EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU PASS/PAES Requirements for Disclosure

10th Industry Stakeholder Platform – Operation of EU pharmacovigilance , London, 3 February 2017

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  - 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

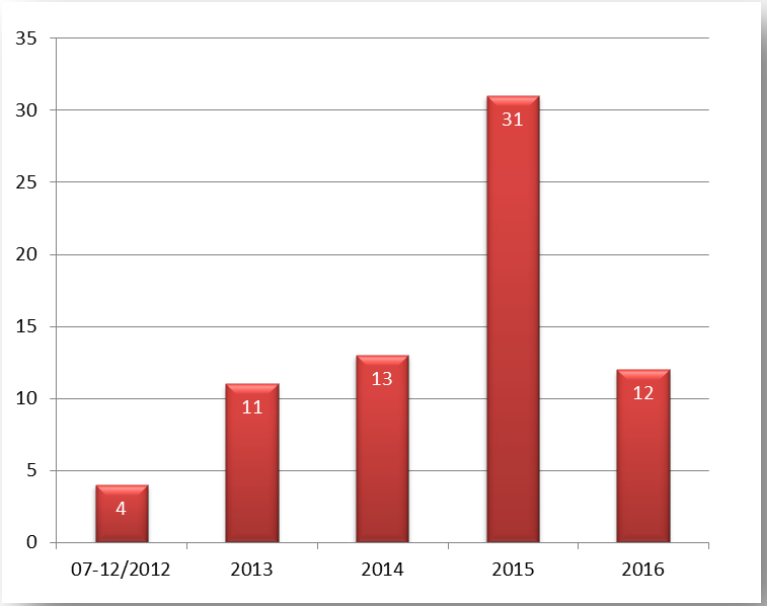
- Study not to promote use of product
- Payments to HCPs […] shall be restricted
- MAH to submit **protocol and progress report** to MS where study is conducted (on request of NCA)
- MAH to send **final study reports** within 12 months of end of data collection to NCA where the study was conducted
- 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

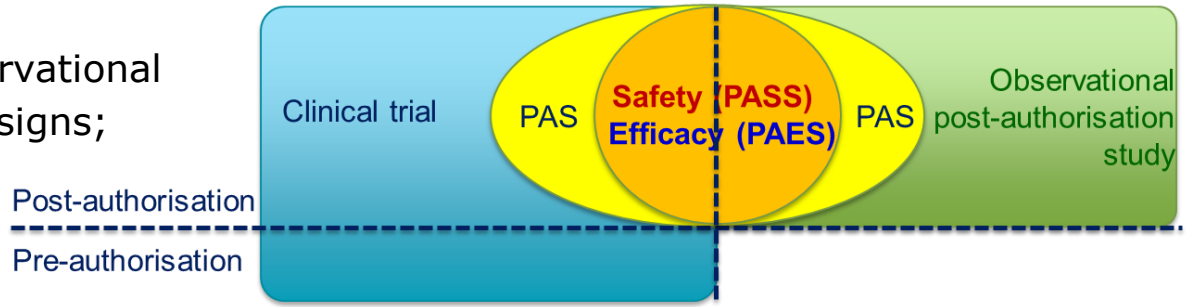
Number of imposed non-interventional PASS protocols reviewed* by PRAC Jul 2012 – Dec 2016



*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) 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)

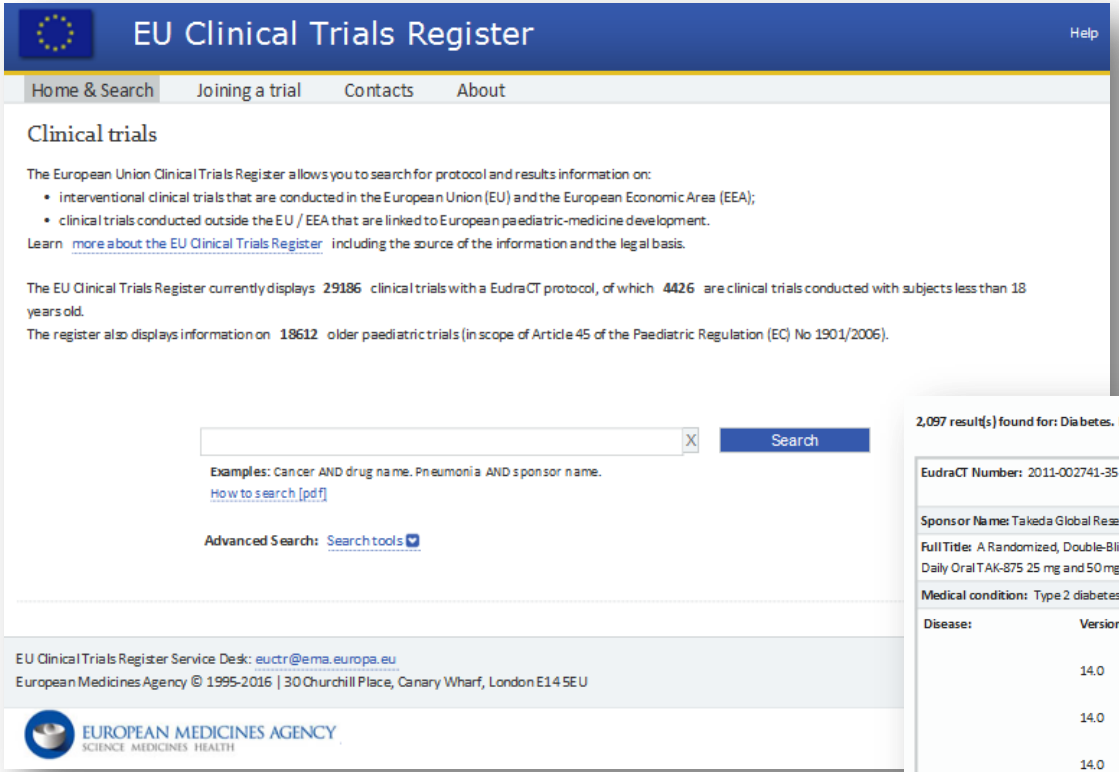
2018 →

European Union Clinical Trials Portal and Database

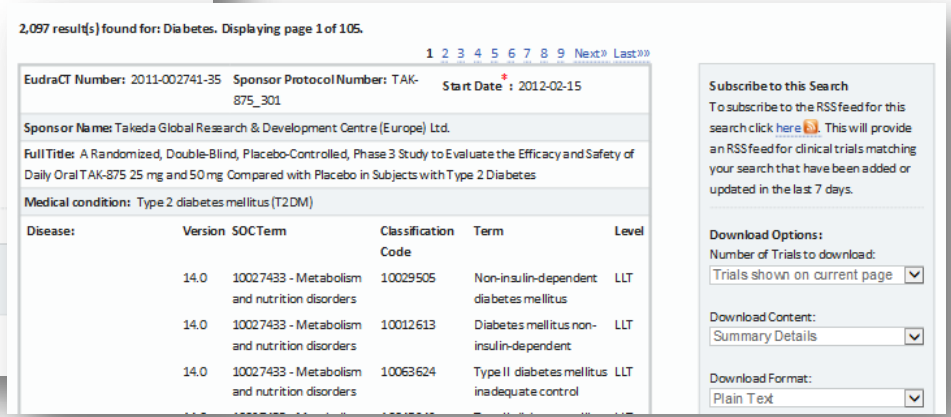
- Portal as **single entry point** for submitting **clinical trial information in the EU**
- EMA makes information stored in the database publicly available subject to transparency and disclosure rules:
  - Appendix on disclosure rules to functional specifications for the EU Portal and Database (EMA/228383/2015)

⇨ **Applies to PASS and PAES falling under the definition of a clinical trial**

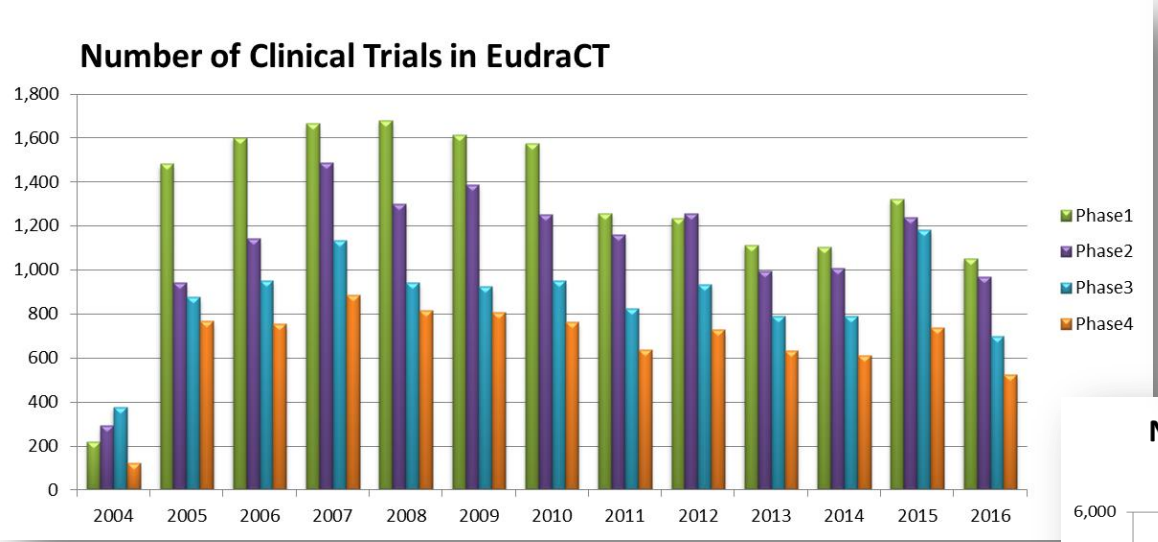
EU Clinical Trials Register (www.clinicaltrialsregister.eu)

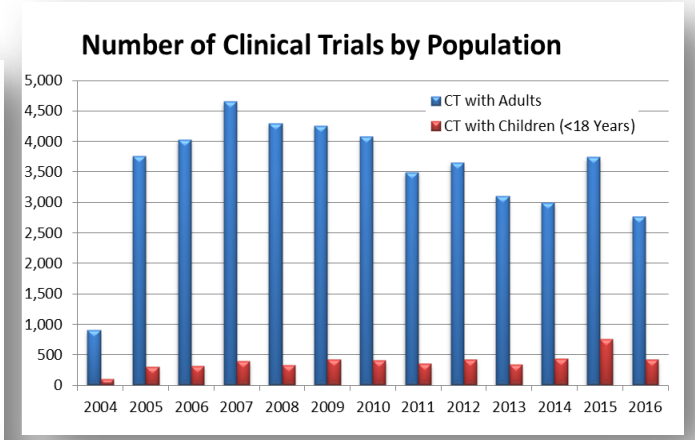


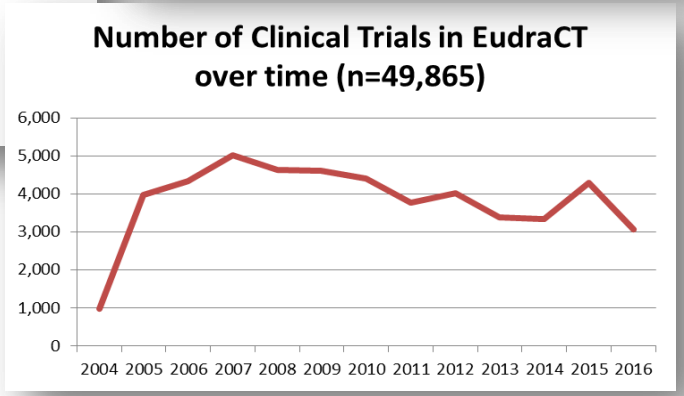
- Contains interventional clinical trials starting after 01/05/2004;
- Results disclosure mandatory since 07/2014;
- Online guidance on searching the register;



EU Clinical Trials Register (EudraCT) – Statistics#







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**

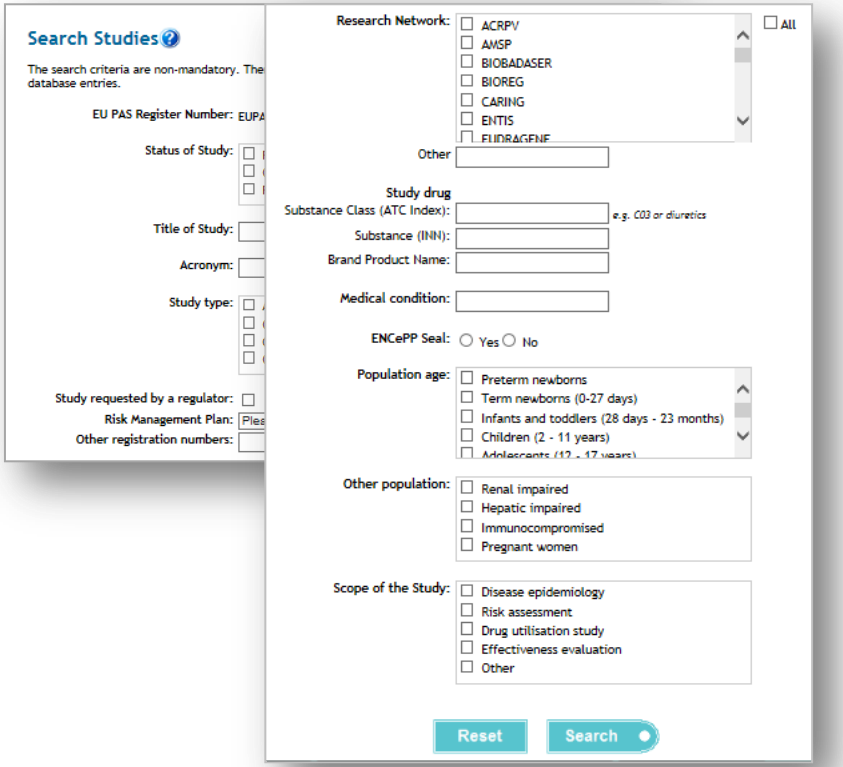
Voluntary registration

- **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

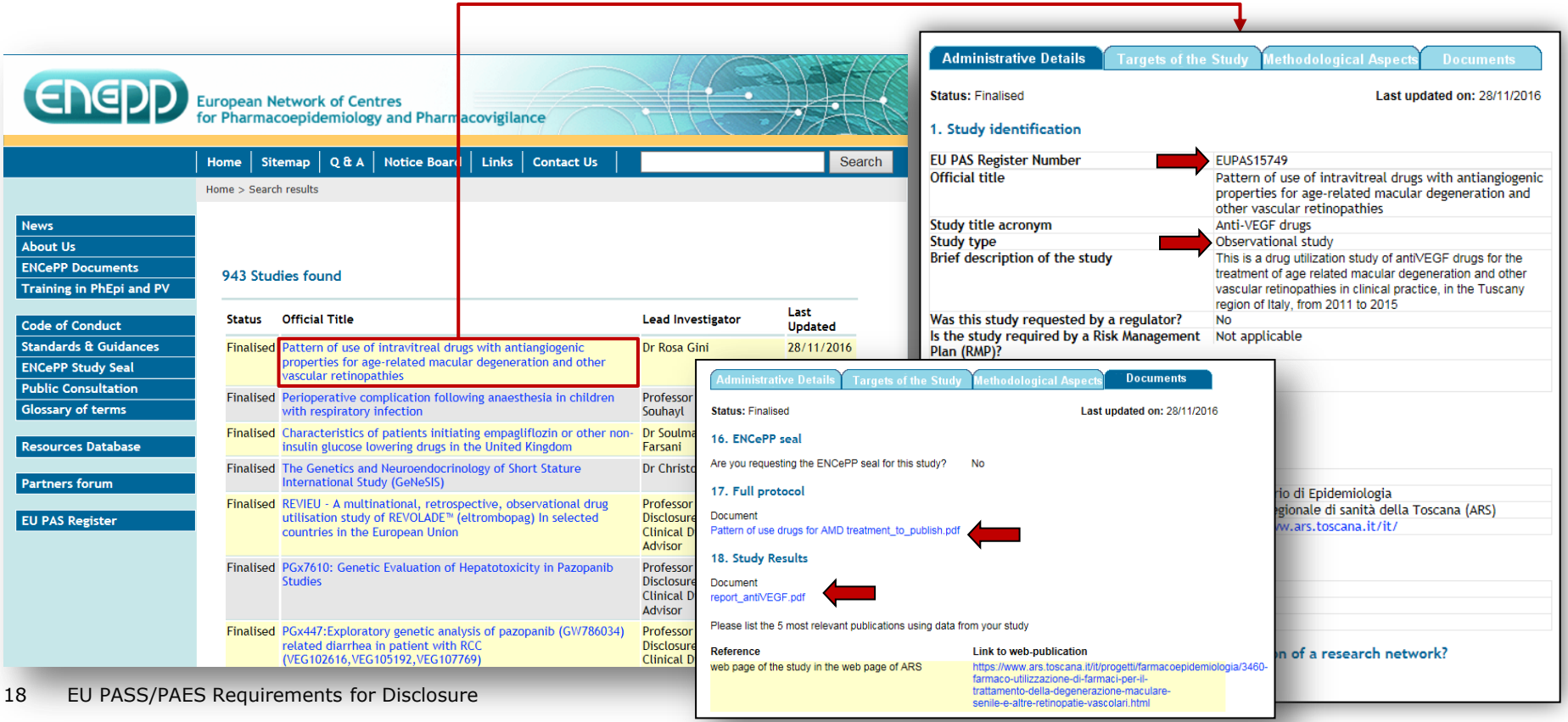
  should be registered to **support the same level of transparency, scientific and quality standards.**
- **Non-interventional PAES** outside the scope of DIR 2001/20/EC (including for studies conducted outside the EU) should also be registered in the EU PAS Register.

EU PAS Register (www.encepp.eu)

- Hosted on ENCePP website;

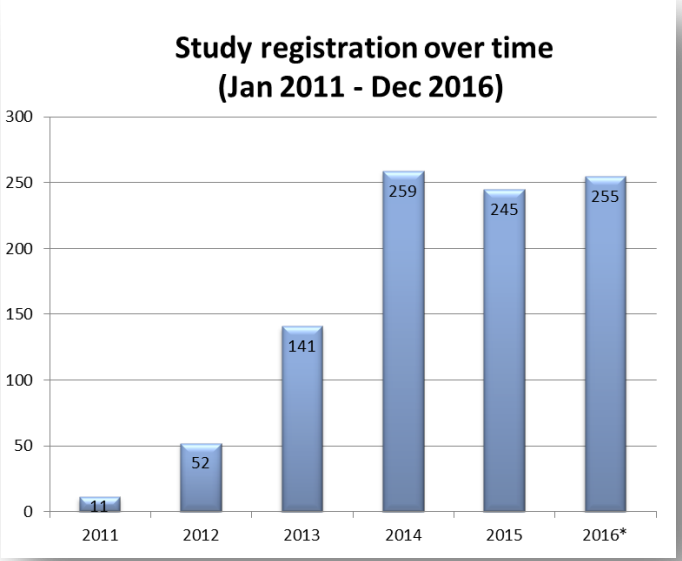


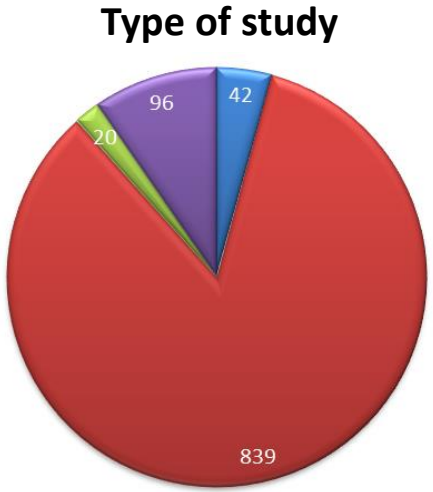
EU PAS Register (www.encepp.eu)

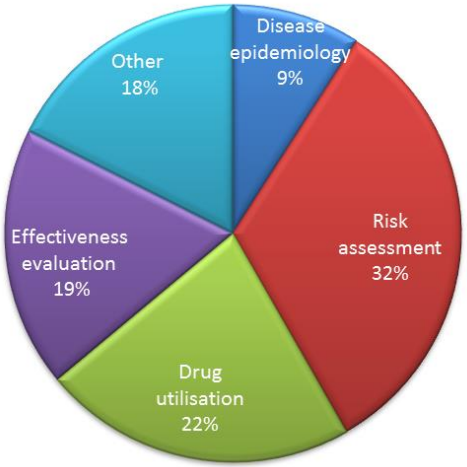


EU PAS Register - Statistics

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





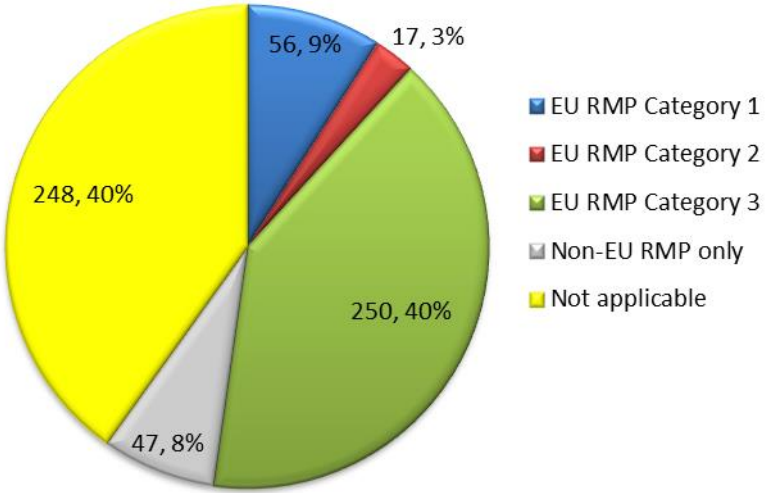


Scope of study

- 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):

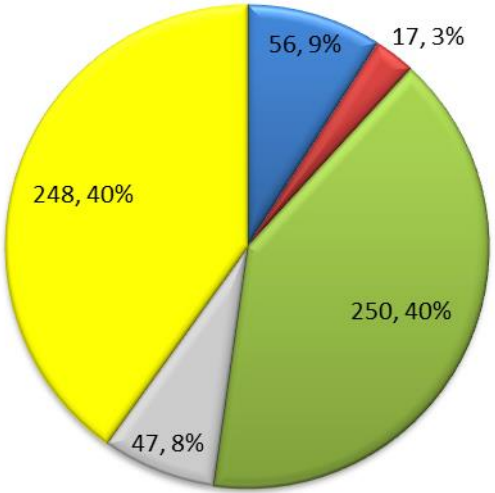
- Legal obligation of MAH to register the study in **EU PAS Register**
  - obligation applies **at the time of study report**
- Legal obligation of MAH as regards the format of the **study protocol**, **study report** and **abstract** of study report (GVP VIII Annex III)
- Recommendations in GVP VIII
  - 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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