Update on activities of ENCePP WG3 "Inventory of EU data sources and methodological approaches for multisource studies"

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Achievements of WG3 in the years 2020-2023

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Different Strategies t
Studies for Medicine
Real-World Setting: A
European Model

Rona Gini[1]*, Miriam C. J. Sturkenboom[2], Ja
Alexandra Pacurariu[4], Giuseppe Roberto[1], Tani
Gianluca Trifirò[8] on behalf of the Working G
and methodological approaches for multisource

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ORIGINAL ARTICLE

Overview of the European
post-authorization studies
September 2010 to Decem

Drug Safety (2022) 45:333–344
https://doi.org/10.1007/s40264-022-01154-7

ORIGINAL RESEARCH ARTICLE

A Landscape Analysis of Post-Ma
PAS Register and ClinicalTrials.g
or Breastfeeding Effects: A Cont

List of suggestions/recommendations for EU-PAS Register improvement from ENCePP WG3

General comments:

1. To implement automatic quality checks as some data are not registered in accurate way and certain combinations of choices are not possible (e.g. scope of the study: disease epidemiology; type of study design: clinical trial - other example: study carried out with an established data source = No; sources of data = claims database); the use of natural language processing (NLP) to check discrepancies between what has been reported in the protocol and what have been recorded in the different fields.
2. To incorporate help text and the following guidance:
   - for those registering the study to facilitate accurate registration;
   - for data users;
   - on what fields have to be filled by the Principal Investigator.
   Such guidance may include a guided wizard, where, based on the answers given, some classifications are automatically generated. It could also be helpful to limit free-text fields by using drop down menus or other tools which limit options in data recording.
3. To make registration of the study protocol compulsory as the study protocol is currently available in less than 50% of the studies registered in the EUPAS register (suggestion: make PRAC assessment of a protocol conditional to having the study registered in the EU PAS). Since it is not legally possible to impose the registration of the study protocol, the only means would be to have a study registered only after the protocol is available and uploading of the protocol mandatory before registration is complete. Moreover, it could be helpful to create Policy/Procedure to automate data extraction from the study protocol.
4. To explore the possibility of linking the registration of the study to the PRAC minutes as well as ENCePP resource database or clinicaltrials.gov.
5. To compare date of already existing field on first registration of a regulatory required study (categories 1-2) and Marketing Authorisation (MA) date (initial MA, renewal, variation of MA), field that should be created, in order to monitor compliance with registration time frame required (within 6 months after MA according to GVP). More generally, a set of compliance checks (automated or semi-automated) should be defined.
6. To add new export functionalities to more easily extract data (.xls, .csv format etc…) including all fields available in the Register.
7. To implement metadata/API fields crosswalks for the EU PAS register like for clinicaltrial.gov (see https://clinicaltrials.gov/api/gui/ref/crosswalks).
8. A significant number of 'unknown' variables in EU PAS register form and they may not represent what was actually designed in study protocols.
9. Revise the list of mandatory fields – agreement has to be sought on what fields have to be mandatory.
10. Check whether there are MS or national competent authorities that have requirements for companies to register studies in catalogues and explore possibilities of link (reporting the ID of the study in the EU PAS Register?). A field could be included in the record to allow providing such links.
11. Implement changes to allow the search for studies targeting a certain type of product or safety concern. This will be very helpful for anyone wanting to know which studies addressed a particular similar safety question (e.g. what designs and data sources were used in studies addressing the safety concern "secondary malignancies"). For this it will be necessary to link with product information (that can be retrieved from EMA product information page) and the summary of the Risk Management Plan (available in the EPARs) where the safety concerns for each product and the studies planned/ongoing to address those can be located (see in the version with comments the findings of a recent study where all the RMPs of products approved in 2017 and 2018 were checked to identify the safety concerns at the initial RMP and the PASS targeting each safety concern).
12. If the above proposition of having all key information in the same source is not possible, then assign a unique ID to studies and use it consistently across all sources where the study is mentioned: Risk Management Plan (which is published in the EPAR), EU PAS, PRAC meeting minutes and EPARs including the "Procedural steps taken and scientific information after the authorisation" file - currently the only possible identifiers across sources are the protocol number and EMA procedure number but they are not available in all sources nor in all studies.
13. Create a "dictionary" with the definitions for each field and each option in the field used in EU PAS to ensure harmonized interpretation across stakeholders: currently, the same term is used by different stakeholders to describe different study aspects (e.g. "prospective" is used by some registrants to mean study direction and by others as a synonym of "primary data collection"). This problem was well acknowledged in the field of Pharmacoepidemiology as illustrated by the following quote from one of the main textbooks in the field: "The same term is sometimes used by different authors to describe different concepts. Unfortunately, when reading a scientific paper, there is no way of determining which usage the author intended" (Strom BL, Kimmel SE, Hennessy S, editors. Pharmacoepidemiology. 5th ed. West Sussex, United Kingdom: John Wiley & Sons, Ltd; 2012).
14. Review guidelines for consistency and accuracy of terms used (e.g. GVP Module VIII). Differentiate prospective/retrospective (epidemiological study design) from primary/secondary data collection (data source); clarify the use of the term registry (currently used as both a design or as data source by different stakeholders); clarify that drug utilization study is not a study design per se but a study scope - have these definitions available for the registrants to avoid ambiguity.
15. Harmonize terminology used in guidelines (e.g. GVP) and EU PAS Register. For example, in GVP Module VIII, "Drug Utilisation study" is defined as a study design. However "drug utilisation" is used as primary scope in EU PAS Register which is more adequate as it is related with the nature of the objectives rather than the nature of the design. It also links with the fact that one of the objectives that makes a study a PASS is ""To assess patterns of drug utilisation that add knowledge on the safety of the medicinal product". Once the "dictionary"/"glossary" with definitions of terminology is built for EU PAS Register, GVP Module VIII should be revised and can refer to the new "dictionary"/"glossary".
16. Have some fields to be entered by the Marketing Authorisation Holder of the institution conducting the research on their behalf and others entered by the EMA (e.g. regulatory outcome, protocol and report PRAC assessment outcome).

Accessibilità: verifica

Focus

Proposal for inclusion in the ENCePP Workplan 2023-2025 - WG3

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- Once it will go alive, further revision of the structure and functionalities of the EMA catalogues RWD sources and non-interventional studies (former ENCePP Resource Database and EU PAS Register)

- Analysis of the studies included in the non-interventional studies register with the final goal to explore better options for: a) the identification of key information for the conduct of observational studies exploring specific research questions; and b) the linkage with other relevant repositories (e.g., PRAC minutes)

- Comparison of EMA catalogues with other observational study register (e.g. clinicaltrials.gov) to explore consistency of information collected

- Liaison with ISOP Big Data and RWE SIG to better explore the role of distributed database networks in the context of signal management and especially of signal detection

ENCePP WG3 – Ongoing articles

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- Secondary use of data in observational studies and its relationship with economic development of the countries: a study based on the analysis of EU PAS Register

- Regulatory outcomes of Non-interventional Post Authorisation Safety Studies (PASS): a review of publicly available information

- Post-Authorisation Studies in Paediatric population: data from the EU-PAS registry

Secondary use of data in observational studies and its relationship with economic development of the countries: a study based on the analysis of EU PAS Register (1)

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Status: Submitted to Pharmacoepidemiology and Drug Safety on 11th October 2023

AIMS:

- To describe the extent of secondary use of data in observational studies registered in the EU PAS Register from November 2010 to December 2018, conducted in Europe, United States and Canada;
- To evaluate possible predictors of their use, such as economic factors and healthcare system performance at the country level.

Descriptive analysis of the observational studies based on secondary use of data

Studies based on secondary use of data, n	698
Data source - country, n (%)	
US & Canada	154 (22.1)
European country	317 (45.4)
From >1 European countries	185 (26.5)
From both US/Canada and European countries	42 (6.0)
Scope, n (%)	
Risk assessment	373 (53.4)
Drug utilization	268 (38.4)
Effectiveness evaluation	153 (21.9)
Disease epidemiology	118 (16.9)

Secondary use of data in observational studies and its relationship with economic development of the countries: a study based on the analysis of EU PAS Register (3)

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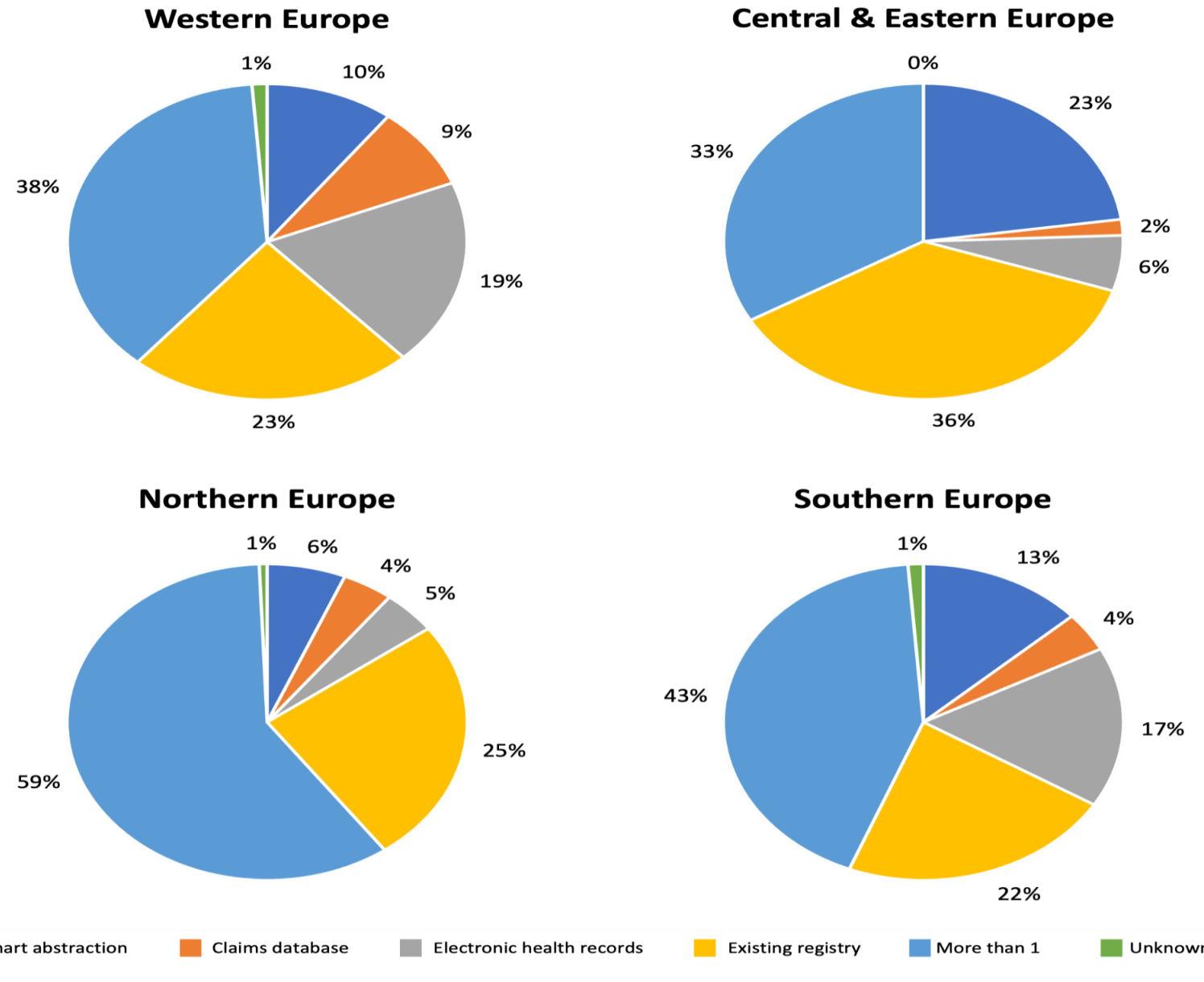
Type of secondary data used in studies conducted in Europe and included in the EU PAS register



Regulatory outcomes of studies requested by Regulators (1)

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Status: Currently drafting the manuscript

AIM: to describe the regulatory outcomes of completed PASS (multiple database studies vs non- multiple database studies) registered in the EU PAS Register and requested by the Regulators, by using publicly available information from the EMA website

Regulatory outcomes of studies requested by Regulators (2)

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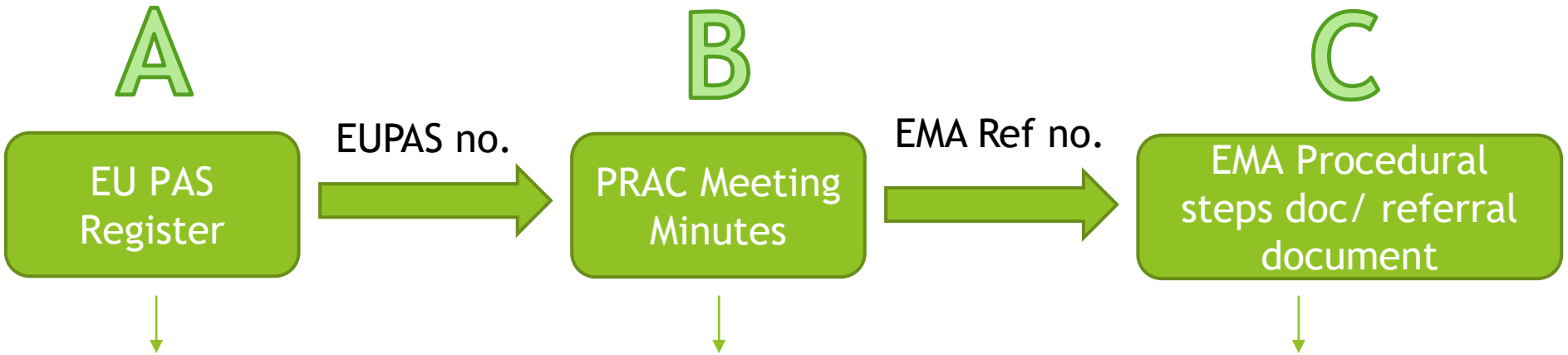
Data Collection Process



Retrieve identifiers and study characteristics:

- Study title
- Study type
- Objectives
- Protocol/Project number
- Study acronym
- EMA Procedure number
- Study drug

Using the identifiers from A) search the studies:

- Is there any PRAC review avaiable?
- Which study identifiers are used?

Using the identifiers from A) or B) search the studies:

- Has Regulatory Outcome available?
- Which study identifiers are used?
- What is the Regulatory Outcome?

Regulatory outcomes of studies requested by Regulators (3)

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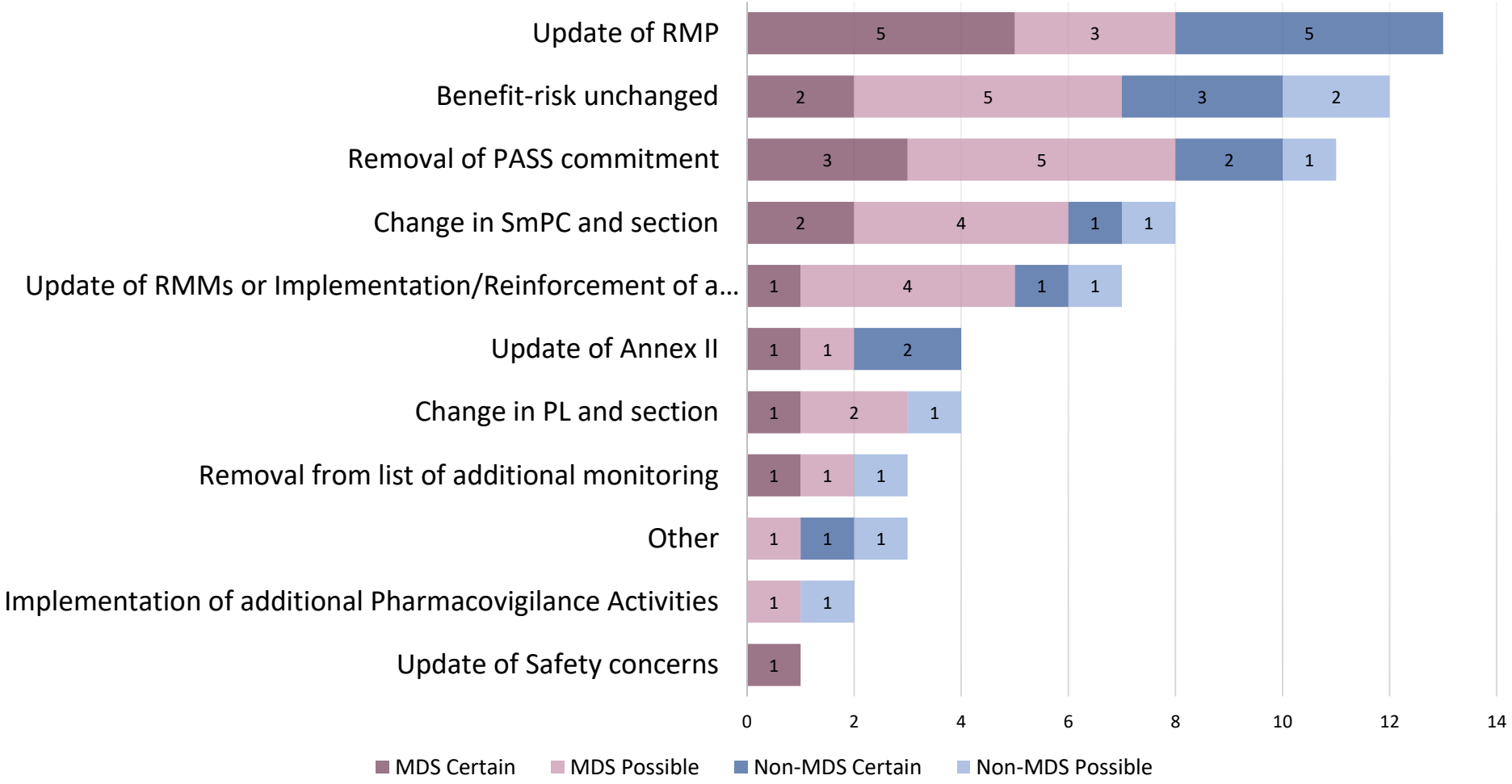
Regulatory outcomes of multidatabase and non-multi-database studies



Post-Authorisation Studies in Paediatric population: data from the EU-PAS registry

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1. Assess	**the possible impact of the recent regulatory initiatives in promoting the clinical research in this population**
2. Describe	**the epidemiological research framework in this population, considering the different class of ages and identifying the still uncovered therapeutic areas for each of them**
3. Evaluate	**the impact of the finalised PASS on the regulatory actions taken on the specific drug (in terms of marketing/SmPC changes)**

- ✓ Study promoted by pharmaceutical company, regulatory drug agency, academy
- ✓ Start of the study based on imposed condition of marketing authorization or on voluntary basis by the marketing holder

- ✓ Age-category according ICH
- ✓ Disease under study
- ✓ Study medicine

- ✓ Changes in the regulatory actions
- ✓ Evidence in paediatric population

A new data extraction has been carried out and analyses will be updated accordingly

Thank you and thanks to all the WG3 members!

Mandate of ENCePP Working Group 3

Inventory of EU data sources and methodological approaches for multi-source studies

Inventory of EU data sources and methodological approaches for multi-source studies	
Chair:	Gianluca Trifirò
• Promote the registration of data sources useful for pharmacoepidemiology and pharmacovigilance research in the already existing ENCePP Resources database and encourage regular update	
• Publish an overview of available EU databases relevant for pharmacovigilance and pharmacoepidemiology research	
• Perform an analysis of regulatory needs to evaluate the extent to which the existing data sources are able to meet them	
• Facilitate the initiation and conduct of observational research through the ENCePP network; develop guidance on conceptual models for multi-national and multi-database studies	
• Assess the impact of forthcoming clinical trials and data protection legislation on ENCePP activities and provide expert input during implementation	

The specific deliverables for the period 2017-2019 may be seen in the corresponding ENCePP Work Plan.