Draft concept paper: Models for multi-database pharmacoepidemiologic studies

On behalf of WG3 members,
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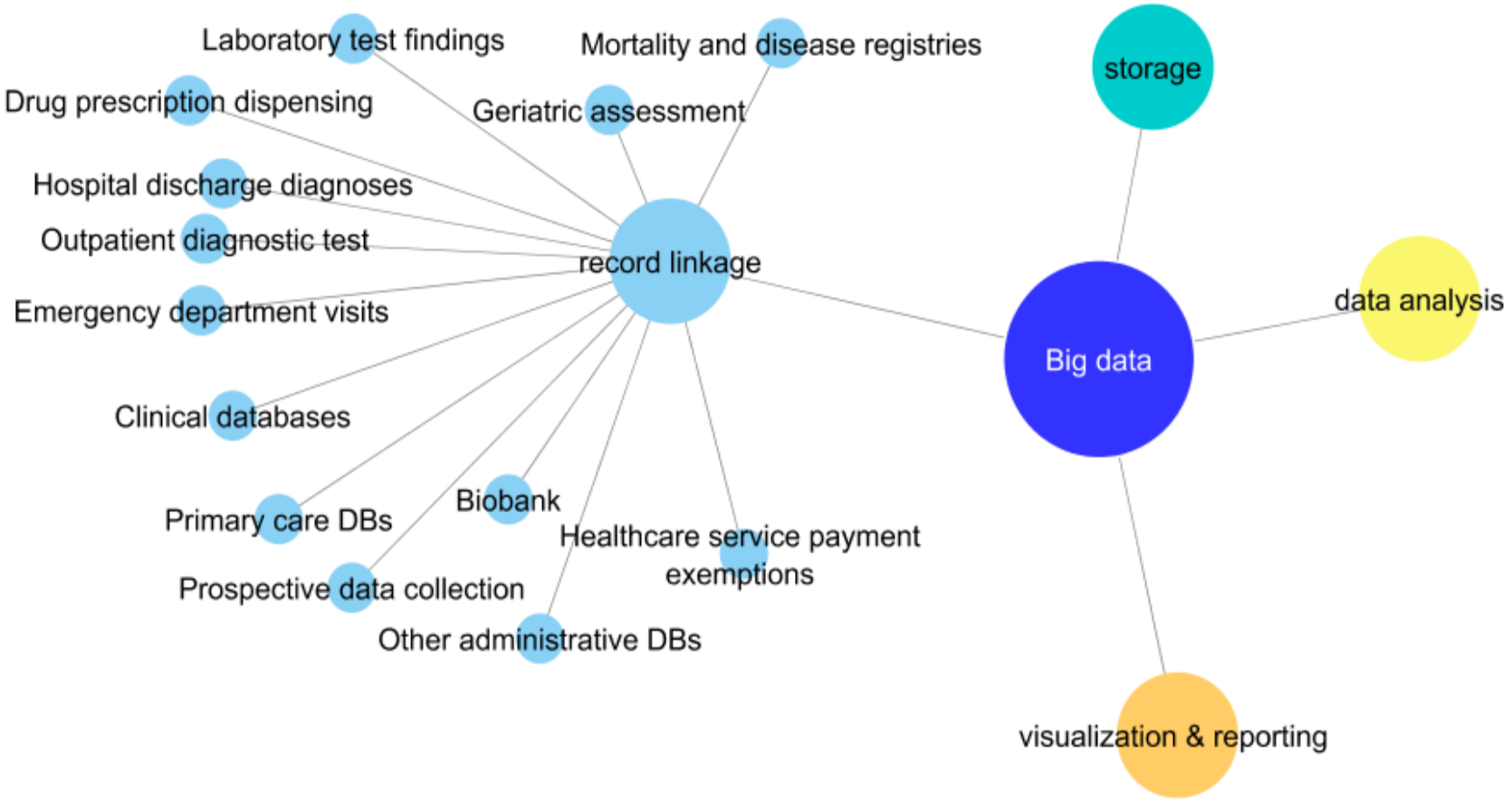
Reactivation of WG3 - Inventory of EU data sources and methodological approaches for multisource studies

IT	University of Messina
IT	Agenzia Reginale di Sanità della Toscana
IT	University of Eastern Piedmont
IT	UNIBO
IT	MediNeos Observational Research
IT	TEDDY Network (Fondazione per la Ricerca Farmacologica Gianni Benzi)
IT	"Vanvitelli" Campania University
NL	Erasmus MC
NL	UMC Utrecht
ES	BIFAP
ES	EpiChron - Instituto Aragonés de Ciencias de la Salud (IACS)
FI	EPID Research
UK	Queen Mary University of London
UK	Evidera
UK	UCL School of Pharmacy
DE	BIPS GmbH (Leibniz Inst. for Prevention Research and Epidem)
GR	University of Thrace
PT	Centre for Health Evaluation & Research (CEFAR)
FR	IMS Health
FR	University of Lyon

Agenda

- Why revitalizing WG3?
- Outline and aim of the concept paper on multi-database studies
- Work in progress:
  - Information retrieval about multi-DB studies
  - Definitions of dimensions to be evaluated for each specific model
  - Identification of research scenarios
  - Next steps

The landscape of healthcare databases



Trifirò G, Sultana S, Bate A. From big data to smart data for pharmacovigilance: the role of healthcare databases and other emerging sources. Drug Saf. 2017 Aug 24. [Epub ahead of print]

Examples of large consortia of multi-DB pharmacoepi studies

US

- VSD
- Sentinel
- OHDSI- Observational Health Data Sciences and Informatics (formerly OMOP)

Canada

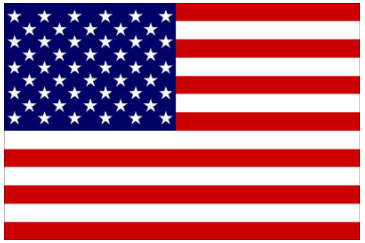
- CNODES

EU

- EU-ADR: www.euadr-project.org
- ARITMO: www.aritmo-project.org
- SAFEGUARD www.safeguard-diabetes.org
- PROTECT: www.imi-protect.eu
- ADVANCE: www.advance-vaccines.eu
- EMIF: www.imi.europa.eu/content/emif

Global

- GRIP: www.grip-network.org



Different models adopted for multi-database studies - 1

A) Local data extraction and analysis, common protocol

B) Local data extraction and central analysis on patient-level raw data

C) Study-specific local data extraction in a common data model and central analysis

D) General local data extraction in a common data model and central analysis

Different models adopted for multi-database studies - 2

A) Local data extraction and analysis, common protocol

- ✓ Data are extracted and analysed locally on the basis of a common protocol;
- ✓ Definitions of exposure, outcomes and covariates, analytical programs and reporting formats are standardised according to a common protocol;
- ✓ the results of each analysis are shared in an aggregated format and may be pooled together through meta-analysis (e.g. the PROTECT project).

Different models adopted for multi-database studies - 3

B) Local data extraction and central analysis on patient-level raw data

Central analysis of fully anonymized or pseudonymized patient-level raw data extracted based on a common extraction protocol;

This is only possible with a high level of trust among partners, and when data have a very similar structure in the first place, usually being from the same country or very similar countries (e.g the Scadinavian databases or Italian multi- DB studies).

Different models adopted for multi-database studies - 4

C) Study-specific local data extraction in a common data model and central analysis

- ✓ Data are extracted from local databases using a study-specific, database-tailored extraction protocol into a common data model and (pre-)processed locally with a common analytic program;
- ✓ The output of the common analytic program is shared among partners (e.g. EU-ADR project, ARITMO; Safeguards).

Different models adopted for multi-database studies - 5

D) General local data extraction in a common data model and central analysis

- ✓ Full set of raw local data is mapped to a common data model;
- ✓ For each study, data are (pre-)processed locally with a common analytic program (e.g. Sentinel initiative; Observational Health Data Sciences and Informatics (OHDSI) community).

Sentinel Common Data Model (CDM)

Administrative

Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Person ID	**Person ID**	**Person ID**	**Person ID**	**Person ID**	**Person ID**
Enrollment start & end dates	Birth date	Dispensing date	Service date(s)	Service date(s)	Service date(s)
Drug coverage	Sex	National drug code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical coverage	ZIP code	Days supply	Encounter type & provider	Encounter type & provider	Encounter type & provider
Medical record availability	Etc.	Amount dispensed	Facility	Diagnosis code & type	Procedure code & type
			Etc.	Principal discharge diagnosis	Etc.

Clinical

Lab Result	Vital Signs
Person ID	**Person ID**
Result and specimen collection dates	Measurement date and time
Test type, immediacy & location	Height and weight
Logical Observation Identifiers Names and Codes (LOINC ®)	Diastolic & systolic BP
Test result & unit	Tobacco use & type
Etc.	Etc.

Registry

Death	Cause of Death	State Vaccine
Person ID	**Person ID**	**Person ID**
Death date	Cause of death	Vaccination date
Source	Source	Admission Type
Confidence	Confidence	Vaccine code & type
Etc.	Etc.	Provider
		Etc.

Different models adopted for multi-database studies - 6

Model	Responsibility for data management	Responsibility for data analysis	Output to be shared with partners
A	Local	Local	Final estimates
B	Central	Central	Raw data
C	Local, study-specific	Central	Analytic dataset or aggregated intermediate dataset or final estimates (according to agreement among partners)
D	Local once every data update, then central	Central	Analytic dataset or aggregated intermediate dataset or final estimates (according to agreement among partners)

Concept paper outline

Aims

- Collect **relevant examples of multi-DB initiatives;**
- Identify relevant **dimensions** to evaluate **feasibility, performance and scientific soundness** of different multi-DB network models;
- **Compare** the **four models** with respect to the dimensions identified;
- Create a **decision model /framework** that would allow researchers deciding which model is better for a particular type of **research scenario**.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

21 October 2014
EMA/651167/2014
ENCePP Secretariat

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) survey of methodologies for European Union publicly funded multi-database safety studies

Current practice in European Union multi-database pharmacoepidemiology research

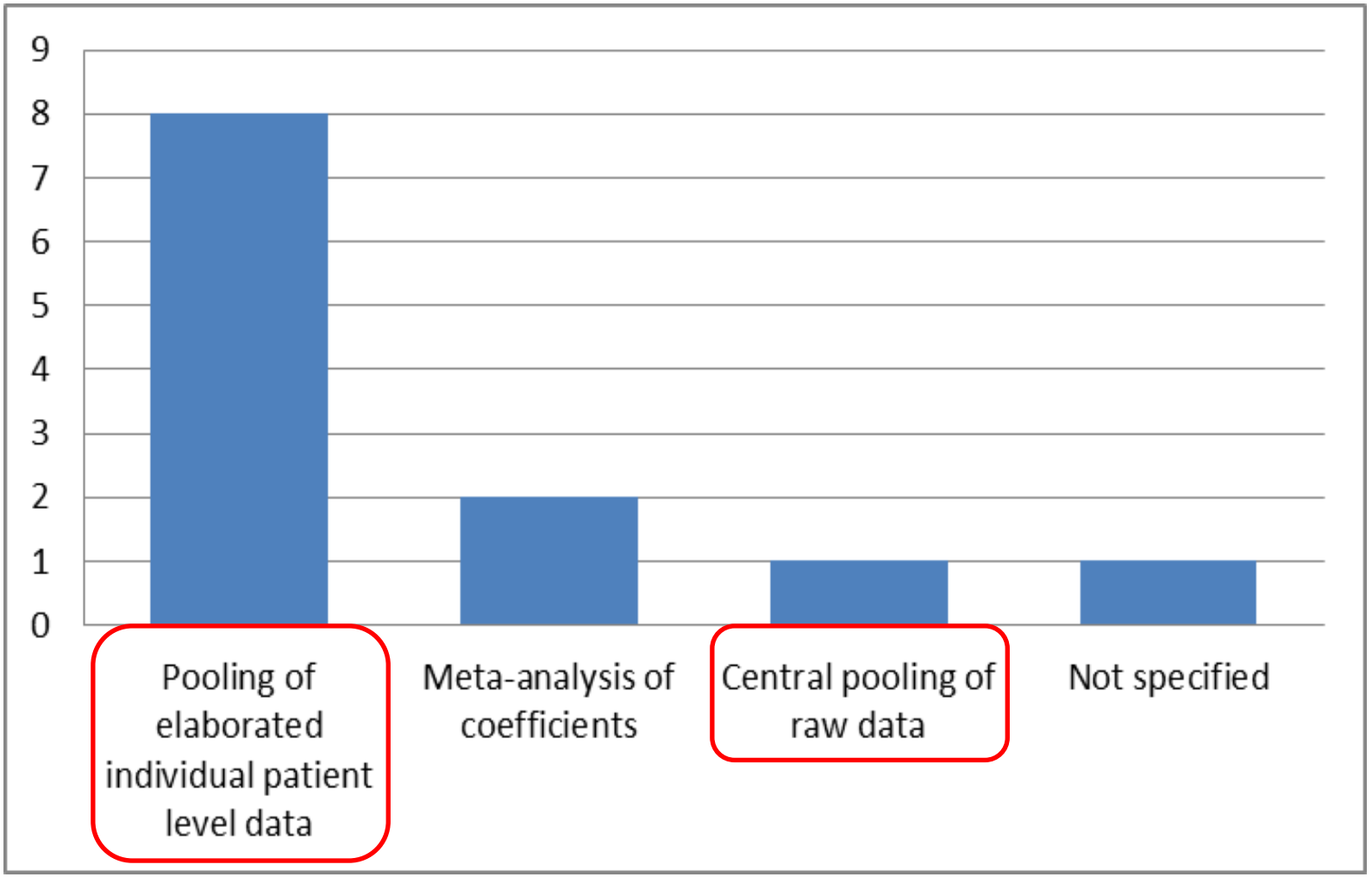
Coordinated by Miriam Sturkenboom on behalf of WG3

Key findings

- ✓ Survey of the research coordinators of consortia funded under FP7 - Health 2007 – 2013 and/or European Medicines Agency and/or IMI projects aimed at conducting multi-DB studies (N=16/18 projects);
- ✓ N. of databases used in individual projects ranged from 2 to 11 and 8 of the projects (44%) involved pooling data from different databases;
- ✓ Large heterogeneity of methods used to combine data from multiple databases; it has yet to be established if a single model is the best approach;

EncePP survey on EU-funded multiple database studies (n=16)

Pooling of data for analysis



ENCePP website

Key findings

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- ✓ N. of databases used in individual projects ranged from 2 to 11 and 8 of the projects (44%) involved pooling data from different databases;
- ✓ Large heterogeneity of methods used to combine data from multiple databases; it has yet to be established if a single model is the best approach;
- ✓ To contact again all coordinators with a structured questionnaire to inquire about: 1) Common data model; 2) Common analytics; 3) Governance; 4) Sustainability; 5) Publications; 6) Lessons learned.

Systematic review

1. Collected relevant papers from experts (SG and WG3 members) thorugh dropbox folder
2. Execute a Pubmed search using specific string
3. Assess sensitivity
4. If sensitivity <80%, search for new keywords and repeat from (2)

Expert opinion and available publications on multiDB studies

- Assess whether proposed models are **exhaustive** and accordingly **categorize** different initiatives into proposed models;

- Create a list of relevant **dimensions** to be evaluated: (a) flexibility; b) need for initial investments; c) velocity in executing many studies; d) sustainability; e) risks of errors/misunderstandings; f) legal constraints; g) ability in addressing diversity of local data; h) others);

- **Score** each **model** with respect to the **relevant dimensions** in relation to different **research scenarios.**

Research scenarios – 1

Why?

"Create a decision model /framework that would allow researchers deciding **which model is better for a particular type of research scenario** (e.g. periodic safety monitoring, drug utilisation studies, disease epidemiology studies, drug safety signal confirmation studies, …..)"

Research scenarios – 2

How?

- **For whom** research scenarios have to be relevant?
- Involvement of **regulatory agencies,** which one? (EMA - EU Member States; Health Canada; FDA; Asian and other Countries regulatory agencies)
- How much **comprehensive** and **specific** (e.g. drug utilisation studies vs. studies on exposure to teratogenic drugs in pregnancy) has to be the list of research scenarios?
- Stand alone publication!
- List of research scenarios has to be considered **dynamic** as priorities of post-marketing assessment evolve over time.

Research scenarios – 3

Planned actions

- **Survey of ENCePP partners** through electronic questionnaires (google form) which was pilot tested by WG3 members;

- Revise studies in the **EU PAS Register**;

- Interview of **regulatory agencies and coordinators of most relevant international multi-DB initiatives** to prioritize the list of proposed research scenarios potentially requiring multiple-DB studies.

Survey of ENCePP partners through electronic questionnaires - 1

Which type of regulatory decisions can profit from evidence generated by multi-database studies?

This survey is conducted in the context of ENCePP Working Group 3 "Inventory of EU data sources and methodological approaches for multi-source studies". The survey is aimed at identifying what are the research questions asked by regulators that can be addressed by conducting observational multi-database studies. More specifically, we are interested in getting a better understanding of the value of multi-database pharmacoepidemiology studies regarding different types of drug-related issues which requires further investigation in post-marketing setting.

Multi-database studies are studies which are carried out using at least two healthcare databases that cannot be linked with each other at individual level.

Please answer the following questions based on your personal experience.

Survey of ENCePP partners through electronic questionnaires - 2

1. Do you currently work mainly in

- ○ Academia
- ○ Contract Research Organization
- ○ Public research agency
- ○ Altro: _____

2. Are you currently participating, or have you participated in the past two years, in a committee which advises or takes regulatory decisions?

- ○ Yes
- ○ No

3. Have you ever been been involved in multi-database pharmacoepidemiology studies?

- ○ Yes
- ○ No

Survey of ENCePP partners through electronic questionnaires - 3

- Irrespective of your involvement in such studies, what type of research questions do you think can profit from the evidence generated by multi-database studies?

Drug Utilization studies

Effectiveness assessment

Risk assessment

Disease epidemiology

Survey of ENCePP partners through electronic questionnaires - 4

- **Drug Utilization studies**
  - Implementation of risk minimization measures
  - Underdosage or overdosage
  - Adherence and persistence to chronic treatments
  - Use of contraindicated drugs in special populations (patients with renal or hepatic impairment, pregnancy or breastfeeding)
  - Off label use of drugs
  - Uptake of generics and biosimilars
  - Appropriate use of high cost drugs
  - Appropriate use of orphan drugs
  - Vaccination coverage

Survey of ENCePP partners through electronic questionnaires - 5

- **Effectiveness assessment**
  - Periodic effectiveness monitoring
  - Effectiveness evaluation in special populations (e.g. children, pregnant women, immunocompromised)
  - Long term effectiveness
  - Comparative effectiveness of drugs with same indication
  - Comparative effectiveness of generics/biosimilars vs. originators
  - Effectiveness of orphan drugs
  - Vaccine effectiveness

Survey of ENCePP partners through electronic questionnaires - 6

- **Risk assessment**
  - Periodic safety monitoring
  - Signal detection
  - Signal strengthening
  - Signal confirmation
  - Safety evaluation in special populations (e.g. children, pregnant women, immunocompromised
  - Long-term safety
  - Rare adverse drug reactions
  - Effects of risks minimization measures
  - Adverse drug reactions due to drug-drug interactions
  - Comparative safety of drugs with same indication
  - Comparative safety of generics/biosimilars vs. originators
  - Safety of orphan drugs
  - Vaccine safety

Survey of ENCePP partners through electronic questionnaires - 7

Overall, can you score (from 1= “no or limited value” to 5= “greatest value”) how much the results of multiple database pharmacoepidemiology studies can drive regulatory decisions?

EU PAS Register - 1

EU PAS Register - 2

Population age:

- [ ] Preterm newborns
- [ ] Term newborns (0-27 days)
- [ ] Infants and toddlers (28 days - 23 months)
- [ ] Children (2 - 11 years)
- [ ] Adolescents (12 - 17 years)

Other population:

- [ ] Renal impaired
- [ ] Hepatic impaired
- [ ] Immunocompromised
- [ ] Pregnant women

Scope of the Study:

- [ ] Disease epidemiology
- [ ] Risk assessment
- [ ] Drug utilisation study
- [ ] Effectiveness evaluation
- [ ] Other

Next steps

- Extended survey of coordinator of EU-funded multi-DB studies
- Systematic review of key publications about multi-DB pharmacoepi studies
- Definition of dimensions to be evaluated
- ENCePP partner survey on reserach scenarios
- Analysis of studies available in EU PAS register
- Interview through semi-structured questionnaire to key regulators and international experts

Thanks for the attention

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