Protocol: Time intervals between key milestones of studies evaluating the effectiveness of Risk Minimisation Measures assessed by PRAC

EMA-UU collaborative project

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1. List of abbreviations

ADR(s)	Adverse drug reaction(s)
ATC	Anatomical Therapeutic Chemical
aRMM(s)	Additional risk minimisation measure(s)
CHMP	Committee for Medical Products for Human Use
DHPC	Direct healthcare professional communication
eCTD	Electronic Common Technical Document
EC	European Commission
EM	Educational material
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies Register
EU-RMP	Product's Risk Management Plan
EURS	European Review System for eCTDs
GVP	Good Pharmacovigilance Practices
HCP(s)	Health care professional(s)
MA	Marketing authorisation
MAH(s)	Marketing authorisation holder(s)
Ms	Microsoft
PASS	Post-authorisation safety studies
PSUR(s)	Periodic safety update report(s)
RMM(s)	Risk minimisation measure(s)

2. Background and rationale

Risk minimisation measures (RMMs) are public health interventions aimed to prevent or reduce the occurrence of adverse drug reactions (ADRs), or to limit the severity of ADRs and their impact on patients (1). In the European context, two types of RMMs exist: routine measures, which are applied to every medicinal product -e.g. a summary of product characteristics, product label and patient information leaflet-, and additional measures (aRMMs), which should only be introduced when they are deemed essential for safe use,-i.e. educational material (EM) for healthcare professionals (HCPs) and patients, controlled access programmes, controlled distribution programmes, pregnancy prevention programmes, direct healthcare professional communication (DHPC)- (2).

As required by the European Medicines Agency's (EMA) Good Pharmacovigilance Practices (GVP) Module XVI, marketing authorisation holders (MAHs) are obligated to measure the effectiveness of RMM for their products (3). This is crucial to examine if the objectives of the RMMs are fulfilled or if amendments are needed to protect health of patients (4). In general, aRMMs can be evaluated using routine (e.g., Periodic Safety Update Reports [PSURs] to regulatory authorities) and/or additional pharmacovigilance activities (i.e., using post-authorisation safety studies). Regarding these additional pharmacovigilance activities, the number of studies that evaluated the effectiveness of aRMMs is growing (5).

The PRAC and the MAHs spend a considerable amount of time and resources on the assessment of RMM effectiveness PASS. The timing and duration of RMM effectiveness studies is challenging as the need for timely data to protect patients' health should be balanced with accurate performance of the studies itself (6,7). Previous research on studies evaluating the effectiveness of aRMM introduced at MA for centrally authorised medicinal products showed that the duration of these studies was relatively long. Of the evaluation studies with at least 18 months follow-up (n = 69), none was finalised and assessed by PRAC within 18 months after MA. Within 60 months after MA (n = 37), the probability that an evaluation study was finalised and assessed by PRAC was 25.2% (95% CI 12.3–36.2) [unpublished results of Essink et al.]. This was despite the fact these timepoints are included as timepoints of interest in GVP Module XVI Rev 2 (8).

Prior work of Essink et al. (9) has provided general insight in the duration of aRMM effectiveness evaluations. This work included a concise oversight of the distribution of the duration amongst three main periods: time from MA to the start of the evaluation study, from the start of the evaluation study to the final report, and from the final report to the PRAC outcome. It was shown that the duration of these distinct time periods varied between individual studies. However, this study was restricted to aRMM evaluation studies in place at MA and many studies were still ongoing (e.g., calculating the median time-to-event was not possible). Based on the prior work, a further study with focus on the distribution of the duration of PASS evaluating the effectiveness of RMM might give valuable insights. Detailed examination of the time needed to evaluate the effectiveness of RMM might be important to identify points for improvement to facilitate timely evaluation of the effectiveness of RMMs and gives insight for the regulatory world. Therefore, this study will systematically assess pharmaceutical industry sponsored PASS evaluating RMM effectiveness assessed by PRAC to provide insight in the time intervals between important milestones of regulatory procedures.

3. Aim and objectives

This retrospective cohort study of PASS overseen/discussed by PRAC is aimed to provide insights in the time intervals between key milestones of regulatory procedures for RMM effectiveness PASS assessed by PRAC 2016-2022 (follow-up on previous expert collaboration project with Utrecht University, EUPAS45978, EUPAS47563) (10-12). Objectives for this research are reached through the following steps:

1. To identify PASS assessed by the PRAC that evaluated the effectiveness of RMM and to review PRAC assessment protocols and study reports;
2. To extract information on timing of and duration of time intervals between key milestones of PRAC regulatory procedures for requesting and assessing protocols and study reports of RMM effectiveness PASS;
3. To determine how many study protocol assessment rounds (first approved study protocol) and final study report assessment rounds were required for these RMM effectiveness PASS.
4. To assess factors potentially associated with the duration of time intervals between key milestones, e.g, PASS study design, PASS indicators, PASS conclusive or inconclusive, type of RMM evaluated.

4. Methods

4.1 Study design

This study is a retrospective cohort study including completed PASS that evaluated RMM effectiveness.
This study involves a quantitative analysis of time intervals between key milestones of PRAC regulatory procedures for requesting and assessing protocols and study reports of RMM effectiveness PASS. We will use a dataset of PASS evaluating RMM effectiveness assessed by PRAC between 2016 and 2022.

4.2 Inclusion of studies between 2016 and 2022

The dataset with completed PASS contains all EU-RMP category 1, 2, or 3 PASS evaluating the effectiveness of RMM submitted to PRAC where the assessment of the final study report was completed between January 1st of 2016 and December 31st of 2022. Gardarsdottir et al. and Grupstra et al. (10-12) identified eligible PASS between 2016 and 2021 based on the agendas of monthly PRAC plenary meetings held between January 1st 2016 and December 31st 2021. For this, unpublished agendas were extracted from DREAM to include information on the detailed scope of the regulatory procedure. The PRAC agendas were searched using the following keywords: “risk-minimisation”, “risk minimisation”, “RMM”, “effectiveness”, “educational”, “material”, “(EM)”, “final report”, “survey”. Additionally, sections 5.2 (Medicines in the post-authorisation phase-RPAC led procedures), 5.3 (Medicines in the post-authorisation phase-Committee for Medical Products for Human Use (CHMP) led procedures), 7.3 (Results of PASS imposed in the marketing authorisation(s)), 7.4 (Results of PASS non-imposed in the marketing authorisation(s)), and 7.6 (Others) of the monthly PRAC agendas were manually scanned for eligible PASS. To determine eligibility of PASS, the scope as described in the PRAC agendas and study objectives of the PASS as presented in the PRAC assessment report were consulted. In addition, documents from other regulatory procedures pertaining to PASS such as EU-RMPs and periodic safety update reports (PSURs) could be used to confirm eligibility (10-12). We will identify eligible PASS in 2022 based on the agendas of monthly PRAC plenary meetings held between January 1st 2022 and December 31st 2022, using the same methods as described before.

Inclusion criterion for this study:

- PASS evaluating the effectiveness of RMM submitted to PRAC with assessment of the final study report completed in 2016-2022 (as identified by Gardarsdottir et al. and Grupstra et al. for 2016-2021 (10-12) and by Essink et al. for 2022).

Exclusion criterion for this study:

- PASS for which the PASS request date could not be retrieved, as this is the start point for the analyses.

4.3 Data sources

(Additional) data will be extracted from documents from both the Documents Records Electronic Archive Management (DREAM) system and the European Review System (EURS) for electronic Common Technical Documents (eCTD). DREAM is an online content filing system used 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 PRAC assessment reports) and PASS documents submitted by MAHs (e.g. EU-RMPs, study protocols and study reports) are filed in DREAM. DREAM will be used to extract, for each study (if available): the assessment report of the procedure in which study was requested, assessment report of the first approved study protocol, and the assessment report of the final study report. Documents that are electronically submitted by MAHs for marketing authorisation applications and post-authorisation applications in the format of the electronic Common Technical Document (eCTD) are stored in EURS, a non-public electronic tool that is accessible to the European Medicines Regulatory Network (EMRN). From EURS, documents as submitted by the MAH relevant for the study request, the final study protocol and final study report were retrieved. If needed, SIAMED was consulted for dates that were not included/missing in the source documents.

4.4 Study outcomes

The primary outcome of this study is time intervals between key milestones of the regulatory procedures related to RMM effectiveness PASS. The following dates will be manually extracted from the corresponding data source and used to calculate time intervals between key milestones of the regulatory procedures for requesting and assessing study protocols and results of RMM effectiveness PASS (Figure 1):

- Study request date: the studies can be requested at various timepoints. Study request date is defined as the date of finalisation (see details below) of the procedure in which the study was requested by PRAC or proposed by the MAH. 1) These procedures will be identified by screening (the assessment report of) the final study report on any leads of the procedure or date where the study was requested. 2) If no leads will be identified, the cover letter of this procedure will be screened for any leads on the study request date/procedure. If leads will be identified, the corresponding procedure was checked if the study was indeed requested within this procedure. 3) If this will not retrieve useful information, the RMP approved with the initial marketing authorisation (MA) will be checked for inclusion of the study. 4) Post-marketing procedures with an RMP update will be checked for inclusion of the study if the study was not requested at MA. For these post-marketing procedures, in which the RMP is updated to include the study, we will check whether the first study request was within this procedure, e.g., type II variation to introduce aRMMs and corresponding studies. If there were indications that the study was added to the RMP based on a recommendation in another procedure, we will identify the procedure in which the study was requested, e.g., implementation of PSUSA outcomes in a type II variation to update the RMP. Once the procedure in which the study was requested is identified, relevant documents will be collected:
    - Study requested at MA: date of issue of marketing authorisation (European Commission (EC) decision). This will be gathered from the EMA website for the specific medicinal products.
    - Study requested post-authorisation: date and date source depend on procedure. See *Table 1*.

Table 1. Dates and data sources of interest for different procedures.

Procedure	Date	Source	Motivation
Variation (type IB/II): e.g., RMP	PRAC Recommend-ation date (PRAC	This will be gathered from the final adopted	EMA decides depending on the scope which committee will be in the lead. Variations are usually led by CHMP. Except for variations

update (solely, related to new safety information, indication extension)	led procedures) or (updated) PRAC assessment report date (CHMP led procedures; e.g., date of final PRAC AR or date on which PRAC endorsed/ adopted assessment)*	assessment reports.	intended to update the RMP. They are sent for adoption to the CHMP and are followed by a CHMP opinion date eventually. Sometimes an EC decision applies to type II variations. This will be difficult to find out and dates are not routinely collected, also CHMP documents are not retrieved in this study. CHMP opinion/EC decision are mostly a formality for decision on studies that evaluate the effectiveness of RMM, as the PRAC most often makes decisions regarding these studies. Therefore, we will stick to the PRAC Recommendation in case of PRAC led procedures and to the PRAC assessment report date (e.g., date of final PRAC AR or date on which PRAC committee endorsed/ adopted assessment) in case of CHMP led procedures. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/type-ii-variations-questions-answers
PSUR	PRAC recommend-dation date	This will be gathered from the PRAC Recommendation	PSUR assessment is done by PRAC for CAPs and NAPs, which is always followed by PRAC recommendation (PRAC meeting). If variation, suspension of revocation of MA is recommended than PRAC recommendation will be received by CHMP or CMDh. If this is the case, this will be followed by an EC decision. This will be difficult to find out and dates are not routinely collected. Therefore, we will stick to the PRAC Recommendation date for all PSUR procedures. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs
Renewal	(updated) PRAC assessment report date (e.g., date on which PRAC endorsed/ adopted assessment)	This will be gathered from the final adopted PRAC assessment reports.	The renewal involves CHMP and PRAC. After the PRAC outcome, there is a CHMP opinion. Eventually, there is a EC decision on renewal of the MA. The CHMP and EC date will be difficult to find out and dates are not routinely collected in our data sources. Therefore, we will stick to the PRAC assessment report date (e.g., the date on which PRAC endorsed/adopted assessment) https://www.ema.europa.eu/en/human-regulatory/post-authorisation/renewal-annual-re-assessment-marketing-authorisation
Referral (safety related)	PRAC Recommendation date*	This will be gathered from the EMA page related to the specific referral.	Safety related referrals are assessed by the PRAC and then either by the CHMP or CMDh. This will follow with an EC decision after CHMP opinion or divergence in the CMDh. Considering the PRAC is mostly in the lead for assessing post-authorisation safety studies evaluating the effectiveness of RMM

	within the referrals and for consistency, the PRAC recommendation date was chosen as the date of interest. https://english.cbg-meb.nl/topics/mah-decision-making-process-at-the-european-level

* In case studies were requested or protocols were assessed in procedures starting in 2012 or earlier, the date of final CHMP AR or date of CHMP opinion was collected as date of interest as the PRAC was not in place at that point in time.

- First version of study protocol assessment start date: start date of the (PRAC) regulatory procedure in which the first version of the study protocol submitted by the MAA/MAH is assessed by the EMA/regulatory authorities. Relevant procedures for protocol assessment will be identified by screening (the assessment report of) the final study report on any leads of the procedure or date where the study protocol was first approved. If leads will be identified, the corresponding procedure will be checked if this indeed involves the assessment of the first study protocol. If this will not retrieve useful information, post-marketing procedures, including standalone PAMs and variations, will be checked for inclusion of the study protocol. Once the procedure is identified in which the study was requested, the date will be gathered from the corresponding first or final adopted assessment report (e.g., section: status of this report and steps taken for the assessment). In case the assessment start date cannot be retrieved from the assessment reports, the assessment start date for this procedure will be retrieved from SIAMED. If protocols were assessed within the same procedure as the study request, this is noted in a separate variable. As the start date of protocol assessment will be before the study request date, the time needed for assessment of the protocol will not be taken into account when calculating durations. Additionally, study protocols might be submitted in procedures as an additional document within the scope of the procedure (e.g., as an annex to an RMP update). The dates related to the assessment of this procedure will then be used, as this is considered an opportunity for assessment where PRAC may provide feedback on the protocol, if needed, which will replace a dedicated separate assessment.
- Final study protocol approval date: date of approval of the final study protocol. However, it is possible that the study protocol has been amended later to reflect changes encountered during conduct of the study, which is not considered for this milestone. A study protocol might be approved during the initial marketing authorisation or in a post-authorisation procedure.
    - Study protocol approved at MA: date of issue of marketing authorisation (European Commission (EC) decision). This will be gathered from the EMA website for the specific medicinal products.
    - Study protocol approved post-authorisation: date and data source depend on procedure. See *Table 1*. Note that imposed studies are followed by a PRAC adoption only as the CHMP is not involved. For these studies, the date of adoption of the PRAC decision will be the date of interest.
    - In addition to these procedures, a PASS protocol can be submitted as a stand-alone PAM. This is possible for non-imposed study protocols. The assessment is performed by PRAC and afterwards closed by CHMP adoption. The date of the endorsement by PRAC or final PRAC assessment report will be used as date of interest, and this will be gathered from the final adopted assessment reports. If dates are not available in the assessment report, SIAMED will be used to retrieve the dates of interest.

If protocols were assessed within the same procedure as the study request, this is noted (see also information provided at First version of study protocol assessment start date).

- Study start date: date of start data collection. This will be gathered from the final study report (extracted based on procedure number of the identified studies in the PRAC agendas), or, if not available there, the latest approved final study protocol.
- Final study report assessment start date: date of start of the (PRAC) regulatory procedure in which the final study report is assessed by the regulatory authorities. This will be gathered from the corresponding (final adopted PRAC) assessment reports (e.g., section: status of this report and steps taken for the assessment).
- PRAC outcome date of assessment of final study report: date of (PRAC) final recommendation or outcome based on assessment of the regulatory procedure in which the final study report was submitted:
    - Final study reports are most likely submitted as a Type II variation (including worksharings), in line with the guidelines. These are often followed by a PRAC outcome. The date of PRAC outcome will be the date of interest.
    - Imposed studies are followed by a PRAC adoption only as the CHMP is not involved. For these studies, the date of adoption of the PRAC decision will be the date of interest.
    - Some final study reports might be submitted as part of a standalone PAM. The date of the endorsement by PRAC or final PRAC assessment report will be used as date of interest, and this will be gathered from the final adopted assessment reports.
    - Some study reports might be submitted as part of a PSUR. The PRAC recommendation date will be used as date of interest. If the PSUR is followed by a LEG, the PRAC assessment report date (e.g., date of final PRAC AR or date on which PRAC endorsed/ adopted assessment) will be used.
    - Lastly, studies for NAPs might be submitted as part of WS. For these, the date of PRAC advice will be the date of interest.

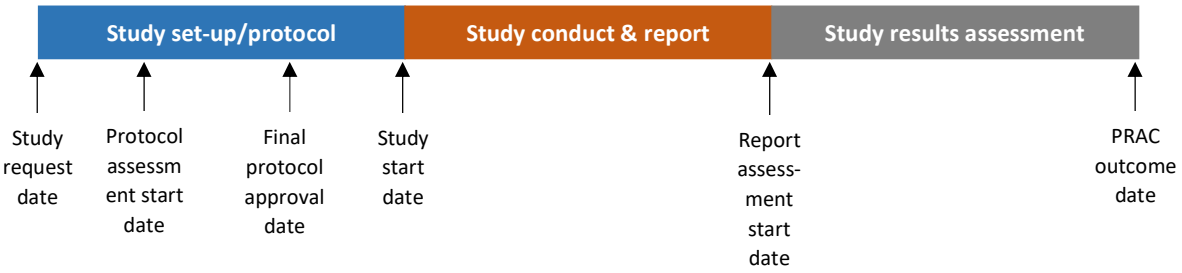

Figure 1. A timeline with the different milestones for studies evaluating the effectiveness of RMM.

The following time intervals will be calculated using the dates described above for which both dates were available and in chronological order:

- Time interval between study request date and first version of study protocol assessment start date
- Time interval between study request date and final study protocol approval date
- Time interval between study request date and study start date
- Time interval between study request date and final study report assessment start date
- Time interval between study request date and PRAC outcome date of assessment of final study report
- Time interval between first version of study protocol assessment start date and final study protocol approval date
- Time interval between final study protocol approval date and study start date
- Time interval between study start date and final study report assessment start date

- Time interval between final study report assessment start date and PRAC outcome date of assessment of final study report
- Time interval between final study protocol approval date and final study report assessment start date

In addition, data on the number of RfSI/assessment round during the PRAC assessment of the first study protocol, and the final study report will be collected if this could be retrieved from the collected documents. Lastly, we will collect data on presence of interim reports if applicable.

For outliers that might be detected for the time interval between study request and PRAC outcome, we will investigate possible reasons for this long duration based on the distinct time periods between key milestones and assessment reports (if needed).

4.5 Study cohort characteristics

Next to the study outcomes, we will collect data to describe our cohort of included studies (see Appendix 1 for detailed information).

Regarding the medicinal products for which the studies were in place, we will describe data on active substance, Anatomical Therapeutic Chemical (ATC) classification. These variables have already been partly extracted in previous projects from (EUPAS45978 and EUPAS47563).

Regarding the regulatory background and studies, we will describe data on the type of RMMs evaluated, study category, study design, data source, PASS objective, type of indicator, number of countries included in study, a priori effectiveness criteria, effectiveness of risk minimisation measures. Most of these variables have already been extracted in previous projects from (10-12). Information was/will be collected from the final study reports and PRAC assessment reports. We will use these variables to assess factors potentially associated with the duration of time intervals between key milestones, e.g., study design, type of indicator, effectiveness of RMM, and type of RMM evaluated.

4.6 Data assembly and extraction

A standardised data extraction form will be used to extract and categorise data from eligible PASS between 2016 and 2022 (see Appendix 1). See for more details on data sources, collected documents and method of identification of relevant document, the information in “4.3 Data sources” and “4.4 Study outcomes”. All the documents are used to extract information about key milestone dates. For each study, a file will be created to describe the steps taken to identify all relevant documents. Relevant dates will be flagged in the source documents and manually transferred into the Microsoft Excel dataset.

4.7 Data analyses

The dataset will be in Microsoft Excel. Data will be processed and analysed with SPSS Statistics. This study mainly involved descriptive statistics to describe the cohort of PASS and duration of the intervals between key milestones.

Categorical variables will be assessed using frequencies and percentages. Continuous variables will be assessed using medians and interquartile ranges or means and standard deviations (in case data follows a normal distribution).

Next to descriptive analyses, data will be analysed stratified on characteristics including study design, type of indicator, effectiveness of RMM and type of RMM evaluated. This is done to evaluate whether these factors influence the duration of time intervals between key milestones.

Variables of interest are:

- ATC code [A/B/C/G/J/L/M/N/S/other], to check for possible differences in the duration of for different indication areas. There might be areas were setting up a study and conducting the study might take more time; for example in indication areas with rare diseases it might take more time to study the effectiveness of RMM. So, it might be of interest to focus on the total duration, the duration of protocol assessment and the duration of study conduct/report.
- Imposed PASS [yes/no], to check for possible differences for imposed and non-imposed PASS. It might be that imposed PASS are being finalised faster as those studies are conditions to the marketing authorisation. So, it might be of interest to focus on the total duration as well as all subperiods.
- Type RMM [aRMM/rRMM/combination], to check for possible differences between rRMM and aRMM. It might be that studies on aRMM are sooner finalised as these are additional measures besides routine measures. So, it might be of interest to focus on the total duration. If differences, are observed it might be needed to study subperiods.
- Data source [primary/secondary], to check for possible differences in the time needed for studies using primary versus secondary data. It might be that studies using secondary data are completed sooner, as it might take less time to collect the data and conduct the study. So, it might be of interest to focus on the total duration and the duration of study conduct/report.
- Study outcome [dissemination, awareness, knowledge, self-reported behaviour/(prescribing) behaviour/health outcomes/combination], to check for possible differences in the time needed for studies assessing the different study outcomes. It might be that studies which assess dissemination, awareness, knowledge, self-reported behaviour are completed sooner compared to studies assessing prescribing behaviour/health outcomes as these might require more sophisticated study designs and time to study the effects. So, it might be of interest to focus on the total duration, the duration of assessment of the protocol and the duration of study conduct/report.
- Study design [cross-sectional/cohort/other], to check for possible differences in the time needed for the cross-sectional versus cohort studies. It might be that cohort studies might require more time to be set-up, conducted and analysed when compared to cross-sectional studies. So, it might be of interest to focus on the total duration, the duration of assessment of the protocol and the duration of study conduct/report.
- Effectiveness of RMM [effective/non-effective/unclear], to check for possible differences in the duration for studies that concluded that RMMs were effective, non-effective versus unclear. It might be that inconclusive studies take more time compared to studies in which it was concluded that RMM were effective or non-effective, also regarding assessment of the final study report. So, it might be of interest to focus on the total duration, the duration of study conduct/report, and the duration of assessment of the final report by PRAC.
- Study request point [at MA, post-marketing], to check for possible differences in the duration for studies requested at MA vs post-marketing. It might be that studies requested at MA might take more time. So, it might be of interest to focus on the total duration, the duration until study start, and the duration of study conduct/report.

4.8 Data management

Data collection will be performed by one researcher and discussed with a second researcher in case of doubt (IZ, TG). Source files, dataset, protocol, analyses and report will be stored in DREAM. For quality control, a random sample of 10% studies will be cross checked and validated by another researcher (TG and VS). We will identify differences between the initial set of collected data and the quality control sample and these will be discussed among SE, TG and VS. In case an inconsistency was identified where no consensus was reached, this will be discussed with a fourth researcher (IZ).

5. Strengths and limitations of the study

5.1 Strengths

A strength of the study is the use of non-public EMA documents related to PASS (e.g., EU-RMPs, PASS protocols, reports and assessment reports) and the access to PASS information that has not been published or registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register), a publicly available register of non-interventional PASS. This research is a continuation and extension of previous research (EUPAS45978, EUPAS47563). Besides, the study will be the first study to provide insight in the duration of specific time periods for conducting evaluation of the effectiveness of RMM.

5.2 Limitations

This study is restricted to PASS evaluated by the PRAC at the European Union (EU) level, meaning that national procedures are only included here if the PASS has been conducted in more than one EU member state and consequently subject to PRAC oversight, or if the responsible national competent authority asked for PRAC Scientific Advice for the respective PASS. The sample set of studies might therefore be incomplete with regards to national PASS procedures. Furthermore, only completed PASS procedures assessing the final study results were included implying that the study protocols for these studies might have been discussed at PRAC prior to latest regulatory and scientific guidance on methods for evaluating RMM effectiveness (e.g., GVP Module XVI, ENCePP Methods Guide) had been published. Another limitation is the fact that only completed studies were included, and thus this might introduce selection of studies that were completed relatively soon. We also limited our study dates to the dates related to PRAC outcome/recommendation in case the assessment of PSURs, variations, and PAMs should also be adopted by CHMP. This is because we only retrieved assessment documents related to PRAC. Lastly, the identification of relevant studies and procedures was performed manually and, even though we implemented a quality control check, errors cannot be completely ruled out.

6. References

1. EMA. PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities (Rev 1). 2017;44(November):1–8. Available from: www.ema.europa.eu/contact
2. European Medicines Agency and Heads of Medicines Agencies. GVP Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 2017;(March). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051.pdf
3. European Medicines Agency and Heads of Medicines Agencies. GVP Module V – Risk Management Systems (Rev 2). Eur Med Agency [Internet]. 2017;(March 2017):PG 7-8. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf [Accessed 23rd March 2023]
4. I Kallio S, Eskola T, Pohjanoksa-Mäntylä M, Airaksinen M. Medication Risk Management in Routine Dispensing in Community Pharmacies. Int J Environ Res Public Health. 2020;17(21).
5. Rubino A, Artime E. A descriptive review of additional risk minimisation measures applied to EU centrally authorised medicines 2006-2015. Expert Opin Drug Saf. 2017;16(8):877-84.
6. Mouchantaf R, Auth D, Moride Y, Raine J, Han SY, Smith MY. Risk Management for the 21st Century: Current Status and Future Needs. Drug Saf. 2021;44(4):409-19.
7. Banerjee AK, Zomerdijk IM, Wooder S, Ingate S, Mayall SJ. Post-approval evaluation of effectiveness of risk minimisation: methods, challenges and interpretation. Drug Saf. 2014;37(1):33-42.
8. 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 2). 2017.
9. Essink SCM, Zomerdijk IM, Straus S, Gardarsdottir H, De Bruin ML. Duration of Effectiveness Evaluation of Additional Risk Minimisation Measures for Centrally Authorised Medicinal Products in the EU Between 2012 and 2021. Drug Saf. 2023.
10. EUPAS45978. Review of studies evaluating the effectiveness of risk minimisation measures assesed by PRAC. https://www.encepp.eu/encepp/viewResource.htm;jsessionid=EMQX7a-rTggLEWytSIXRNmH6R_htDQ0jWZKLr0WPqSdKEZBblrml!154413270?id=45979
11. EUPAS47563. Review of PRAC assessed PASS evaluating risk minimisation measures (RMM). https://www.encepp.eu/encepp/viewResource.htm?id=47564
12. Grupstra RJ, Goedecke T, Scheffers J, Strassmann V, Gardarsdottir H. Review of Studies Evaluating Effectiveness of Risk Minimization Measures Assessed by the European Medicines Agency Between 2016 and 2021. Clin Pharmacol Ther. 2023.

7. Appendix 1

Standardised extraction table overview on PASS characteristics and milestones (partly previously collected in prior collaborative projects EUPAS45978 and EUPAS47563 for studies completed between 2016 and 2022 (10-12))

Product information	Product name
	International Non-proprietary Name (INN)
	ATC code
Regulatory background	Registration in EU PAS Register [yes/no]
	EU PAS Register number (if applicable)
	PASS category • 1 • 2 • 3
	PASS objective • Measuring extent of dissemination • Measuring healthcare professional awareness/behaviour/knowledge • Measuring patient awareness/behaviour/knowledge • Measuring patterns of use in clinical practice • Measuring health outcomes • Measuring health system utilisation (e.g., laboratory testing, monitoring, etc) • Other
	Type of RMM evaluated • Routine • Additional • Both
	Type of routine RMM evaluated (if applicable) • SmPC • Labelling information (information on immediate or outer packaging) • Package leaflet • Pack size • Legal status

	Type of additional RMM evaluated (if applicable)
	• Educational material
	  ○ HCP Guide
	  ○ Patient Guide
	  ○ HCP Checklist
	  ○ Risk awareness form
	  ○ Demonstration kit, training module/program
	  ○ Patient diary
	  ○ Patient card
	• Pregnancy prevention programme
	• Controlled access programme
	• Controlled distribution programme
	• DHPC

Study characteristics	Data source • Primary data collection

• Secondary data collection • Both
Source for primary data collection (if applicable) • Survey • Interview • Focus group • Prospective observational study • Registry
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
Number of countries included in a study
Study design • Cohort study • Cross-sectional study • Interventional RCT • Case control study • Time series
Study outcome • Extent of dissemination • Awareness, knowledge, self-reported behaviour or attitudes • Drug use based on prescription/dispensing date and/or prescribing behaviour in adherence to PI • Health outcomes (e.g., safety outcomes) • Changes in ADR reporting • Other
Effectiveness indicator • Process indicator • Outcome indicator • Both
Process indication (if applicable) • Receipt of RMM/awareness • Clinical knowledge • Self-reported behaviour • Clinical action/behaviour, including prescribing behaviour
RMM effectiveness criterion as defined a prior (yes/no) • Threshold • Change before/after • Descriptive assessment • Threshold and descriptive assessment
Effectiveness of risk minimization (according to MAH and PRAC) • Effective • Non-effective • Inconclusive
Regulatory action

	• New PASS • New/revised RMM • Remove existing RMM • Change to term of marketing authorisation • Other
Timepoints of interest (see 4.4 Study outcomes)	Study request at MA
	Study request date (including source) • Study request date: MA • Study request date: PRAC recommendation (PSUSA, referral, PRAC led variations) • Study request date: PRAC assessment report (CHMP led procedures) • Study request date: CHMP opinion (CHMP led variations)
	Protocol assessed
	Protocol assessment report available
	Protocol assessed during or before study request
	First version of study protocol assessment start date (including source)
	Final study protocol approval date (including source) • Study protocol approval date: MA • Study protocol approval date: PRAC recommendation/adoption (PSUSA, referral, PRAC led variations, including imposed study protocols) • Study protocol approval date: PRAC assessment report/ endorsement by PRAC (CHMP led procedures, standalone PAM) • Study protocol approval date: CHMP opinion (CHMP led variations) • Study protocol approval date: CHMP adoption (standalone PAM)
	Protocol assessment rounds number and timetable
	Study start date (including source)
	Final study report assessment start date (including source)
	PRAC outcome date of assessment of final study report • Study report assessment end date: PRAC recommendation/adoption (imposed studies, PSUSA). • Study report assessment end date: PRAC outcome (Type II variations, LEG) • Study report assessment end date: PRAC assessment report/ endorsement by PRAC (standalone PAM) • Study report assessment end date: CHMP opinion (Type II variations, LEG) • Study report assessment end date: CHMP adoption (standalone PAM)
	Study report assessment round number and timetable
	Interim reports submitted