8th March 2021

Real World research on medicinal products: key contribution of the European Network of Centres in Pharmacoepidemiology and Pharmacovigilance (ENCePP)

The EU register of post-authorisation studies: why is it important to register studies and lessons learned?

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Disclosure of interest

- I have been part of advisory boards on topics not related to this presentation and organized by several pharmaceutical companies on topic not related to this presentation;

- As scientific leader of an academic pharmacoepi team I have been coordinating observational studies on medicines which have been funded by several pharmaceutical companies to University of Messina the and the spin-off INSPIRE (e.g. Amgen, Novartis, AstraZeneca, Daiichi Sankyo, IBSA);

- In the last 5 years I have been scientific coordinator of a Master program at UNIME, which received unconditional grant from several pharmaceutical companies.

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EU PAS Register

About EU PAS Register

The European Union electronic Register of Post-Authorisation Studies (EU PAS Register)

The EU PAS Register® is a publicly available register of **non-interventional post-authorisation studies (PAS)**.

The Register has a focus on observational research, and its purpose is to:

- increase transparency,
- reduce publication bias,
- promote the exchange of information and facilitate collaboration among stakeholders, including academia, sponsors and regulatory bodies,
- ensure compliance with EU pharmacovigilance legislation requirements.

EU pharmacovigilance legislation requires the European Medicines Agency (EMA) to make public the protocols and abstracts of results of **non-interventional post-authorisation safety studies (PASS) imposed as an obligation of marketing authorisation** by a competent authority in accordance with Article 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC. Annex III of the Commission Implementing Regulation (EU) No 520/2012 further specifies that the final report of imposed non-interventional PASS must provide the date of making it public (in EU PAS Register).

PASS initiated, managed or financed **voluntarily** by a marketing authorisation holder and which are required in a **Risk Management Plan (RMP)** to further investigate safety concerns or to evaluate the **effectiveness of risk minimisation activities**, and any other PASS should also be entered into the EU PAS Register to support the same level of transparency, scientific and quality standards. Further information about the requirements for the registration of PASS is available in the guideline on Good Pharmacovigilance Practices (GVP) module VIII.

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 884–893 884

DRUG SAFETY

Lessons learned on the design and the conduct review c

F1000Research F1000Research 2017, 6:1447 Last updated: 20 NOV 2017

Check for updates

RESEARCH ARTICLE

REVISED An analysis of characteristics of post-authorisation studies registere referees: 2 appro

Robert Carroll[1], Sreera
Laura McDonald[2]

Received: 14 November 2017 | Revised: 8 March 2018 | Accepted: 12 March 2018
DOI: 10.1002/pds.4434

REVIEW

WILEY

A review of studies evaluating the effectiveness of risk minimisation m electronic Regi

Pareen Vora[1] | Esth
Vineet Singh[4] | Alex A

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 476–491 476

REVIEW

Study design, process and outcome indicators of post-authorization studies aimed at evaluating the effectiveness of risk minimization measures in the EU PAS Register

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Stepwise approach from EU-PAS register data collection to analysis

Development of data collection form for transferring key information from EU PAS register into the analytical dataset

Distribution of studies across 14 centres for completion of data collection form with information from 1,426 studies from EU PAS register inception up to 31 December 2018

Quality check, re-evaluation and descriptive analysis of collected data

For key variables, independent validation of random sample of studies and inter-rater agreement analysis

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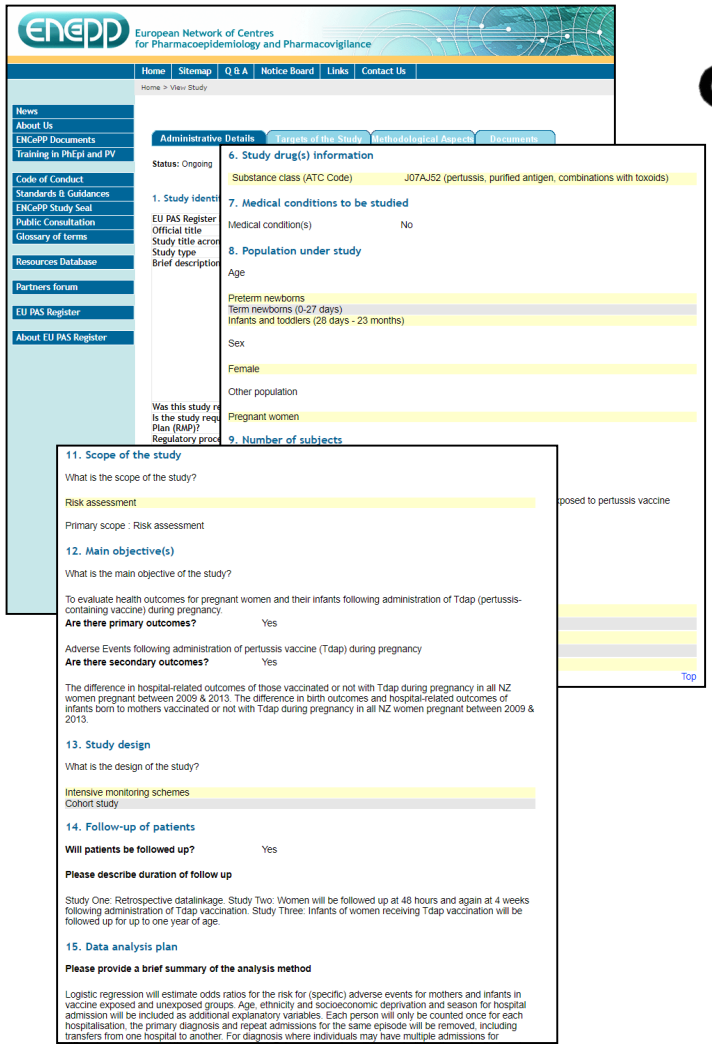


Title	Status_of_Study	Funding_source	Data_collection	Secondary_data	Multiple_database_study	Study_type_new_classification
Current raltegravir use: clinical practice in UK centres	ONGOING	Funded by pharmaceutical company	Mixed	More than 1	Yes	Observational study
Post-market clinical follow-up study – Retrospective evaluation o	FINALISED	Funded by pharmaceutical company	Secondary	EHR	Yes	Observational study
Validation of a US Health Care Claims Database for the Study of	FINALISED	Funded by pharmaceutical company	Secondary	More than 1	Yes	Observational study
Organization of Teratology Information Specialists (OTIS) Vedol	ONGOING	Funded by pharmaceutical company	Mixed	More than 1	Yes	Observational study
Forteo/Forsteo post-approval osteosarcoma surveillance study	FINALISED	Funded by pharmaceutical company	Secondary	More than 1	Yes	Observational Study
Outpatient care with long-acting bronchodilators:	ONGOING	Funded by pharmaceutical company	Mixed	Existing registry	Yes	Observational study
Non-interventional Cohort Study to Investigate Sertindole Prescri	FINALISED	Funded by pharmaceutical company	Secondary	Chart abstraction	Yes	Observational study
MULTICENTER PROSPECTIVE OBSERVATIONAL STUDY OI	FINALISED	Funded by pharmaceutical company	Primary	Not applicable	No	Clinical trial
CONTOUR Australia: Condition of Submental Fullness and Trea	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Observational study
An Observational Post-Authorisation Safety Specialist Cohort M	FINALISED	Funded by pharmaceutical company	Primary	Not applicable	No	Observational study
An observational multicenter study on antibiotic resistance of He	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Observational study
A Prospective, Observational Study of Individuals Who Serocon	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Observational study
Multi-centre study of the in vitro activity of ceftolozane/tazobactar	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Other
A Cross-sectional Survey of Patients and Caregivers (20150228)	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Survey
Post-marketing study of ropinirole prolonged release tablets in F	FINALISED	Funded by pharmaceutical company	Mixed	More than 1	Yes	Observational Study
Evaluation of the effectiveness of the abatacept (ORENCIA®) int	FINALISED	Funded by pharmaceutical company	Mixed	Chart abstraction	Yes	Observational Study
Mabthera Drug Utilisation Study and Patient Alert Card Evaluatic	FINALISED	Funded by pharmaceutical company	Mixed	Chart abstraction	No	Other
An observational, multi-center study to evaluate the safety of def	ONGOING	Funded by pharmaceutical company	Secondary	More than 1	Yes	Observational Study
EUROmediCAT: Safety of Medication Use in Pregnancy in Relat	ONGOING	More than one	Mixed	More than 1	Yes	Observational Study
Isotretinoin and the effectiveness of the pregnancy prevention pr	FINALISED	Funded by national/international drug agency	Mixed	More than 1	Yes	Observational study
Comparative effectiveness of insulines vs analogues to prevent	FINALISED	More than one	Secondary	More than 1	No	Other
A/H1N1 pandemic vaccines and pregnancy outcomes	FINALISED	Funded by national/international drug agency	Secondary	EHR	No	Other
Pertussis in Pregnancy Safety (PIPS) Study	ONGOING	More than one	Mixed	More than 1	Yes	Observational Study
Assessment of the safety of LABAs in asthma in routine care by	FINALISED	More than one	Mixed	More than 1	Yes	Observational Study
A prediction model for future exacerbation risk in children	PLANNED	Self-funded	Secondary	More than 1	Yes	Observational Study
205639 - Meta-analysis of the risk of autoimmune thyroiditis dise	FINALISED	Funded by pharmaceutical company	Mixed	Not applicable	No	Review or meta-analysis
ADVANCE POC I Risk pillar - Testing new approaches to monitc	FINALISED	Funded by public entities, excluding drug agencies	Secondary	More than 1	Yes	Observational study
ADVANCE POC I Benefit-Risk pillar – testing new approaches tc	FINALISED	Funded by public entities, excluding drug agencies	Secondary	More than 1	Yes	Observational study
Prospective non-interventional cohort study to assess safety anc	FINALISED	Funded by pharmaceutical company	Secondary	More than 1	Yes	Observational Study
A prospective observational registry study to characterise norma	FINALISED	Funded by pharmaceutical company	Primary	Not applicable	No	Observational Study
Descriptive Study of the Incidence of Malignancy in Patients wit	PLANNED	Funded by pharmaceutical company	Mixed	Existing registry	Yes	Observational Study
Post-authorisation safety study to assess the risk of urinary tract	ONGOING	Funded by pharmaceutical company	Secondary	More than 1	Yes	Observational Study
A non-interventional post-authorisation safety study (PASS) of v	ONGOING	Funded by pharmaceutical company	Secondary	More than 1	Yes	Observational Study
Retrospective Cohort Study of Certolizumab Pegol (Cimzia®) ar	ONGOING	Funded by pharmaceutical company	Secondary	Chart abstraction	Yes	Observational Study
A description of the UK NHS hospital resource use and patient q	ONGOING	Funded by pharmaceutical company	Mixed	EHR	Yes	Observational Study
Multi-component assessment systems and predicting future risk	PLANNED	More than one	Mixed	EHR	Yes	Observational Study
Can social listening data be used to provide meaningful insights	FINALISED	Funded by pharmaceutical company	Secondary	Unknown	No	Observational Study
Post-Marketing Observational Cohort Study of Patients with Infla	ONGOING	Funded by pharmaceutical company	Mixed	EHR	Yes	Observational Study
Characterising the risk of major bleeding in patients with Non-Va	FINALISED	Funded by national/international drug agency	Mixed	More than 1	Yes	Observational Study
Risk of lactic acidosis associated with metformin use in patients	ONGOING	Funded by public entities, excluding drug agencies	Mixed	More than 1	Yes	Observational Study
Post Authorisation Safety Study (PASS): an European observati	ONGOING	Funded by pharmaceutical company	Mixed	Not applicable	No	Survey
Evaluation of the potential for and clinical impact of increased Al	ONGOING	Funded by pharmaceutical company	Mixed	More than 1	No	Observational Study
A Retrospective Evaluation of PD-L1 expression on primary non-	PLANNED	Funded by pharmaceutical company	Mixed	Existing registry	No	Observational Study
Observational Study of the Effectiveness of Vedolizumab on Tre	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Observational Study
A multi-centre observational study to describe the impact of vedo	ONGOING	Funded by pharmaceutical company	Mixed	EHR	Yes	Observational Study
A 5-year enhanced Pharmacovigilance surveillance initiative to s	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Survey
Prospective observational study to describe routine use of XGEV	PLANNED	Funded by pharmaceutical company	Primary	Not applicable	No	Observational Study
PRJ2282 / 201491: CHESS: CPRD-COPD Hawthorne Effect Study	FINALISED	Funded by pharmaceutical company	Mixed	Existing registry	Yes	Observational Study
Assessment of physical functioning and handling of Spiolto® R	ONGOING	Funded by pharmaceutical company	Primary	Not applicable	No	Observational Study

Inter-rater agreement analysis

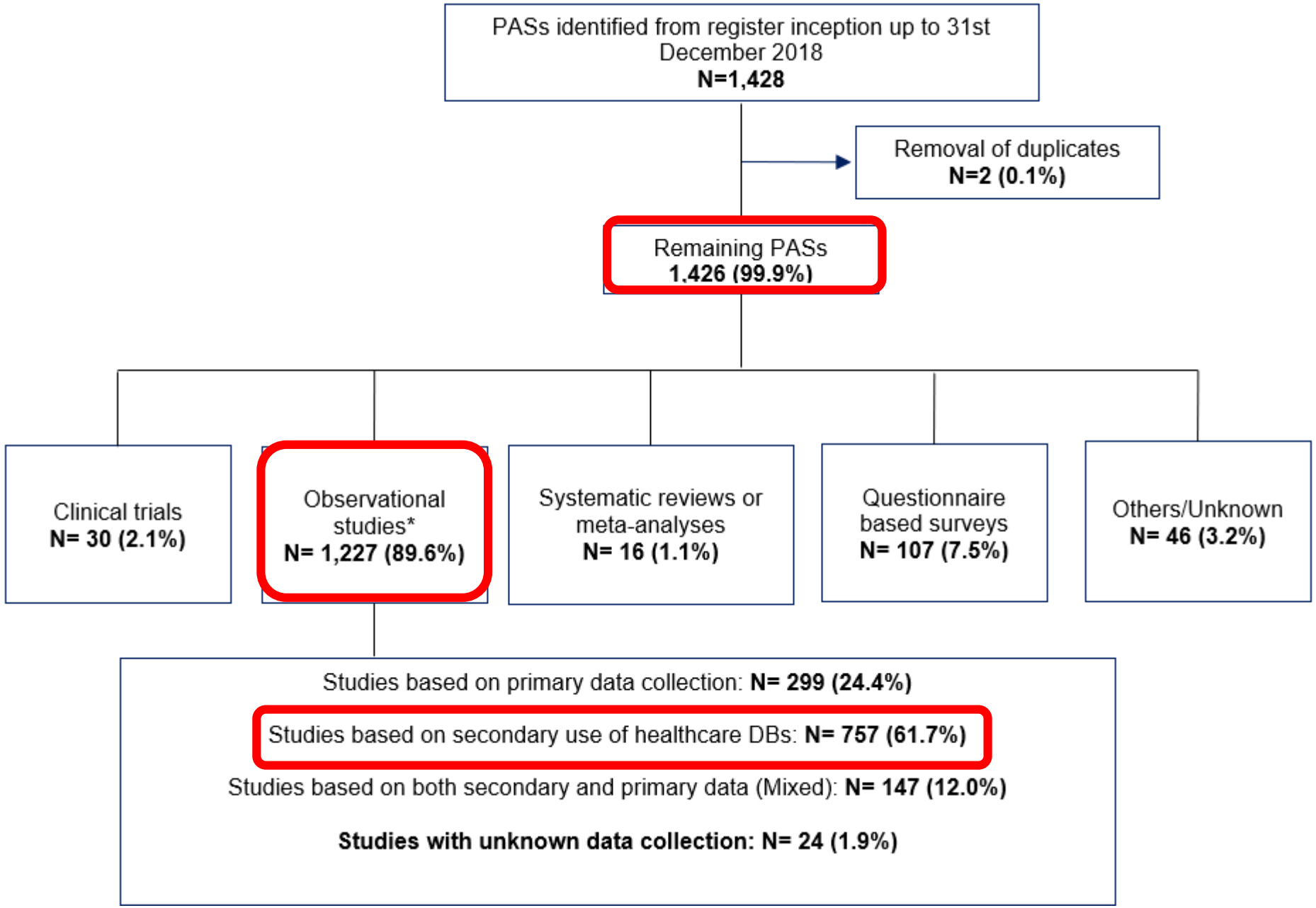
Substantial agreement (k= 0.61-0.80)

Moderate agreement (k= 0.41-0.60)

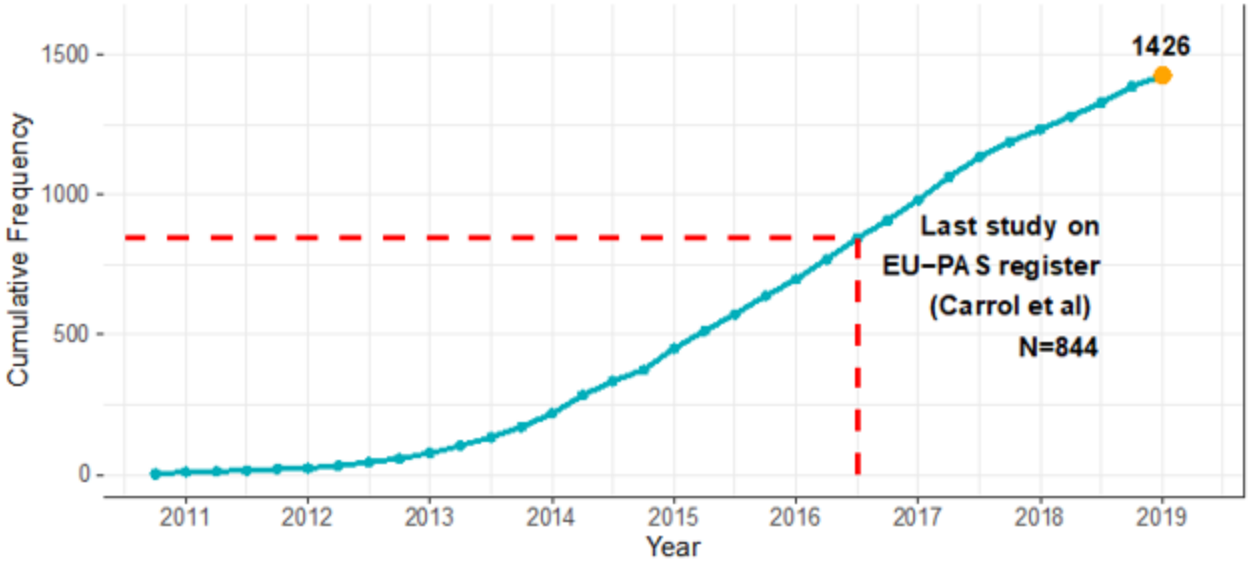
Fair agreement (k= 0.21-0.40)

Variables	Categories	Kappa coefficient*	Agreement N 214 (%)	Total kappa coefficient*
Study type	Clinical trials	0.795	200 (93.5)	**0.769**
	Observational studies	0.758		
	Systematic reviews/ Meta-analyses	1.000		
	Questionnaire-based surveys	0.769		
	Others	0.795		
	Unknown	-		
Data Collection	Primary	0.717	171 (79.9)	**0.649**
	Secondary	0.666		
	Primary and secondary (mixed)	0.562		
	Unknown	-		
Drug type	Non-biologic	0.685	176 (82.2)	**0.646**
	Biologic	0.827		
	Both biologic and non-biologic	-		
	None	0.497		
	Unknown	-		
Use of reference drug for formal comparison	Yes	0.659	171 (79.9)	**0.587**
	No	0.621		
	Unknown	0.127		
Setting	Routine	0.493	193 (90.2)	**0.509**
	Experimental	0.829		
	Unknown	-		
	Not applicable	0.509		
Secondary data	Chart abstraction	0.481	145 (67.8)	**0.496**
	Claims database	0.131		
	EHR	0.457		
	Existing registry	0.505		
	Not applicable/ not secondary data	0.728		
	More than 1	0.579		
	Unknown	0.314		
Multiple database study	Yes	0.503	176 (77.6)	**0.479**
	No	0.478		
	Unknown	0.274		
Orphan drug	Yes	0.478	179 (83.6)	**0.382**
	No	0.422		
	Unknown	-		

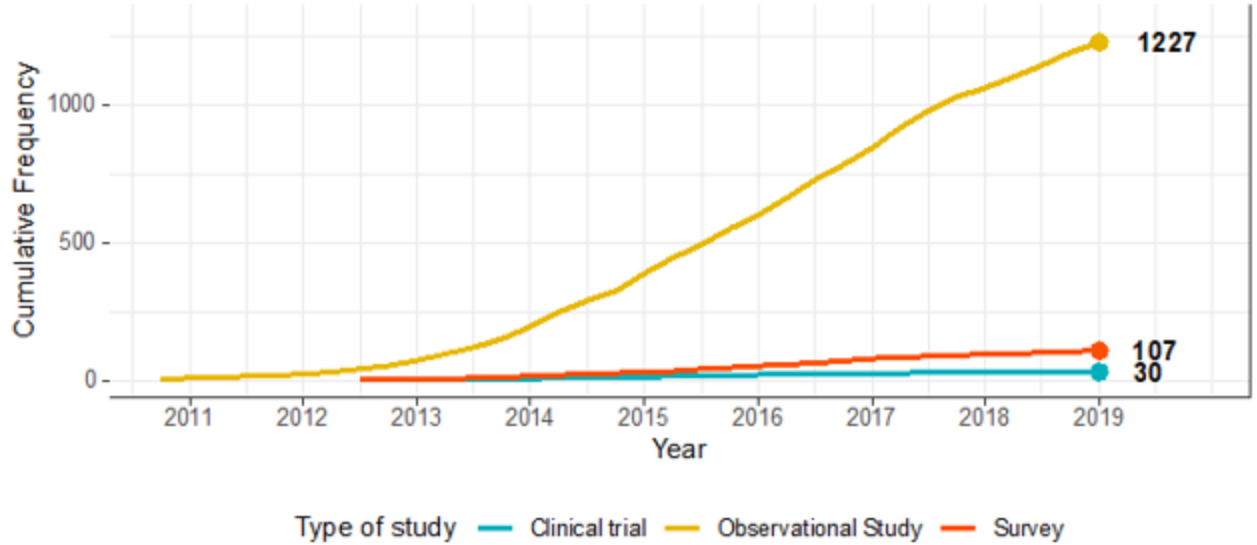
Flowchart of studies registered in the EU PAS register till Dec 2018



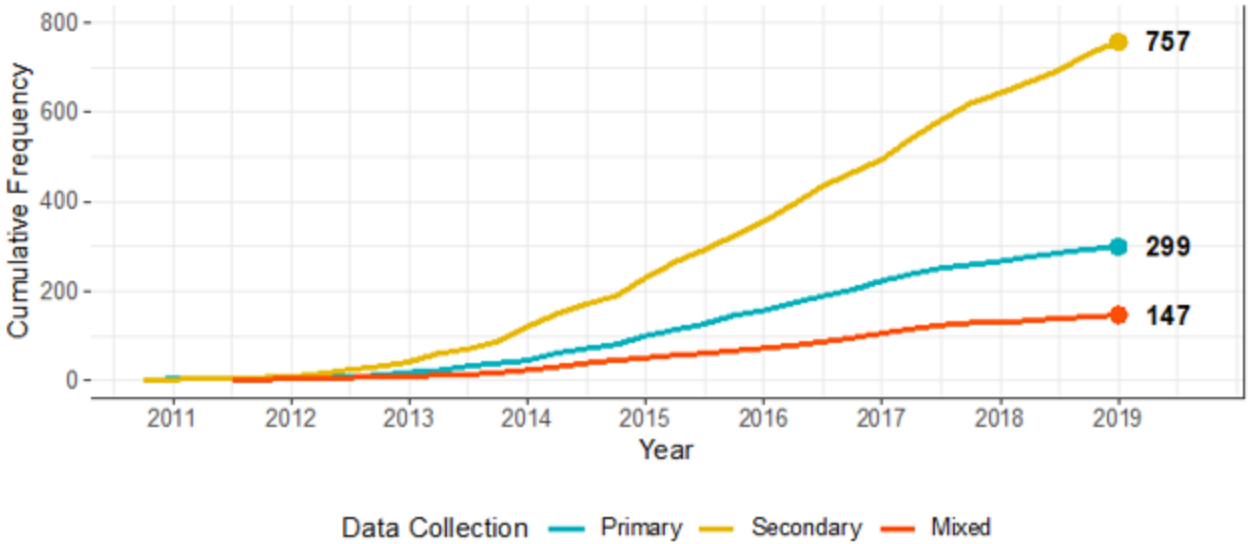
a) Cumulative frequency of studies registered in the EU PAS Register from its inception to 31 Dec 2018



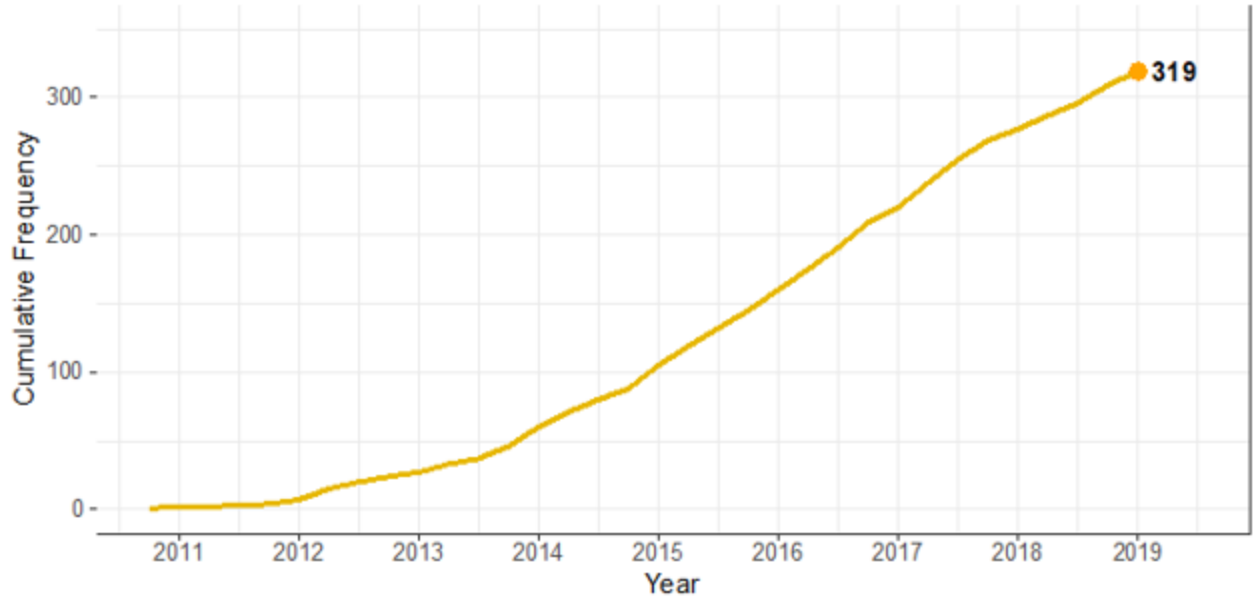
b) Cumulative frequency of studies in the EU PAS Register: Study type



c) Cumulative frequency of observational studies in the EU PAS Register: Data collection



d) Cumulative frequency of MDS registered in the EU PAS Register



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	Clinical trials N=30 (%)	Observational studies N=1227 (%)	Systematic reviews/ Meta-analyses N=16 (%)	Questionnaire-based surveys N=107 (%)
	N (%)	N (%)	N (%)	N (%)
Requested by a regulator				
Yes	10 (33.3)	571 (46.5)	5 (31.3)	68 (63.6)
No	18 (60.0)	637 (51.9)	11 (68.8)	39 (36.4)
Unknown	2 (6.7)	19 (1.5)	0 (0.0)	0 (0.0)
Source of funding				
Pharmaceutical company	20 (66.7)	1005 (81.9)	10 (62.5)	97 (90.7)
National/international drug agency	0 (0.0)	53 (4.3)	3 (18.7)	1 (0.9)
Public entities excluding drug agencies	8 (26.7)	65 (5.3)	2 (12.5)	5 (4.7)
Self-funded	1 (3.3)	23 (1.9)	1 (6.2)	0 (0.0)
More than one source	0 (0.0)	62 (5.1)	0 (0.0)	4 (3.7)
Unknown	1 (3.3)	19 (1.5)	0 (0.0)	0 (0.0)
Secondary data				
Chart abstraction	0 (0.0)	55 (4.5)	0 (0.0)	1 (0.9)
Claims database	0 (0.0)	165 (13.4)	0 (0.0)	0 (0.0)
EHR	1 (3.3)	182 (14.8)	0 (0.0)	1 (0.9)
Existing registry	3 (10.0)	136 (11.1)	0 (0.0)	1 (0.9)
Not applicable-not secondary data	25 (83.3)	376 (30.6)	16 (100)	104 (97.2)
More than 1	0 (0.0)	286 (23.3)	0 (0.0)	0 (0.0)
Unknown	1 (3.3)	27 (2.2)	0 (0.0)	0 (0.0)

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	Clinical trials N=30 (%)	Observational studies N=1227 (%)	Systematic reviews/ Meta-analyses N=16 (%)	Questionnaire-based surveys N=107 (%)
	N (%)	N (%)	N (%)	N (%)
Use of reference drug for formal comparison				
Yes	7 (23.3)	336 (27.4)	4 (25.0)	5 (4.7)
No	22 (73.4)	844 (68.8)	10 (62.5)	100 (93.5)
Unknown	1 (3.3)	47 (3.8)	2 (12.5)	2 (1.9)
Scope of the study *				
Disease epidemiology	4 (13.3)	212 (17.3)	2 (12.5)	8 (7.5)
Risk assessment	13 (43.3)	696 (56.7)	11 (68.8)	36 (33.6)
Drug utilisation	4 (13.3)	444 (36.2)	1 (6.3)	23 (21.5)
Effectiveness evaluation	17 (56.7)	855 (69.7)	15 (93.8)	77 (72.0)
Other	14 (46.7)	246 (20.0)	3 (18.8)	40 (37.4)
Population of interest – age*				
Children	5 (16.7)	442 (36.0)	7 (43.8)	25 (23.4)
Adults	27 (90.0)	1103 (89.9)	15 (93.8)	105 (98.1)
Elderly persons	19 (63.3)	1008 (82.2)	13 (81.3)	98 (91.6)
Pregnant women	2 (6.7)	132 (10.8)	2 (12.5)	3 (2.8)
Breast-feeding women	0 (0.0)	13 (1.1)	0 (0.0)	0 (0.0)

* Multiple options are possible

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Characteristics of studies based on secondary use of existing healthcare data (± primary data collection)

	Chart abstraction N=60 (%)	Claims database N=169 (%)	EHRs N=186 (%)	Existing registry N=144 (%)	More than one type of data N=290 (%)
	N (%)	N (%)	N (%)	N (%)	N (%)
Protocol deposited					
Yes	34 (56.7)	82 (48.5)	123 (66.1)	87 (60.4)	209 (72.1)
No	26 (43.3)	87 (51.5)	63 (33.9)	57 (39.6)	81 (27.9)
Scope of the study					
Disease epidemiology	5 (8.3)	26 (15.4)	34 (18.3)	38 (26.4)	49 (16.9)
Risk assessment	17 (28.3)	30 (17.8)	29 (15.6)	28 (19.4)	53 (18.3)
Drug utilisation	28 (46.7)	57 (33.7)	72 (38.7)	45 (31.3)	117 (40.3)
Effectiveness evaluation	24 (40.0)	37 (21.9)	52 (28.0)	32 (22.2)	54 (18.6)
Other*	17 (28.3)	30 (17.8)	29 (15.6)	28 (19.4)	53 (18.3)
Drug of interest					
Biologic	24 (40.0)	32 (18.9)	32 (17.2)	34 (23.6)	57 (19.7)
Both biologic and non-biologic	2 (3.3)	3 (1.8)	1 (0.5)	6 (4.2)	5 (1.7)
Orphan drugs	8 (13.3)	14 (8.3)	16 (8.6)	24 (16.7)	20 (6.9)
Publication available					
Yes	18 (30.0)	62 (36.7)	73 (39.2)	40 (27.8)	94 (32.4)
No	42 (70.0)	107 (63.3)	113 (60.8)	104 (72.2)	196 (67.6)

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Factors associated to the registration of MDSs vs non-MDSs among observational studies based on secondary use of already existing healthcare data

	Multiple Database Studies
	OR [95% CI]
Protocol deposited	2.012 [1.461 - 2.768]
ENCePP seal	3.004 [1.696 - 5.308]
Requested by a regulator	2.883 [2.117 - 3.918]
RMP status*	
EU RMP 1	2.609 [1.414 - 4.804]
EU RMP 2	1.127 [0.354 - 3.580]
EU RMP 3	2.086 [1.506 - 2.887]
Non-EU RMP only	0.581 [0.285 - 1.181]
Not applicable	0.508 [1.414 - 4.804]
Missing - no info at all	0.477 [0.354 - 3.580]
Population of interest – (Age)	
Children	2.522 [1.846 - 3.444]
Adults	1.048 [0.639 - 1.717]
Elderly persons	1.157 [0.764 - 1.748]
Unknown	1.581 [0.316 - 7.878]

*** EU RMP 1: EU risk management plan 1 (imposed as condition of marketing authorisation); EU RMP 2: EU risk management plan 2 (specific obligation of marketing authorisation); EU RMP 3: EU risk management plan 3 (required)**

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Reviev
Out

Introduction

- Description of 'main' study: E
- MDS and strategies, reference

Methods

- Brief reference to results of th
- Refined definition of MDS
- Methods to estimate sensitivi define the final list of studies
- Data extraction
- Data analysis

Regulatory c pharmacoepidemiolc studies requeste

BACKGROUND:

One of the goals of the new Pharmacovigi increase transparency of the regulatory proc PRAC oversight, specific procedures and tim of the monthly meeting minutes and the endo database for PASS registration represent maj This was a response to previous concerns v Risk Management activities such as protocols A review of publicly available information on P new Pharmacovigilance legislation, highlight had been achieved but there were still some partial availability of information (limited info limited registration of studies in the EU PA different sources (different study type inform limited use of study identification elements across the EU PAS Registrants.(3)

According to the EMA website "Non-inte answers": *Protocols and public abstracts of are publicly available in the EU PAS Regis Pharmacoepidemiology and Pharmacovigila imposed non-interventional PASS final study found only in centrally authorised medicines European public assessment report (EPA medicinal products included in 'mixed' proc were also involved can be found on the Co publishes the outcomes of final study re authorisation safety studies (PASS) for NAPs*

The aim of this study is to understand the re multidatabase studies performed in Europe.

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

Name	Institution

Pregnancy and lactation

Lead: Leonardo Pereira

One of the objectives in ConcePTION, an IMI-funded international study, is to provide important innovations to move beyond product-specific pregnancy registries and/or related observation studies to enhance our understanding of medica strategy: an assessment Post-Authorisation Studies observational studies focu registries studies publishe data from highest level to the summary of product studies led to update the r

population in order to:

- assess the possible i research in this popu
- describe the epidem different class of age them;
- evaluate the impact drug (in terms of mar

Assessment of the utilization of secondary data in European countries based on the EU PAS Register

Step 1: Data collection

Apart from the data that is already collected regarding the studies of the EU PAS Register, we need to document in which countries each study was conducted. This can happen using the appropriate search field on the EU PAS Register website. A series of columns will be added, titled by each country's name and a drop-down choice of "Yes" or "No" will be available to point out if the study was or not conducted in this country. This is considered necessary, since there are studies conducted in multiple countries.

Step 2: Inclusion criteria

Only studies conducted in European countries will be included, since Europe is the region with the most admissions in EU PAS Register and comparisons could be more relevant. (This criterion will be set during the data collection, implementing the search in European countries only.) Furthermore, only observational studies will be included, since both clinical trials and surveys naturally use primary data and reviews/meta-analyses are not relevant for this research question.

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Conclusions

- Assessing the studies registered in the EU PAS register requires multidisciplinary and advanced expertise;
- Availability of protocols is essential for correct interpretation of the studies and rapidly sharing methodological approaches (e.g. COVID-19);
- A large number of studies are based on primary data collection, without any comparator and just descriptive;
- In general, pharmaceutical companies are the main sponsor, irrespective of whether the studies are imposed by regulatory agencies;
- Number of MDSs is increasing and assessing their impact in relation to the adopted methodological strategies may inform regulatory agencies as well as scientifc community.

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Thank you for the attention

UniME/UniVR

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Vera Ehrenstein

University of Thrace

Christos Kontogiorgis

Georgios Poulentzas

Panagiotis Nikolaos Lalagkas

EMC

Christel Hoeve

Esme Baan

Remi Francesca

Katia Verhamme

University of Bordeaux

Anne Fourier-Réglat

University of Campania

Annalisa Capuano

Carmen Ferrajolo

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