



**PROTECT**



Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

# Lessons learned from PROTECT on common protocols for multi-database studies

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# Disclosures

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, [www.imi-protect.eu](http://www.imi-protect.eu)) which is a public-private partnership funded by the Innovative Medicines Initiative (IMI) and coordinated by the European Medicines Agency.
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# 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



# Main objectives

- Explain differences in drug-adverse event associations due to choices in methodology and databases
- Replication program of studies
  - Same study EU database
  - Different study database, specifically US data source

Abbing-Karahagopian V, et al. Curr Clin Pharmacol 2014;9:130-8



# Drug-AE pairs and designs

Drug-AE pair	Descriptive	Cohort	Nested case control	Case crossover	Self-Controlled case series
AB-ALI	All Databases	CPRD BIFAP	CPRD BIFAP	CPRD	CPRD
AED-Suicidality	All Databases	CPRD DKMA			
AD- Hip	All Databases	THIN Mondriaan BIFAP	THIN Mondriaan BIFAP	THIN Mondriaan	THIN Mondriaan
BZP-Hip	All Databases	CPRD BIFAP Mondriaan	CPRD BIFAP Mondriaan	CPRD BIFAP	CPRD BIFAP
B2A-AMI	All Databases	CPRD Mondriaan			
CCB-Cancer	All Databases	CPRD			



# 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 NPCRD AHC	NL	0.7 Mio 0.26 Mio	0.34 Mio 0.17 Mio	GP GP/Pharmacy	ICPC ICPC	ATC ATC	Prescribing 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 in-parallel and replication analyses
  - Stepwise unblinding after completion of each design
- Registration of protocols at ENCePP to guarantee transparency



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ORIGINAL REPORT

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## Hip/femur fractures associated with the use of benzodiazepines (anxiolytics, hypnotics and related drugs): a methodological approach to assess consistencies across databases from the PROTECT-EU project

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2015)

Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3822

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ORIGINAL REPORT

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## Do case-only designs yield consistent results across design and different databases? A case study of hip fractures and benzodiazepines<sup>†</sup>

Gema Requena<sup>1\*,‡</sup>, John Logie<sup>2‡</sup>, Elisa Martin<sup>3</sup>, Nada Boudiaf<sup>2</sup>, Rocío González González<sup>3</sup>, Consuelo Huerta<sup>3</sup>,  
Arturo Alvarez<sup>3</sup>, David Webb<sup>2</sup>, Andrew Bate<sup>4</sup>, Luis A. García Rodríguez<sup>5</sup>, Robert Reynolds<sup>6</sup>,  
Raymond Schlienger<sup>7</sup>, Helga Gardarsdottir<sup>8</sup>, Mark de Groot<sup>8</sup>, Olaf H. Klungel<sup>8</sup>, Fancisco de Abajo<sup>1,9</sup>  
and Ian J. Douglas<sup>10</sup>



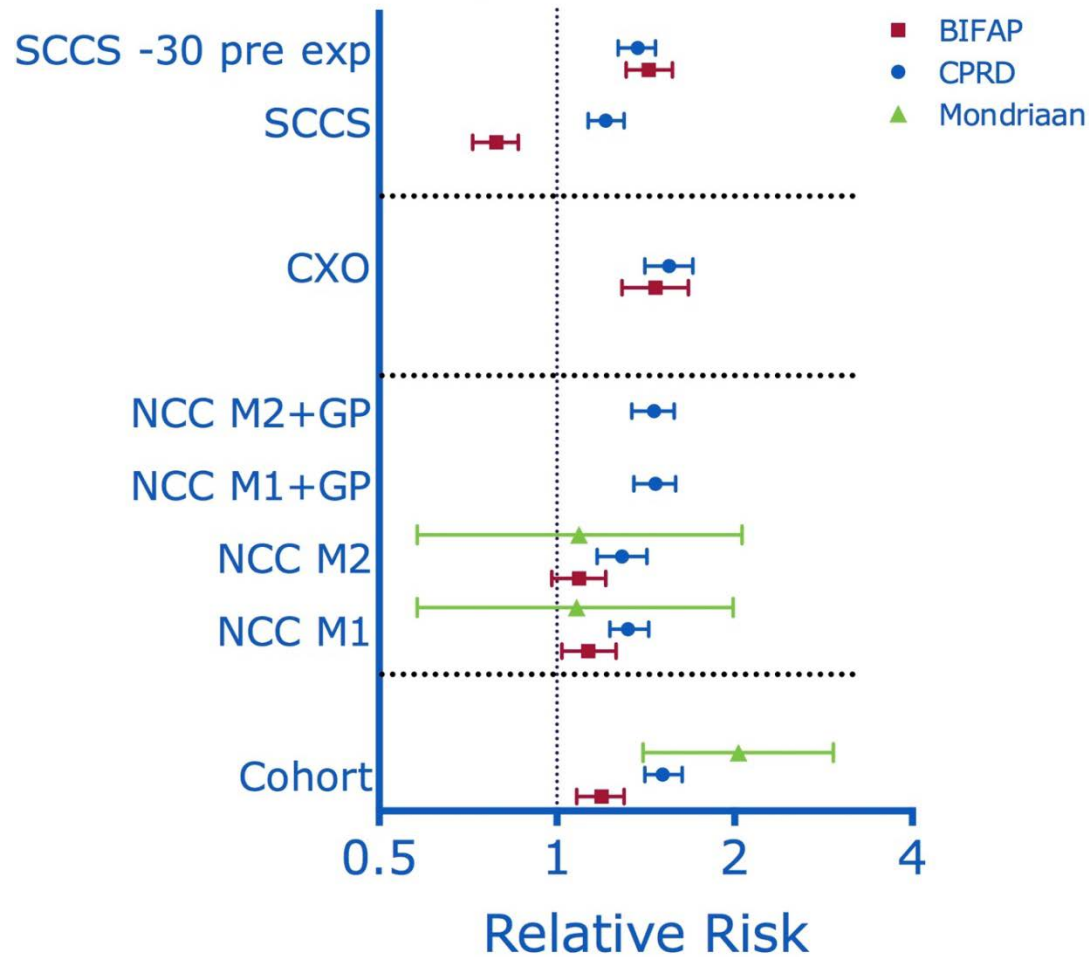


Table 1. Baseline demographics and characteristics of patients initiating prescription of anxiolytic or hypnotic medication

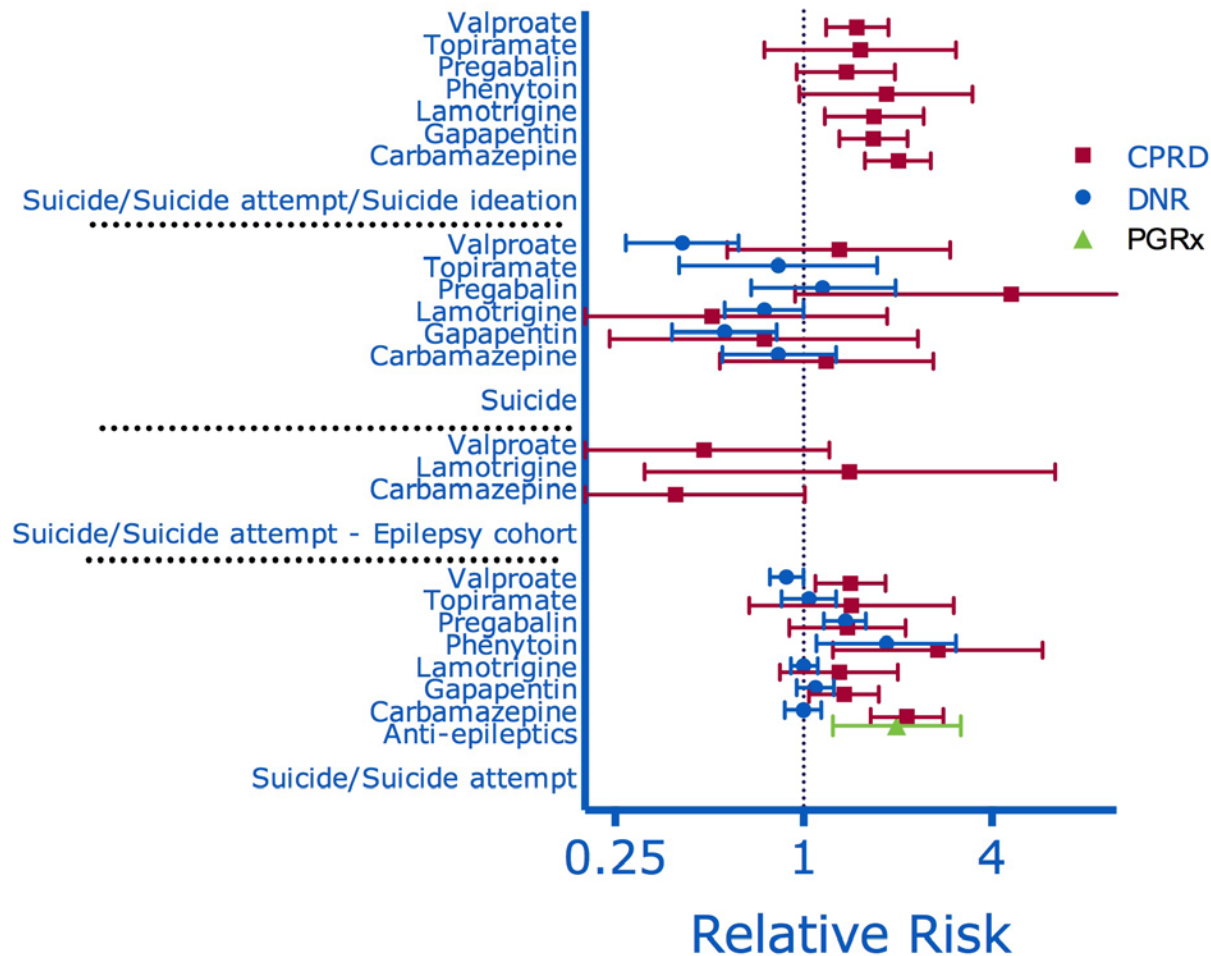
	BIFAP	CPRD	MONDRIAAN
	<i>N</i> = 558 599	<i>N</i> = 663 894	<i>N</i> = 50 464
Duration of follow-up (after start date) years	1 695 045	2 430 138	146 455
Age, year Mean (SD)	<i>n</i> (%) 55.14 (18.7)		
18–29	75 264 (13.5)	Unknown	98 652 (14.9)
30–39	105 270 (18.8)	BMI (kg/m <sup>2</sup> )	
40–49	107 332 (19.2)	<18.5	3838 (0.7)
50–59	98 620 (17.7)	18.5–24.9	14 816 (2.2)
60–69	71 976 (12.9)	25–30	69 796 (12.5)
70–79	62 765 (11.2)	>30	228 910 (34.5)
80+	37 372 (6.7)	Unknown	180 089 (27.1)
Sex		Co-morbidity	115 113 (17.3)
Male	192 519 (34.5)	Previous fractures	124 966 (19.8)
Female	366 080 (65.5)	Rheumatoid arthritis	
Smoking		Osteoporosis	2212 (4.4)
Yes	84 224 (15.1)	Paget's disease	2886 (0.5)
No	173 543 (31.1)	Anemia	10 363 (1.6)
Past	8240 (1.5)	Epilepsies/seizures	16 710 (2.5)
Unknown	292 592 (52.4)		432 (0.1)
Alcohol use			34 196 (6.1)
Yes			5013 (0.9)
No			20 553 (3.1)
			493 (1.0)
		133 628 (20.1)	

(Continues)

# Benzodiazepines and risk of Hip Fracture



# Antiepileptics and suicide



# Challenges/lessons learned

- **Substantial time** (+/-1 year) reach agreement on common protocol
  - Consensus/buy-in on approach between stakeholders!
- Research question determined **choice of database and design** of data collection
- **Detailed data-specification** documents are needed to harmonize procedures and analyses
- **Frequent communication** between research centres to reduce variation in “interpretation” of protocol
- During programming and analysis phase **further clarification** is required and needs documentation



# Methodological determinants of drug-AE associations

- Databases
- Study design
- Outcome definition
- Exposure definition
- Methods to control for confounding



# Recommendations

- Develop common protocol with great detail to reduce methodological differences and “interpretation” by researchers
- Solid infrastructure for communication/collaboration
- Conduct analysis in parallel in multiple DBs versus “a priori” pooling of DBs
  - Cherish heterogeneity and explore its sources



# Recommendations

- To test robustness of findings conduct multiple sensitivity analyses:
  - Multiple designs (e.g. Cohort/case-control vs case-only)
  - Exposure (e.g. Individual AEDs), outcome (e.g SUI), confounding adjustment
- Replication needed if parallel analysis consistent?



# What's next ?

- Network for observational safety and effectiveness studies
  - Common protocol in multiple databases may increase confidence in investigations
  - Testing of existing network
    - New safety signals
    - Platform for methods development and testing
  - Further development of network infrastructure
    - Library of codes/programs
    - Governance of network
    - Structure for collaboration/communication
    - **Collaboration with other networks**





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