



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 November 2017
EMA/165407/2017
Pharmacovigilance Risk Assessment Committee

PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1)

Executive Summary

Pharmacovigilance activities and regulatory interventions are designed to lead to changes in the knowledge and behaviour of individuals (i.e. patients, consumers, care-givers and healthcare professionals) and of organisations in healthcare practice to achieve the best possible health outcomes through safe and effective use of medicines. However, the possibility of unintended consequences of regulatory interventions remains if measures are not adequately implemented or fail to achieve their intended objectives.

The PRAC strategy aims to bridge this gap with a concept for systematically measuring patient-relevant health outcomes of major regulatory interventions, shifting the focus of pharmacovigilance to activities and regulatory tools that make a difference in daily healthcare. Moving forward from the initial conceptual approach, the revised strategy is building on past achievements in each of the four key areas (i.e. effectiveness of risk minimisation activities, pharmacovigilance processes, stakeholder engagement, and methodologies for impact research). The revised strategy is focused on a combination of measures of patient and healthcare professional knowledge of risks, changes in behaviour and drug use in terms of risk reduction, and changes in morbidity and mortality as intended and patient-relevant health outcomes of major regulatory interventions and key pharmacovigilance processes.

1. Introduction

Pharmacovigilance activities contribute to the protection and promotion of public health through preventing harm caused by medicines as well as by enabling the safe and effective use of medicines. In Europe, pharmacovigilance activities are performed by regulators and pharmaceutical companies, including risk management planning, collecting and managing suspected adverse reaction (ADR) reports, signal detection and management, and post-authorisations studies that enable the generation of new information about marketed medicines. Regulators have several key tools available that allow for taking action whenever new information emerges and regulatory actions are taken to either *inform* prescribers or patients of newly emerged information on the safety or effectiveness of a medicine, to *advise* them to modify their behaviour in order to prevent or minimise adverse events, to *restrict*



access to medicines when the benefit-risk profile of a product is no longer positive for a certain patient population, or a combination of these actions.

It is important to measure the impact of pharmacovigilance activities for two principle reasons:

- Firstly this information can be used to inform the review of the benefits and risks of individual medicines that have been the subject of major risk minimisation efforts (effectiveness of risk minimisation);
- Secondly, measuring impacts allows regulators to determine what activities are successful and which are not and therefore to identify enablers and barriers for generating positive impacts which will contribute to the development of the EU proactive pharmacovigilance system.

In this way, measurement of pharmacovigilance impact can support monitoring of individual products and support efforts to continuously improve and optimise functioning of pharmacovigilance activities (Fig. 1).

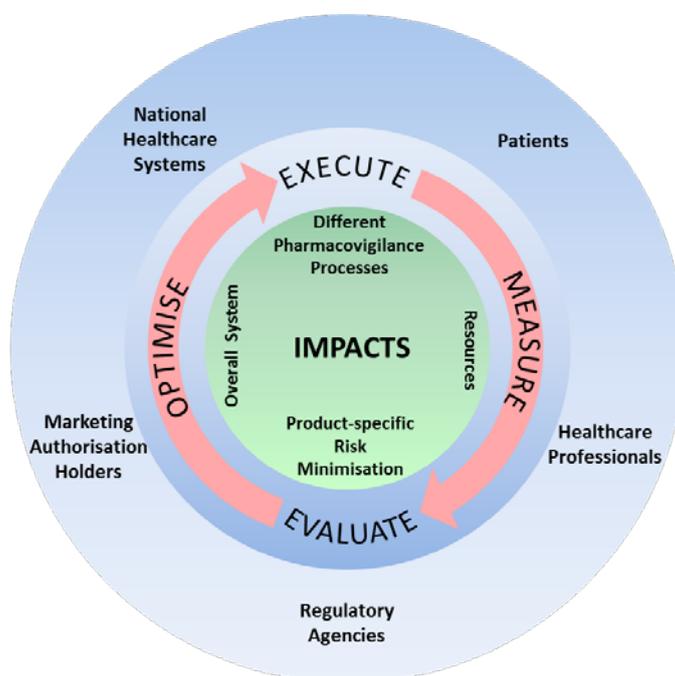


Figure 1: Conceptual approach to impact measurement of pharmacovigilance activities. Important pharmacovigilance outputs and regulatory actions are monitored and their impact in terms of health outcomes is measured with the aim to improve the functioning of the pharmacovigilance system.

2. Objective and guiding principles

The objective of this strategy is to establish a long-term approach for measuring the impact of pharmacovigilance activities which delivers data, information and knowledge on major product- or therapeutic class-specific regulatory actions and decisions, and on enabling factors. The strategy outlines the conceptual approach, principles, stakeholders, priorities, and planning of the collection of data, information, and knowledge on how pharmacovigilance activities are translated into measurable health outcomes (e.g. reduction of harm from adverse reactions) and potential unintended consequences in daily healthcare (e.g. switching patterns, conditions left untreated etc.).

The following guiding principles underpin the strategy's approach:

- Health outcome-focused;
- Science-based;
- Embedded in the work of the network of National Competent Authorities;
- Collaborative with academia, patient associations, healthcare professional associations, and industry;
- Leveraging existing resources;
- Targeting key pharmacovigilance activities where improvements are likely to benefit patients;
- Focussing on product or therapeutic class-specific actions in a risk proportionate way.

3. Conceptual approach – key areas for measuring impact

The strategy is focused on four key areas:

- I) *Effectiveness of risk minimisation activities;*
- II) *Effectiveness of specific pharmacovigilance processes;*
- III) *Enablers of effective pharmacovigilance and stakeholder engagement;*
- IV) *Identification and development of analytical methods.*

3.1. Effectiveness of risk minimisation activities

In line with GVP Module XVI requirements¹ Marketing Authorisation Holders (MAHs) perform studies that measure the effectiveness of additional risk minimisation activities for their products, and the results are reported to regulatory agencies e.g. in PSURs. The systematic collection of these results allows for better understanding of the types of data collection, study designs and analytical methods used by MAHs, the criteria to define successful risk minimisation and to determine the effects of different types of risk minimisation efforts. Such case studies can improve regulatory decision-making and understanding of success factors as highlighted at EMA's workshop on risk minimisation measures².

National competent authorities and the Agency have a legal obligation to monitor the outcomes of risk minimisation measures contained in risk management plans³. In this context, National Competent Authorities and the Agency have established collaborative research projects conducted within the EU regulatory network to assess the effectiveness of risk minimisation measures. The collaborative study of the impact of risk minimisation measures implemented with the EU referral on the use of codeine for pain relief in children in 2013 served as pilot for the generation of post-referral evidence. This pilot also provided an opportunity to assess the feasibility of multi-database studies with a common protocol. Other examples include the ongoing post-referral studies on the use of combined hormonal contraceptives in Europe with a qualitative study on regulatory communication and risk awareness and a quantitative study on prescribing patterns.

To prioritise key regulatory decisions and activities for EU collaborative impact research PRAC has developed a [checklist](#) with criteria for the identification and selection of safety topics which require the

¹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf

² http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/12/WC500198810.pdf

³ Directive 2001/83/EC, Art. 107h; Regulation (EC) No 726/2004 Art. 28a and Art. 56(1).

generation of data, information and knowledge to monitor impact beyond the data submitted by MAHs in context of regulatory procedures.

These prioritisation criteria are based on a clear understanding of the research question (i.e. which information about a safety concern is required), how the data generated by the study will be used (i.e. does the study reduce uncertainty or provide answers to relevant questions), and of the feasibility of the study and generalisability of the study outcome(s) to better inform regulatory decisions.

In a 12-months pilot a process for routine screening of PRAC agenda topics has been set up and the prioritisation takes into account the public health importance of the regulatory action, the potential impact on clinical practice and whether the study delivers decision relevant data.

3.2. Effectiveness of specific pharmacovigilance processes

Pharmacovigilance activities involve a number of complex processes in relation to spontaneous reporting of suspected adverse reactions, signal detection and management, risk management planning, periodic safety update reporting, post-authorisation studies etc.; however, the impact of this broad range of activities cannot be measured in a systematic way and the strategy focusses therefore on post-authorisation safety studies (PASS) as key activity to support continuous process improvement. Since 2012 a number of imposed PASS and PASS evaluating the effectiveness of risk minimisation have been requested which provide the basis for reviewing the various steps from the regulatory request to perform a study to protocol development and evaluation of the results. A review of the current PASS process will help to identify opportunities for process improvement.

3.3. Enablers of effectiveness pharmacovigilance

The effectiveness of pharmacovigilance processes and risk minimisation measures both depend on 'enablers' for engaging patients and healthcare professionals in medicines regulation and pharmacovigilance activities in daily healthcare. These key stakeholders have a critical role in several pharmacovigilance activities, e.g. in providing information through reporting suspected adverse reactions and in modifying their behaviours in response to risk minimisation interventions.

Understanding enablers for patient and healthcare professional engagement is essential in generating positive health impacts of pharmacovigilance. Data on key stakeholders' response to risk minimisation measures are needed to identify areas of stakeholders' concerns or potential for misunderstandings in the dialogue between stakeholders and regulators which, if remedied, could increase the effectiveness of pharmacovigilance and risk minimisation activities.

In this context, a healthcare professional survey⁴ on the effectiveness of safety communications performed in nine Member States within the SCOPE Joint Action focused on Direct Healthcare Professional Communications (DHPCs), national regulatory agency communications and educational materials. Based on the results good practice recommendations have been produced and one important finding was the preference to receive safety communications directly from the national competent authority as a more trusted source. Further survey reports delivered by [SCOPE Work Package 6 Risk Communications](#) can be found [here](#).

In addition, qualitative explorations are needed to understand how the dialogue between patients' and healthcare professionals' representatives can be strengthened and how their input can most effectively inform regulatory decision-making on risk minimisation measures. As a case example, the input collected through various engagement mechanisms used during the valproate safety referrals in 2014 and 2017, in particular the [public hearing](#) on 26 September 2017, is currently subject to a content

⁴ [http://www.scopejointaction.eu/assets/files/WP6-HCP-Survey-Report\(1\).pdf](http://www.scopejointaction.eu/assets/files/WP6-HCP-Survey-Report(1).pdf)

analysis with a view to derive good practice recommendations for routine engagement and dialogue for the evaluation of risk minimisation measures.

3.4. Identification and development of analytical methods

Currently, there are no broadly accepted methods for measuring how pharmacovigilance activities are translated into health outcomes. To support the implementation of the PRAC strategy and the conduct of collaborative impact research further method identification and development is required. Surveys and drug utilisation studies frequently conducted for regulatory purposes may be able to measure changes in behaviour and drug use; however they cannot measure changes in actual health outcomes which may require different methodologies to be combined.

A systematic review of methodologies for measuring the impact of regulatory interventions showed significant heterogeneity in study conduct and reporting, and highlighted the need for scientific guidance to ensure robust methodologies are applied, and systematic dissemination of the results of impact research occurs⁵.

Methods for modelling health impact of pharmacovigilance decisions based on epidemiological parameters (such as population attributable risk, prevalence of exposure, behavioural changes data, data on switch of therapies) are being explored by the ENCePP Special Interest Group (SIG) on Impact which has been established for this purpose.

4. Activities

The PRAC strategy for measuring the impact of pharmacovigilance is expected to move towards systematically measuring patient-relevant health outcomes of major regulatory interventions through systematic data collection from ongoing activities, the conduct of independent collaborative impact studies, and the further development of methodologies for impact research.

4.1. Completed activities

The PRAC Interest Group (IG) on Impact established in January 2016 has the mandate to oversee the implementation of the strategy with the following key deliverables of the initial work plan:

- A workshop on measuring the impact of pharmacovigilance activities held in December 2016 concluded with a set of recommendations to streamline ongoing initiatives from regulators, academia, patient and healthcare professional organisations, and industry to support the implementation of the strategy in the long term. A number of recommendations highlighted in the [workshop report](#) have been reflected in the revised work plan for 2018 (Annex).
- An ENCePP Special Interest Group (SIG) on Impact was established with the [mandate](#) to provide recommendations to the PRAC IG on the key methodologies for measuring health outcomes of pharmacovigilance activities.
- The identification of impact relevant data sources which allow measuring health outcomes focus on electronic health records, drug prescription, dispensing and utilisation data, and on patient registries. In this regard the implementation of the strategy has been supported by a number of complementary initiatives:

⁵ Goedecke T, Morales D, Pacurariu A and Kurz X. Measuring the impact of medicines regulatory interventions – systematic review and methodological considerations. Br J Clin Pharmacol 2017; DOI: 10.1111/bcp.13469

- Results of a survey⁶ conducted amongst Member States in context of the [SCOPE Work Package 8 Lifecycle Pharmacovigilance](#) on available data sources for pharmacovigilance purposes other than spontaneous reporting databases;
- Inventory of data sources registered by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)⁷;
- Inventory of European databases for longitudinal patient-based studies (EMA/533991/2017) currently under development by EMA in collaboration with ENCePP Working Group 3.
- Following a 12-months pilot a process to prospectively identify safety topics for collaborative impact research has been established based on [prioritisation criteria](#) agreed by PRAC. The criteria consider the public health importance of the regulatory action, the potential impact on clinical practice and whether a collaborative impact study will be able to deliver decision relevant data in addition to the data submitted routinely or upon request in the context of regulatory procedures for authorised medicines.

4.2. Ongoing activities

The following activities are ongoing:

- Collect and collate available data on existing activities within the EU regulatory network relevant to measurement of the impact of pharmacovigilance activities;
- Conduct independent collaborative impact studies of key regulatory actions and decisions;
- Conduct targeted studies of key pharmacovigilance processes (e.g. PASS);
- Develop good practice recommendations for stakeholder engagement in the evaluation of risk minimisation measures;
- Develop guidance on methodologies for measuring the impact of pharmacovigilance activities in the [ENCePP Guide on Methodological Standards in Pharmacoepidemiology](#) (routine revision 2018).

⁶ http://www.scopejointaction.eu/_assets/files/SCOPE-WP8-Survey-Report-Annex-1.pdf

⁷ <http://www.encepp.eu/encepp/resourcesDatabase.jsp>

5. Annex - Work plan

This Annex contains an overview of activities and deliverables to implement the PRAC strategy.

5.1. Data on pharmacovigilance activities and decisions (regulatory outputs)

The following table lists data that are compiled periodically in context of the EU regulatory network's pharmacovigilance activities and regulatory decisions. The quantitative data are gathered via the quarterly collection of pharmacovigilance system workload and performance measures collected at EU level.

Pharmacovigilance data	Regulatory tools	Regulatory decisions	Additional risk minimisation
<ul style="list-style-type: none"> • Proportion of ADR reports from patients (EEA origin)* • PASS imposed, non-interventional* 	<ul style="list-style-type: none"> • Signals* • PSUSA • PASS/PAES Results (type II variations)* • Referrals (Article 20, 31, 107i)* • Annual reassessments • Renewals 	<ul style="list-style-type: none"> • Variation • Restriction of indication • Withdrawal • Suspension/ revocation 	<ul style="list-style-type: none"> • Competent authorities communications • DHPCs* • Additional risk minimisation measures • Additional monitoring*

*Routinely collected EU pharmacovigilance system performance measures with impact relevance.

5.2. Activities in 2018

The following table provides an overview of planned activities and deliverables in 2018 to implement specific workshop recommendations in line with the strategy's key areas of focus.

Workshop Recommendation (focus area ¹)	Activity	Deliverable	Development Forum	Target
Conduct of collaborative impact research (I)	Based on PRAC prioritised topics, evaluate the impact of product-specific regulatory interventions	<ul style="list-style-type: none"> • Consultation on draft technical specification for two EMA tendered or EU regulatory network collaborative studies • Consultation on two draft protocols 	PRAC IG	Q2/2018
Revision of the framework for impact evaluation (I; II)	Define process and outcome indicators for measuring impact of key pharmacovigilance activities;	<ul style="list-style-type: none"> • Methodological guidance for impact research (impact chapter in ENCePP methods guide) • Revision of GVP XVI Risk Minimisation Measures 	PRAC IG/ ENCePP SIG	Q4/2018
Active engagement and capacity building with patient communities and healthcare professional	Establish process for systematic involvement of patient and HCP organisations and healthcare	<ul style="list-style-type: none"> • Process for routine engagement with patient and HCP organisations/ medical bodies on 	PRAC IG/ EMA	Q2/2018

Workshop Recommendation (focus area ¹)	Activity	Deliverable	Development Forum	Target
bodies to support impact research (III)	providers in evaluation of effectiveness of risk minimisation	evaluating effectiveness of risk minimisation		
	Establish impact relevant criteria for targeted benefit/ risk communications, based on SCOPE JA reports	<ul style="list-style-type: none"> • Consultation on draft revision of GVP XV Safety Communication 	PRAC IG/ EMA	2019
Develop methodologies for measuring health impacts of pharmacovigilance activities (III)	Explore concepts and techniques to measure patient and HCP engagement in risk minimisation;	<ul style="list-style-type: none"> • Report on case study with recommendations on patient and HCP engagement in risk minimisation • Consultation on draft manuscript on conceptualising and measuring engagement ² 	PRAC IG/ EMA	Q1/2018
Develop methodologies for measuring health impacts of pharmacovigilance activities (IV)	Explore methods for predictive modelling of drug utilisation data to measure changes in morbidity or mortality	<ul style="list-style-type: none"> • Methodological guidance for impact research (impact chapter in ENCePP methods guide) 	ENCEPP SIG	Q3/2018
	Explore interrupted time series (ITS) and similar regression methods to identify trend changes		ENCEPP SIG	Q3/2018
	Explore real time monitoring of drug use patterns in population-based electronic health records		ENCEPP SIG	Q3/2018
Systematic collection of impact relevant data considering the need for, the nature of and the approach to collection (I; II; III; IV)	Support transparency and sharing of impact relevant data among stakeholders of the EU regulatory network	<ul style="list-style-type: none"> • Explore models for multi-stakeholder collaboration • Establish platform for sharing impact relevant information 	PRAC IG/ EMA	Q2/2018
Revision of the framework for impact evaluation (III)	Update framework for EU pharmacovigilance impact research to include multiple stakeholders e.g. healthcare system providers, medical councils, HTA bodies etc.;	<ul style="list-style-type: none"> • Revision of PRAC strategy with recommendations on patient and HCP engagement and multi-stakeholder collaboration 	PRAC IG	Q4/2018

¹ See section 3;

² Deliverable led by University of Amsterdam;