



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## EU PASS/PAES Requirements for Disclosure

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10<sup>th</sup> Industry Stakeholder Platform – Operation of EU pharmacovigilance , London, 3 February 2017

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An agency of the European Union





# Content

- **Post-authorisation study (PAS)**
  - PASS - PAES
- **Regulatory requirements for PAS** initiated, managed or financed by MAH
  - Objectives for requesting PAS
  - PASS supervision
- **Disclosure requirements for PASS and PAES**
  - European Union Clinical Trials Register (EudraCT)
  - European Union Post-Authorisation Study (EU PAS) Register

## Post-Authorisation Study (PAS)

**Post-authorisation study (PAS)** may be requested by competent authorities in EU Member States or the EMA in accordance with DIR 2001/83/EC or REG (EC) 726/2004, or conducted voluntarily by MAHs, and could either be

⇒ **Clinical trial**

Requirements of DIR 2001/20/EC apply

⇒ **Non-interventional post-authorisation study**

Requirements of DIR 2001/83/EC and REG (EC) 726/2004 apply



# Post-Authorisation Safety Study

## Post-authorisation **Safety** Study (PASS)

Legal definition DIR 2001/83/EC Article 1(15):

*'Any study relating to an **authorised medicinal product** conducted with the aim of **identifying, characterising or quantifying a safety hazard**, confirming the **safety profile** of the medicinal product, or of measuring the **effectiveness** of risk management measures'.*

- May cover **clinical trials** and **non-interventional studies**;
- May be imposed as an obligation of marketing authorisation or conducted voluntarily;
- Covered by a specific chapter of the pharmacovigilance legislation, Implementing Regulation (EC) 520/2012 chapter VIII and GVP Module VIII on PASS;

# PASS – MAH Initiated, Managed or Financed

## A) Pursuant to an **obligation** imposed by a Competent Authority

- as a condition to the granting of the marketing authorisation, or after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product [*REG Art 10 and 10a, DIR Art 21a and 22a*] [GVP V.B.6.3: **Category 1**]
  - as part of a marketing authorisation granted under exceptional circumstances or conditional MA [GVP V.B.6.3: **Category 2**]
- ⇒ **DIR 2001/83/EU Articles 107m-q** apply (non-interventional **PASS oversight** by PRAC)
- ⇒ **IR 520/2012 Articles 36-38** apply for **format of study protocol, abstract and study results** for non-interventional PASS)
- ⇒ **GVP Module VIII (Rev 2)** requirements for non-interventional PASS

# PASS – MAH Initiated, Managed or Financed

## B) Voluntarily

- Studies required in the Risk Management Plan to investigate a safety concern or evaluate the effectiveness of risk minimisation activities [**Category 3**]
  - Any other PASS
- ⇒ **DIR 2001/83/EU Art 107m applies** to non-interventional PASS (submission of protocol and final study report to Competent Authority of the Member State where the study is conducted)
- ⇒ **GVP Module VIII (Rev 2)** requirements for imposed non-interventional PASS (e.g. format of study protocol, abstract and study results) are NOT mandatory but recommended

# PASS Categories in EU RMP

## GVP V.B.6.3 Summary table of additional pharmacovigilance activities (Rev 2)

	Type of activity	In annex II of MA (CAPs only)	Study category (PhV Plan)	Status	Supervised under	
					Article 107m	Article 107 n-q
Imposed PASS	"Interventional"*	Yes, in Annex IID	1	Mandatory and subject to penalties	No	No
	Non-interventional	Yes, in Annex IID			Yes	Yes
Specific obligation	"Interventional"*	Yes, in Annex IIE	2	Mandatory and subject to penalties	No	No
	Non-interventional	Yes, in Annex IIE			Yes	Yes
Required	"Interventional"*	No	3	Legally enforceable	No	No
	Non-interventional	No			Yes	No

# Non-interventional PASS - PRAC Supervision

## Article 107m – all PASS

- Study not to promote use of product
- Payments to HCPs [...] shall be restricted
- MAH to submit **protocol and progress report** to MS where study is conducted (on request of NCA)
- MAH to send **final study reports** within 12 months of end of data collection to NCA where the study was conducted
- MAH to monitor data and implication on **B/R**
- Recommendation to follow **format and content** of protocol and study report in line with IR (EC) 520/2012

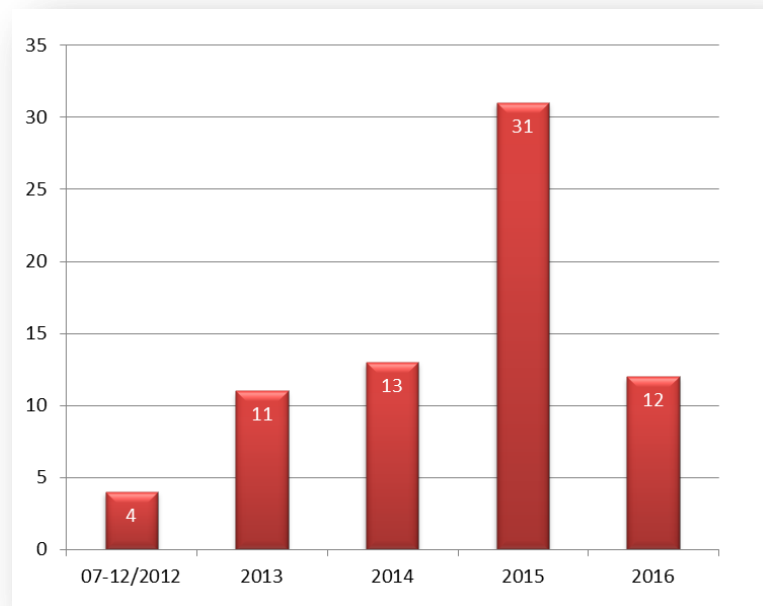
## Article 107n-q – **only imposed** PASS

- + Prior to study start MAH to submit draft **protocol** to PRAC (or NCA when conducted in only 1 MS) for **endorsement** (or objection) with 60 days TT
- + After study start **protocol amendments** require PRAC/NCA **endorsement** (or objection)
- + **Final study report** submitted to the PRAC/NCA **within 12 months** of the end of data collection + electronic abstract of study results
- + Based on results **PRAC makes recommendations**



# Imposed non-interventional PASS since 07/2012

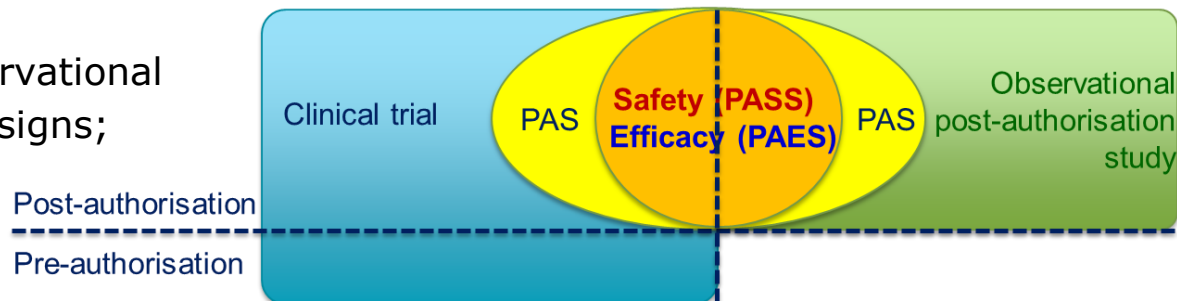
Number of imposed non-interventional PASS protocols reviewed\* by PRAC Jul 2012 – Dec 2016



\*Protocol review procedure started

# Post-Authorisation Efficacy Studies I

- A **Post-Authorisation Efficacy Study (PAES)** may be **imposed** for
  - **Conditional** marketing authorisations *[REG (EC) 726/2004 Article 14(7)]*
  - Marketing authorisation under **exceptional circumstances** *[REG (EC) 726/2004 Article 14(8) or DIR 2001/83/EC Article 22]*
  - Marketing authorisation for **ATMP** *[REG (EC) 1394/2007 Article 14]*
  - **Paediatric use** of medicinal product *[REG (EC) 1901/2006 Article 34(2)]*
  - Pharmacovigilance **referral** procedure for safety reasons *[Articles 31 or 107i of DIR 2001/83/EC; Article 20 of REG (EC) 726/2004 ]*
- Covers clinical trials and observational (non-interventional) study designs;



## Post-Authorisation Efficacy Studies II

- In addition, PAES may be **imposed** as an obligation of MA within the scope of **Delegated Regulation (EU) 357/2014** which lays down the **specific situations**
  - when it may be **necessary to complement the data** available at the time of authorisation with additional information concerning the **efficacy** of a medicinal product;
  - when **post-authorisation** information may require significant **revision of previous efficacy evaluations** and call for **additional, confirmatory efficacy data**, while the marketing authorisation is maintained.
- **EMA scientific guidance on post-authorisation efficacy studies** ([EMA/PDCO/CAT/CMDh/PRAC/CHMP/261500/2015](https://www.ema.europa.eu/en/documents/scientific-guideline/ema-pdco-cat-cmdh-prac-chmp-261500-2015_en.pdf)) includes a 'working' definition of PAES (no legal definition);
- Since June 2014, **29 PAES** have been imposed by CHMP, all are clinical trials;

# Disclosure of Clinical Trials information

03/2011



## European Clinical Trials Register (EU CTR)

- The EU CTR, launched in March 2011 containing **protocol information** and since Jul'14 also **results information**, allows to search for
  - interventional clinical trials that are conducted in the EEA/EU;
  - clinical trials conducted outside the EU/EEA linked to European paediatric-medicine development (PIP)

2018

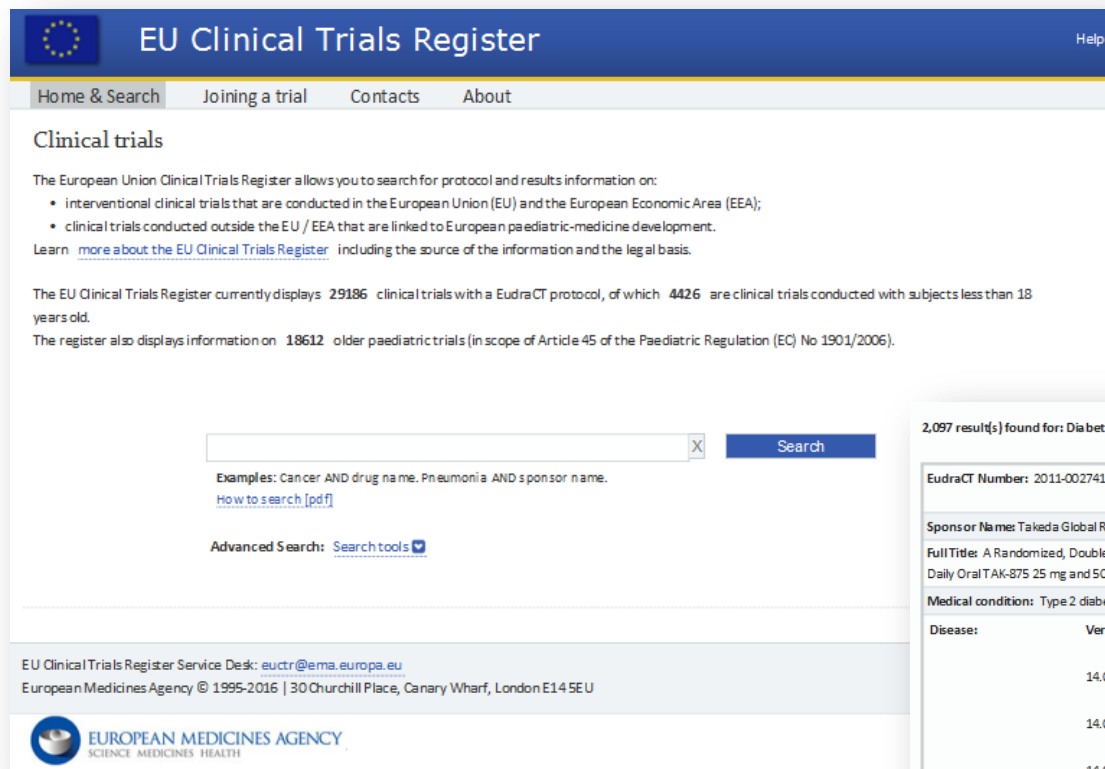


## European Union Clinical Trials Portal and Database

- Portal as **single entry point** for submitting **clinical trial information in the EU**
- EMA makes information stored in the database publicly available subject to transparency and disclosure rules:
  - Appendix on disclosure rules to functional specifications for the EU Portal and Database (EMA/228383/2015)



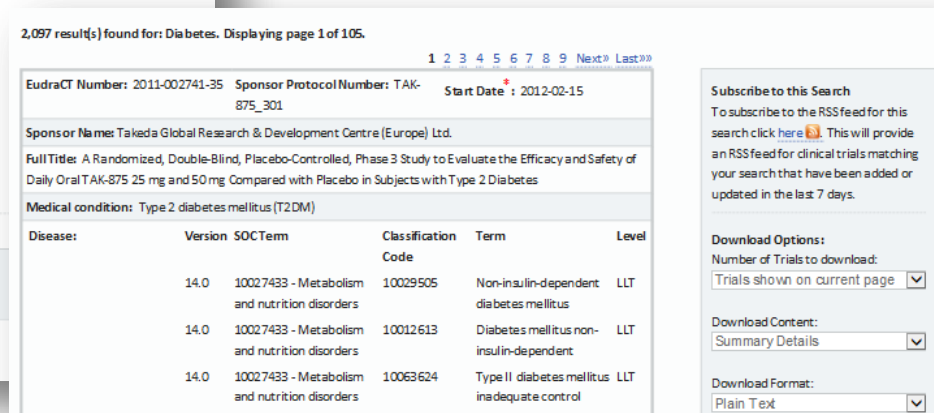
# EU Clinical Trials Register (www.clinicaltrialsregister.eu)



The screenshot shows the homepage of the EU Clinical Trials Register. At the top is a blue header with the European Union flag and the text "EU Clinical Trials Register" and a "Help" link. Below the header is a navigation bar with links: "Home & Search", "Joining a trial", "Contacts", and "About". The main content area is titled "Clinical trials" and contains text explaining the register's purpose and search capabilities. It lists the types of trials included: interventional clinical trials in the EU/EEA and clinical trials outside the EU/EEA linked to European paediatric-medicine development. It also provides statistics: 29186 clinical trials with a EudraCT protocol, 4426 of which are conducted with subjects less than 18 years old, and 18612 older paediatric trials. A search bar is visible with a search button and examples of search terms. Below the search bar are links for "Advanced Search" and "Search tools". At the bottom, there is contact information for the EU Clinical Trials Register Service Desk and the European Medicines Agency.

EU Clinical Trials Register Service Desk: [euctr@ema.europa.eu](mailto:euctr@ema.europa.eu)  
European Medicines Agency © 1995-2016 | 30 Churchill Place, Canary Wharf, London E14 5EU

- Contains interventional clinical trials starting after 01/05/2004;
- Results disclosure mandatory since 07/2014;
- [Online guidance](#) on searching the register;



The screenshot shows search results for "Diabetes". It indicates 2,097 results found, displaying page 1 of 105. The results are organized into a table with columns: Disease, Version, SOCTerm, Classification Code, Term, and Level. The table lists three entries for Type 2 diabetes mellitus (T2DM) with different classification codes and levels. To the right of the table, there is a section for "Subscribe to this Search" and "Download Options".

2,097 result(s) found for: Diabetes. Displaying page 1 of 105.

Disease	Version	SOCTerm	Classification Code	Term	Level
	14.0	10027433 - Metabolism and nutrition disorders	10029505	Non-insulin-dependent diabetes mellitus	LLT
	14.0	10027433 - Metabolism and nutrition disorders	10012613	Diabetes mellitus non-insulin-dependent	LLT
	14.0	10027433 - Metabolism and nutrition disorders	10063624	Type II diabetes mellitus inadequate control	LLT

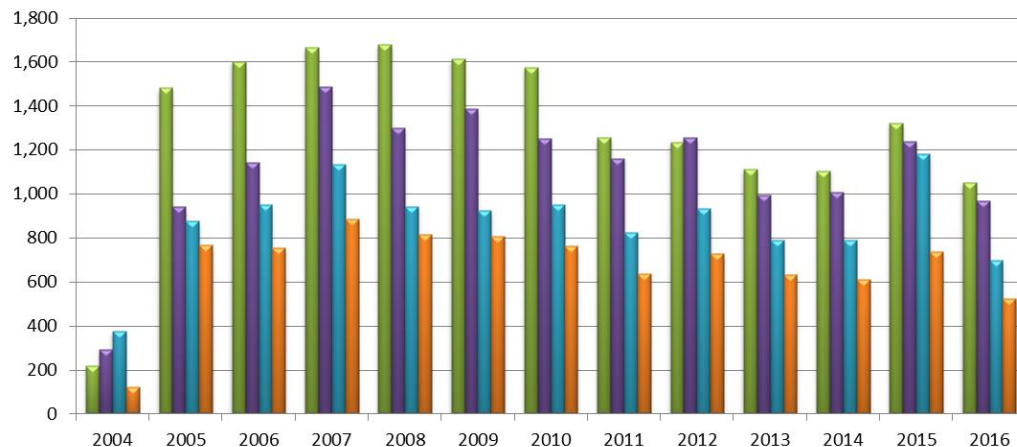
Subscribe to this Search  
To subscribe to the RSS feed for this search click [here](#). This will provide an RSS feed for clinical trials matching your search that have been added or updated in the last 7 days.

Download Options:  
Number of Trials to download:  
  
Download Content:  
  
Download Format:

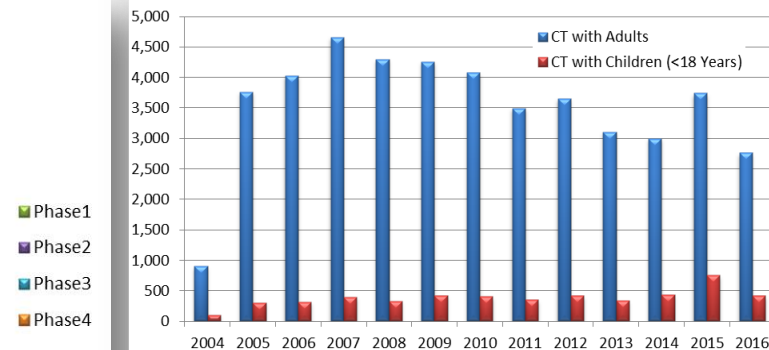


# EU Clinical Trials Register (EudraCT) – Statistics<sup>#</sup>

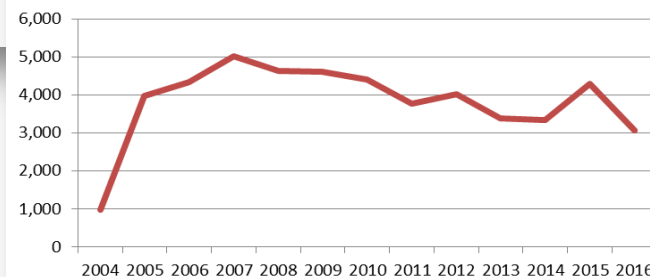
## Number of Clinical Trials in EudraCT



## Number of Clinical Trials by Population



## Number of Clinical Trials in EudraCT over time (n=49,865)



<sup>#</sup> The counts refer to the number of CT in EudraCT authorised by an EU NCA

# Registration of Non-Interventional Studies

07/2012



**European Union Post-Authorisation  
Study (EU PAS) Register**

**Mandatory registration**

- Public register of **non-interventional post-authorisation studies (PAS)** hosted and maintained by EMA;
- EU pharmacovigilance legislation requires EMA to make public the **protocols** and abstracts of **results** of **non-interventional post-authorisation safety studies (PASS)** imposed in accordance with Article 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC [**EU RMP Category 1 + 2**].
- 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).

# Registration of Non-Interventional Studies

07/2012



**European Union Post-Authorisation  
Study (EU PAS) Register**

**Voluntary registration**

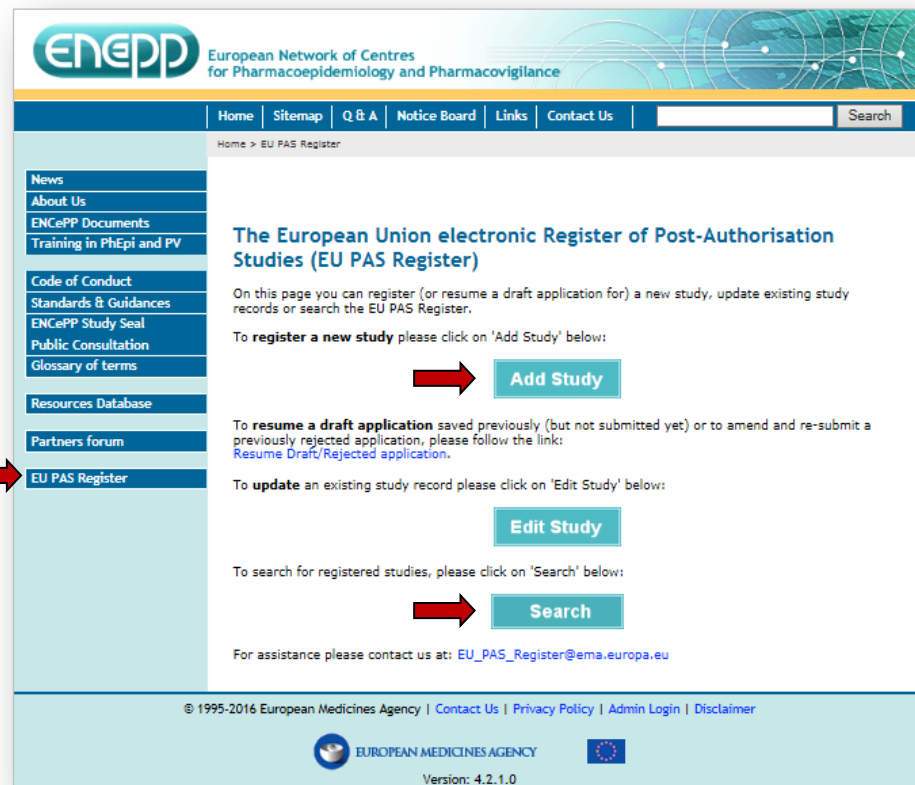
- **PASS initiated, managed or financed voluntarily** by a MAH
  - required in a Risk Management Plan (RMP) [**Category 3**] to further investigate safety concerns **or**
  - to evaluate the effectiveness of risk minimisation activities, and
  - any other PASS

should be registered to **support the same level of transparency, scientific and quality standards.**

- **Non-interventional PAES** outside the scope of DIR 2001/20/EC (including for studies conducted outside the EU) should also be registered in the EU PAS Register.



# EU PAS Register (www.encepp.eu)



**ENePP** European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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Home > EU PAS Register

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

On this page you can register (or resume a draft application for) a new study, update existing study records or search the EU PAS Register.

To **register a new study** please click on 'Add Study' below:

**Add Study**

To **resume a draft application** saved previously (but not submitted yet) or to amend and re-submit a previously rejected application, please follow the link:  
[Resume Draft/Rejected application.](#)

To **update** an existing study record please click on 'Edit Study' below:

**Edit Study**

To search for registered studies, please click on 'Search' below:

**Search**

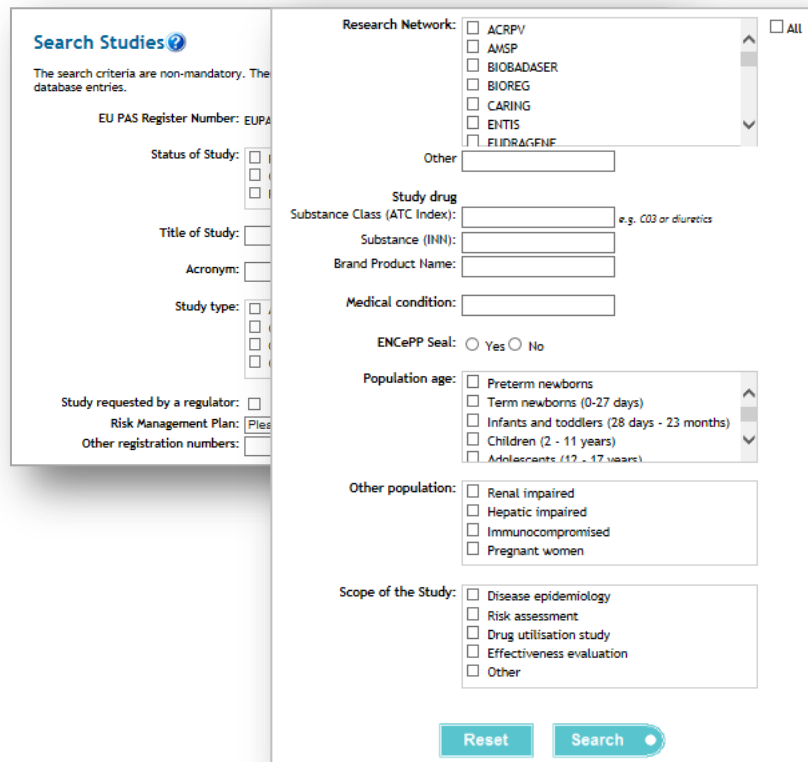
For assistance please contact us at: [EU\\_PAS\\_Register@ema.europa.eu](mailto:EU_PAS_Register@ema.europa.eu)

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EUROPEAN MEDICINES AGENCY

Version: 4.2.1.0

- Hosted on ENCePP website;



**Search Studies**

The search criteria are non-mandatory. The database entries.

EU PAS Register Number: EUPA

Status of Study: ☐ ☐ ☐ ☐

Title of Study:

Acronym:

Study type: ☐ ☐ ☐ ☐

Study requested by a regulator: ☐

Risk Management Plan: ☐

Other registration numbers:

**Research Network:** ☐ ACRPV ☐ AMSP ☐ BIOBADASER ☐ BIOREG ☐ CARING ☐ ENTIS ☐ FLINDRAGFNF ☐ All

Other:

**Study drug**

Substance Class (ATC Index):  e.g. C03 or diuretics

Substance (INN):

Brand Product Name:

**Medical condition:**

**ENCePP Seal:** ☐ Yes ☐ No

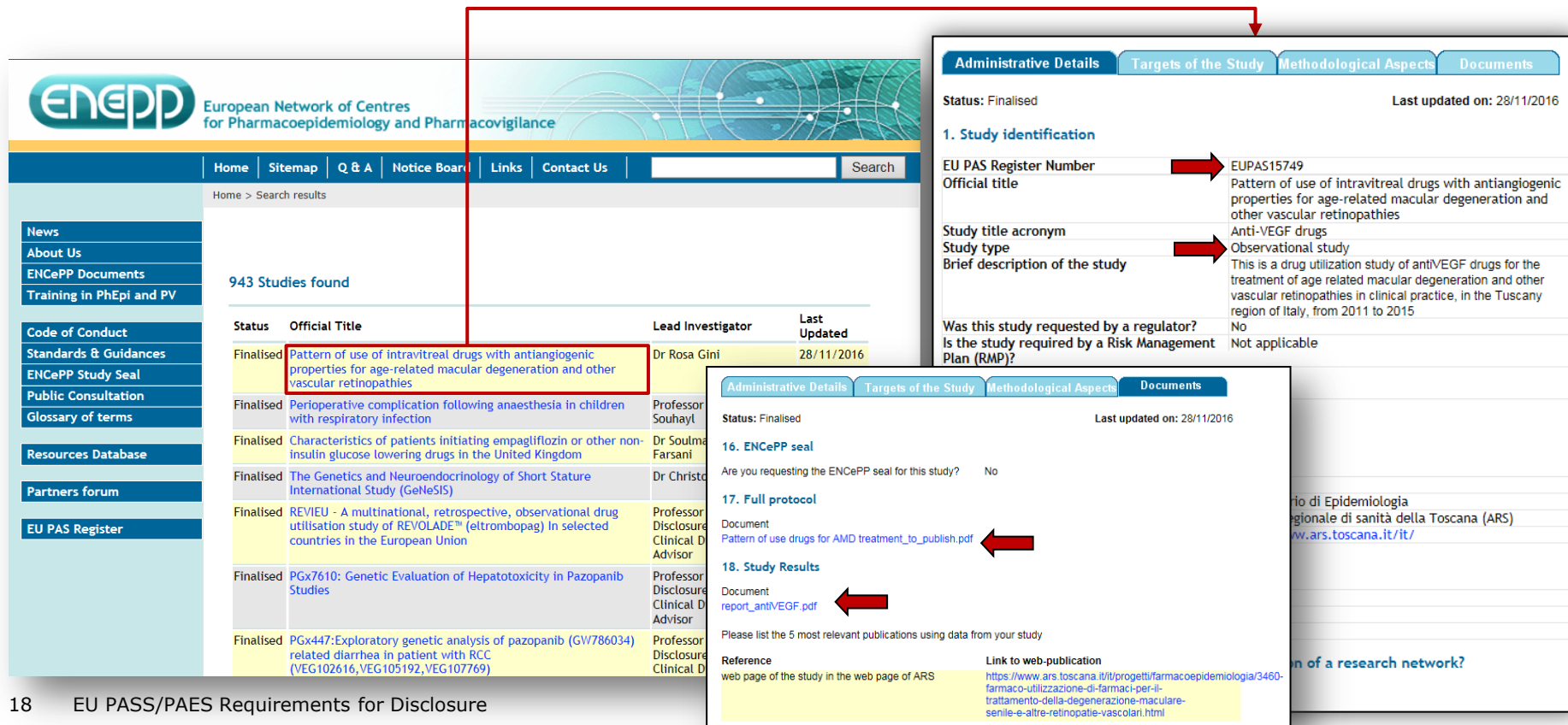
**Population age:** ☐ Preterm newborns ☐ Term newborns (0-27 days) ☐ Infants and toddlers (28 days - 23 months) ☐ Children (2 - 11 years) ☐ Adolescents (12 - 17 years)

**Other population:** ☐ Renal impaired ☐ Hepatic impaired ☐ Immunocompromised ☐ Pregnant women

**Scope of the Study:** ☐ Disease epidemiology ☐ Risk assessment ☐ Drug utilisation study ☐ Effectiveness evaluation ☐ Other

**Reset** **Search**

# EU PAS Register (www.encepp.eu)



The screenshot displays the ENCePP website interface. On the left is a navigation menu with links such as Home, Sitemap, Q & A, Notice Board, Links, Contact Us, News, About Us, ENCePP Documents, Training in PhEpi and PV, Code of Conduct, Standards & Guidances, ENCePP Study Seal, Public Consultation, Glossary of terms, Resources Database, Partners forum, and EU PAS Register. The main content area shows search results for '943 Studies found'. A table lists several studies, with the first one highlighted: 'Pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies'. A red box highlights this study title, and a red arrow points from it to a detailed view of the study on the right. The detailed view shows administrative details, targets of the study, methodological aspects, and documents. Red arrows indicate specific fields: 'EU PAS Register Number' (EUPAS15749), 'Official title' (Pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies), 'Study title acronym' (Anti-VEGF drugs), 'Study type' (Observational study), 'Brief description of the study' (This is a drug utilization study of antiVEGF drugs for the treatment of age related macular degeneration and other vascular retinopathies in clinical practice, in the Tuscany region of Italy, from 2011 to 2015), 'Was this study requested by a regulator?' (No), 'Is the study required by a Risk Management Plan (RMP)?' (Not applicable), '16. ENCePP seal' (Are you requesting the ENCePP seal for this study? No), '17. Full protocol' (Document: Pattern of use drugs for AMD treatment\_to\_publish.pdf), '18. Study Results' (Document: report\_antiVEGF.pdf), and 'Reference' (web page of the study in the web page of ARS: https://www.ars.toscana.it/it/progetti/farmacoevidenza/3460-farmacoevidenza-di-farmacoevidenza-per-il-trattamento-della-degenerazione-maculare-senile-e-altre-retinopatie-vascolari.html).

**ENCePP** European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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Home > Search results

943 Studies found

Status	Official Title	Lead Investigator	Last Updated
Finalised	Pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies	Dr Rosa Gini	28/11/2016
Finalised	Perioperative complication following anaesthesia in children with respiratory infection	Professor Souhail	
Finalised	Characteristics of patients initiating empagliflozin or other non-insulin glucose lowering drugs in the United Kingdom	Dr Souma Farsani	
Finalised	The Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS)	Dr Christa	
Finalised	REVIEW - A multinational, retrospective, observational drug utilisation study of REVOLADE™ (eltrombopag) in selected countries in the European Union	Professor Disclosure Clinical D Advisor	
Finalised	PGx7610: Genetic Evaluation of Hepatotoxicity in Pazopanib Studies	Professor Disclosure Clinical D Advisor	
Finalised	PGx447: Exploratory genetic analysis of pazopanib (GW786034) related diarrhea in patient with RCC (VEG102616, VEG105192, VEG107769)	Professor Disclosure Clinical D Advisor	

**Administrative Details** | Targets of the Study | Methodological Aspects | Documents

Status: Finalised Last updated on: 28/11/2016

**1. Study identification**

EU PAS Register Number → EUPAS15749

Official title → Pattern of use of intravitreal drugs with antiangiogenic properties for age-related macular degeneration and other vascular retinopathies

Study title acronym → Anti-VEGF drugs

Study type → Observational study

Brief description of the study → This is a drug utilization study of antiVEGF drugs for the treatment of age related macular degeneration and other vascular retinopathies in clinical practice, in the Tuscany region of Italy, from 2011 to 2015

Was this study requested by a regulator? No

Is the study required by a Risk Management Plan (RMP)? Not applicable

**Administrative Details** | Targets of the Study | Methodological Aspects | Documents

Status: Finalised Last updated on: 28/11/2016

**16. ENCePP seal**

Are you requesting the ENCePP seal for this study? No

**17. Full protocol**

Document

Pattern of use drugs for AMD treatment\_to\_publish.pdf →

**18. Study Results**

Document

report\_antiVEGF.pdf →

Please list the 5 most relevant publications using data from your study

Reference

web page of the study in the web page of ARS

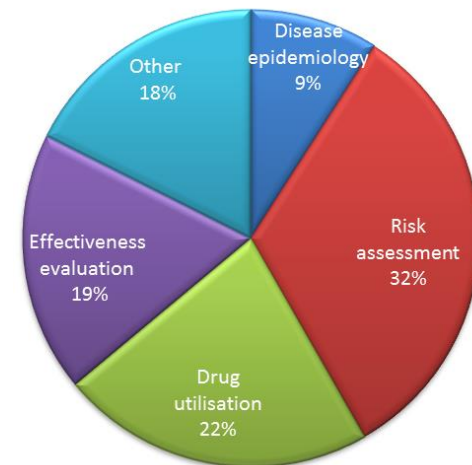
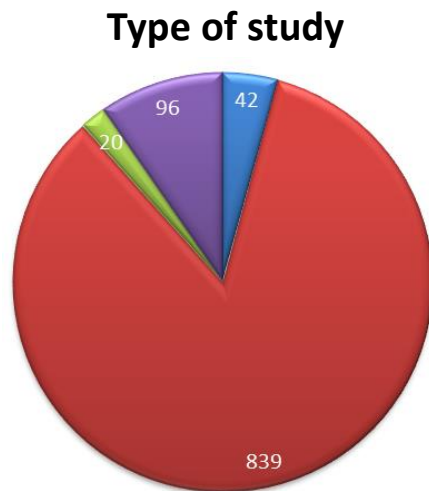
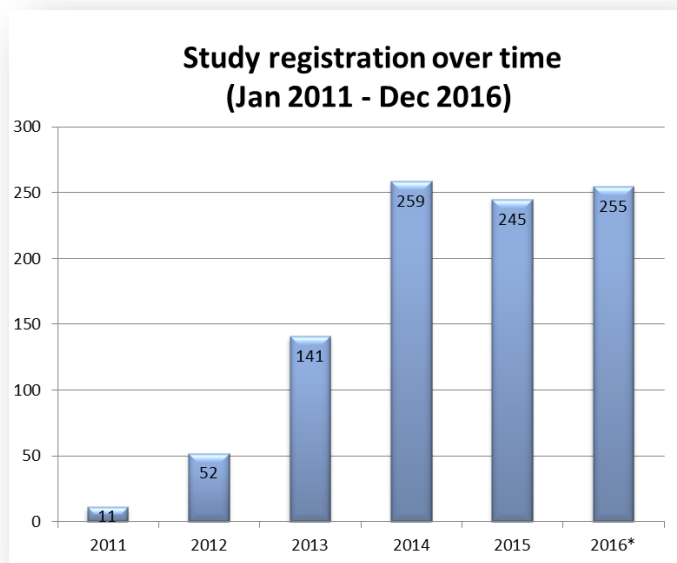
Link to web-publication

https://www.ars.toscana.it/it/progetti/farmacoevidenza/3460-farmacoevidenza-di-farmacoevidenza-per-il-trattamento-della-degenerazione-maculare-senile-e-altre-retinopatie-vascolari.html



## EU PAS Register - Statistics

- 997 studies registered by 3 Feb 2017
- 508 (51%) requested by regulator (EU and non-EU)



■ Active surveillance

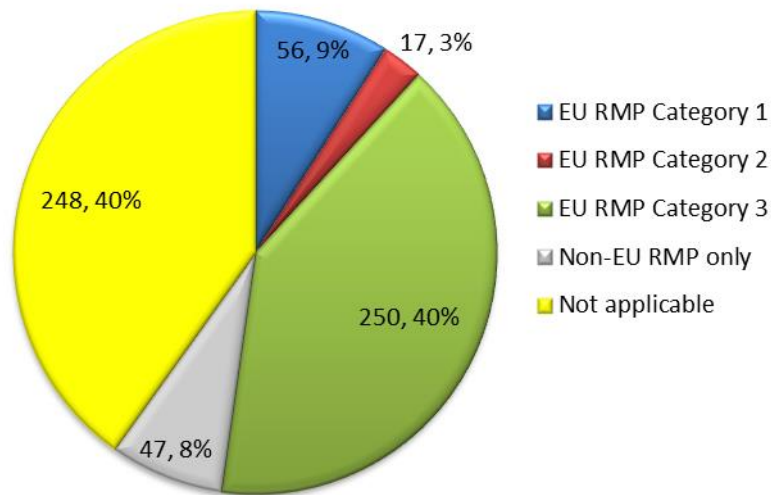
■ Non-interventional  
(observational)

■ Clinical trial

■ Other

## EU PAS Register – RMP Studies

- 618 (62%) of studies provide this information (feature available since 07/2016)
- 370 (37%) studies are part of a pharmacovigilance plan (EU or non-EU RMP) by 3 Feb 2017 (n=997)



# Disclosure requirements for PASS – Summary I

**Non-interventional PASS imposed** as a legal obligation by a regulatory authority (EU RMP Category 1):

- Legal obligation of MAH to register the study in **EU PAS Register**
  - obligation applies **at the time of study report**
- Legal obligation of MAH as regards the format of the **study protocol, study report** and **abstract** of study report (GVP VIII Annex III)
- Recommendations in GVP VIII
  - MAH to upload the **study protocol prior to start of data collection** or data extraction
  - MAH to upload study **report within two weeks of finalisation**

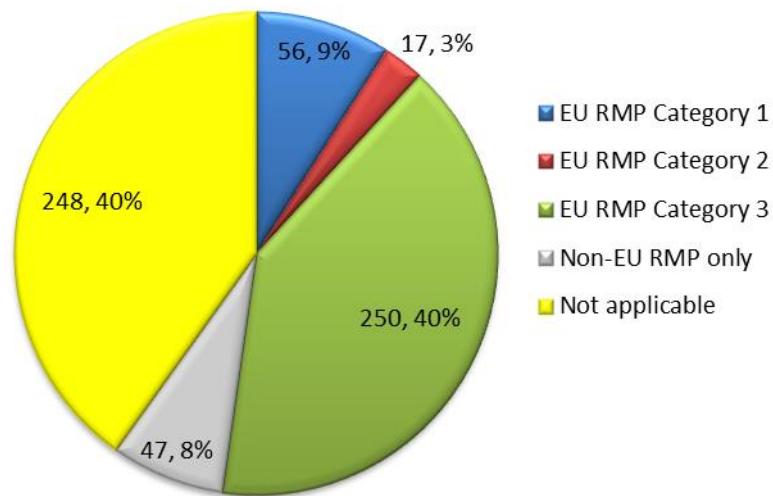
## Disclosure requirements for PASS – Summary II

- To be encouraged to **upload** in the EU PAS Register the **protocols** and **results** of **non-interventional imposed PASS after PRAC recommendation** has been issued.
  - EMA will otherwise upload the protocols and public abstracts of results into the EU PAS Register on its own initiative in order to fulfil its legal obligations\* unless alternative timelines are agreed.
- PASS protocols and full study reports may be publicly available via the Agency's obligation to provide **Access to Documents** under Regulation (EC) No 1049/2001 (subject to the exceptions set out in Article 4).
- If PASS is a **clinical trial** it should be registered in the **EU Clinical Trial Register** and a **summary of the results** should be uploaded to be made public.

\*Article 26(1)(h) of Regulation (EC) No 726/2004 requires the Agency to make public "protocols and public abstracts of results of the post-authorisation safety studies referred to Articles 107n and 107p of Directive 2001/83/EC".



# EU PAS Register – Disclosure Imposed PASS (3 Feb 2017)



## EU RMP Category 2

### 7 Finalised

- 4 with protocol & report
- 1 with protocol only

### 6 Ongoing

- 3 with protocol

### 4 Planned

- 1 with protocol

## EU RMP Category 1

### 7 Finalised

- 3 with protocol & report
- 1 with protocol only
- 2 with report only

### 35 Ongoing

- 19 with protocol

### 14 Planned

- 7 with protocol

## Disclosure requirements for PAES – Summary

**PAES initiated, managed or financed by a MAH voluntarily, or pursuant to an obligation imposed** by a competent authority [within or outside the scope of Delegated Regulation (EU) No 357/2014]:

- PAES which fall under the definition of a **clinical trial** in line with DIR 2001/20/EC should be registered in the **EU Clinical Trial Register**;
- **Non-interventional** PAES should be registered in the **EU PAS Register**;





# Questions?

Thank you for your attention.

## Further information

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[[www.ema.europa.eu](http://www.ema.europa.eu)]

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