PROTECT

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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PROTECT: Work Package 6

PROTECT: An Innovative Public-Private Partnership for New Methodologies in Pharmacovigilance and Pharmacoepidemiology

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WP6 Participants of WP2 replicability research plan

Institutions	*Names*
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Work Package 6 – Specific objectives

- To validate and test the transferability and feasibility of methods developed in PROTECT (WP2 to 5) to other data sources and population groups
- To determine the added value of using other data sources as a supplement or alternative to those generally used for drug safety studies, in order to investigate specific aspects or issues.

Started in September 2010 (Year 2)

WP2 Replicability research plan: Study Objectives, Rationale and Design

Research plan designed from defined study objectives applied to WP2 drug-event pairs

- Replication in same database
- Replication in different database
- Negative control study
- Use of alternative outcome definition
- Validation of outcome
- Assessment of confounders

Key principles

- Common protocol applied for each drug pair event
- Blinding procedure

WP2 Replicability research plan: Study Objectives, Rationale and Design

Defined Study Objective	Scientific Question	DB identification	Study design
Objective 1 **Replication study in same database**	Is the study replicable when conducted independently in the same database?	• CPRD • Danish Psychiatric, Somatic Hospital Discharge & Mortality Registers (DMR)	Cohort study
Objective 2 **Replication study in different database**	Do the results have external validity?	• LabRx/Premier • MarketScan and Medicare • E3N • PGRx • UPOD	• Nested case control • Population case control • Cohort • Descriptive study

WP2 Replicability research plan: Study Objectives, Rationale and Design

Defined Study Objective	Scientific Question	DB identification	Study design
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?	• LabRx/Premier • PGRx	• Nested case control (AMI) • Population case control
Objective 4 **Use of alternative outcome definition**	What is the impact of different levels of certainty of the outcome (e.g. definite, probable, possible) on the effect estimate?	• GPRD • PGRx • DMR	• Population case control

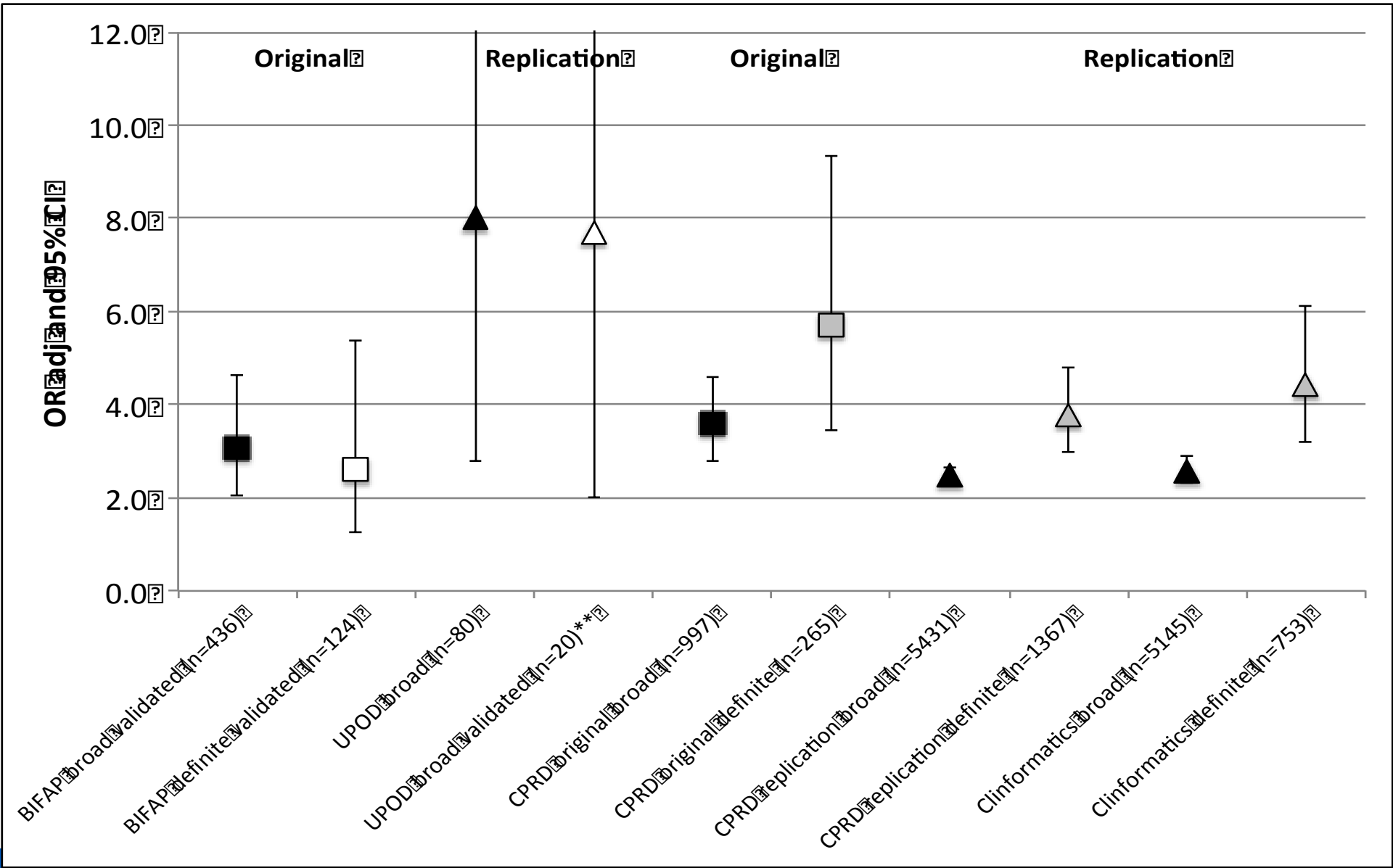
WP2 Replicability research plan: Study Objectives, Rationale and Design

Defined Study Objective	Scientific Question	DB identification	Study design
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?	• GPRD • LabRx/Premier • UPOD • DMR • CPRD	• Population case control • Nested case control • Cohort study
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?	• UPOD • PGRx • DMR	• Descriptive study • Population case control • Cohort study

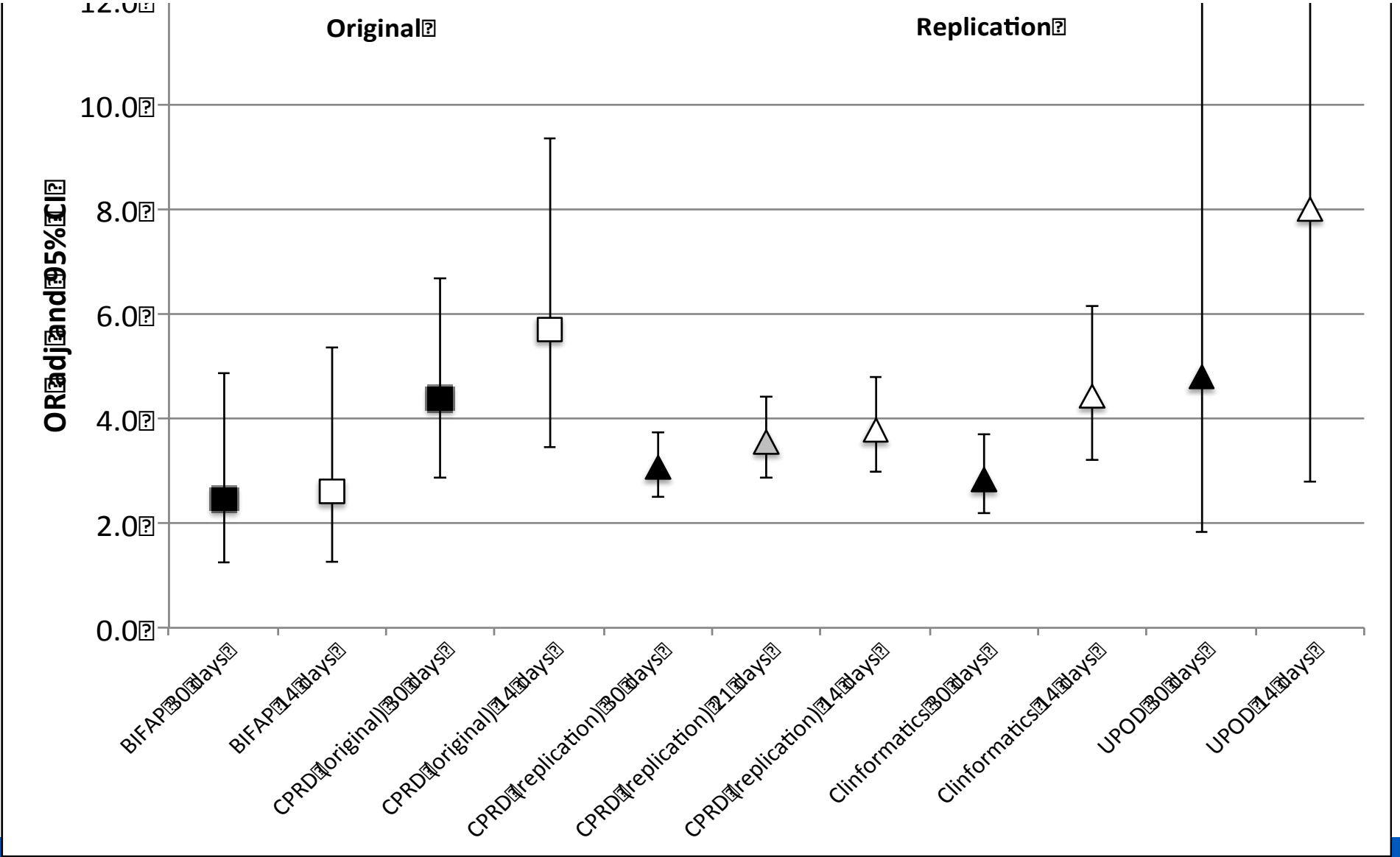
Antibiotics and acute liver injury (ALI)

- Used for replication in the same database, assessment of alternate definition (CPRD)
- Used for replication in another database (Clinformatics)
- Used for validation of outcomes: UPOD
  - UPOD (WP6) and BIFAP (WP2) used validated cases (definite validated cases in BIFAP and broad validated cases in UPOD)

Adjusted odds ratios of ALI associated with current antibiotic use across databases according to case definitions.



Adjusted odds ratios of definite cases** of ALI associated with antibiotic use across databases and different definitions of time window at risk



Beta2 agonists and myocardial infarction

- Used as replication in another database
  - PGRx
  - Clinformatics

Results: Beta2 agonists & AMI

Drug-event pair	Database	Design	Status	Who?
Beta2 agonists & AMI	PGRx	Case-control	Completed	LASER
	LabRx	Cohort	Completed	Sanofi

Exposure to Beta2 agonists		
PGRx	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
2 months before index date		
Exposure in this time window	1.23 (0.95 - 1.58)	1.19 (0.75 – 1.89)
12 months before index date		
Exposure in this time window	1.14 (0.91 - 1.44)	1.01 (0.66 – 1.55)

LabRx		
Cohort 325,377	**Crude HR**	**Adjusted HR**
Current users of LABA	1.09 (0.93-1.29)	0.93 (0.79-1.10)
Recent (90 days)	1.30 (1.10-1.53)	1.26 (1.04-1.21)

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Antibiotics and acute myocardial infarction (AMI)

- Used as an exercice around negative control using case-control design
  - PGRx
  - Clinformatics

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Results: Antibiotics and AMI (negative control)

Drug-event pair	Database	Design	Status	Who?
Antibiotics and AMI	LabRx	Case-control	Completed	Sanofi
	PGRx	Case-control	Completed	LASER

Exposure to antibiotics	Crude OR (95% CI)	Adjusted OR (95% CI)
PGRx		
2 months before index date		
Exposure in this time window	1.22 (0.98 - 1.51)	1.24 (0.99 - 1.56)
12 months before index date		
Exposure in this time window	1.07 (0.94 – 1.22)	1.06 (0.92 – 1.24)
LabRx		
2 months before index date		
Exposure in this time window	1.45 (1.40-1.50)	1.35 (1.30-1.39)
12 months before index date		
Exposure in this time window	1.25 (1.23-1.28)	1.13 (1.11-1.16)

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Antiepileptics and suicidality

- Used as replication in the same database and validation of outcome (Danish register)
- Used as replication in another database, use of alternate definition (PGRx)

Results: Antiepileptic & Suicidality

Drug-event pair	Database	Design	Status	Who?
Antiepileptic & Suicidality	Danish register	Cohort	Completed	AU
	PGRx	Case-control	Completed	LASER

Exposure to antiepileptic drugs		
PGRx	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
2 months before index date		
Exposure in this time window	3.10 (2.05 - 4.69)	1.98 (1.24 - 3.18)
12 months before index date		
Exposure in this time window	3.08 (2.12 - 4.49)	1.85 (1.21 - 2.85)
Danish Registry (Carbamazepine)	**Crude HRR**	**Standard covariate adjustment**
Cohort study (N=43,035)	**(IR current/IR past)**	**HRR (95% CI)**
Current use	2.14	0.99 (0.87-1.13)
CPRD (Carbamazepine) (N=46,364)		
Current use	2.17	2.16 (1.65-2.83)

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Results: Comparison of cases and controls by exposure to antiepileptic drugs according to current depression episode

	Patients with current major depressive episode			Patients without current depression		
	Cases (n=298)	Controls (n=249)		Cases (n=163)	Controls (n=2202)	
	n (%)	n (%)	**Adj OR [95%CI]**	n (%)	n (%)	**Adj OR [95%CI]**
2-month time window						
Use of any AED (vs. none)	31 (10.4)	14 (6.3)	**2.2 [1.1 - 4.3]**	8 (4.9)	64 (2.6)	**1.4 [0.6 - 3.1]**
12-month time window						
Use of any AED (vs. none)	41 (13.8)	19 (8.1)	**2.2 [1.2 - 4.0]**	10 (6.1)	79 (3.3)	**1.3 [0.6 - 2.8]**

Among those with depression, cases were more than twice as likely to be exposed to any AEDs than controls, whereas no difference observed in those without depression

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Results: Comparison of cases and controls by exposure to antiepileptic drugs according to the presence of a neurologic condition*

	Patients with a neurologic condition*			Patients without any neurologic condition*		
	Cases (n=89)	Controls (n=201)		Cases (n=417)	Controls (n=2628)	
	n (%)	n (%)	**Adj OR [95%CI]**	n (%)	n (%)	**Adj OR [95%CI]**
2-month time window						
Use of any AED (*vs.* none)	15 (16.9)	38 (18.1)	**1.2 [0.5 – 2.5]**	29 (7.0)	53 (1.8)	**3.1 [1.8 - 5.3]**
12-month time window						
Use of any AED (*vs.* none)	17 (19.1)	39 (18.2)	**1.3 [0.6 - 2.8]**	39 (9.4)	74 (2.6)	**3.0 [1.9 - 4.8]**
12-month time window						
Use of any AED (except clonazepam only) (vs. none)	-	-	-	8 (1.9)	42 (1.6)	**1.0 [0.4 – 2.3]**

*Epilepsy, migraine, chronic neuropathic pain

WP2 Replicability research plan: Conclusions

Defined Study Objective	Conclusion
Objective 1 **Replication study in same database**	Case control analysis of ATB & ALI, replicated in the CPRD • same point estimates, different CI due to fewer cases retained • The study is replicable when conducted independently in the same database
Objective 2 **Replication study in different database**	2 drug-event pairs: ATB & ALI and β2agonists & AMI • Replication in different databases with different methods (using the same protocol for each method) • Point estimates very consistent with each other • Results have an external validity

WP2 Replicability research plan: Conclusions

Defined Study Objective	Conclusion
Objective 3 **Negative control study**	Case control analysis of ATB & AMI • Similar trend towards an increased risk of AMI in recent antibiotic users (one significant and the other NS): **true negative?** • Interpretation with caution
Objective 4 **Use of alternative outcome definition**	• Misclassification / case definition • In the case of ATB&ALI: point estimate increased with more precise definitions for non validated cases

WP2 Replicability research plan: Conclusions

Defined Study Objective	Conclusion
Objective 5 **Validation of outcome**	- Few cases left after validation - Analysis not possible
Objective 6 **Assessment of confounders**	-Antiepileptic drugs and SA: taking into account confounding by indication showed large differences in results - Otherwise generally minimal effect.