ENCePP Work Group 3 – Inventory of EU data sources and methodological approaches for multisource studies

Chair: Prof. Gianluca Trifirò,
University of Messina

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

STUDIORUM UNIVERSITAS MESSANAE

WG 3 Objectives

To explore and compare models for the conduct of multiple database studies in regulatory environment:

Preparation of a **commentary** to define and compare the strategies adopted to conduct European multi-database studies;

Systematic review of all pertinent **literature** and other sources concerning models for the conduct of multiple database studies which have been published so far

Review of all the studies which have been registered into the **EU-PAS register** plus PRAC minutes and assessment reports, with a special emphasis on the multiple database studies and their **contribution to regulatory actions**.

Preparation of commentary

- Coordinated by Rosa Gini (ARS Toscana), Miriam Sturkenboom (Utrecht Medical Centre) and myself;
- Supported by **several other WG3 members** from, University of Messina, ARS, University of Bremen, Benzi Foundation, EMA;
- Several TCLs were organised to prepare the final draft, which was recently **thoroughly revised by EMA;**
- Contains **detailed description of four strategies** used to conduct multi-database studies in European comparison of these approaches from an operational point of view;
- Preparing for submission to BMJ.

Features of common strategies for performing multiple database studies

Strategy	First step	Data extraction	Transformation into CDM	Analysis programs	Level of data sharing
A **Local analysis**	Each protocol is the starting point of activity	Each site extracts a dataset specific for the study	Not done	Programmed locally by each site, not shared by design	Final results
B **Sharing of raw data**	As for A	As for A	Not done	Programmed by one site, existing standard programs can be re-used, not shared by design	Raw data
C **Study specific CDM**	As for A	As for A	Specific for the study. Once a CDM has been implemented, standard procedures can be re-used for subsequent studies with a CDM of the same format	Programmed by one site, existing standard programs can be re-used, shared with sites	Anonymized analytic dataset or aggregated data or final results
D **General CDM**	The starting points of the activity is the regular mapping to the CDM, then each protocol starts a study	The entire dataset is extracted regularly, whenever the local data are refreshed	Periodically refreshed. Standard procedures are put in place once the CDM is adopted and re-used periodically	As for C	As for C

Systematic review of published multiple database studies

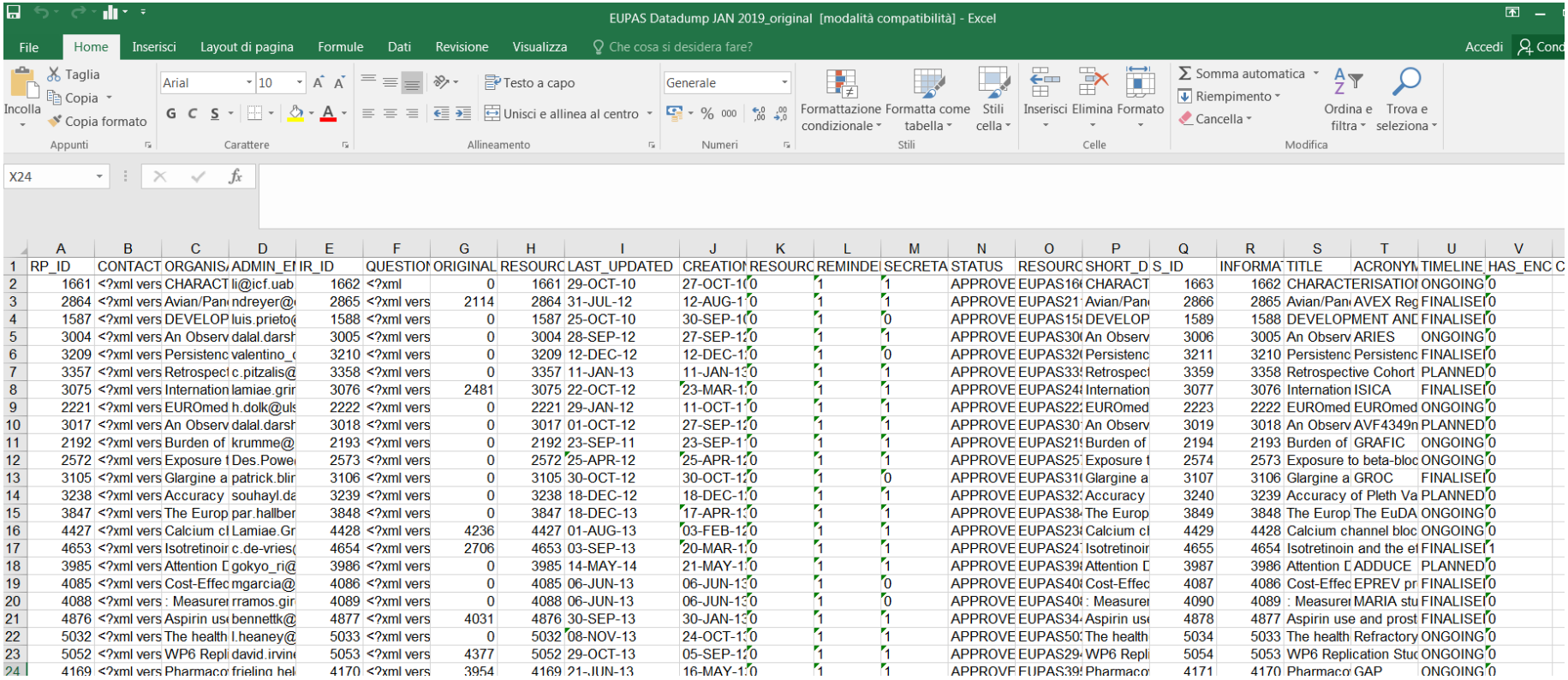
- Development and validation of a specific Pubmed search using specific strings to identify key publications describing models of multiDB studies;
- Preliminary results: 150 papers identified;
- Work in progress – to be finalized after commentary submission.

Field	Field options	Selection	Comments
Study type	☐ Active surveillance ☐ Observational study ☐ Clinical trial ☐ Other	Select all. For clinical trials, minimal data will be collected, enough to give an overview.	This selection is aimed at maximum sensitivity at the cost of lower selectivity; "other" includes systematic reviews, surveys, drug utilisation studies (for example, using IMS Disease Analyser) *as well as post-authorisation safety studies. Based on final manual validation only observational studies will be included in the end. New categorization of study types will be proposed.*
Study requested by a regulator	Yes / No	No selection	This selection is aimed at maximum sensitivity at the cost of lower selectivity
Risk Management Plan	☐ Not applicable ☐ EU risk minimisation plan (RMP) category 1 (imposed as condition of marketing	No selection	Stratification by category will considered in analytical phase. The category "EU risk minimisation

Review of the EU PAS Register (2)

1. **Expression of interest** to screen studies in EU-PAS register from **10 partners**;

2. **Collaboration with EMA** to obtain automatically extracted data from EU-PAS register and converted to usable format by data



EUPAS Datadump JAN 2019_original [modalità compatibilità] - Excel

File Home Inserisci Layout di pagina Formule Dati Revisione Visualizza Che cosa si desidera fare? Accedi

Taglia Copia Copia formato Incolla — Appunti

Arial 10 — Carattere

Testo a capo Unisci e allinea al centro — Allineamento

Generale — Numeri

Formattazione condizionale Formatta come tabella Stili cella — Stili

Inserisci Elimina Formato — Celle

Somma automatica Riempimento Cancella Ordina e filtra Trova e seleziona — Modifica

X24

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
1	RP_ID	CONTACT	ORGANIS/	ADMIN_EI	IR_ID	QUESTION	ORIGINAL	RESOURC	LAST_UPDATED	CREATION	RESOURC	REMINDEI	SECRETA	STATUS	RESOURC	SHORT_D	S_ID	INFORMA	TITLE	ACRONYM	TIMELINE	HAS_ENC C
2	1661	<?xml vers	CHARACT	li@icf.uab	1662	<?xml	0	1661	29-OCT-10	27-OCT-10	0	1	1	APPROVE	EUPAS16	CHARACT	1663	1662	CHARACTERISATIOI		ONGOING	0
3	2864	<?xml vers	Avian/Pan	ndreyer@	2865	<?xml vers	2114	2864	31-JUL-12	12-AUG-1	0	1	1	APPROVE	EUPAS21	Avian/Pan	2866	2865	Avian/Pan	AVEX Reg	FINALISE	0
4	1587	<?xml vers	DEVELOP	luis.prieto@	1588	<?xml vers	0	1587	25-OCT-10	30-SEP-10	0	1	0	APPROVE	EUPAS15	DEVELOP	1589	1588	DEVELOPMENT ANI		FINALISE	0
5	3004	<?xml vers	An Observ	dalal.darsh	3005	<?xml vers	0	3004	28-SEP-12	27-SEP-12	0	1	1	APPROVE	EUPAS30	An Observ	3006	3005	An Observ	ARIES	ONGOING	0
6	3209	<?xml vers	Persistenc	valentino_(	3210	<?xml vers	0	3209	12-DEC-12	12-DEC-12	0	1	0	APPROVE	EUPAS32	Persistenc	3211	3210	Persistenc	Persistenc	FINALISE	0
7	3357	<?xml vers	Retrospect	c.pitzalis@	3358	<?xml vers	0	3357	11-JAN-13	11-JAN-13	0	1	1	APPROVE	EUPAS33	Retrospect	3359	3358	Retrospective Cohort		PLANNED	0
8	3075	<?xml vers	Internation	lamiae.grir	3076	<?xml vers	2481	3075	22-OCT-12	23-MAR-1	0	1	1	APPROVE	EUPAS24	Internation	3077	3076	Internation	ISICA	FINALISE	0
9	2221	<?xml vers	EUROmed	h.dolk@uls	2222	<?xml vers	0	2221	29-JAN-12	11-OCT-1	0	1	1	APPROVE	EUPAS22	EUROmed	2223	2222	EUROmed	EUROmed	ONGOING	0
10	3017	<?xml vers	An Observ	dalal.darsh	3018	<?xml vers	0	3017	01-OCT-12	27-SEP-12	0	1	1	APPROVE	EUPAS30	An Observ	3019	3018	An Observ	AVF4349n	PLANNED	0
11	2192	<?xml vers	Burden of	krumme@	2193	<?xml vers	0	2192	23-SEP-11	23-SEP-1	0	1	1	APPROVE	EUPAS21	Burden of	2194	2193	Burden of	GRAFIC	ONGOING	0
12	2572	<?xml vers	Exposure t	Des.Powe	2573	<?xml vers	0	2572	25-APR-12	25-APR-12	0	1	1	APPROVE	EUPAS25	Exposure t	2574	2573	Exposure to beta-bloc		ONGOING	0
13	3105	<?xml vers	Glargine a	patrick.blir	3106	<?xml vers	0	3105	30-OCT-12	30-OCT-12	0	1	0	APPROVE	EUPAS31	Glargine a	3107	3106	Glargine a	GROC	FINALISE	0
14	3238	<?xml vers	Accuracy	souhayl.da	3239	<?xml vers	0	3238	18-DEC-12	18-DEC-1	0	1	1	APPROVE	EUPAS32	Accuracy	3240	3239	Accuracy of Pleth Va		PLANNED	0
15	3847	<?xml vers	The Europ	par.hallber	3848	<?xml vers	0	3847	18-DEC-13	17-APR-1	0	1	1	APPROVE	EUPAS38	The Europ	3849	3848	The Europ	The EuDA	ONGOING	0
16	4427	<?xml vers	Calcium cl	Lamiae.Gr	4428	<?xml vers	4236	4427	01-AUG-13	03-FEB-1	0	1	1	APPROVE	EUPAS23	Calcium cl	4429	4428	Calcium channel bloc		ONGOING	0
17	4653	<?xml vers	Isotretinoir	c.de-vries(	4654	<?xml vers	2706	4653	03-SEP-13	20-MAR-1	0	1	1	APPROVE	EUPAS24	Isotretinoir	4655	4654	Isotretinoin and the el		FINALISE	1
18	3985	<?xml vers	Attention D	gokyo_ri@	3986	<?xml vers	0	3985	14-MAY-14	21-MAY-1	0	1	1	APPROVE	EUPAS39	Attention D	3987	3986	Attention D	ADDUCE	PLANNED	0
19	4085	<?xml vers	Cost-Effec	mgarcia@	4086	<?xml vers	0	4085	06-JUN-13	06-JUN-13	0	1	0	APPROVE	EUPAS40	Cost-Effec	4087	4086	Cost-Effec	EPREV pr	FINALISE	0
20	4088	<?xml vers	: Measurer	rramos.gir	4089	<?xml vers	0	4088	06-JUN-13	06-JUN-13	0	1	0	APPROVE	EUPAS40	: Measurer	4090	4089	: Measurer	MARIA stu	FINALISE	0
21	4876	<?xml vers	Aspirin us	bennettk@	4877	<?xml vers	4031	4876	30-SEP-13	30-JAN-13	0	1	1	APPROVE	EUPAS34	Aspirin us	4878	4877	Aspirin use and prost		FINALISE	0
22	5032	<?xml vers	The health	l.heaney@	5033	<?xml vers	0	5032	08-NOV-13	24-OCT-13	0	1	1	APPROVE	EUPAS50	The health	5034	5033	The health	Refractory	ONGOING	0
23	5052	<?xml vers	WP6 Repli	david.irvine	5053	<?xml vers	4377	5052	29-OCT-13	05-SEP-13	0	1	1	APPROVE	EUPAS29	WP6 Repli	5054	5053	WP6 Replication Stuc		ONGOING	0
24	4169	<?xml vers	Pharmaco	frieling.hel	4170	<?xml vers	3954	4169	21-JUN-13	16-MAY-1	0	1	1	APPROVE	EUPAS39	Pharmaco	4171	4170	Pharmaco	GAP	ONGOING	0

Review of th

1. **Expression of interest** to s
   partners;

2. **Collaboration with EMA** t
   EU-PAS register and conver
   programmers in-house;

3. Development and revision
   collection to be **pilot teste**

A	B
Automatically extracted data	EU_PAS_Register_number
	LAST_UPDATED
	Study_type_original
	Status of Study
	Study requested by a regulator
	ENCePP Seal
	Funding
Data to be manually extracted from EU PAS Register	Funding source
	Risk Management Plan
	PI employed by study funder
	Data collection
	Secondary data
	Multiple database study
	Data models
	Study type_new classification
	Product lifecycle
	Study design
	Use of comparator drug
	Setting
	Scope_Disease epidemiology
	Scope_Risk assessment
	Scope_Drug utilisation study
	Scope_Effectiveness evaluation
	Scope_Other
	Population age
	Special populations
	Drug type
	Orphan drug
	Protocol_in_English
Data to be manually extracted from other sources	Regulatory action
	Publications available
	Publication DOI or URL

Review of the EU PAS Register (2)

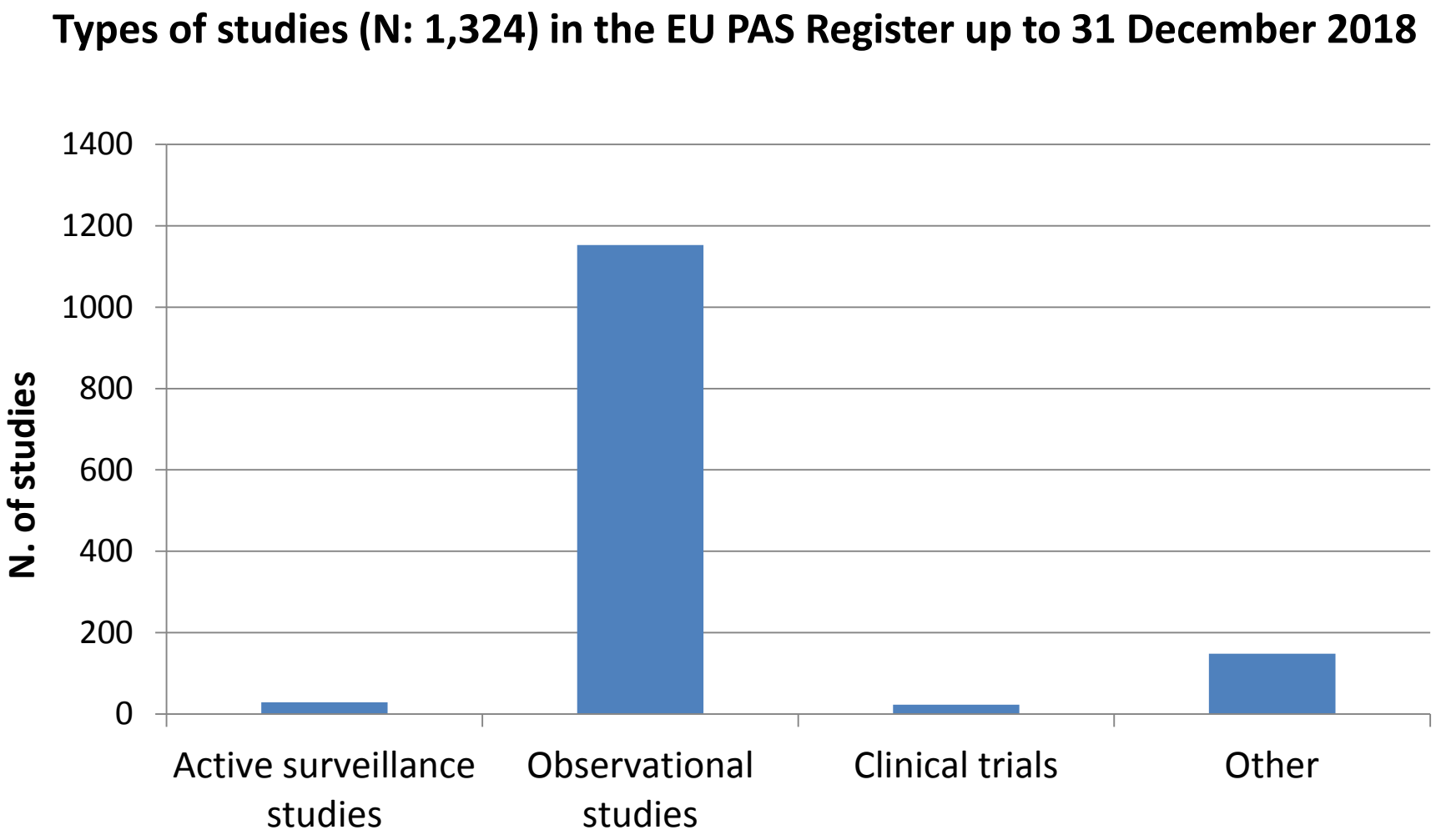
1. **Expression of interest** to screen studies in EU-PAS register from **10 partners**;

2. **Collaboration with EMA** to obtain automatically extracted data from EU-PAS register and converted to usable format by data programmers in-house;

3. Development and revision of a spreadsheet for **standardized data collection** to be **pilot tested** in a training session;

4. Liaison with EMA colleagues to assess **feasibility of screening PRAC minutes and assessment reports** to explore impact of studies on regulatory actions.

Preliminary results (1)



Preliminary results (2)

Information on risk management plan and study scope for studies registered in the EU-PAS register after new classifications

	Clinical trials N=25 (%)	Observational studies N=1,284 (%)	Systematic reviews/Meta-analyses N=9 (%)	Questionnaire-based surveys N=38 (%)	Others* N=17 (%)
RMP status					
Not applicable	8 (32.0)	527 (41.0)	5 (55.6)	3 (7.9)	6 (35.3)
EU RMP 1	1 (4.0)	89 (6.9)	0 (0.0)	6 (15.8)	0 (0.0)
EU RMP 2	2 (8.0)	32 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
EU RMP 3	3 (12.0)	370 (28.8)	3 (33.3)	18 (47.4)	4 (23.5)
Non-EU RMP only	1 (4.0)	79 (6.2)	0 (0.0)	5 (13.2)	1 (5.88)
Missing	10 (40.0)	187 (14.6)	1 (11.1)	6 (15.8)	6 (35.3)
Scope of the study					
Disease epidemiology	3 (12.0)	201 (15.7)	1 (11.1)	1 (2.6)	1 (5.9)
Risk assessment	3 (12.0)	638 (49.7)	8 (88.9)	7 (18.4)	7 (41.2)
Drug utilisation	5 (20.0)	428 (33.3)	1 (11.1)	9 (23.7)	0 (0.0)
Effectiveness	11 (44.0)	359 (28.0)	3 (33.3)	21 (55.3)	2 (11.8)
Other scopes	18 (72.0)	327 (25.5)	2 (22.2)	11 (29.0)	10 (58.8)

* e.g. analysis based on spontaneous reporting systems, post-hoc analysis of clinical trial data, in vitro analysis of antibiotic susceptibility

Thanks to all the WG3 members

Centre	Lead
ARS Toscana	Rosa Gini
Erasmus Medical Centre	Katia Verhamme
University of Bordeaux	Annie Fourier
IQVIA	Massoud Toussi
TEDDY	Letizia Carrara
Aarhus University	Vera Ehrenstein
University of Messina	Gianluca Trifirò
Democritus University of Thrace	Christos Kontogiorgis
Università di Campania	Annalisa Capuano
RTI Health Solutions	Joan Fortuny
EMA	Thomas Goedecke
EPID Research	Katja Hakkaraine