fewer data, the outcome of the study should allow to conclude on the added value and feasibility of data collection directly from consumers using modern communication techniques.	light of the limited time, now the study will start as soon as possible in all 4 countries. The timescales for data cleaning and statistical analysis have been shortened enabling a longer recruitment period. Furthermore, as a worst-case scenario, an application for extension of the project timelines is being considered.	monitored to see if further corrective action is needed
4-09	We will not recruit the planned number of women via the IVRS system. However since one of the study questions was to look at which method was best suited to collect data, this can be answered. One of the planned analyses was to compare the demographics of women choosing the web and IVRS. With one women choosing to use IVRS this comparison cannot be done	VH	L	Red	We will not recruit the planned number of women via the IVRS system. However since one of the study questions were to look at which method was best suited to collect data, this can be answered. One of the planned analyses was to compare the demographics of women choosing the web and IVRS. With one women choosing to use IVRS this comparison cannot be done	No corrective action is possible since women choose which method they wish to use to contribute data. The system has been repeatedly checked to ensure that it was not a system malfunction leading to this and we are confident that it is purely choice. For this reason the IVRS recruitment was shut down at the planned date of the 1 st September 2013. Web recruitment continues.	N/A
4-10	Data Linkage of study data in the UK with THIN data: . Leaflets went to pharmacies in areas with above average numbers of doctors contributing data to the THIN database to increase the chances of being able to link women. However, since most recruitment in the UK has been via website (and not pharmacies) this means that possible linkage will revert to the norm. (THIN has about 6% of the UK patients in its database). Doctors have to opt in to allow linkage in general of their data (ie not specific to this study). Uptake of this has been lower than expected and only about 30% of THIN practices	M	M	Yellow	The number of women whose data we can link is reduced. This along with the slower than hoped for recruitment means that we will only be able to link a small number of women's data. Whereas we can still compare the data as planned, small numbers mean that firm conclusions may be difficult.	None possible.	

	are currently enrolled.						
4-11	At a very late stage of the project, it became apparent that there were major issues with getting consent from the Polish data protection agency.				This had the potential to prevent any recruitment of women from Poland	PUMS had multiple meetings and discussions with the DPPO in Poland. Final agreement on requirements meant that considerable changes to the website and work flow needed to be undertaken with subsequent protocol changes. This led to a considerable delay in starting recruitment but the successful outcome meant that Poland were able to continue their participation in WP4.	Recruitment in Poland started in May 2013.
5-01	The project manager of WP5 had to leave the Work Package end of 2010.	M	M	Green	The period of time without project management has resulted in delays but strategies are in place to minimise these and WP5 timelines have been amended accordingly.	Project management is now in place from Imperial	ASAP. To be finalised in September 2013.

VH= Very High, H = High, M = Medium, L = Low

5. Finance - Cost

5.1. Cost summary

All participants have provided a financial statement (Form C) and an *explanation on the use of the resources* for the reporting period.

A compilation of all available ***explanations of the use of the resources*** is provided in Annex 7.1. Breakdown of the costs by WP for EFPIA participants is only an estimate as they are not required to report their cost on WP level.

5.2. Description of deviation from original budget

The overview is based on the costs of all participants as reported in the financial statements (Forms C; see also Annex 7.1) and the consequent update of the project budget (table below).

The costs declared for the 1st, 2nd, 3rd and 4th project year have been updated in line with a number of adjustments to the financial statements received from PROTECT participants. Namely from: DHMA (1st, 2nd and 3rd period), UU (3rd period), UMC (2nd period), Imperial (1st, 2nd, 3rd period), UNEW (2nd, 3rd period), Pfizer (3rd period), Amgen (all previous periods), Bayer (3rd period) and AZ (3rd period).

A significant move of the resources took place during the 4th project year in WP6. As explained with the latest amendment of the Annex I to the grant agreement, the unallocated funds have now been redistributed to the partners additionally involved in WP6.

The estimated project cost for a new partner, UMCG- also involved in WP6, was covered by the unallocated funds.

Additionally, Witten University (Wuppertal, Germany) joined the PROTECT consortium. However, the accession of this new partner did not have any budgetary implications since their cost was covered by reallocation of funds from LMU (partner no. 6). An exact description of the tasks of Witten University and updated tasks of LMU along with the corresponding shifting of resources from LMU to Witten University are included in Annex 1 to the Grant Agreement (revision 7).

Table 5-1 Overview of the project costs – public beneficiaries*

		A	B	A-B	A/C		C
Partner No	Partner Name	Cumulative Actual costs years 1-4	Cumulative Budget years 1-4	Deviation	Current budget status	Forecast Remaining Periods	Total
1	EMA	200,489.81	241,758.25	-41,268.44	50.60%	195,768.19	396,258.00
2	DHMA	394,335.08	481,939.52	-87,604.45	77.13%	116,934.93	511,270.00
4	IAPO	30,985.33	113,219.50	-82,234.17	37.39%	51,884.98	82,870.31
5	Outcome	418,529.27	813,202.27	-394,673.00	42.55%	565,148.07	983,677.34
6	LMU Muenchen	182,307.98	276,433.99	-94,126.01	52.89%	162,362.98	344,670.96
7	AEMPS	335,414.67	387,882.31	-52,467.64	89.45%	39,576.33	374,991.00
8	FICF	497,896.01	504,401.83	-6,505.82	80.25%	122,497.99	620,394.00
9	CEIFE	231,057.23	274,150.00	-43,092.77	82.58%	48,749.77	279,807.00
10	INSERM	496,381.41	459,823.12	36,558.29	83.69%	96,718.81	593,100.22
11	PGRx (LASER)	1,036,078.32	978,139.25	57,939.07	73.97%	364,582.26	1,400,660.58
12	IRFMN	195,491.22	181,697.12	13,794.11	83.60%	38,352.27	233,843.49
13	RUG	149,493.31	258,855.39	-109,362.08	60.71%	96,760.46	246,253.77
14	UU	1,151,778.86	1,469,785.56	-318,006.70	80.62%	276,916.14	1,428,695.00
15	UMC	644,455.62	1,013,065.76	-368,610.14	73.56%	231,662.18	876,117.80
16	MHRA	403,005.00	323,760.90	79,244.10	75.04%	134,078.60	537,083.60
17	Imperial	381,168.24	506,963.35	-125,795.11	52.41%	346,122.53	727,290.77
18	UNEW	92,726.67	191,240.39	-98,513.72	37.86%	152,163.33	244,890.00
30	PUMS	36,212.97	47,500.47	-11,287.50	63.52%	20,801.03	57,014.00
32	AU	217,896.40	338,543.70	-120,647.30	67.65%	104,190.60	322,087.00
34	WHU	0.00	18,810.00	-18,810.00	0.00%	38,820.00	38,820.00
35	UMCG	13,740.00	117,359.00	-103,619.00	4.92%	265,441.00	279,181.00
	Unallocated						430,739.17
Total							11,009,715

Note: * For beneficiaries only the IMI JU requested contribution is show.

Table 5-2 Overview of the project costs – EFPIA Partners

		A	B	A-B	A/C		C
Partner Number	Partner Name	Cumulative Actual costs years 1-4	Cumulative Budget years 1-4	Deviation	Current budget Status	Forecast Remaining Periods	Total (<i>inc.EU and non EU contribution</i>)
3	GSK	556,417	713,796	-157,379.49	58.99%	386,827	943,244.00
19	SARD	773,839	976,553	-202,714.63	77.85%	220,121	993,960.25
20	Pfizer	844,319	1,003,999	-159,679.80	84.09%	159,732	1,004,051.16
21	Roche	861,434	786,240	75,194.00	87.65%	121,366	982,800.00
22	Novartis Pharma	447,670	415,170	32,500.23	78.30%	124,100	571,769.82
23	Amgen	632,215	799,288	-167,073.45	70.23%	268,000	900,215.00
24	Genzyme	474,806	513,678	-38,871.90	82.81%	98,571	573,377.00
25	ME	1,093,901	1,092,519	1,381.87	83.89%	210,000	1,303,901.00
26	Bayer	469,325	995,212	-525,887.41	75.78%	150,000	619,324.92
27	AZ	452,172	491,575	-39,402.70	80.65%	108,501	560,673.00
28	HLU	113,064	84,839	28,225.22	97.00%	3,500	116,564.22
29	Novo	323,581	313,071	10,510.06	98.18%	6,000	329,581.00
31	TGRD (Europe)	136,589	134,791	1,797.73	95.12%	7,000	143,588.73
33	Eli Lilly	53,211	45,055	8,156.50	63.72%	30,296	83,507.21
	Total	7,232,542.07	8,365,785.84	-1,133,243.77		1,894,015.24	9,126,557.31

6. Form C and Summary Financial Report

Copies of the financial statement of all participants are provided in Annex 7.1 and the signed originals are sent by post. DHMA, UU, UMC, Imperial, UNEW, Pfizer, Amgen, Bayer and AZ notified adjustments to the financial statements (see section above, 5.2.). The attached set of Forms C thus includes Adjustments to the Form C for the previous reporting periods for these 9 participants.

The summary financial report is also annexed to this report (Annex 7.1). The interest yielded by the pre-financing on the account of the Managing Entity of the IMI JU funding (DHMA) is declared for the fourth year of the project. The summary financial report also reflects all adjustment to Forms C for the previous reporting periods.

Six partners went through the audit exercise within the last reporting period: DHMA, INSERM, UU, Imperial, UMC and La-Ser. Enclosed are in this report Independent Auditor's Reports of Factual Findings on costs claimed / declared under the IMI JU agreement. The detailed reports can be found in the Annex 7.1- Financial Reporting Documents.

7. Annexes

All Annexes are provided with the submission of the periodic report as separate documents.

7.1. Financial reporting documents

- Explanation on the use of the resources for 4th period (from all participants)
- Compiled Forms C for the 4th reporting period and Adjustments to Forms C for the previous reporting period (DHMA, UMC, Imperial, UNEW, Pfizer, Novartis Pharma, Amgen, Bayer and AZ)
- Independent Reports of Factual Findings on costs claimed under Grant Agreement (115004) from DHMA, INSERM, UU, Imperial and UMC.
- Summary financial report for 4th period

7.2. PROTECT Global Work Plan Year 4

7.3. Other relevant documents

- 4th half-year Report covering months 37-42 (inclusive)
- List of publications
- List of presentations
- List of meetings in 4th project year
- PROTECT Meeting Plan Year 5
- Program of the PROTECT Consortium Assembly in October 2013 in London, (EMA offices).