EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The PRAC Strategy for Measuring Impact of Pharmacovigilance Activities

Workshop: Measuring the Impact of Pharmacovigilance Activities
London, 5-6 December 2016

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Legislative framework and legal basis

Pharmacovigilance legislation provides the basis for collaboration between EMA and EU Member States' competent authorities **to continuously develop pharmacovigilance systems** capable of **achieving high standard**s of public health protection for all medicinal products, and monitor the **outcomes of risk minimisation measures** *[Article 107h DIR 2001/83/EC]*.

The **EU Regulatory Network** and **its stakeholders** all have a role in collecting data and information on **regulatory measures**

- to ensure they are **effective and efficient** *[Article 28a REG (EC) 726/2004]*
- to continuously drive **process improvement** *[Article 28e REG (EC) 726/2004].*

Why measuring impact of regulatory actions?

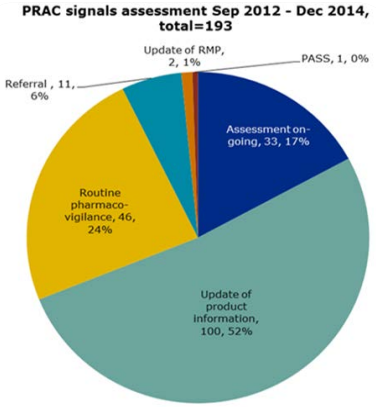
Key objectives in pharmacovigilance:

- To inform the **review of the benefits and risks of individual medicines** that have been the subject of **major risk minimisation efforts** (effectiveness);
- To determine what activities are successful and which are not, and therefore **identify enablers and barriers for generating positive impacts** which would contribute to the development of proactive pharmacovigilance in the EU;
- Support to **continuously improve and optimise** the functioning of the pharmacovigilance system (‘evidence-based process improvements’);

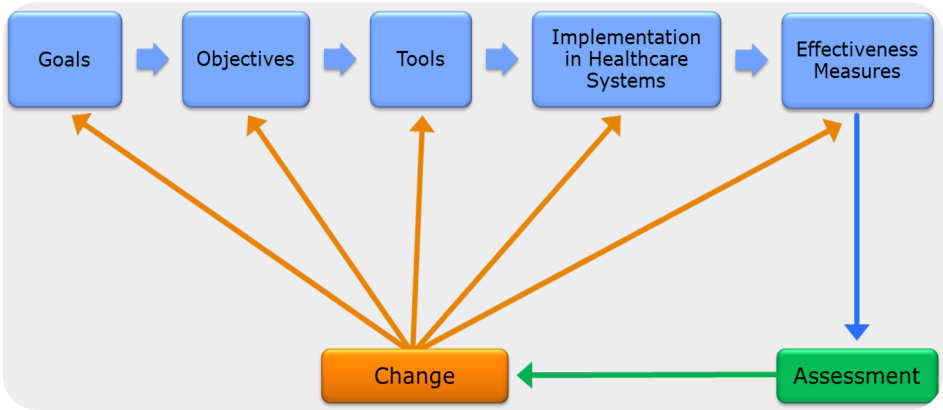
Evaluating impact

Evaluation of health impacts is an **iterative science** and **evidence-based** process assessing the implementation and effectiveness of regulatory actions in healthcare systems, including monitoring use of medicines and stakeholder engagement.

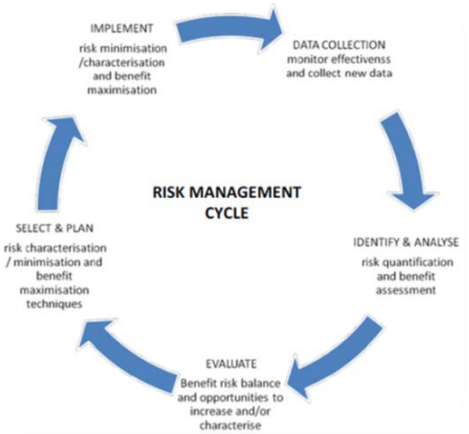
Pharmacovigilance Activities



Effectiveness of Risk Minimisation



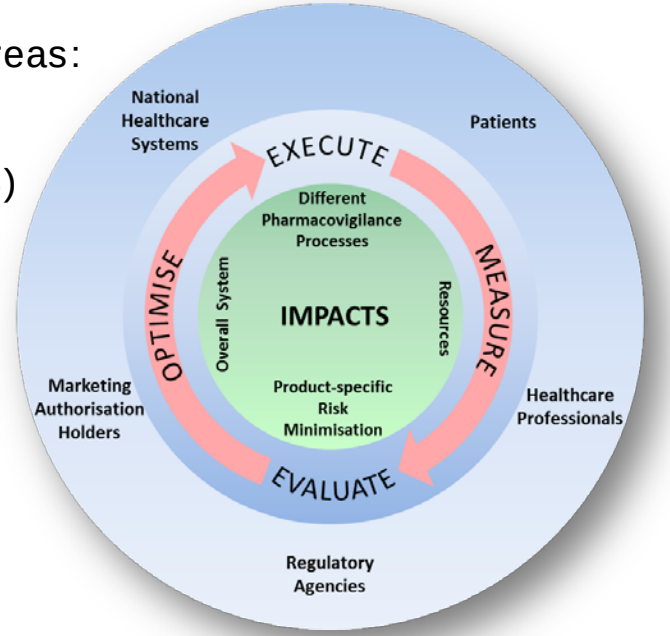
Risk Management Planning



PRAC Strategy for measuring pharmacovigilance impact

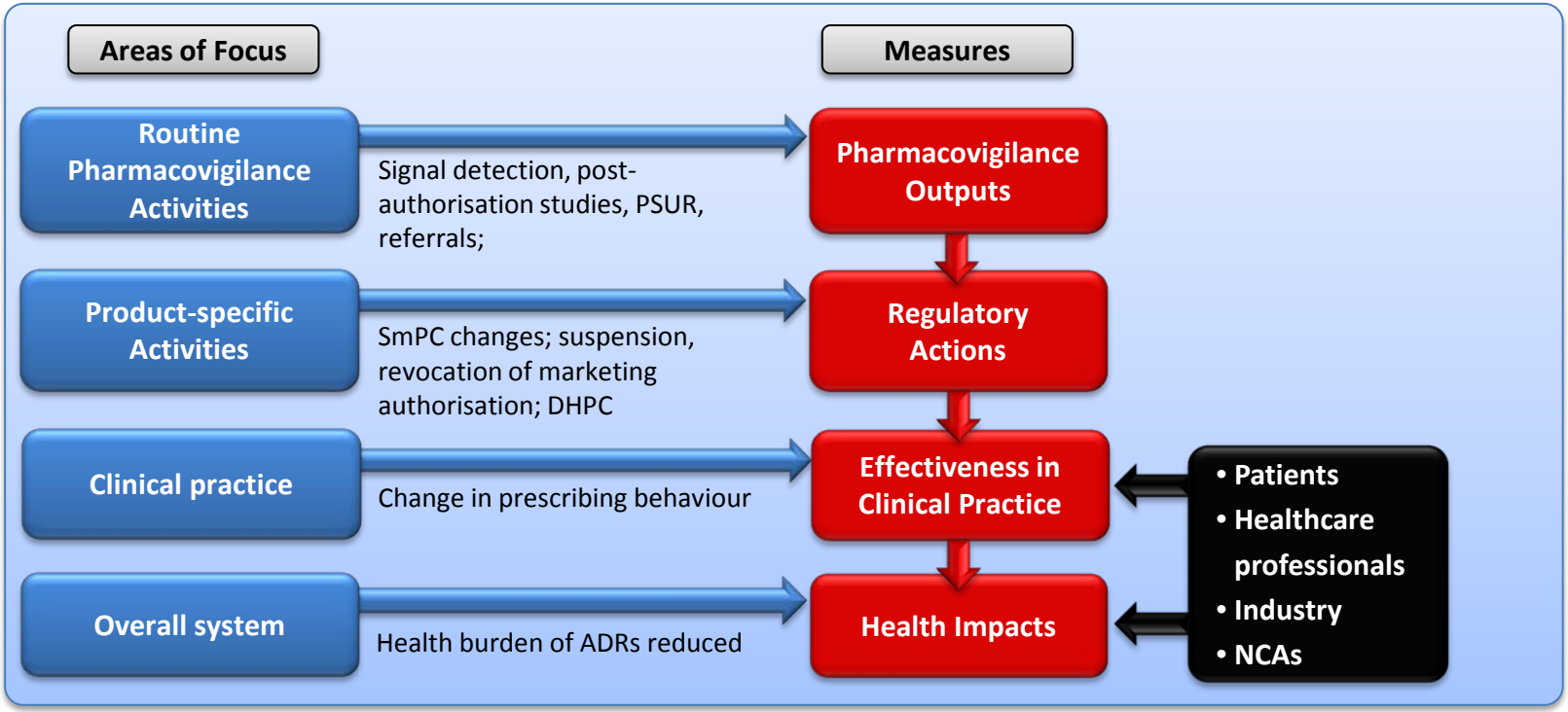
The PRAC Strategy (EMA/790863/2015) focusses on 4 key areas:

- Effectiveness of **pharmacovigilance processes** (e.g. ADR reporting, signal detection & management, PAS)
- Effectiveness of **product-specific risk minimisation** (e.g. measures following major referrals)
- Enablers of effective pharmacovigilance such as **stakeholder engagement**;
- Collaboration on **methodologies**, e.g. modelling methods for measurement of impact on health outcomes;

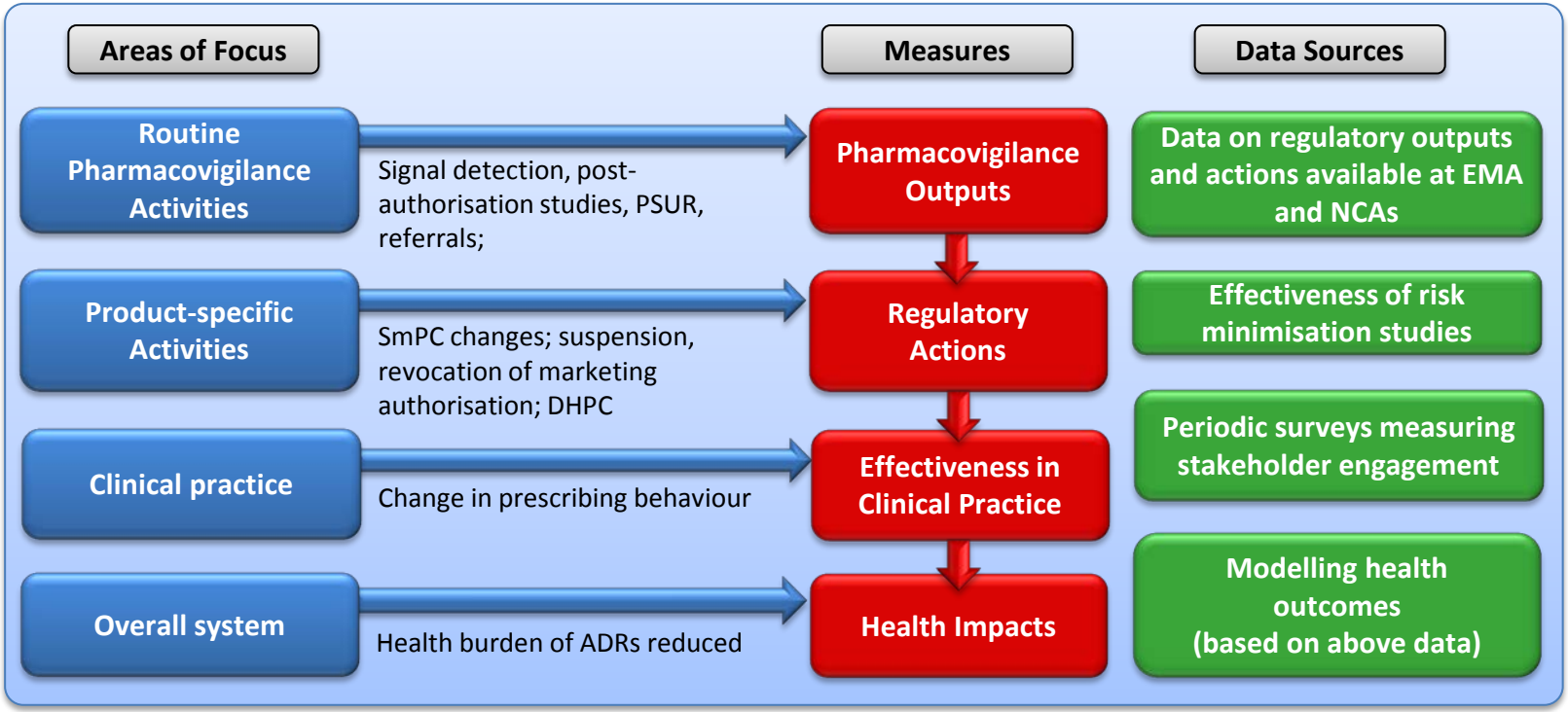


→ Leverage of ongoing work by regulators (NCAs + EMA), industry and academia;

How does the pharmacovigilance system generate impacts?



How does the pharmacovigilance system generate impacts?



How can we measure health impacts?

- Based on available data on effectiveness of key regulatory actions, **health impacts of regulatory actions may be estimated**:
  - i.e. patient and HCP **knowledge** of risks following communication;
  - i.e. change of patient and HCP **behaviour** (e.g. prescribing patterns) in clinical practice;
  - i.e. change of **morbidity / mortality** due to prevention of ADRs before and after regulatory intervention;
  - [Data sources: patient exposure, drug utilisation, electronic health records, patient registries, stakeholder surveys, etc.]
- If no data is available, evidence-based assumptions on the effectiveness of regulatory actions may be made through **modelling health impacts** e.g. based on population attributable risk, prevalence of exposure, data on behavioural changes etc.;

PRAC Strategy – work plan 2016/2017

Objective	Deliverable
Establish prioritisation criteria for collaborative impact study topics	• Reflection paper (EMA/153279/2016) ✓
Collection of data elements on EU pharmacovigilance activities	• Annual report on key activity indicators
Stakeholder (patients, HCPs, industry) survey on engagement	a) Conduct survey b) Report survey results
ENCePP collaboration on methodologies for impact research	a) Set up ENCePP Special Interest (SIG) Group, including mandate and work plan ✓ b) Inventory of PhV activities relevant for impact research ✓ c) Review of survey studies published in EU PAS Register ✓ d) Review of methodologies for effectiveness of RMM studies

PRAC Strategy – work plan 2016/2017

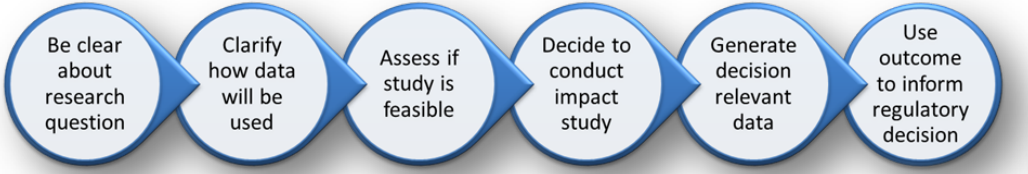
Objective	Deliverable
Study on ADR reporting by patients/HCPs	Final study report ✓
Post-referral best evidence pilot: • Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism *(EMA/2014/50/RE/1)*; • Study of utilisation of combined hormonal contraceptives in Europe *(EMA/2014/50/RE/4)*; • Prescribing of codeine for the treatment of pain in children (collaborative multi-database regulatory study with common protocol);	Final study reports

PRAC Interest Group (IG) Impact - mandate

- **Prioritise** design, methods and choice of outcomes for **studies measuring the effectiveness of risk minimisation** measures at EU and Member State level;
- Establish **criteria for the prioritisation of PRAC regulatory decisions** for collaborative impact studies;
- Assess the feasibility of **multi-database regulatory impact studies** by means of a common core protocol;
- Collaborate with ENCePP Special Interest Group (SIG) on Impact on **methodological aspects** of studies;
- **Composition:** 14 PRAC members with expertise and experience in impact research chaired by Marieke De Bruin, University of Copenhagen, DK

PRAC IG Impact deliverables – prioritisation criteria (I)

- Reflection paper on criteria to prioritise collaborative impact research adopted Sep'16;
- Criteria are based on **key considerations**:



- Prioritisation of safety topics is based on:
  - **I. Public health importance of the regulatory action**
  - **II. Potential impact on clinical practice**
  - **III. Delivery of decision relevant data**
- 6 months pilot testing started in December 2016;
- For review in Q2/2017;

Criteria	Explanation	High / Yes	Low / No	Not clear
Public health importance of the regulatory action				
1. Nature and severity of the risk in the affected population;	*How serious are the consequences for the patient? How is the risk perceived by the general public in terms of intensity (mild, moderate, severe)?*	□	□	□
2. Magnitude of the risk (absolute and relative) in the population where the product is used;	*How big is the risk in the treated, compared to the untreated population? How big is the population using the product in the EU taking into account exposure data from several Member States where the product is marketed, and if available recommendations in national clinical guidelines.*	□	□	□
3. Amount of public concern, e.g. due to risk in vulnerable populations, public debate, disagreement within the scientific community etc.;	*Are affected populations perceived as particularly vulnerable (children, pregnant women, elderly people)? Has the safety concern been subject to public debate in the media? Is there conflicting evidence about the safety concern in the scientific literature?*	□	□	□
Potential impact on clinical practice				
4. Extent of the regulatory intervention;	*Is the regulatory action expected to lead to changes in patient and/or HCP behaviour, to change the way the product is used in clinical practice or to changes in clinical guidelines? Regulatory interventions may include label changes e.g. addition of adverse reaction(s), warnings and/or contraindications to SmPC, additional risk minimisation measures, restriction of the indication, suspension or revocation.*	□	□	□
Delivery of decision relevant data				
5. Regulatory action is amenable to research generating impact relevant data?	*Are there any measurable effects of the regulatory intervention which allow to assess if the intended outcome (e.g. lower risk incidence) has been delivered in clinical practice or did any unintended consequences occur?*	□	□	□
6. Suitable data sources and methodologies are available in several Member States to allow generalisability of results?	*Are suitable data sources available and accessible for impact research or can they be generated within reasonable time frames? Do these data sources allow for generalisability of the results across different healthcare systems for the whole EU?*	□	□	□
7. Does the study fill gaps in knowledge and understanding of the safety issue?	*Are there clearly defined knowledge gaps about the risk to patients under real world conditions, about the effectiveness of risk minimisation measures or how the product is used in practice which could be answered by collaborative impact research?*	□	□	□
8. Does the study add to the evidence beyond the studies conducted by MAH(s)?	*Are there any other ongoing or planned studies from MAH(s) which provide evidence on the impact of the regulatory action in question? Are MAH(s) in the position to conduct such a study e.g. as joint study?*	□	□	□
Topic prioritised for impact research: □ **Yes** □ **No**		**Comment:**		

PRAC IG Impact deliverables – prioritisation criteria (II)

Applied to safety topics under the following **PRAC agenda items**:

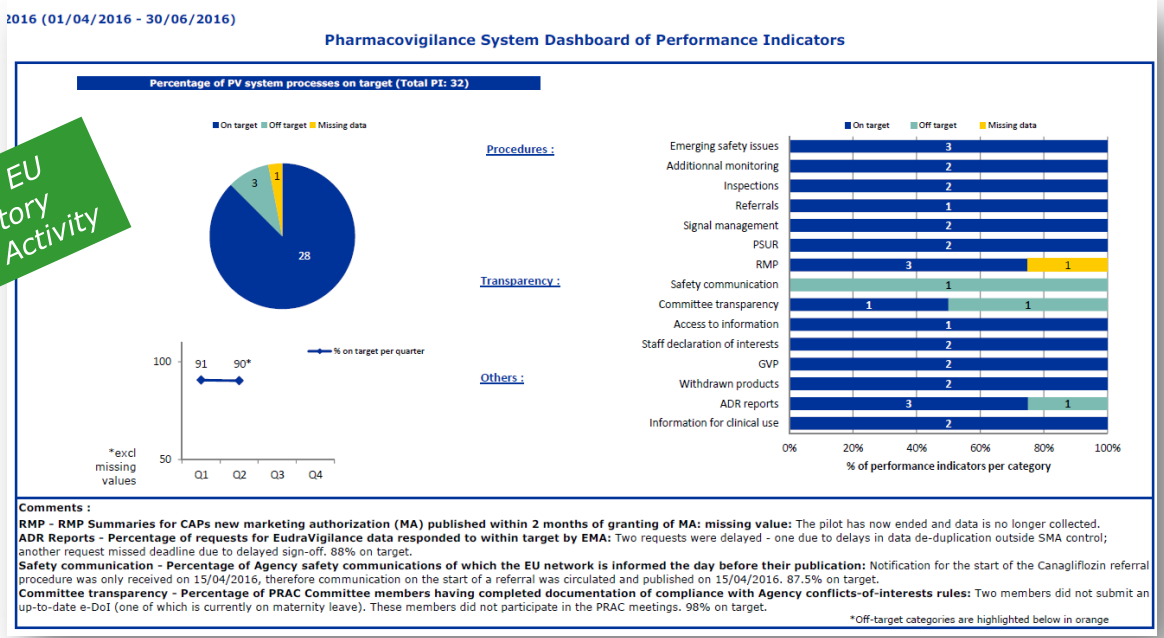
- **Urgent EU referral procedures** for safety reasons: for finalisation
- **Other EU referral procedures** for safety reasons: for finalisation
- **Signals assessment and prioritisation** - Signals follow-up and prioritisation where PRAC recommends **changes to Product Information and/or RMP** including:
  - New contraindication(s),
  - New warning(s),
  - Restriction of the indication or
  - Additional risk minimisation measures
- After pilot: **PSURs** resulting in variation, suspension or revocation

To be reviewed after the pilot

PRAC IG Impact deliverables – routine data collection

- Pharmacovigilance activity areas relevant for impact research where information is continuously generated and available in terms of procedure or work load counts (**activity indicators**):
  - ADR reporting
  - PASS/PAES protocols
  - PASS/PAES results
  - Signals
  - Referrals (Art 20, 31, 107i)
  - Additional risk minimisation

Ongoing EU Regulatory Network Activity



How to measure stakeholder engagement?

- **Patient reporting of ADRs** → number and proportion of patient-reported ADRs in EV and at national level;
- **Patients seeking regulatory information** → regulatory websites views; social media monitoring;
- **Attitude and knowledge of patients and HCPs on medicines regulation** → social media monitoring, surveys and other methods;

This activity includes **collaboration with PCWP and HCPWP** on:

- Patient reporting and relevance to safety monitoring of medicines
- Scope and methods of surveys
- Other methods to measure trust and engagement in medicines regulation

Looking ahead

Today's workshop is a key milestone of the PRAC Strategy with various possible outputs:

- **Recommendations on methods** for measuring health outcomes of pharmacovigilance activities
- Identification of methodological **gaps and limitations** (e.g. what is missing to be able to predict if regulatory actions will achieve positive health outcomes)
- Areas for **further development** (e.g. methods, regulatory and scientific guidance, data sources, networking)
- Recommendations on **stakeholder collaboration and engagement**
- Identification of the **key pharmacovigilance processes** which do have an impact

Thank you for your attention

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