EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Overview of GVP modules V (risk management systems), VIII (post-authorisation safety studies) and ENCePP

EU 28: Science, medicines, health – a regulatory system fit for the future, 6-8 May 2013, Dubrovnik

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Pharmacovigilance and Risk Management

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Outline of the presentation

- **Legal Basis**
- GVP V - The new EU Risk Management Plan (EU-RMP)
- GVP VIII - Post-authorisation Safety Studies (PASS)
- ENCePP

Legal Basis

- The application for MA shall be accompanied by [DIR Article 8(3)(iaa)]:

  (ia) A summary of the applicant's **pharmacovigilance system** which shall include the following elements [...]:

  (iaa) The **risk management** plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a **summary** thereof.
  The risk management system [...] shall be **proportionate** to the risks and the need for post-authorisation data.

- Definition

  Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.

New RMP Requirements for MAH (I)

- As part of the pharmacovigilance system, the marketing authorisation holder shall operate a **risk management system for each medicinal** product [DIR Article 104]
- Holders of MA **granted before 2 July 2012** shall **not** be required to operate a risk management system for each medicinal product [REG Article 21]
- Legal basis for older MA: 'The Agency may **impose the obligation to operate risk management system…'**
  [REG Article 21 (2)]

New RMP Requirements for MAH (II)

The marketing authorisation holder shall incorporate any **conditions or requirements** referred to in Articles 9(4) points (c)(ca)(cb)(cc), 10a, 14(7) and 14(8) in his **risk management system** [REG Article 14a]:

- Conditions and restrictions for safe and effective use
- Recommended measures for safe use
- Post-Authorisation Safety Studies (PASS)
- Post-Authorisation Efficacy Studies (PAES)
- Post-approval obligation for PASS / PAES
- Specific Obligations
- Exceptional Circumstances

New RMP Requirements for MAH (III)

As part of the pharmacovigilance system, the marketing authorisation holder shall [DIR Article 104]:

3(d) monitor the outcome of risk minimisation measures which are contained in the risk management plan or which are laid down as conditions of MA.

3(e) update the risk management system and monitor pharmacovigilance data to determine

- if there are new risks
- if risks have changed
- if benefit-risk balance has changed (PSUR + EU-RMP)

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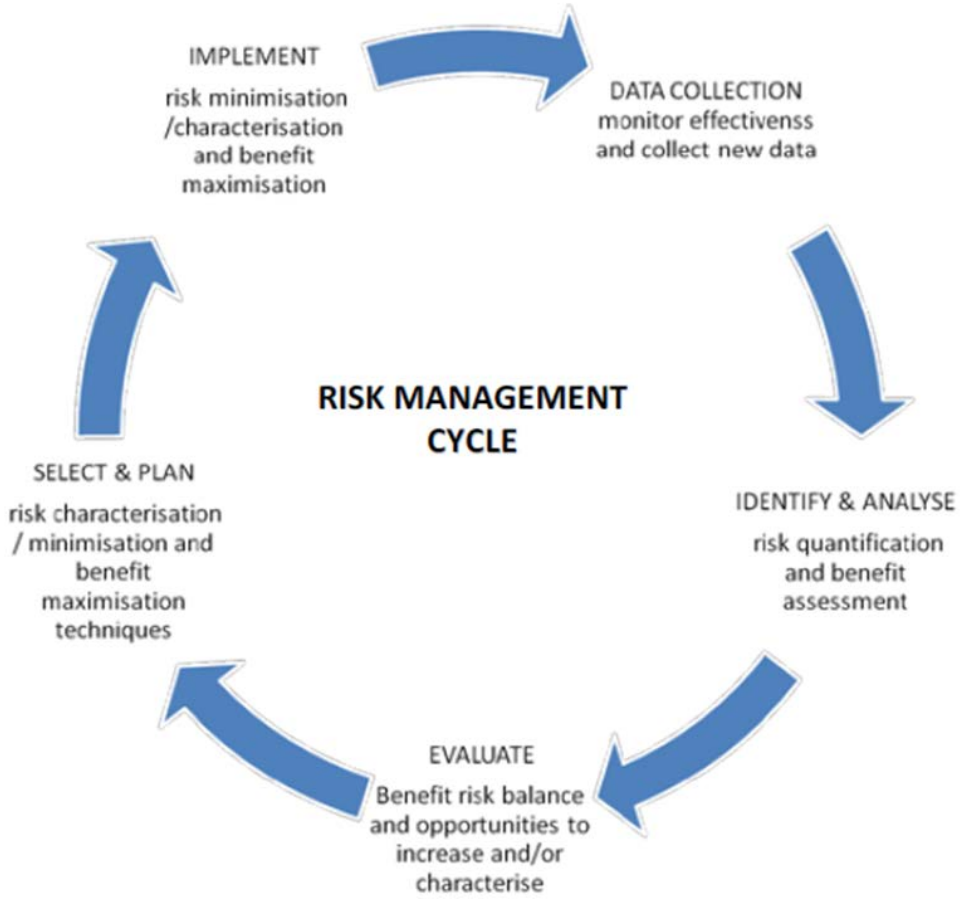
Principles of Risk Management

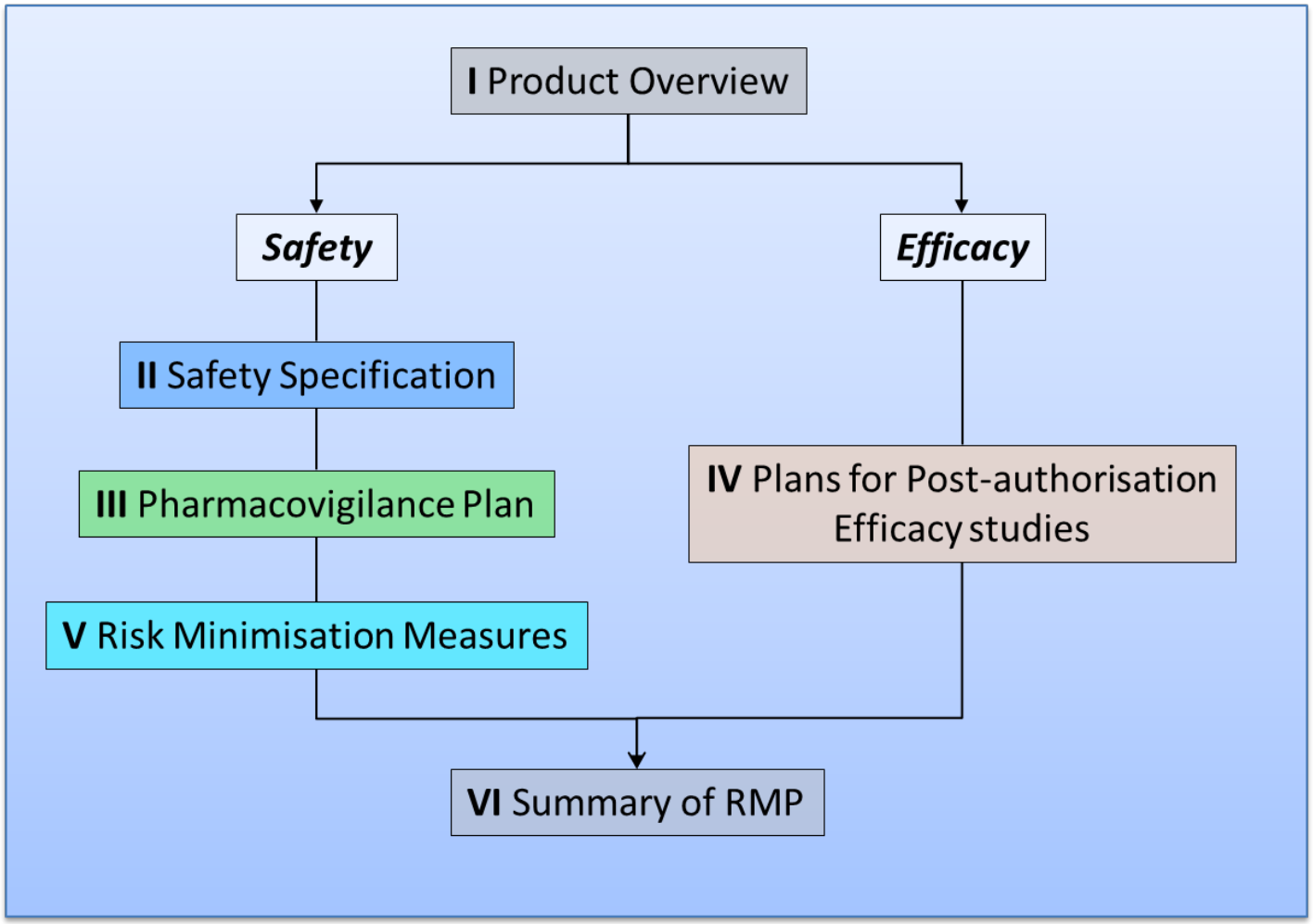


New RMP Structure - Parts and Modules

Part I	**Product Overview**
Part II	**Safety Specification** Module SI Epidemiology of indication and target population Module SII Non-clinical part of Safety Specification Module SIII Clinical trial exposure Module SIV Populations not studied in clinical trials Module SV Post-authorisation experience Module SVI Additional EU requirements for Safety Specification Module SVII Identified and potential risks (non-ATMPs) Module SVIIa Identified and potential risks (ATMPs) Module SVIII Summary of safety concerns
Part III	**Pharmacovigilance Plan**
Part IV	**Plans for post-authorisation efficacy studies**
Part V	**Risk Minimisation Measures**
Part VI	**Summary of the risk management plan**
Part VII	**Annexes**

GVP modules V (risk management systems), VIII (post-authorisation safety studies) & ENCePP

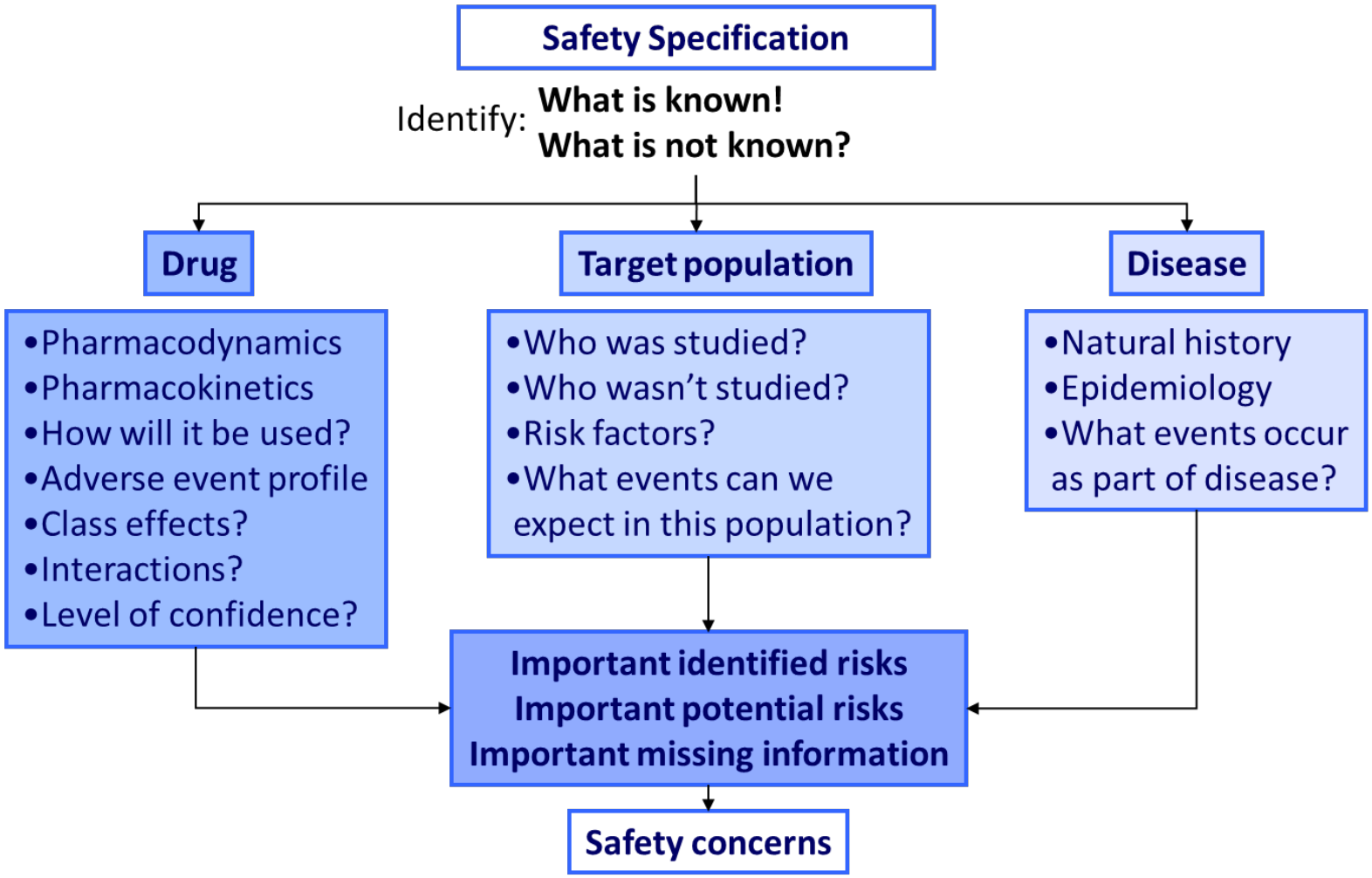
Information flow in the RMP



Part I Product Overview

- Active substance (INN) – RMP is substance-based
- Pharmaco-therapeutic group (ATC)
- MAH
- Products concerned
- Data lock point - RMP version
- Date when each part/module was last submitted
- Authorisation procedure - QPPV
- Product description (mode of action)
- Indication
- Posology
- Pharmaceutical forms/strengths

Part II Safety Specification Information Flow

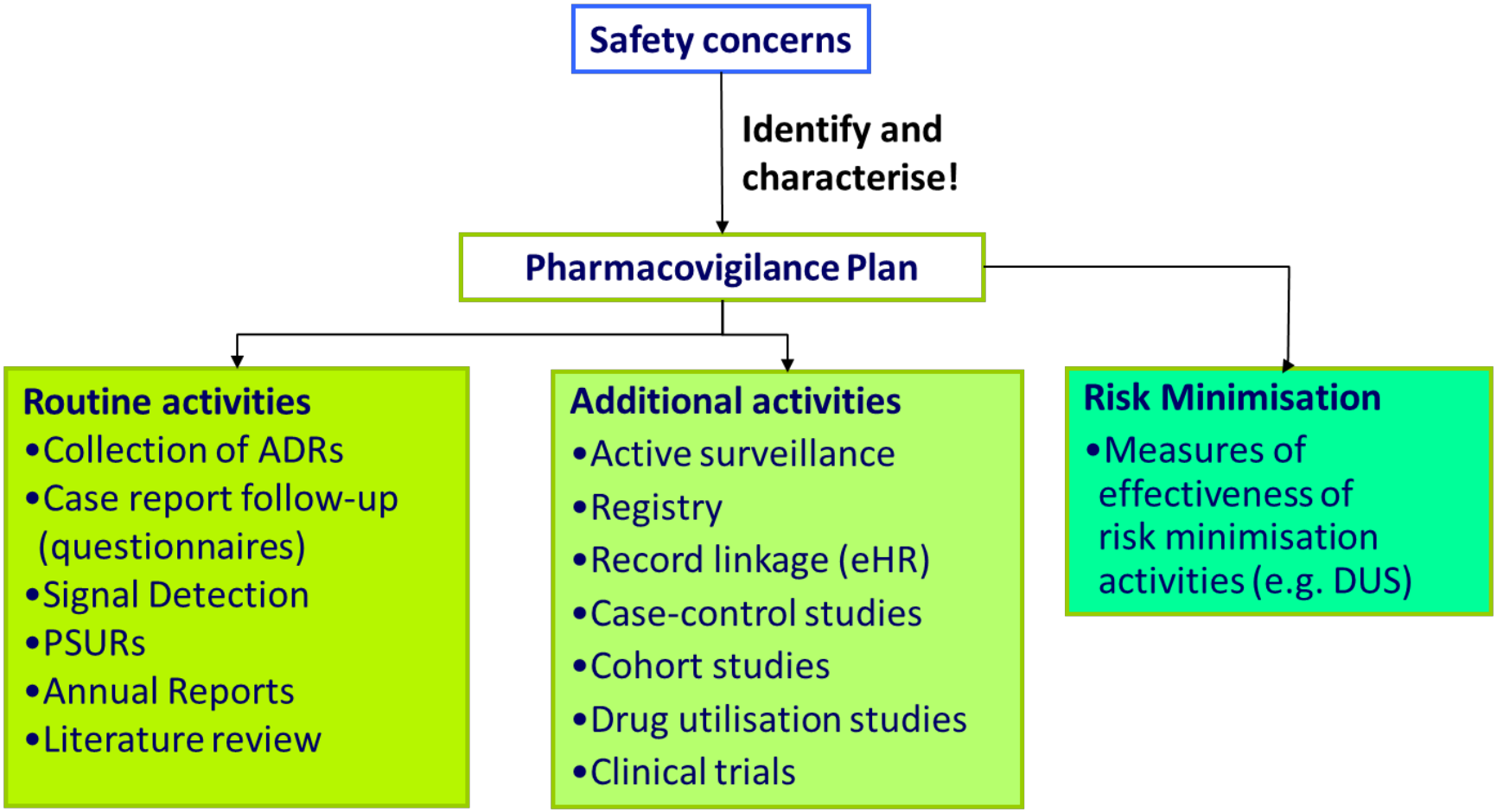


Part II Module SVI Additional EU requirements

Covers potential safety concerns not included in ICH E2E:

- Harm from overdose
- Transmission of infectious agents
- Misuse for illegal purposes
- Medication errors
  - Any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer (wrong medication, dose, route of administration or patient)
  - Assess potential for ME during development and design phase of the product with regard to naming, presentation, instructions for use and labelling
- (Paediatric) off-label use
- Paediatric safety and efficacy issues identified in PIP

Part III Pharmacovigilance Plan

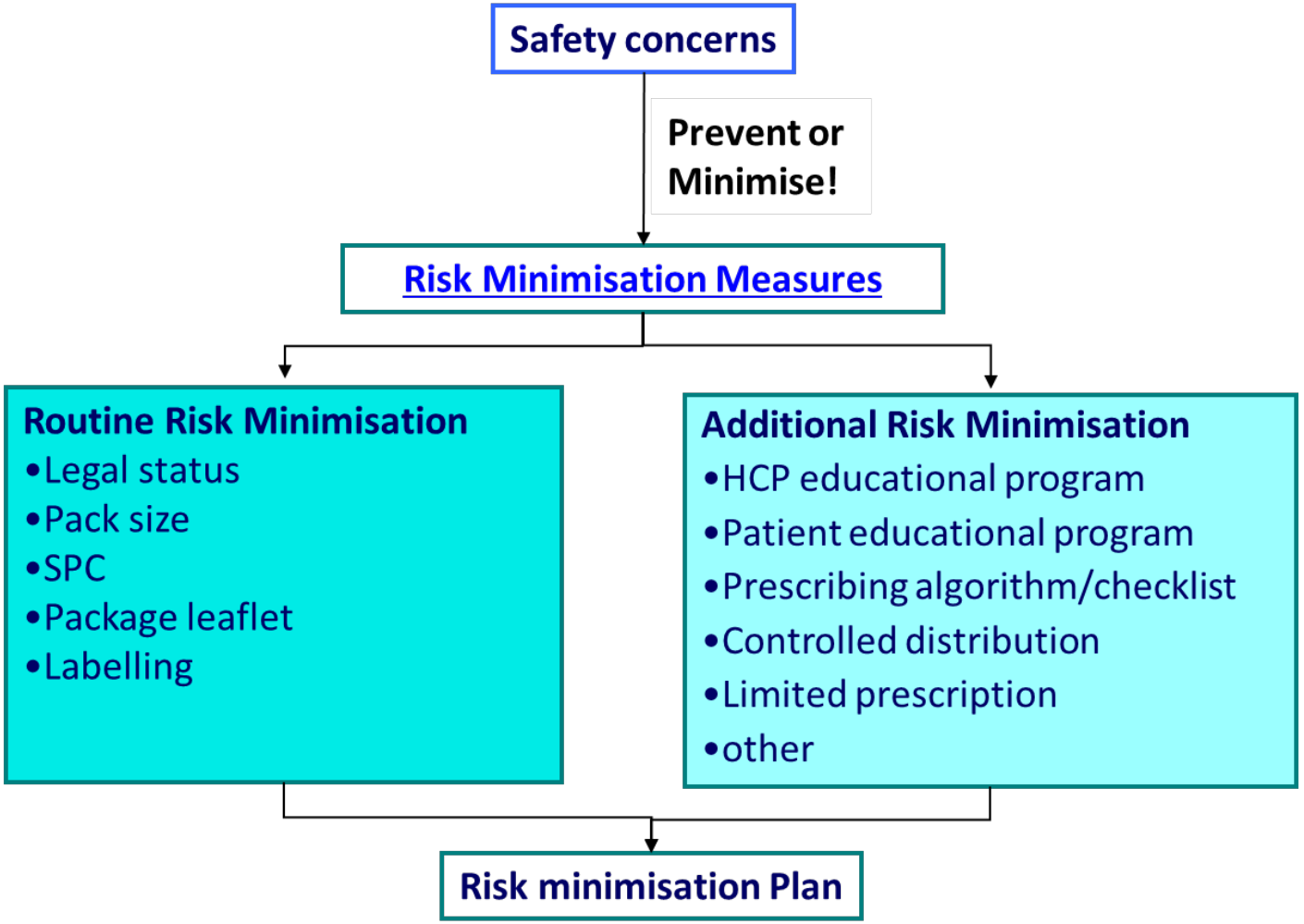


Part IV Plan for post-authorisation efficacy studies (PAES)

- In line with RMP definition, but scope is expanded to include elements of benefit/real world efficacy
- EC Delegated Act on PAES determines situations when needed
- Part IV contents
  - Summary of efficacy data based on clinical trials and their endpoints
  - Short review how the product fits in the therapeutic armamentarium compared to standard treatment
  - Discussion of robustness of endpoints and need for further studies
  - Applicability of efficacy data to all patients in target population in everyday medical practice
  - Consideration of studies to ascertain which patients benefit most

GVP modules V (risk management systems), VIII (post-authorisation safety studies) & ENCePP

Part V Risk Minimisation Measures



Part V EU-specific Aspects of Risk Minimisation

- In EU risk minimisation activities (e.g. restricted access, educational programmes, control of prescription, named patients registries) depend in many cases on national legislation
- **Principles applied at CHMP Opinion**:
  - Only **key components of educational material** considered essential for the safe use of the product are adopted
  - Obligation (MAH/MS) to implement components, but practical aspects may differ across Member States
  - No marketing in Member States without implementation
  - Educational programme must not be promotional
  - Agreement on **key message(s)** of educational programme; details left to National decision

Part V EU-specific Aspects of Risk Minimisation

Effectiveness of risk minimisation activities should be **measured**

- Legislation requires **active monitoring of the outcome** of risk minimisation measures
- Crucial aspect of continuous pharmacovigilance
- Criteria to assess the effectiveness of each (additional) activity should be **outcome measures** that **indicate the success or failure** of the process implemented based on agreed standards
- Define regular intervals with milestones included in RMP
- Consider burden on patients/prescribers and performance in healthcare system

→ Further guidance will be provided in GVP Module XVI

Part VI Public Summary of the RMP

- Overview of disease epidemiology
- Summary of benefits/efficacy and uncertainties
- Summary of safety concerns (including preventability)
- Summary of risk minimisation measures by safety concern
  - Routine & additional measures
- Planned post-authorisation development plan
  - Studies which are a condition of MA
- Summary of major changes to RMP over time
- Written in lay scientific language

→ Template for RMP Summary is currently under development

→ Routine consultation of Patient and HCP Organisations

PRAC Mandate on RMPs

REG Article 56(1)

(aa) […] the PRAC, which shall be responsible for providing recommendations to the CHMP and the CMD on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on **risk management systems** and it shall be responsible for **monitoring the effectiveness of those risk management systems**;

→ **PRAC ADVICE** to CHMP/CMDh on **Risk Management Plans**

→ For CHMP adoption but CHMP can also amend/reject

Outline of the presentation

- EU Legislation
- GVP V - The new EU Risk Management Plan (EU-RMP)
- **GVP VIII - Post-authorisation Safety Studies (PASS)**
- ENCePP

Post-authorisation Safety Studies (PASS)

Definition [DIR Article 1(c)]

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.

Objectives

- To quantify potential or identified risks
- To evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment)
- To provide evidence about the absence of a risk
- To assess patterns of drug utilisation that add knowledge on the safety (e.g. indications, dosage, co-medication, medication errors)
- To measure the effectiveness of a risk minimisation activity

PASS Categories and Supervision

GVP Module V.B.9.4: Summary table of additional pharmacovigilance activities

	Type of activity	In Annex II of Opinion (CAPs only)	Category in Summary table of PhV activities	Status	Supervised under Article 107m	Supervised under Article 107 n-q
Imposed PASS	"Interventional"*	X	1	Mandatory and subject to penalties		
	Non-interventional	X	1	Mandatory and subject to penalties	X	X
Specific obligation	"Interventional"*	X	2	Mandatory and subject to penalties		
	Non-interventional	X	2	Mandatory and subject to penalties	X	X
Required	"interventional"*		3	Legally enforceable		
	Non-interventional		3	Legally enforceable	X	
Stated	"interventional"*		4	Not enforced		
	Non-interventional		4	Not enforced	X	

PASS - MAH initiated, managed or financed

1 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) [*Category 1*]
- as part of a marketing authorisation granted under exceptional circumstances [*Category 2*]

→ **PASS oversight by PRAC** [DIR Articles 107m-q]

→ **Mandatory format of study protocol, abstract and study results** [IR Articles 36-38]

Supervision of PASS Category 1+2

DIR Articles 107n-q

- Articles 107n - 107q apply **exclusively to imposed PASS**

(n) **Prior to study start** the MAH has to **submit draft protocol to PRAC** (or national competent authority when conducted in only 1 MS) **for endorsement** (or objection) within a 60 days TT

(o) After study start **protocol amendments require PRAC/NCA endorsement** (or objection)

(p) Final study report submitted to the PRAC/NCA **within 12 months** of the end of data collection + electronically submit an abstract of the study results

(q) Based on results PRAC makes recommendations

PASS - MAH initiated, managed or financed

2 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

→ **Submission of protocol and final report** [DIR Art 107m]

→ Provisions for imposed studies (e.g. format of study protocol, abstract and study results) are not mandatory but recommended

Supervision of PASS Category 3

DIR Article 107m

- Applies to **all non-interventional post-authorisation safety studies**
- The studies shall not promote the use of a medicinal product
- MAH required to **submit protocol and progress report to MS** where study is conducted (on request of national competent authority)
- MAH required to send **final study reports within 12 months of end of data collection**
- MAH required to **monitor** data and implication on **B/R balance** while study is conducted

→ **PRAC assessment of protocols and study results** in context of RMP

→ For same quality standards the MAH should follow format and content of protocol and study report in line with IR

PASS Protocol – General Provisions for MAH

For Studies imposed as obligation by Competent Authority

- Imposed format
- Draft protocol to be submitted to PRAC before study is conducted
- PRAC decision within 60 days
- Study may commence only after written endorsement of protocol and transmission of endorsed protocol to the NCAs
- Any substantial amendment to the protocol to be submitted to PRAC
- Registration of study in **EU PAS register** recommended

For studies conducted voluntarily by MAH

- Format of study protocol and final report recommended
- Registration of study in **EU PAS register** recommended

PRAC Mandate on PASS

REG Article 61

The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use**, the design and evaluation of post-authorisation safety studies** and pharmacovigilance audit.

→ **PRAC RECOMMENDATION** to CHMP/CMDh on **PASS**

→ Directly implementable and legally binding for protocols if PASS is a condition of MA ('imposed')

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- **ENCePP**

What is ENCePP?

ENCePP, the European Network of Centers for Pharmacoepidemiology & Pharmacovigilance is a **collaborative scientific network** coordinated by the European Medicines Agency and developed in collaboration with European experts;

The aim:

- Bring together expertise in the fields of pharmacoepidemiology and pharmacovigilance across Europe.
- Strengthen further the post-authorisation monitoring of medicinal products in Europe.
- Facilitate conduct of post-authorisation studies (PAS)
  - high quality
  - independent
  - multi-centre
- Focus on academia and not-for-profit organisations.

Who are the ENCePP Partners?

- Research centres located in EU
- Universities, medical-care centres, owners of healthcare databases and/or electronic registries;
- Other public/not for profit research centres specialised in pharmacoepidemiology and pharmacovigilance;
- Existing European networks covering certain rare diseases, therapeutic fields and adverse drug events of interest;
- For-profit clinical research organisations (CROs)
  - ✓ provided that they perform studies commissioned by third parties and their main focus is pharmacoepidemiology and pharmacovigilance research

ENCePP Partners (as of 25 April 2013)

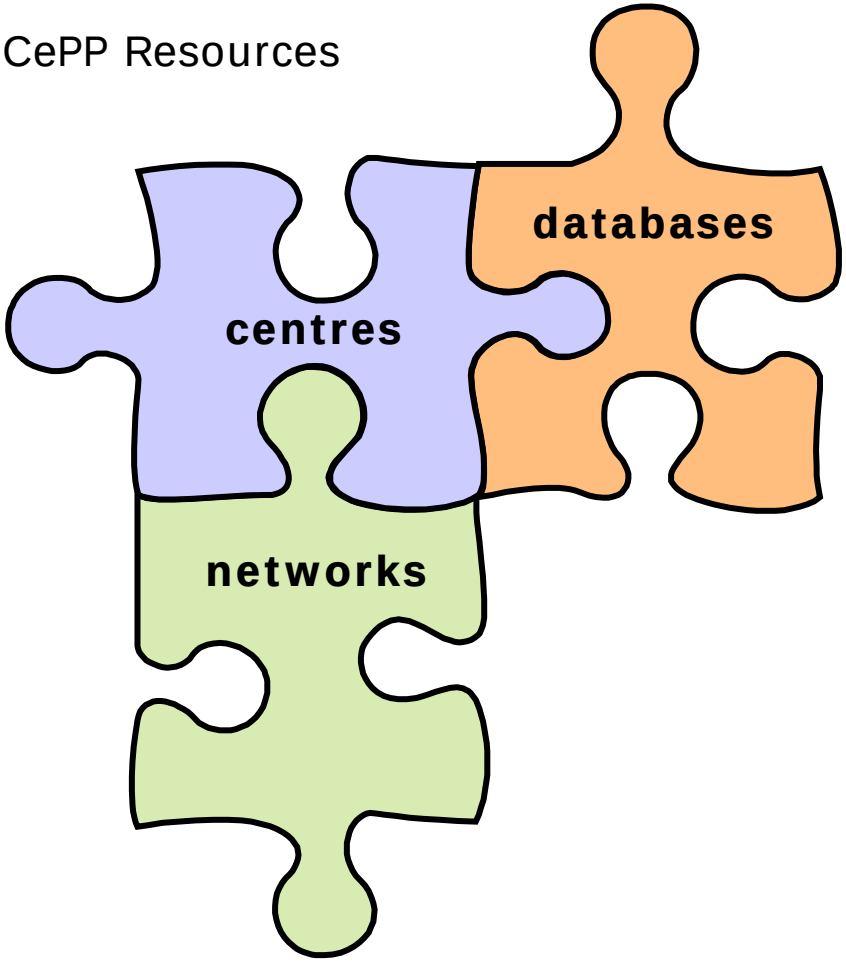
- **117 Centres**
  - 93 not for profit (university, hospital, government, charities)
  - 24 for profit (CROs, consultancies)
- **17 Networks**
  - 10 International
  - 7 National (France, Italy , Spain, Belgium, Austria, Sweden)

    Special interests: Psychiatry, rheumatology, teratology, congenital abnormalities, pharmacogenetics, women's health, paediatrics, psoriasis, severe cutaneous adverse reactions to drugs
- **46 Data sources**
  - Total (cumulative) number of persons with actual data: > 116 million
  - Number of persons with active data collection in past calendar year: > 100 million

ENCePP Database of Resources

Public Database of ENCePP Resources

- Searchable database to identify who the best placed research partners to conduct a particular study might be;
- Offers information on the available sources of expertise and research experience across Europe;
- Facilitates collaboration in the conduct of pharmaco-epidemiology and pharmacovigilance studies;



ENCePP Guiding Principles

✓**Independence**

Clear roles and responsibilities of researcher & funder

Freedom to publish

Code of Conduct

✓**Standards**

Stimulate consideration of important study principles in design of studies

Methodological Standards Checklist & Guide

✓**Transparency**

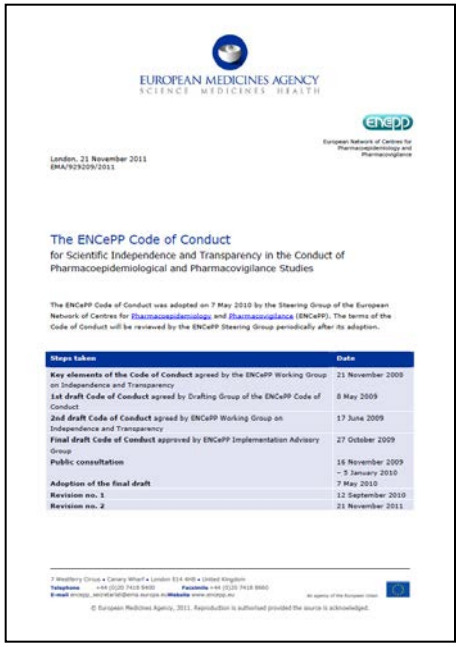
Registration of studies

Publication of protocols and results

ENCePP E-Register of Studies (EU PAS Register)

ENCePP Code of Conduct - Rationale

- It is recognised that there are areas in pharmacoepidemilogy and pharmacovigilance research which would benefit from a higher level of **openness, communication** and **accountability**.
- There is a need to have **clarity of roles and responsibilities** in studies of both investigator and study funder.
- Transparency in the design and the conduct of studies is a cornerstone in **building trust and confidence**.
- Main focus is on **contract research / privately funded studies**.


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 21 November 2011
EMA/929209/2011

The ENCePP Code of Conduct
for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies

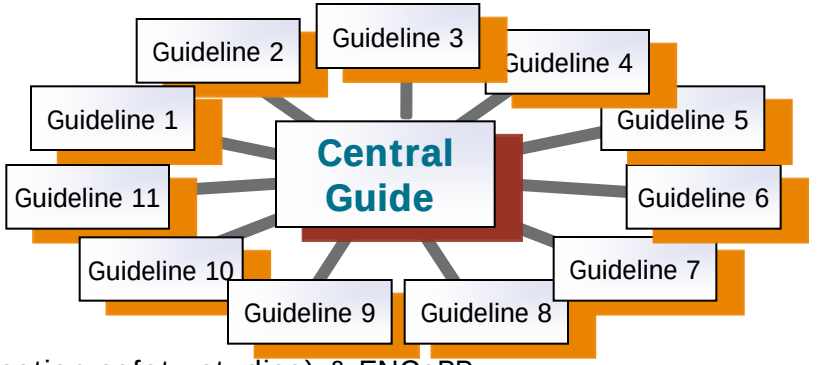
Steps taken	Date
Key elements of the Code of Conduct agreed by the ENCePP Working Group on Independence and Transparency	21 November 2009
1st draft Code of Conduct agreed by Drafting Group of the ENCePP Code of Conduct	8 May 2009
2nd draft Code of Conduct agreed by ENCePP Working Group on Independence and Transparency	17 June 2009
Final draft Code of Conduct approved by ENCePP Implementation Advisory Group	27 October 2009
Public consultation	16 November 2009 – 5 January 2010
Adoption of the final draft	7 May 2010
Revision no. 1	12 September 2010
Revision no. 2	21 November 2011

ENCePP Code of Conduct - Content

- Set of principles and rules for the conduct of studies to maximise transparency and promote **scientific independence** throughout the research process (good practice);
- "Charter of rights and obligations" covering essential aspects of the study **conduct and dissemination** of the outcome;
- Integral part of the "**ENCePP Study Seal**";
- Applies primarily to **non-interventional post-authorisation studies** (PAS) as outlined in GVP Module VIII;
- The Code is NOT a guarantee for high scientific quality or a replacement for existing legislation or guidance;

ENCePP Guide on Methodological Standards in Pharmacoepidemiology

- Key achievement of the ENCePP network
- **Single overview document** and web resource gathering:
  - an overview of internationally acknowledged recommendations,
  - key points from other existing English-language guidelines and standards in pharmacoepidemiology, and
  - directions for learning on study design and methods.
- The intention is not to duplicate but complement the text from existing guidelines and textbooks.



GVP modules V (risk management systems), VIII (post-authorisation safety studies) & ENCePP

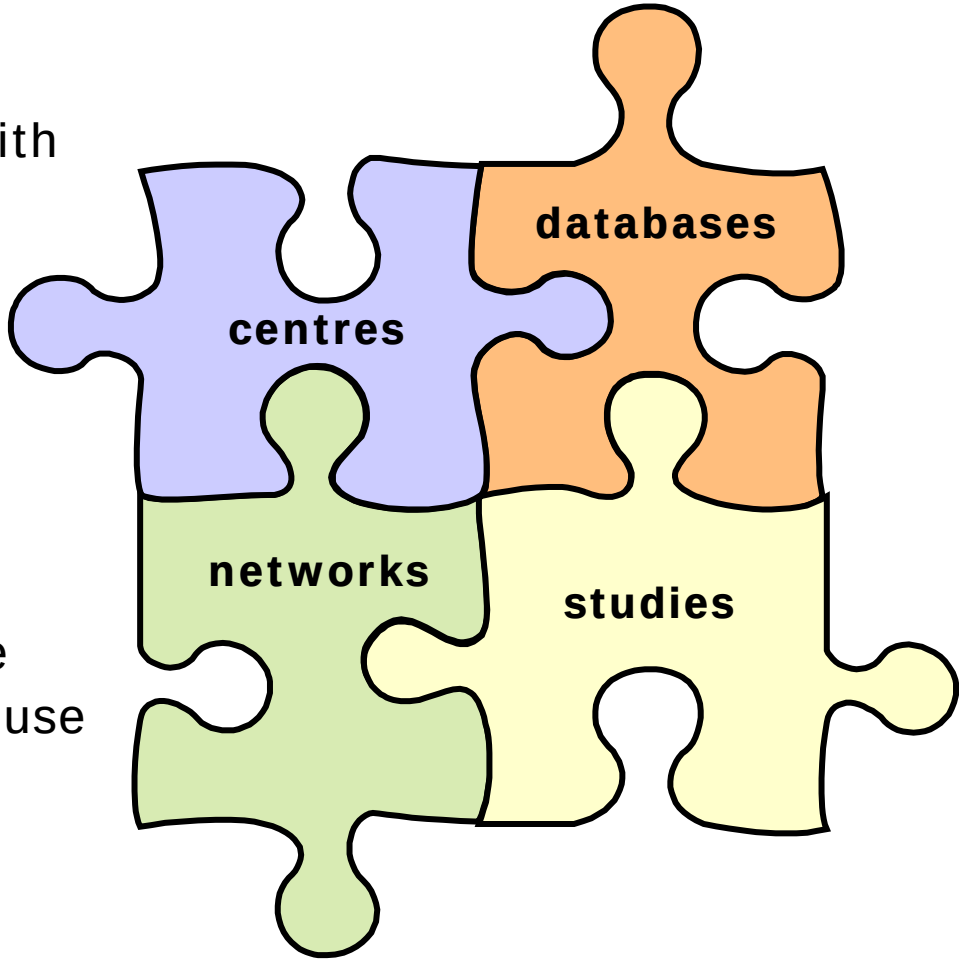
ENCePP Checklist for Study Protocols

- Reflects accepted **standards and good practice** in pharmacoepidemiology studies as identified by ENCePP;
- Purpose is to ensure **consideration of important epidemiological principles for designing a study**;
- Intention is to **promote quality** not uniformity;
- Innovation and new methods welcome so some questions may be 'not applicable';
- Reflected in Implementing Regulation 520/2012, Annex III (format and content of protocol, abstract and final study report) and **GVP Module VIII (PASS)**;

ENCePP E-Register of Studies

Public database of studies

- Searchable database of studies with focus on post-authorisation safety studies (PASS)
- Increase transparency
- Reduce publication bias
- Promote information exchange
- Facilitate collaborations within the scientific community and optimal use of PhEpi expertise in Europe
- Completely voluntary



EU PAS Register and ENCePP

- New legislation requires a public register of protocols, abstracts and results of PASS imposed as an obligation of MA;
- For MAH-sponsored non-interventional PASS required by a regulatory authority EMA informs all EU Member States of the study registration with: title, name of sponsor, countries, link to registry;
- **ENCePP E-Register acts temporarily as 'EU PAS Register'** for all post-authorisation studies
  - initiated, managed or financed by a MAH (imposed and voluntary)
  - conducted by a (ENCePP) research centre within the EU
- Further guidance: EU PAS Register Guide on ENCePP Website and GVP chapter VIII.B.4

http://www.encepp.eu/publications/documents/EUPASRegisterGuide.pdf

ENCePP Study Seal

The seal is a symbol that the study is conducted in adherence to the ENCePP guiding principles:

- Maximum level of **transparency** which justifies increased trust of the public, researchers and regulators in the robustness of the research;
- Use of agreed **methodological standards** in the study protocol, the development and agreement of the study protocol, and the communication of the results;
- Research is as far as possible **free from biases and commercial, financial and personal influences**;

ENCePP Study Seal - Requirements

1. Lead investigator belongs to an ENCePP centre

2. The **CoRe** requirements are met:

   + ENCePP Code of Conduct

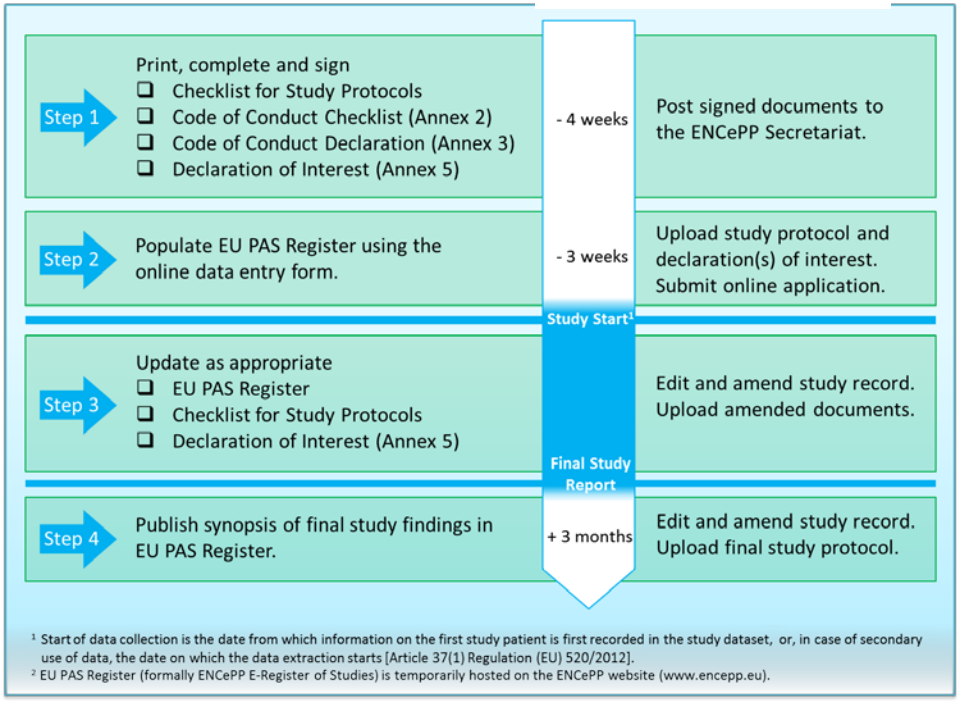
   ✓ *Signed declaration & checklist*

   + Checklist for Study Protocols

   ✓ *Signed checklist*

   + E-Register of Studies

   + *Registration prior to study start*



http://www.encepp.eu/publications/documents/ENCePPStudySealGuide.pdf

ENCePP supports EU regulatory decision making

- **In context of referrals**
  - Provision of expertise in pharmacoepidemiology for ad-hoc expert groups [e.g. re-examination of calcitonin Art 31]
  - Provision of data in response to an EMA request [e.g. tetrazepam Art 107i, combined oral contraceptives (COC) Art 31, Diane Art 107i]
  - Final studies feeding into referrals e.g. SOS consortium NSAIDs study and NSAIDs Art 5(3) + Art 31 (diclofenac), and an EMA-funded ENCePP study on COC.
- **In context of safety issues**
  - Provision of information/data in response to EMA request, e.g. hypnotics and risk of death, fluoroquinolones and retinal detachment;
  - Amendment of protocols for existing/on-going studies to include further endpoints/ exposures and/or confounders e.g. SAFEGUARD consortium and safety of oral T2DM therapy;
  - PASS request for pan-European study to characterise the nature and size of the risk of bladder cancer associated with pioglitazone in T2DM patients (seal);

For further information:

ENCePP Homepage
www.encepp.eu

ENCePP Code of Conduct (Revision 2)
http://www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf

ENCePP E-Register (EU PAS Register)
http://www.encepp.eu/encepp/studiesDatabase.jsp

Guide on Methodological Standards in Pharmacoepidemiology (Revision 1)
http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_2.pdf

Call for Expression of Interest (Safety Studies)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000320.jsp&mid=WC0b01ac05800a3991

Thank you for your attention!

Questions?