PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

# Impact of Methodological Choices on Findings from Pharmacoepidemiological Studies in Electronic Healthcare Data

## Final Results from Work Packages 2 and 6 of the IMI-PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) Project

Robert Reynolds (Pfizer) on behalf of PROTECT participants

PROTECT Symposium

London, United Kingdom

# PROTECT Goal

**To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods**

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

These methods are being tested in real-world situations

# WP2 & WP6 Partners

## Public

**Regulators:**
EMA
DKMA
AEMPS
MHRA

**Academic Institutions:**
Aarhus University
FICF (Barcelona)
University of Munich
University of Utrecht
Witten University

**Others:**
CPRD
CEIFE

**SMEs:**
La-Ser

## Private

**EFPIA companies:**
GSK
Sanofi
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Astra Zeneca
Eli Lilly

# WP2: Participants and their roles

| | WG1<br>Databases | WG2<br>Confounding | WG3<br>Drug utilization |
|---|---|---|---|
| Number of participants | n=51<br>37 public, 14 private | n=10<br>8 public, 2 private | n=10<br>7 public, 3 private |
| Public partners | EMA, LMU-Muenchen, Witten University[4], AEMPS, CEIFE, CPRD, DKMA and UU | UU | FIFC, LMU and Witten University[4] |
| Private partners | Amgen, AZ, Genzyme, GSK, La-Ser, Merck, Novartis, Roche and Pfizer | Amgen, Novartis and Pfizer | Amgen, Novartis and Roche |
| WG Coordinators | Raymond Schlienger [1] (Novartis)<br>Mark de Groot[2] (UU) | Nicolle Gatto (Pfizer)<br>Rolf Groenwold (UU) | Joan Fortuny [3,5] (Novartis)<br>Luisa Ibanez (FIFC) |
| WP2 coleaders | Olaf Klungel (UU) - Robert Reynolds (Pfizer) | | |
| WP2 coleaders alternates | Tjeerd van Staa (LSHTM) - Jamie Robinson (Roche) | | |
| WP2 Project Manager | Ines Teixidor (UU) | | |

[1] from October 2010 replacing John Weil (GSK), [2] from 1 February 2011 replacing Frank de Vries (UU), [3] from 15 March 2012 replacing Hans Petri (Roche),
[4] New partner, accession approved by SC in January 2013 [5] Departed Novartis in 2014

# WP6: Participants and their roles

| | WP6 |
|---|---|
| Number of participants | n= 20<br>5 public, 5 private |
| Public partners | European Medicines Agency, Universiteit Utrecht, Aarhus University, Medicines and Healthcare products Regulatory Agency, University of Groningen |
| Private partners | LA-SER, Sanofi-Aventis Research and Development, Takeda Global Research and Development Centre (Europe) Ltd, H. Lundbeck A/S, Merck KGaA |
| WP6 coleaders | Lucien Abenhaim (LA-SER) - Laurent Auclert (Sanofi-Aventis Research and Development, co-leader until June 2014 [1] ) |
| WP6 coleaders alternates | Lamiae Grimaldi (LA-SER) - Juhaeri Juhaeri & Stéphanie Tcherny-Lessenot (Sanofi-Aventis Research and Development) |
| WP6 Project Manager | Laurence Mazuranok (Sanofi-Aventis Research and Development) |

[1] retired from Sanofi-Aventis in June 2014

# Background

- Increased use of large-scale, "real world" electronic healthcare databases
- Studies in same database generate different results
  - e.g., oral bisphosphonates-esophageal cancer, or statins-fractures
- Studies in different databases generate different results
  - e.g., antibiotics-sudden death, or NSAIDs-cardiovascular risk
- Debate about value of epidemiology for understanding medicines' benefits and risks

# Main objectives

- Explain differences in drug-adverse event associations due to choices in methodology and databases (WP2)
- WP6 replication program of WP2 studies
  - Same study EU database
  - Different study database, specifically US data source
  - Use of alternative outcome definition
  - Negative control study

Abbing, V et al. Bridging differences in findings from pharmacoepidemiological studies: The PROTECT project. *Current Clin Pharmacol.* 2014 May;9(2):130-8.

# Rationale for Drug-Adverse Event Pairs

Criteria

- AEs that caused regulatory decisions
- Public health impact (both rare and common events), seriousness of the event, prevalence of drug exposure, etiologic fraction
- Feasibility for assessment of AEs in databases
- Possibility to investigate broad range of relevant methodological issues, i.e. variable results across at least two databases

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# Seven Drug – Adverse Event Pairs Selected

- Antidepressants/benzodiazepines and hip fracture
- Inhaled long-acting β2-agonists and acute myocardial infarction
- Anti-epileptics and suicide / suicide attempts
- Antibiotics and acute liver injury
- Calcium channel blockers and cancer
- Antibiotics and myocardial infarction ("negative" control)

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# Characteristics of healthcare databases

| Database | Country | Cumulative population (2008) | Active population (2008) | Data source | Coding diagnoses | Coding drugs | Recording of drug use |
|---|---|---|---|---|---|---|---|
| BIFAP | ES | 3.2 Mio | 1.6 Mio | GP | ICPC | ATC | Prescribing |
| CPRD | UK | 11.0 Mio | 3.6 Mio | GP | READ | BNF | Prescribing |
| THIN | UK | 7.8 Mio | 3.1 Mio | GP | READ | BNF | Prescribing |
| Mondriaan | NL | | | | | | |
| NPCRD | | 0.7 Mio | 0.34 Mio | GP | ICPC | ATC | Prescribing |
| AHC | | 0.26 Mio | 0.17 Mio | GP/Pharmacy | ICPC | ATC | Prescribing + dispensing |
| The Danish national registries | DK | 5.2 Mio | 5.2 Mio | Hospital/ Pharmacy | ICD-8/10 | ATC | Dispensing |
| PGRx | FR/ UK/ CN | 10 k | 10 k | GP + Specialist Registries | ICD-9 | ATC/ EPH MRA | Prescribing + Patient Interview |
| Clinformatics | US | 47 Mio | 15 Mio | Claims health insurance | ICD-9 | NDC | Claims |

# Procedures

- Common protocol for each drug-AE pair
  - Extensive sensitivity analyses on main methodological issues
- Common standards, templates, procedures
  - Detailed data specification including definitions of exposures, outcomes, and confounders for each database.
- Blinding of results of analyses within drug–AE teams and across WPs

# Members of PROTECT WP2 and WP6

**WP2: J. Slattery, Y. Alvarez, G. Candore, J. Durand, X. Kurz** (European Medicines Agency); **J. Hasford, M. Rottenkolber** (Ludwig-Maximilians-Universität-München); **S. Schmiedl (**Witten University**); F. de Abajo Iglesias, M. Gil, C. Huerta Alvarez, G. Requena, E. Martin (**Agencia Espanola de Medicamentos y Productos Sanitarios); **R. Brauer, G. Downey, M. Feudjo-Tepie, M. Schoonen** (Amgen NV); **S. Johansson** (AstraZeneca); **J. Robinson, M. Schuerch, I. Tatt** (Roche); **L.A. Garcia, A. Ruigomez** (Fundación Centro Español de Investigación Farmacoepidemiológica); **J. Campbell, A. Gallagher, E. Ng, T. Van Staa** (General Practice Research Database); **O. Demol** (Genzyme); J**. Logie, D. Webb, J. Pimenta, K. Davis** (GlaxoSmithKline Research and Development LTD); **L. Bensouda-Grimaldi** (L.A. Sante Epidemiologie Evaluation Recherche); **U. Hesse** (Lægemiddelstyrelsen (Danish Medicines Agency) ); **M. Miret** (Merck KGaA ); **P. Primatesta, R. Schlienger, E. Rivero, J. Fortuny** (Novartis); **A. Bate, N. Gatto, R. Reynolds** (Pfizer); **E. Ballarin, L. Ibañez, J.R. Laporte, M. Sabaté, P. Ferrer** (Fundació Institut Català de Farmacologia); **V. Abbing-Karahagopian, A. Afonso , M.L. de Bruin, F. de Vries, A.C.G. Egberts, B. Leufkens, P. Souverein, L. van Dijk, M. De Groot, H. Gardarsdottir, R. Van den Ham, O. Klungel, S. Belitser, A. De Boer, R. Groenwold, A. Hoes, W. Pestman, K. Roes, S. Ali, J. Uddin** (Universiteit Utrecht).

**WP6: L. Abenhaim, L. Grimaldi** (LA-SER); **L. Auclert, J. Juhaeri, S. Tcherny-Lessenot, L. Mazuranok** (Sanofi-Aventis Research and Development); **X. Kurz, A. Beyer** (European Medicines Agency); **L. Wise, D. Irvine, P. Dolin** (Takeda Global Research and Development Centre (Europe) Ltd); **M. De Bruin, I. Teixidor** (Universiteit Utrecht); **C. Gasse** (Aarhus University); **P. Verpillat** (H. Lundbeck A/S); **A. Micaleff** (Merck KGaA); **W. Richardson, A. Thomson** (Medicines and Healthcare Products Regulatory Agency); **H. Hillege, A. Beyer** (University of Groningen)