REVIEW OF STUDIES EVALUATING THE EFFECTIVENESS OF RISK MINIMISATION MEASURES ASSESSED BY PRAC

Study information

Title	Review of studies evaluating the effectiveness of risk minimisation measures evaluated by PRAC
Version identifier	2.0
Date of last version of the final protocol	31 Oct 2019
EU PAS® Register	EUPAS45978
Active substance	Multiple (review)
Medicinal product(s)	Multiple (review)
Product reference	Not applicable
Product number	Not applicable
Joint PASS	Not applicable
Research question and objectives	This study is a deliverable of the Pharmacovigilance Risk Assessment Committee (PRAC) Interest Group (IG) on Impact at the European Medicines Agency to support the implementation of the PRAC strategy for measuring the impact of pharmacovigilance activities (Rev 1) (EMA/165407/2017).
	The aim of this review of industry-sponsored post-authorisation safety studies (PASS) evaluating the effectiveness of risk minimisation measures (RMM) assessed by PRAC between 2016 and 2019 is to improve regulatory decision-making by providing a better understanding of factors associated with effectiveness PASS that allow (or not) a conclusion on RMM effectiveness, such as methodological issues, and factors associated with effective or ineffective RMM.
	The main objectives of this study are to
	1) identify industry-sponsored PASS assessed by the PRAC that evaluate the effectiveness of RMM and to describe their designs and analytical methods and chosen measures for effectiveness evaluation,
	2) determine the type of RMM addressed by these PASS, the proportion of effective RMM and criteria used to define if these were effective,

	3) compare characteristics of effective RMM with non-effective RMM as measured by the PASS,
	4) identify factors allowing to draw a conclusion on RMM effectiveness as measured by the PASS
Countries of studies	Not applicable
Authors	Helga Gardarsdottir[1], Jet Scheffers[1], Jarno Hoekman[1], Simone Bergner[2], Wiebke Seemann[2], Valerie Straßmann[3], Thomas Goedecke[3];
	[1]Division Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, 3584 CG Utrecht, The Netherlands
	[2]Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 53175 Bonn, Germany
	[3]European Medicines Agency, 1013 DP, Amsterdam, The Netherlands
Market authorisation holder(s)	Not applicable

TITLE
Review of studies evaluating the effectiveness of risk minimisation measures assessed by PRAC

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

- ADR Adverse drug reaction

- BfArM Federal Institute for Drugs and Medical Devices

- DHPC Direct Healthcare Professional Communication

- DREAM Document Records Electronic Archive Management

- eCTD electronic Common Technical Document

- EMA European Medicines Agency

- EM Educational material

- EU European Union

- EU PAS Register European Union electronic Register of Post-Authorisation Studies

- EURS European Review System for eCTDs

- GVP Good Pharmacovigilance Practices

- HCP Healthcare Professional

- MAH Marketing Authorisation Holder

- PRAC Pharmacovigilance Risk Assessment Committee

- PAM Post-authorisation measure

- PASS Post-authorisation safety study

- PSUR Periodic safety update report

- RCT Randomised clinical trial

- RMM Risk minimisation measure

- RMP Risk management plan

- SmPC Summary of product characteristics

3. RESPONSIBLE PARTIES

Name	Role
Dr. Helga Gardarsdottir[1,2,3]	Principal Investigator
Dr. Jarno Hoekman[1]	Co-investigator
Ms. Jet Scheffers[1]	PhD student
Dr. Simone Bergner[3],	Co-investigator
Dr. Wiebe Seemann[3],	Co-investigator
Dr. Valerie Straßmann[4]	Co-investigator
Dr. Thomas Goedecke[4]	Co-investigator

1. Universiteit Utrecht, David de Wiedgebouw, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands (UU)
2. University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands (UMCU)
3. University of Iceland, Department of Pharmaceutical Sciences, Reykjavik, Iceland
4. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 53175 Bonn, Germany
5. European Medicines Agency, 1013 DP, Amsterdam, The Netherlands

Contact principal investigator Dr. Helga Gardarsdottir: h.gardarsdottir@uu.nl

4. ABSTRACT

Title: Review of studies evaluating the effectiveness of risk minimisation measures assessed by PRAC

Protocol version: 2.0. Date: 31 Oct 2019.

Main author: Helga Gardarsdottir, PhD, Utrecht University, Netherlands.

Co-authors: Dr. Thomas Goedecke, Dr. Valerie Straßmann, European Medicines Agency, 1013 DP, Amsterdam, The Netherlands. Dr. Jarno Hoekman, Ms. Jet Scheffers, Universiteit Utrecht, David de Wiedgebouw, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands; Dr. Simone Bergner, Dr. Wiebe Seemann, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), 53175 Bonn, Germany

Rationale and background: Risk minimisation measures (RMM) are public health interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient. The impact of these interventions are assessed by conducting post-authorisation safety studies (PASS). A systematic review of industry sponsored PASS evaluating RMM effectiveness assessed by the PRAC between 2016 and 2019 is conducted to provide better understanding of the types of data collected, the study designs and analytical methods used, and to provides a better understanding of those PASS where a conclusion on RMM effectiveness could be drawn in order to help improve regulatory decision-making.

This study is a deliverable of the Pharmacovigilance Risk Assessment Committee (PRAC) Interest Group (IG) on Impact at the European Medicines Agency to support the implementation of the PRAC strategy for measuring the impact of pharmacovigilance activities (Rev 1) (EMA/165407/2017).

Research question and objective:

The aim of this review of industry-sponsored PASS evaluating the effectiveness of RMM assessed by PRAC between 2016 and 2019 is to improve regulatory decision-making by providing a better understanding of factors associated with RMM effectiveness PASS that allow (or not) a conclusion on RMM effectiveness, such as methodological issues, and factors associated with effective or ineffective RMM.

The main objectives of this study are to

- identify industry-sponsored PASS assessed by the PRAC that evaluated the effectiveness of RMM and to describe their designs and analytical methods, and chosen measures for effectiveness evaluation,

- determine the types of RMM addressed by these PASS, the proportion of effective RMM and how RMM effectiveness was defined,

- compare characteristics of effective RMM with non-effective RMM as measured by the PASS,

- identify factors allowing to draw a conclusion on RMM effectiveness as measured by the PASS

Population: All EU-RMP category 1, 2, or 3 PASS evaluating the effectiveness of RMM that were submitted to and assessed by the PRAC between 1 January 2016 and 31 December 2019 were included in the study cohort.

Study design: This is a descriptive, cross-sectional study

Variables: The following variables will be extracted from the data source and categorised into: medicinal product information, regulatory background, study characteristics and PASS performance information

Data sources: Data used in this study will be retrieved from protocols, study reports and assessment reports held in EMA's Document Records Electronic Archive Management (DREAM) system which is an online content filing system used internally by EMA to save and share information and from the European Review System (EURS) for the submission of electronic Common Technical Document (eCTD).

Study size: NA

Data analysis: A review will be performed and extracted variables were analysed with descriptive statistics. Variables were summarised by the number and percentage per category.

Milestones:

Start of data collection: September 2020.

Planned end of data collection: March 2021.

Registration in the EU PAS register: February 2022.

Planned final report of study results: December 2021.

5. AMENDMENTS AND UPDATES

N/A.

6. MILESTONES

Milestone	Planned date
Start of data collection	September 2020
End of data collection	March 2021
Registration in the EU PAS register	February 2022
Final report of study results	December 2021

7. RATIONALE AND BACKGROUND

Risk minimisation measures (RMM) are public health interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient. The PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (1) focuses on the effectiveness of RMM and specific pharmacovigilance processes, two key areas for measuring the impact of pharmacovigilance activities.

The conduct of post-authorisation safety studies (PASS) is a key pharmacovigilance activity. In line with GVP Module XVI requirements, marketing authorisation holders (MAHs) perform PASS that measure the effectiveness of RMM for their products. The results of these studies are reported by the MAHs for centrally authorised products as part of the post-authorisation requirements laid down in the risk management plan's (RMP) pharmacovigilance plan. Since 2012, a number of PASS evaluating the effectiveness of RMM have been requested and assessed by the PRAC and other regulatory agencies. A systematic review of PASS information evaluating RMM effectiveness assessed by the PRAC between 2016 and 2019 allows a better understanding of the types of data collected, the study designs and analytical methods used by MAHs to assess the effectiveness of RMM for their products, and provides a better understanding of those PASS where a conclusion on RMM effectiveness could be drawn in order to help improve regulatory decision-making. In addition, criteria to define factors associated with PASS that demonstrate (or not) that RMM are effective and factors associated with effective and non-effective RMM may be determined as well as impacts of different types of risk minimisation efforts on (patient) relevant outcomes. Information from these PASS provide the basis for reviewing the various steps from the regulatory request to protocol development, evaluation of the results and decision making.

8. RESEARCH QUESTIONS AND OBJECTIVE

The aim of this review of industry-sponsored post-authorisation safety studies (PASS) evaluating the effectiveness of risk minimisation measures (RMM) assessed by PRAC between 2016 and 2019 is to improve regulatory decision-making by providing a better understanding of factors associated with effectiveness PASS that allow (or not) a conclusion on RMM effectiveness, such as methodological issues, and factors associated with effective or ineffective RMM.

The main objectives of this study are to

•   identify industry-sponsored PASS assessed by the PRAC that evaluated the effectiveness of RMM and to describe their designs and analytical methods and chosen measures for effectiveness evaluation,

•   determine the types of RMM addressed by these PASS, the proportion of effective RMM and how RMM effectiveness was defined,

•   compare characteristics of effective RMM with non-effective RMM as measured by the PASS,

•   identify factors all

owing to draw a conclusion on RMM effectiveness as measured by the PASS

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a descriptive, cross-sectional study assessing characteristics of industry-sponsored post-authorisation safety studies (PASS) evaluating the effectiveness of risk minimisation measures (RMM) assessed by PRAC between 2016 and 2019.

9.2 SETTING

NA

9.3 STUDY POPULATION

Data will be considered eligible when originating from industry-sponsored PASS evaluating the effectiveness of RMM submitted and assessed by PRAC between 2016 and 2019.

All EU-RMP category 1, 2, or 3 PASS evaluating the effectiveness of RMM that were submitted to and assessed by the PRAC between 1 January 2016 and 31 December 2019 will be included in the study cohort. A PASS may be required at different stages of the regulatory life cycle. Category 1 PASS are imposed as a condition of the marketing authorisation, while category 2 PASS are imposed as a specific obligation in the context of a marketing authorisation granted under exceptional circumstances and both categories require PRAC assessment in line with EU pharmacovigilance legislation. PASS may also be required in the EU-RMP to investigate safety concern(s) or to evaluate the effectiveness of RMM (category 3) (2).

Agendas of monthly PRAC plenary meetings held between 1 January 2016 and 31 December 2019 will be screened (SB, VS) to identify PASS evaluating the effectiveness of RMM. PRAC agendas are published on the EMA public website, however, for this study unpublished agendas will be extracted from DREAM to include information on the detailed scope of the regulatory procedure. PRAC agendas will be searched using the following keywords: "risk-minimisation", "risk minimisation", "RMM", "effectiveness", "educational", "material", "EM", and "(EM)". In addition, additional documents from other regulatory procedures pertaining to PASS such as EU-RMPs, periodic safety update reports (PSURs), PRAC plenary minutes or other relevant documents identified in the PRAC plenary agendas will be consulted to confirm eligibility of the PASS (section 5.1.), by the PASS title, rationale and/or research question and study objectives, or to retrieve relevant study protocols or study reports related to these documents.

For each identified PASS evaluating the effectiveness of RMM, the corresponding regulatory procedure number found in the PRAC agenda will be used to retrieve related documents such as the study protocol, the final study report and the PRAC assessment report from DREAM and/or EURS.

9.4 VARIABLES

A standardised data extraction form will be created a priori for the variables of interest. The following variables will be extracted from study reports and assessment reports (and protocols as appropriate for further verification) and categorised into product information, regulatory background, study characteristics and PASS performance information:

- **Product information**

- o International Non-proprietary Name (INN)
- o MAH
- o ATC code

- **Regulatory Background**
  - o Registration in EU PAS Register [yes/no]
  - o EU PAS Register number (if applicable)
  - o Joint PASS [yes/no]
  - o PASS category [1/2/3]
  - o PASS objective(s)
    - Measuring healthcare professional awareness/behavior/knowledge
    - Measuring patient awareness/behavior/knowledge
    - Measuring patterns of use in clinical practice
    - Measuring health outcomes
    - Measuring health system utilisation (e.g., laboratory testing, monitoring, etc)
  - o Type of RMM evaluated
    - Routine
    - Additional
    - Both
  - o Type of Routine RMM evaluated (if applicable)
    - SmPC
    - Labelling information (information on immediate or outer packaging)
    - Package leaflet
    - Pack size
    - Legal status
  - o Type of Additional RMM evaluated (if applicable)
    - Educational material
      - HCP Guide
      - Patient Guide
      - HCP Checklist
      - Risk awareness form
      - Demonstration kit
      - Patient diary
      - Patient card
    - DHPC
    - Pregnancy prevention progamme
    - Controlled access programme

- **Study characteristics**
  - o Data Source
    - Primary data collection
    - Secondary data collection
    - Both
  - o Source for primary data collection (if applicable)
    - Survey
    - Interview
    - Focus group
    - Prospective observational study
    - Registry
  - o Source for secondary data collection (if applicable)
    - Patient medical records (including prescribing data)
    - Administrative claims records/pharmacy records (dispensing data)
    - Healthcare records linkage
    - Spontaneous reports of ADRs
    - Registry/registry-based study
  - o Number of countries included in a study
    - Single
    - Multiple 2-5

- Multiple >5
  - o Geographical region included in a study (as defined by United Nations Geoscheme, see Appendix 10.1)
    - Eastern Europe
    - Southern Europe
    - Northern Europe
    - Western Europe
    - Countries from all regions included
  - o Outcome
    - Extent of dissemination
    - (Change in) awareness/knowledge, self-reported behavior, attitudes
    - (Change in) prescribing/dispensing patterns
    - Health outcome (mortality, morbidity, etc)
    - Change in ADR reporting
    - Other
  - o Time period covered
    - Pre- and post-intervention
    - Post-intervention
  - o Study design
    - Interventional RCT
    - Cohort study
    - Case control study
    - Cross-sectional study
    - Time series
  - o Analytical method
    - Descriptive with comparator
    - Descriptive without comparator
    - Descriptive statistics with significant testing with comparator
    - Descriptive statistics with significant testing without comparator
    - Regression models
    - Time series analysis
    - Thematic analysis

- **PASS performance**
  - o RMM effectiveness criteria
    - Measurable criterion defined a priori [yes/no]
      - Threshold
      - Change before/after
      - Descriptive assessment
      - Threshold and descriptive assessment
  - o Planned sample size met
  - o Planned response rate (surveys) met
- Effectiveness of risk minimisation
  - o Effective
  - o Non-effective
  - o Inconclusive
- Further regulatory action for those evaluated as non-effective/inconclusive
  - o New PASS
  - o New/revised RMM
  - o Existing RMM discontinued
  - o Change to terms of marketing authorization
  - o Other

In addition, information (free text) about limitations of the PASS will be extracted from the assessment reports and when applicable coded into the following categories: Limitations related to 1) not reaching target audience or sample size; 2) limited use of product in country; 3) imbalanced country

distribution of included subjects; 4) suboptimal study population; and 5) study design flaws or limitations.

9.5 DATA SOURCES

Data used in this study will be retrieved from EMA's Document Records Electronic Archive Management (DREAM) system which is an online content filing system used internally by EMA to save and share information. DREAM allows access to documents for meetings organised by EMA, thereby facilitating paperless meetings and providing a single source for up-to-date documents. PRAC meeting documents (e.g., agendas, minutes, and assessment reports) are stored in DREAM. PASS documents (e.g., study protocols and study reports) are submitted electronically by MAHs in the format of the electronic Common Technical Document (eCTD) and stored in the European Review System for eCTDs (EURS). EURS is a non-public electronic tool that is accessible to both EMA and national competent authorities. For this study, we will use documents related to the assessment of industry-sponsored PASS evaluating the effectiveness of RMM stored both in DREAM and EURS.

9.6 STUDY SIZE

NA

9.7 DATA MANAGEMENT

Data extraction will be performed from the included study protocols, study reports and assessment reports in WORD or PDF format into Microsoft EXCEL (see 5.2. for inclusion criteria). A random sample including a subset of 20 PASS will be selected and double coded to cross check and validate the data extraction. Any unclarities in relation to the extraction and/or coding and classification will be discussed and agreed by the co-authors.

9.8 DATA ANALYSIS

A review of PASS meeting the inclusion criteria (see 5.2) will be performed and extracted variables will be analysed with descriptive statistics. Variables will be summarised by the number and percentage (%) of PASS in each category. Additionally, free text information extracted from study protocols, study reports and assessment reports will be used to determine if the RMM was concluded effective, non-effective or inconclusive by the MAH or PRAC, as well as to identify limitations of the PASS as reported by PRAC.

9.9 QUALITY CONTROL

Data extraction will be performed from the included study protocols, study reports and assessment reports in WORD or PDF format into Microsoft EXCEL (see 5.2. for inclusion criteria). A random sample including a subset of 20 PASS will be selected and double coded to cross check and validate the data extraction. Any unclarities in relation to the extraction and/or coding and classification will be discussed and agreed by the co-authors.

9.10 LIMITATIONS OF THE RESEARCH METHODS

The study will be restricted to PASS evaluated at the European Union level by the PRAC. National procedures are therefore only included in this review if the PASS is conducted in more than one Member State and consequently subject to PRAC oversight or if the competent authority has asked for

PRAC Advice for the respective PASS because it was deemed important at European level. The sample set of studies might therefore be incomplete with regards to national PASS procedures.

Only PASS procedures assessing the final study results will be included implying that the study protocols for these studies might have been discussed at PRAC prior to regulatory and scientific guidance on methods for evaluating RMM effectiveness had been published (e.g. GVP Module XVI, ENCePP Methods Guide) had been published.

10. PROTECTION OF HUMAN SUBJECTS

NA

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

NA

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol as well as the study results will be submitted to the EU-PAS register. In addition, the study will be presented to the PRAC and is planned for publication in a scientific journal. Authorship is decided according to the *International Committee of Medical Journal Editors (ICJME) 'Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals'*.

13. REFERENCES

1. Pharmacovigilance Risk Assessment Committee (PRAC). PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1) (EMA/165407/2017) [Internet]. 2017 [cited 2021 Sept 20]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf

2. European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP) Module XVI- Risk minimisation measures: selection of tools and effectiveness indicators (Rev 1). 2014. [cited 2021 Sept 20]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf