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## Background

In the EU-funded project "Safety evaluation of adverse drug reactions in diabetes" (SAFEGUARD) a multi-database observational study with information of several healthcare databases (DBs) from Europe and the USA will be conducted under a common protocol to evaluate selected safety outcomes in users of non-insulin glucose lowering medications. An important step prior to this study is the harmonization of the definitions and algorithms to extract outcome events between DBs.

## Objectives

To describe the harmonization process for outcome events across DBs involved in the SAFEGUARD project.

## Methods

- Eight population-based cohorts were extracted without any exclusion criteria from eight European DBs. One additional cohort was extracted among subjects aged 65 years and older from a US DB. (**Table 1**)

Table 1: Characteristics of the DBs involved in the SAFEGUARD project

Database	Country	DB Type	Coding system	Study period	Total pop. (millions)
BIFAP	Spain	GP	ICPC + FT	2001-2009	3.2
CPRD	United Kingdom	GP	Read code	2000-2011	8
IPCI	Netherlands	GP	ICPC+ FT	2000-2012	1.1
HSD	Italy	GP	ICD-9 CM + FT	2000-2010	1.4
PHARMO	Netherlands	RL	ICD-9 CM	1998-2010	4
MEDICARE	USA	Admin	ICD-9 CM	2005-2008	4
PUGLIA	Italy	Admin	ICD-9 CM	2002-2009	5
LOMBARDY	Italy	Admin	ICD-9 CM	2000-2010	9
GePaRD	Germany	Admin	ICD-10 GM	2004-2009	17

Admin – administrative, CM – clinical modification, DB – database, FT – free text, GM – German modification, GP – general practitioner, ICD – International Classification of Diseases, ICPC – International Classification of Primary Care, RL – record linkage

- Clinical and DB-specific operational definitions of outcome events were created.
- Based on these definitions, data was extracted and processed locally from each DB using standardized software (Jerboa) to obtain event coding rates (ECRs) (stratified by age and sex) and the distribution of observed outcome event codes in each DB.
- The aggregated data from each DB was uploaded to a central remote research environment (RRE) at the Erasmus University Medical Center in Rotterdam for a combined analysis.
- ECRs were described across DBs and compared to relevant published information from each country. The distribution of outcome event codes was compared between DBs using the same coding dictionary.

## Results

- From an overall source population of almost 42 million subjects, we studied ECRs and the distribution of codes for ischemic and hemorrhagic stroke, bladder and pancreatic cancer, acute myocardial infarction, heart failure, acute pancreatitis and total mortality within approximately 240,000,000 person years over all DBs.
- Overall, the age and sex specific ECRs and the distribution of codes seemed consistent for most DBs and outcomes.

- However, discrepancies for some outcomes were observed between DBs, coding systems and countries. **Figure 1** provides the sex and age specific ECRs for ischemic stroke for each DB as an example.

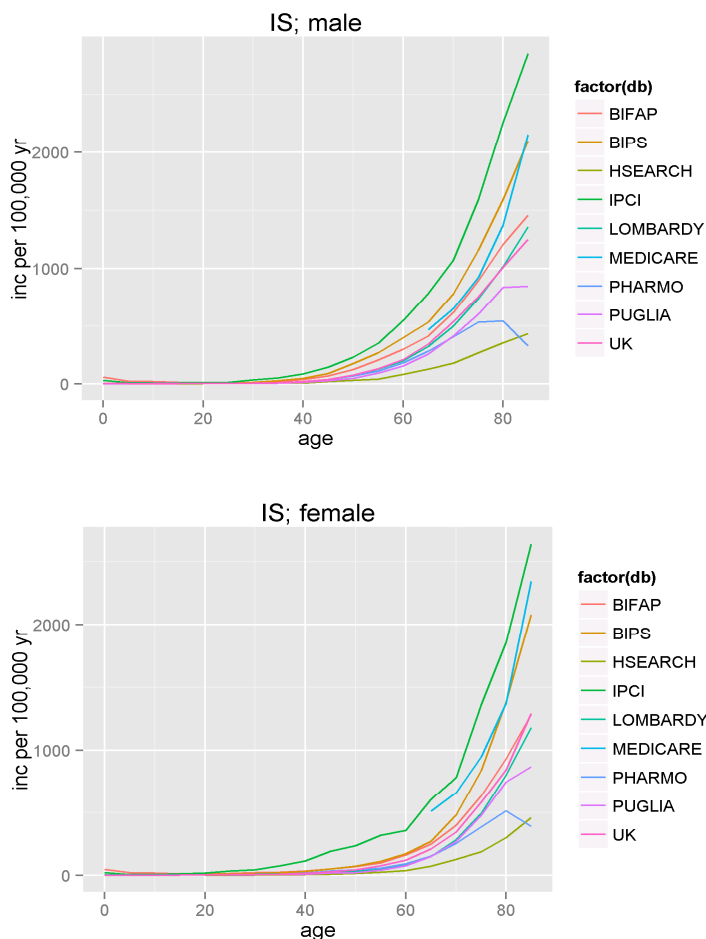


Figure 1: Event coding rates of ischemic stroke (IS) diagnoses stratified by age and sex

- All estimates were recalculated three times. If necessary, modifications of preliminary proposed codes and free-text algorithms were applied in order to obtain final operational definitions.

## Conclusions

- Benchmarking of definitions and algorithms to extract outcome events is crucial to detect inconsistencies between DBs and to reduce heterogeneity of outcomes in multi-database studies in drug safety and healthcare research.
- Observed differences of the ECRs and the distribution of codes across DBs might be explained by diverging characteristics of source populations (e.g. different background incidences of outcome events), different coding practices and different types of DBs (electronic medical record DBs, record-linkage systems and administrative DBs).
- Further validation efforts will be applied to verify the accuracy of algorithms used to identify outcome events.

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