



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Revision 2)

Executive Summary

Pharmacovigilance activities and the regulatory actions taken by competent authorities based on emerging pharmacovigilance data are designed to lead to changes in knowledge and behaviour of individuals (i.e. patients, consumers, care-givers and healthcare professionals) and of healthcare provider organisations to achieve the best possible health outcomes through safe and effective use of medicines. However, the possibility of unintended consequences remains if regulatory actions are not adequately implemented or fail to achieve their intended objectives.

The PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities ('PRAC Impact Strategy') has closed this gap with a concept for systematically measuring patient-relevant health outcomes of major regulatory interventions, shifting the focus of pharmacovigilance to those activities and regulatory tools that make a difference in daily healthcare.

The second revision of the PRAC Impact Strategy integrates the achievements over a five-year period since its launch in the four activity areas: effectiveness evaluation of risk minimisation measures, effectiveness of pharmacovigilance processes, enablers of effective pharmacovigilance and stakeholder engagement, and analytical methods for impact research. It describes the conceptual approach, principles and stakeholders, as well as the processes for prioritisation and conduct of impact research implemented by the EU Medicines Regulatory Network (EMRN) to systematically investigate the public health impact of major regulatory actions and to determine potential unintended consequences in daily healthcare that may counteract risk minimisation efforts.

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. 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 tools for taking action when new



information based on pharmacovigilance data emerges. Regulatory actions are aimed at *informing* prescribers, healthcare providers or patients of new information on the quality, safety or efficacy of a medicine, to *advise* them to modify their behaviour or how to use medicines in order to prevent or minimise adverse events, to *restrict* to the use of medicines when the benefit-risk profile of a product is no longer positive for a certain patient population, or a combination of these actions.

The PRAC Impact Strategy describes the conceptual approach, principles and stakeholders, as well as the processes for prioritisation and conduct of impact research implemented by the EU Medicines Regulatory Network (EMRN) to systematically investigate how pharmacovigilance activities and major regulatory actions translate into measurable positive health outcomes (e.g. through reduction of harm from adverse reactions) and to determine potential unintended consequences in daily healthcare that may counteract risk minimisation efforts.

2. Conceptual approach, objectives and principles

Pharmacovigilance impact research is a key pillar to support monitoring of the benefits and risks of individual medicines and to continuously improve the functioning of pharmacovigilance systems as described in Fig. 1.

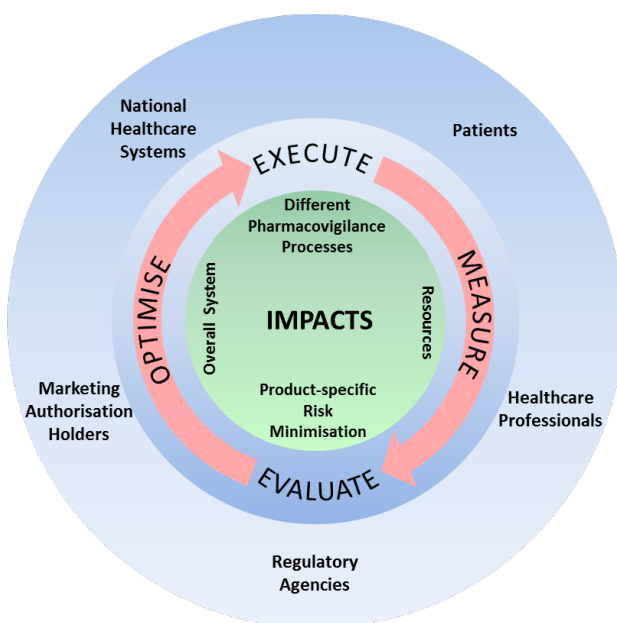


Figure 1: Conceptual approach to measuring the impact of pharmacovigilance activities and regulatory actions. Important pharmacovigilance activities and regulatory actions are monitored and their impact in terms of patient-relevant health outcomes is measured with the aim to improving the functioning of the pharmacovigilance system.

EU regulators conduct impact research to generate data, information and knowledge on the public health impact of major product- or therapeutic class-specific regulatory actions, and on enablers for engaging patients and healthcare professionals in pharmacovigilance activities with the **objectives**:

1. to inform the review of the benefits and risks of authorised medicinal products that have been subject to major risk minimisation efforts by evaluating the effectiveness of risk minimisation;
2. to determine successful pharmacovigilance activities and those requiring strengthening, and to identify enablers and barriers for the development of efficient pharmacovigilance systems.

To achieve these objectives the strategy's conceptual approach is underpinned by the following guiding **principles** for impact research being:

- health outcome-focused;
- scientific evidence-based, applying robust methodologies;
- embedded in core pharmacovigilance activities of the EU medicines regulatory network and the Agency;
- conducted in collaboration with regulators, academia, patient- and healthcare professional associations;
- targeting key pharmacovigilance activities where improvements are likely to benefit patients;
- focussed on product- or therapeutic class-specific regulatory actions in a risk proportionate way.

3. Key activity areas for measuring impact

Since its launch in 2016 the PRAC Impact Strategy has been implemented through four key activity areas (Fig. 2) with initial focus on the development of methodological guidance and setup of a regulatory framework for prioritising and conducting impact research. With the first public hearing¹ in 2017 qualitative research was initiated to better understand enablers for patient and healthcare professional engagement in pharmacovigilance activities. In 2019 a review of industry-sponsored post-authorisation safety studies (PASS) evaluating risk minimisation effectiveness was launched to explore options for pharmacovigilance process improvements.

Measuring the impact of major regulatory interventions is a key objective of the PRAC annual work programme and the PRAC Interest Group (IG) Impact has been established with the mandate to oversee the strategy's four activity areas.

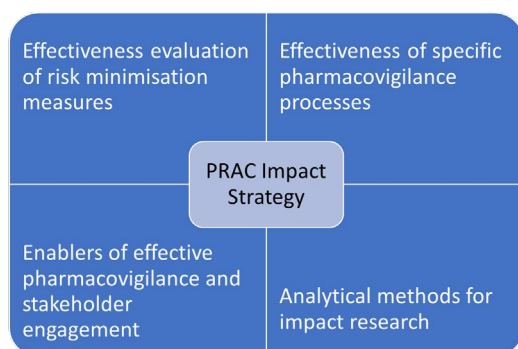


Figure 2: The four key activity areas of the PRAC Impact Strategy.

3.1. Effectiveness evaluation of risk minimisation activities

In line with GVP Module XVI requirements² Marketing Authorisation Holders (MAHs) conduct and report to competent authorities PASS that evaluate the effectiveness of risk minimisation measures (RMM) for authorised medicinal products. This effectiveness evaluation guides the discussion in the RMP on whether risk minimisation activities need to be strengthened or may be discontinued and is based on estimates of product-specific targeted effects in relation to RMM dissemination, changes in knowledge and behaviour and improved health outcomes, and of potential non-targeted effects such as unintended changes in prescribing, health outcomes or healthcare practices as a consequence of the

¹ https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy_en.pdf

² http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf

regulatory action. This approach extends to other medicinal products not subject to specific risk minimisation efforts where other knowledge, behaviour or health-related outcomes may have occurred that could counteract product-specific RMM effectiveness (e.g. spill-over effects) (Fig.3).

The systematic collection and review of the results of MAH sponsored PASS evaluating the effectiveness of RMM contributes to a better understanding of the requirements for data collection, study designs and analytical methods, as well as the interpretation of study results, factors associated with success or failure of RMM and impact of individual RMM tools in clinical practice.

Monitoring the outcomes of risk minimisation may be complemented with impact research on regulatory actions of major public health importance, e.g. in context of referral procedures based on pharmacovigilance data (i.e. Article 31 and Article 107i of Directive 2001/83/EC, Article 20 of Regulation (EC) No 726/2004) where several different products and MAHs are involved.

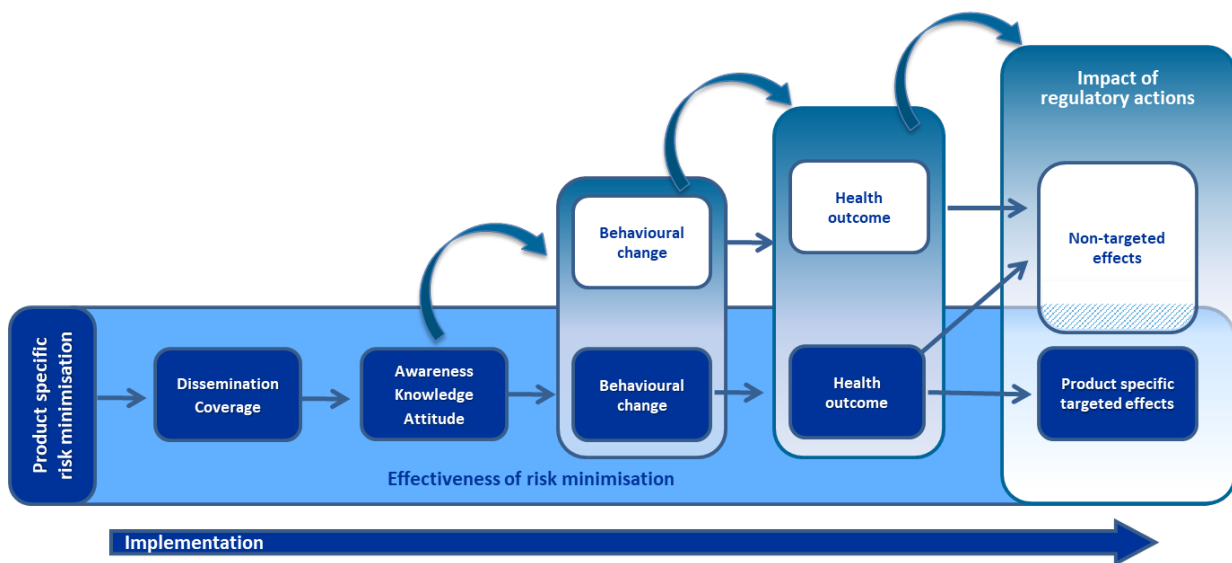


Figure 3: The approach to effectiveness evaluation of risk minimisation measures in GVP Module XVI.

For example, the 2013 EU label changes for diclofenac-containing medicinal products due to the risk of cardiovascular events were associated with a significant fall in diclofenac initiation in the Netherlands, England and Scotland, but not in Denmark. The regulatory action was associated with modest differences in switching to other pain medicines such as NSAIDs, paracetamol, opioids, and other chronic pain medication³. For hydroxyzine-containing medicines label changes in 2015 due to pro-arrhythmogenic risks were associated with an immediate fall and negative trend in hydroxyzine initiation in England and Scotland, but limited impact in the Netherlands and Denmark to only certain age groups. The regulatory action was not associated with switching to other antihistamines, benzodiazepines or antidepressants⁴.

Overall, impact research may confirm that there is no need for further regulatory action despite geographical variation in impact which may be associated with the type of regulatory action and method of dissemination.

³ Morales, DR, Morant, SV, MacDonald, TM, et al. Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and The Netherlands. *Pharmacoepidemiol Drug Saf.* 2020; 29: 296– 305.

⁴ Morales, DR, Macfarlane, T, MacDonald, TM, et al. Impact of EMA regulatory label changes on hydroxyzine initiation, discontinuation and switching to other medicines in Denmark, Scotland, England and the Netherlands: An interrupted time series regression analysis. *Pharmacoepidemiol Drug Saf.* 2021; 30: 482– 491.

3.2. Effectiveness of specific pharmacovigilance processes

Pharmacovigilance activities involve several complex processes in relation to spontaneous reporting of suspected adverse reactions, signal detection and management, risk management planning, periodic safety update reporting and post-authorisation studies (see Annex). In 2018 the PRAC Interest Group Impact identified PASS measuring effectiveness of risk minimisation as process most relevant to the strategy's key activity areas (see Fig. 2) where continuous improvement is expected to have tangible benefits. Since 2012 a significant number of PASS evaluating the effectiveness of RMM have been imposed or requested by PRAC. However, a systematic review of these PASS assessed by PRAC between 2016 and 2019 showed marked heterogeneity in quality and methodology which may be the reason that almost half of the studies included in this review were unable to conclude whether RMM was effective or not⁵. The continuous review of PASS evaluating RMM effectiveness is an ongoing activity with focus on factors why PASS are inconclusive or RMM ineffective and includes also procedural aspects.

3.3. Enablers of effective pharmacovigilance and stakeholder engagement

The effectiveness of pharmacovigilance processes and RMM depends on 'enablers' for engaging patients and healthcare professionals in medicines regulation and pharmacovigilance activities, both at regulatory level and 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 implementing RMM through behavioural change. Conceptualising stakeholder engagement for pharmacovigilance purposes provided the basis for further progressing this activity area⁶. Specifically, input from stakeholders is needed for informing regulatory-decision-making on RMM during risk management planning and benefit-risk life-cycle management of medicinal products. A content analysis of the stakeholder input to the public hearing for valproate in 2017 identified the value as well as gaps in input from an RMM implementation perspective⁷. Further qualitative research analysed EMA's pharmacovigilance engagement for major safety concerns by means of conceptual and risk governance frameworks and provided recommendations for strengthening the dialogue between regulators and patients' and healthcare professionals' representatives⁸. Together this research provides the basis for *points to consider* for selecting tools, setting objectives and applying different discourse types in different risk scenarios with a view to derive good practice recommendations for routine engagement and dialogue for informing and evaluating RMM effectiveness, taking into account the enablers for RMM implementation in healthcare.

3.4. Analytical methods for impact research

There is no single commonly accepted method for measuring the impact of pharmacovigilance activities or to evaluate the effectiveness of risk minimisation measures. In 2017, 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 for stakeholders on methods for impact research⁹. The development of methodological guidance was a

⁵ Gardarsdottir et al. Review of studies evaluating the effectiveness of risk minimisation measures assessed by PRAC (EMA/37857/2021).

⁶ Brown P, Bahri P. 'Engagement' of patients and healthcare professionals in regulatory pharmacovigilance: establishing a conceptual and methodological framework. *Europ J Clin Pharmacol.* 2019; 75: 1181-1192.

⁷ Bahri P, Morales DR, A Inoubli, Dogné JM, Straus SMJM. Proposals for engaging patients and healthcare professionals in risk minimisation from an analysis of stakeholder input to the EU valproate assessment using the novel Analysing Stakeholder Safety Engagement Tool (ASSET). *Drug Saf.* 2021; 44: 193-209 (epub 30 Oct 2020)

⁸ Bahri P, Pariente A. Systematising pharmacovigilance engagement of patients, healthcare professionals and regulators: a practical decision guide derived from the International Risk Governance Framework for engagement events and discourse. *Drug Saf.* 2021; 44: 1193-1208.

⁹ 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.* 2018; 84:419-433.

priority from the outset and revision 7 of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology included an addendum dedicated to methods for impact research which is now fully integrated in the current version¹⁰. For pharmaceutical industry and regulators GVP Module XVI¹¹ includes guidance on the principles, objectives and assessment of RMM effectiveness evaluation, and a new addendum on methods for effectiveness evaluation. The guidance on analytical methods for impact research continues to be updated with latest developments in the area of impact research.

4. Prioritisation of impact research

In accordance with GVP Module XVI principles for RMM effectiveness evaluation, regulatory impact research should focus on regulatory actions of major patient and public health importance, taking into account the nature, severity and seriousness of the risk, the magnitude of population exposure and the amount of public concern.

PRAC has established a process for prioritisation and regulatory follow-up of impact research¹² based on criteria that consider the public health importance of the regulatory action, the potential impact on clinical practice and whether new decision relevant data can be generated. A clear understanding of the research question (i.e. which data or information is required), how the data generated by the study will be used (i.e. is the study expected to reduce uncertainty), feasibility of the study and generalisability of the study results are key aspects to be taken into account.

Prioritisation allows regulators to direct resources to major regulatory actions that require additional evidence beyond data generated by routine pharmacovigilance processes, i.e. through expedited and periodic safety reporting, post-authorisation safety studies or studies measuring the effectiveness of RMM included in the EU RMP.

The output of the prioritisation process is the adoption of a technical specification for tender describing the service required by the Agency with regulatory background, research question, study objectives and methodological considerations which provides the basis for a formal PRAC request to commission the study under EMA's framework contract. Alternatively, PRAC may endorse an outline for an impact study conducted as EU regulatory network collaborative project.

5. Framework for regulatory impact research

National competent authorities and the Agency have a legal obligation to monitor the outcomes of RMM and other regulatory actions for authorised medicinal products ([DIR Art 107h (1), REG Art 28a]). While scientific evidence generated by MAH remains at the core of regulatory evaluation, additional data and information available from alternative sources or new data may need to be generated to further inform regulatory decision-making based on the best available scientific evidence.

Pharmacovigilance impact research is a multi-stakeholder undertaking that involves measuring the effects of European Union (EU) pharmacovigilance activities and regulatory actions in Member States' national healthcare settings. This often involves several marketing authorisations in a therapeutic class of medicines e.g. for regulatory actions taken in context of EU referral procedures. In this context, commissioning impact research centrally has several advantages with regards to access to impact-

¹⁰ https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

¹¹ Revision 3, currently under review following public consultation: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf

¹² Process for prioritisation and regulatory follow-up of impact research (EMA/621879/2020)

relevant national health data and accounting for national variation in healthcare practices, regulatory communication strategies and implementation of product-specific regulatory actions.

At EU level the Agency has established a framework contract with research organisations to perform pre- and post- authorisation quality, efficacy and safety research to generate data and information to support regulatory decision-making. Under the framework contract qualitative and pharmacoepidemiological research of the impact of pharmacovigilance activities and regulatory actions may be commissioned to shortlisted contractors. PRAC advises on the research question, objectives and methodological aspects of commissioned impact research and contributes to the evaluation of the study protocol, study report and manuscript for publication submitted by the contractor. Moreover, the Data Analysis and Real World Interrogation Network (DARWIN EU)¹³ launched in 2022 will drive the conduct of impact research with real-world evidence from across Europe on the uses, safety and efficacy of medicines with an expanding catalogue of healthcare databases and standard analyses, for example on drug utilisation.

Alternatively, competent authorities in Member States may conduct impact studies on their own initiative or establish research collaborations within the EMRN, e.g. following the model of a common protocol for multi-database studies where each regulator conducts the research in national or regional database or via transformation of data from different databases into a common data model. Examples are the EMA collaboration with the national agencies from Spain and United Kingdom on a study that evaluated the impact of EU label changes in 2013 for the use of codeine in children for pain indications using a common protocol¹⁴ and the EU collaborative study of changes in alternative treatments for pain and cough in children after introduction of RMM for codeine in 2015¹⁵.

All publicly funded impact research has to follow the rules of the ENCePP Code of Conduct¹⁶ in its entirety to ensure maximal levels of scientific independence and transparency, and adherence to the highest methodological standards in line with Annex 2 of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology¹⁷.

6. Continuous activities

The PRAC Impact Strategy provides the basis for systematically measuring patient-relevant health outcomes of major regulatory interventions through systematic data collection in the four key activity areas outlined above. This includes the following continuous activities:

- Based on PRAC prioritised topics evaluate the impact of product-specific regulatory interventions by commissioning impact research through EMA's framework contracts for qualitative research and pharmacoepidemiological research; alternatively, collaborative impact research may be conducted within the EU medicines regulatory network;
- Collect and collate data from ongoing pharmacovigilance activities within the EU regulatory network which are relevant for measuring the impact of pharmacovigilance activities;
- Engage with patients and HCPs for measuring the impact of regulatory interventions and for providing input to RMM;

¹³ <https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu#timelines-section>

¹⁴ Hedenmalm, K., Kurz, X. & Morales, D. Effect of withdrawal of fusafungine from the market on prescribing of antibiotics and other alternative treatments in Germany: a pharmacovigilance impact study. *Eur J Clin Pharmacol.* 2019; 75:979–984.

¹⁵ EU collaborative study: Changes in alternative treatments for pain and cough in children after introduction of risk minimisation measures for codeine (EMA/37857/2021). Manuscript submitted for publication.

¹⁶ https://www.encepp.eu/code_of_conduct/documents/ENCEPPCodeofConduct.pdf

¹⁷ https://www.encepp.eu/standards_and_guidances/documents/1.ENCEPPMethodsGuideRev.9.pdf

- Provide training to pharmacovigilance assessors on methods for measuring the impact of regulatory interventions.

Annex

Table 1 lists data that are compiled periodically in context of the EMRN 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.

Table 1: Data compiled on pharmacovigilance activities.

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