Review of Studies Evaluating Effectiveness of Risk Minimization Measures Assessed by the European Medicines Agency Between 2016 and 2021

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The European Medicines Agency (EMA) supervises medicines' safe and effective use throughout the product's life cycle by, for example, monitoring the implementation of risk minimization measures (RMMs). Limited information is available on factors associated with effectiveness of RMMs. This study reviews post-authorization safety studies (PASS) evaluating the effectiveness of RMMs assessed by the Pharmacovigilance Risk Assessment Committee (PRAC) between 2016 and 2021. PASS assessment reports finalized by PRAC between January 1, 2016, and December 31, 2021, were compiled from non-public EMA databases and PASS characteristics were extracted. Of the 93 PASS included, 62.4% aimed to measure healthcare professionals' awareness, knowledge, and behavior regarding RMMs. There were 67.7% of the 93 PASS that used primary data, 24.7% used secondary data sources, and 7.5% used both. A cross-sectional study design was most frequently applied (77.4%), followed by a cohort study design (29.0%). Nearly 40% of the included PASS did not render a conclusion on RMM effectiveness. Of the 60% that did render a conclusion, 82.1% were deemed effective. Only minor differences in characteristics were found when stratified by outcome (i.e., effective RMM, ineffective RMM, and no conclusion on RMM effectiveness). To conclude, 4 out of 10 PASS assessing impact of RMMs did not render a conclusion on RMM effectiveness. No clear differences in PASS characteristics were found in relation to their outcomes, indicating that additional research is needed to understand better the underlying reasons for PASS being inconclusive.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The European Union pharmacovigilance legislation implemented in 2012 emphasizes risk management, including conduct of post-authorization safety studies (PASS) evaluating risk minimization measure's (RMM's) effectiveness by marketing authorization holders. Reviews of PASS evaluating RMM effectiveness have been conducted, describing PASS characteristics, such as study design and outcome measures.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study reviewed PASS evaluating the effectiveness of RMMs assessed by the Pharmacovigilance Risk Assessment Committee between 2016 and 2021, focusing on PASS characteristics and conclusiveness for regulatory decision making.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Four out of 10 PASS evaluating RMM effectiveness did not render a conclusion, with higher likelihood of rendering a conclusion for PASS with predefined effectiveness criteria.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Determining predefined effectiveness criteria positively affects success of RMM effectiveness evaluation.

Medicinal products are rigorously assessed by regulators before being authorized for use in populations. However, not all aspects of their safety are known upon market authorization, such as their long-term effect and safety, as well as their safety in specific populations. As a result, regulators have pharmacovigilance systems in place to monitor safety throughout a medicine's life cycle and to detect any change in its benefit–risk balance. A positive benefit–risk balance is a prerequisite for a medicine's approval and

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continued use in the general population. Activities monitoring safety in the postmarketing authorization phase are referred to as pharmacovigilance activities.[1]

In the European Union, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) is responsible for monitoring and supervising the safety of medicinal products authorized in the European Union. Through the implementation of public health interventions known as risk minimization measures (RMMs), among other things, the benefit–risk balance of medicinal products is safeguarded.[1] Two types of RMMs exist: (i) routine RMMs, which are in place for all medicinal products, including the summary of product characteristics (SmPC), the patient information leaflet, and product labeling; and (ii) additional RMMs, which are required for some medicinal products to ensure safe use and optimize the benefit–risk balance.[1] Examples of additional RMMs include educational materials regarding the medicinal product for healthcare professionals (HCPs) and patients, pregnancy prevention programs, and pre-prescription patient screening.[2] RMMs are described in the product's risk management plan (EU-RMP), which is a mandatory requirement for all new marketing authorization applications and for some applications involving significant changes to an existing marketing authorization.[3]

In 2012, an amended pharmacovigilance legislation came into force in the European Union, which made the EU-RMP legally enforceable. It requires marketing authorization holders (MAHs) to monitor the effectiveness of their risk management activities, including routine and additional RMMs, for instance, in post-authorization safety studies (PASS).[4] Measuring RMM effectiveness is essential for the PRAC to establish whether public health interventions have been effective or not and to implement corrective actions if necessary.[1] The EMA guideline on good pharmacovigilance practices (GVPs) Module XVI provides guidance on risk minimization tool evaluation, stating which RMM outcomes should be addressed (e.g., the process of disseminating the RMM to target audiences, its impact on knowledge and behavior, or its impact on health outcomes) and what potential unintended outcomes should be considered. Additionally, in line with the legislation and GVP Modules VIII and XVI, PRAC evaluates the outcomes of both routine and additional RMMs by assessing study protocols and the results of imposed PASS evaluating the effectiveness of RMMs, and making recommendations for any necessary regulatory action.[1] Several systematic reviews of PASS evaluations of RMMs have been published in the last decade. For instance, describing the design of PASS evaluating RMMs combining process and outcome indicators,[5] alignment with GVP guideline recommendations,[6] used sampling methodologies,[7] types of RMMs evaluated and which process and outcome indicators were used,[8] and the extent to which the PRAC assessed the protocols of such PASS.[9] These studies of PASS evaluating RMM effectiveness were all based on public information available in, among others, the EUPAS Register, and these reviews offer a descriptive overview of PASS design, types of data collected, and analytical methods performed by MAHs, which provides a better understanding of the design and conduct of such PASS. However, no insights have been provided into whether the PASS allowed the PRAC to draw conclusions on RMM effectiveness. The assessment of PASS characteristics associated with conclusive RMM evaluation, either through clarifying what constitutes a successful study design to measure RMM effectiveness or by gaining insights into the effectiveness of specific RMMs, may provide learnings for designing PASS that evaluate RMM effectiveness. To our knowledge, this is the first review of industry-sponsored PASS that evaluate the effectiveness of routine and/or additional RMMs assessed by the PRAC between 2016 and 2021 with full access to information held in the EMA databases. The primary objectives of our study were (i) to describe the design, analytical method(s), and outcome(s) of PASS evaluating RMM effectiveness assessed by the PRAC; (ii) to determine the types of RMMs addressed by these PASS, the proportion of PASS with a conclusion on RMM effectiveness, and how effectiveness was defined; and (iii) to describe the characteristics of PASS in relation to the final outcome of the PRAC assessment (i.e., effective RMM, ineffective RMM, and inconclusive PASS).

METHODS

Data sources and eligibility

All category 1 (imposed as condition of marketing authorization), 2 (imposed as specific obligation of marketing authorization), and 3 (required as part of the EU-RMP) industry-sponsored PASS evaluating the effectiveness of routine and/or additional RMMs with the PRAC's assessment of the PASS report finalized between January 1, 2016, and December 31, 2021, were included in this study.[3] Assessments of interim or annual reports and assessments that were not completed by PRAC within the study period were excluded. PASS assessment reports were identified from the PRAC monthly plenaries' public agendas and compiled from non-public EMA databases to also include confidential information on the detailed scope of the regulatory procedure (i.e., Documents Records Electronic Archive Management System (DREAM) and the European Review System (EURS) for electronic Common Technical Documents (eCTDs)). PRAC agendas were screened using the following keywords: "risk-minimization," "risk minimization," "RMM," "effectiveness," "educational," "material," "(EM)," "final report," and "survey." Additionally, PRAC agenda sections 5.2 (Medicines in the post-authorization phase—PRAC-led procedures), 5.3 (Medicines in the post-authorization phase—Committee for Medicinal Products for Human Use- (CHMP-) led procedures), 7.3 (Results of PASS imposed in the marketing authorization(s)), 7.4 (Results of PASS non-imposed in the marketing authorization(s)), and 7.6 (Others) were manually screened for eligible PASS. The PASS scope and study objectives as presented in the PRAC agendas and assessment reports were consulted to determine eligibility.

Study outcome

The primary outcome of this study was the PASS final assessment outcome. The PASS evaluating RMMs were defined based on the PRAC's final conclusion in the assessment report as follows: conclusive with effective RMM evaluation, conclusive with ineffective RMM evaluation, or inconclusive (i.e., PASS did not allow drawing firm conclusions on RMM effectiveness). An example of information rendering a PASS inconclusive is as follows: "Regarding the results of the Physician Survey Analysis, conclusions are difficult due to the low number of respondents." An example of text from an assessment report demonstrating conclusiveness of a PASS is as follows: "Overall, it is agreed that the results of the HCP knowledge and understanding survey confirm that the educational materials are effective."

Collected PASS data

Information about PASS characteristics was extracted, including the regulatory background, PASS study characteristics, and PASS performance. The PASS regulatory background included the publication year of the

PRAC's final opinion about the PASS report, EUPAS Registration (yes/no), and the PASS category. PASS study characteristics included study objectives, type of RMM assessed, utilized data sources (primary, secondary, or both), outcome variables, study design information, and used analytical methods. Whether predefined effectiveness criteria were in place and what they entailed were also captured, as well as whether RMM were deemed effective according to the PRAC, and whether regulatory follow-up actions were required.

Data extraction and analysis

The original data were extracted by authors Jet Scheffers and Renske J. Grupstra into a predefined coding matrix. A random sample of six PASS was selected and coded in duplicate by authors Valerie Strassmann and Thomas Goedecke to cross-check and validate the data extraction. Any unclarities regarding the extraction and/or coding and classification were discussed and agreed upon by the co-authors (J.S., R.G., V.S., T.G., and H.G.).

Data were presented using descriptive statistics based on extracted study variables. Variables were summarized by number and percentage (%) of PASS in each category. Additionally, variables were stratified per effectiveness evaluation (i.e., effective RMM, ineffective RMM, and inconclusive PASS).

RESULTS

PASS characteristics

Table 1 demonstrates the characteristics of the 93 industry-sponsored PASS included (further information on the included PASS can be found in Table S1). The majority of PASS were registered in the EUPAS Register (82.8%), and most were category 3 PASS (80.6%). Nearly two-thirds (62.4%) aimed to measure HCPs' awareness, behavior, and knowledge regarding RMMs; 30.1% assessed patterns of use in clinical practice; 28.0% measured the extent of RMM dissemination; and 25.8% measured patients' awareness, behavior, and knowledge regarding RMMs. Regarding data collection, 67.7% of PASS used primary data only, 24.7% made use of secondary sources of data only, and 7.5% used both primary data and secondary data analysis. Amongst the studies utilizing primary data ($n = 70$), surveys were the most prevalent source (85.7%), followed by prospective observational studies (11.4%). Sources for PASS utilizing secondary data ($n = 30$) included electronic health records (73.3%), administrative claims (50.0%), and healthcare records linkage (26.7%). The most common study outcomes investigated in the PASS included (change in) awareness/knowledge, self-reported behavior, and attitudes (63.4%); (change in) prescribing/dispensing pattern (35.5%); and health outcomes (mortality, morbidity, etc.; 33.4%). PASS frequently used descriptive statistics without a comparator (75.3%) and, to a lesser extent, descriptive statistics with significance testing with a comparator (12.9%), descriptive statistics with a comparator (6.5%), or descriptive statistics with significant testing without a comparator (5.4%).

RMMs addressed in included PASS

Nearly two-thirds (62.4%) of the evaluated RMMs were additional, 29.0% were a combination of routine and additional RMMs, and 8.6% were routine. Types of routine and/or additional RMMs are not mutually exclusive; the following percentages may exceed 100%. The majority of the routine RMMs evaluated concerned the SmPC (91.4%), whereas fewer PASS pertained to the package leaflet (17.1%), labeling (text on the inner and outing packaging[5]; 11.4%), and legal status of the medicinal product (i.e., details of any conditions or restrictions on the supply or use of the medicinal product[3]; 5.7%). Regarding additional RMMs, the effectiveness of educational materials was frequently evaluated (87.0%). In particular, an HCP guide or patient guide as educational material was frequently evaluated (69.4% and 30.6%, respectively). Other additional RMMs included direct HCP communication (30.6%) and—in a small selection of PASS—pregnancy prevention programs (1.2%).

Half of the PASS defined effectiveness criteria *a priori*, which often consisted of a predefined threshold (66.6%) of, for instance, 80% compliance with the conditions for safe and effective use and/or correct answers. Overall, the PRAC was able to draw a conclusion on RMM effectiveness in 56 out of 93 PASS (60.2%). Of those conclusive PASS, RMMs were deemed effective in 46 studies (82.1%) and ineffective in 10 studies (17.9%). By contrast, the PRAC was unable to clearly conclude on RMM effectiveness based on the results of 37 PASS (39.8%); these PASS were therefore considered inconclusive in this study. Regulatory follow-up was requested in one third (32.3%) of the PASS, including new or revised RMM (10.8%), a combination of a new PASS and new or revised RMM (6.5%), removal of existing RMM (6.5%), a new PASS (3.2%), or other changes to the terms of the marketing authorization (3.2%).

Stratification per effectiveness evaluation

Inconclusive PASS more frequently intended to measure patterns of use in clinical practice (45.9%) and health system utilization (18.9%; e.g., patient monitoring, diagnostic tests, etc.) compared to conclusive PASS with effective RMM (17.3% and 6.5%, respectively) or ineffective RMM (30.0% and 10.0%, respectively; Table 1). Additionally, PASS with ineffective RMM evaluation and inconclusive PASS included "(change in) prescribing/dispensing pattern" as a study outcome more frequently (50.0% and 45.9%) compared to PASS with effective RMM evaluation (23.9%). PASS that led to a conclusion on RMM effectiveness more frequently used descriptive statistics with a comparator (10.0% of the PASS that evaluated RMM as ineffective and 8.7% of the PASS that evaluated RMM as effective) compared to inconclusive PASS (2.7%). Educational materials were most frequently studied in the three groups, that is, inconclusive PASS, conclusive PASS evaluating RMM as effective, and conclusive PASS evaluating RMM as ineffective. Comparing specific types of educational materials, PASS with effective RMM evaluation included HCP checklists more often than PASS with ineffective RMM evaluation (14.6% compared to 11.1%, respectively). An HCP guide as well as a patient guide was frequently evaluated in PASS resulting in an ineffective RMM evaluation (88.8% and 55.6%, respectively) and, to a lesser extent, in PASS resulting in an effective RMM evaluation (63.% and 29.3%, respectively). Of the 45 PASS for which effectiveness criteria were predefined, nearly half resulted in an effective evaluation of RMM ($n = 20$, 43.5%). A threshold was the most common predefined effectiveness criterion used in effective, ineffective, and inconclusive PASS (85.0%, 57.1%, and 50.0%, respectively). Ineffective RMM resulted twice as often

Table 1 Characteristics of industry-sponsored PASS evaluating RMM effectiveness finalized by the PRAC between January 1, 2016, and December 31, 2021

Category	Subcategory	Total, *n* (%) (*n* = 93)	Effective, *n* (%) (*n* = 46)	Ineffective, *n* (%) (*n* = 10)	Inconclusive, *n* (%) (*n* = 37)
EU PAS registration		77 (82.8)[a]	37 (80.4)	9 (90.0)	31 (83.8)
PASS category	Category 1 (imposed)	15 (16.1)	6 (13.0)	2 (20.0)	7 (18.9)
	Category 2 (specific obligation)	2 (2.2)	1 (2.2)	1 (10.0)	0 (0.0)
	Category 3 (required)	75 (80.6)	38 (82.6)	7 (70.0)	30 (81.1)
	Not applicable	1 (1.1)	1 (2.2)	0 (0.0)	0 (0.0)
PASS objective[b]	Measuring extent of dissemination	26 (28.0)	12 (26.0)	2 (20.0)	12 (32.4)
	Measuring HCP awareness/ behavior/knowledge	58 (62.4)	28 (60.8)	7 (70.0)	23 (62.2)
	Measuring patient risk awareness/behavior/ knowledge	24 (25.8)	14 (30.4)	4 (40.0)	6 (16.2)
	Measuring patterns of use in clinical practice	28 (30.1)	8 (17.3)	3 (30.0)	17 (45.9)
	Measuring health outcomes	12 (12.9)	6 (13.0)	1 (10.0)	5 (13.2)
	Measuring health system utilization	10 (10.8)	3 (6.5)	0 (0.0)	7 (18.9)
	Other[c]	3 (3.2)	3 (6.5)	0 (0.0)	0 (0.0)
Year of PRAC outcome	2016	19 (20.4)	8 (17.4)	2 (20.0)	9 (24.3)
	2017	11 (11.8)	4 (8.7)	3 (30.0)	4 (10.8)
	2018	17 (18.3)	8 (17.4)	1 (10.0)	8 (21.6)
	2019	20 (21.5)	11 (23.9)	1 (10.0)	8 (21.6)
	2020	15 (16.1)	10 (21.7)	1 (10.0)	4 (10.8)
	2021	11 (11.8)	5 (10.19)	2 (20.0)	4 (10.8)
Data source	Primary data source	63 (67.7)	36 (78.3)	7 (70.0)	20 (54.1)
	Secondary data source	23 (24.7)	7 (15.2)	3 (30.0)	13 (35.1)
	Both	7 (7.5)	3 (6.5)	0 (0.0)	4 (10.8)
Primary data source (*n* = 70)[b]	Survey	60 (85.7)	31 (67.4)	7 (70.0)	22 (59.5)
	Interview	3 (4.2)	2 (4.4)	1 (10.0)	0 (0.0)
	Prospective observational study	8 (11.4)	6 (13.0)	0 (0.0)	2 (5.4)
	Registry	1 (1.4)	1 (2.2)	0 (0.0)	0 (0.0)
Secondary use of data (*n* = 30)[b]	Electronic health records (including prescribing data)	22 (73.3)	6 (13.0)	3 (30.0)	13 (35.1)
	Administrative claim records/pharmacy records	15 (50.0)	3 (6.5)	1 (10.0)	11 (29.7)
	Healthcare record linkage	8 (26.7)	2 (4.4)	1 (10.0)	5 (13.5)
	Spontaneous ADR reports	2 (6.7)	1 (2.2)	0 (0.0)	1 (2.7)
	Registry	4 (13.3)	2 (4.4)	0 (0.0)	2 (5.4)
Study design[b]	Cohort study	27 (29.0)	14 (30.4)	3 (30.0)	10 (27.0)
	Case control study	1 (1.1)	1 (2.2)	0 (0.0)	0 (0.0)
	Cross-sectional study	71 (77.4)	34 (73.9)	7 (70.0)	30 (81.1)
	Time series	2 (2.1)	0 (0.0)	1 (10.0)	1 (2.7)
Number of countries	Single	6 (6.5)	2 (4.4)	0 (0.0)	4 (10.8)
	Multiple (2–5)	44 (47.3)	22 (47.8)	4 (40.0)	18 (48.6)
	Multiple (>5)	43 (46.2)	22 (47.8)	6 (60.0)	15 (40.5)

(Continued)

Table 1 (Continued)

Category	Subcategory	Total, *n* (%) (*n* = 93)	Effective, *n* (%) (*n* = 46)	Ineffective, *n* (%) (*n* = 10)	Inconclusive, *n* (%) (*n* = 37)
Study outcomes[b]	Extent of dissemination	31 (33.3)	18 (39.1)	2 (20.0)	11 (29.7)
	(Change in) awareness/ knowledge, self-reported behavior, attitudes	59 (63.4)	30 (65.2)	7 (70.0)	22 (59.4)
	(Change in) prescribing/dispensing pattern	33 (35.5)	11 (23.9)	5 (50.0)	17 (45.9)
	Health outcome (mortality, morbidity, etc.)	31 (33.4)	12 (26.1)	3 (30.0)	16 (43.2)
	Change in ADR reporting	4 (4.3)	2 (4.4)	0 (0.0)	2 (5.4)
	Other	14 (15.1)	7 (15.2)	1 (10.0)	6 (16.2)
Analytical method[b]	Descriptive with a comparator	6 (6.5)	4 (8.7)	1 (10.0)	1 (2.7)
	Descriptive without a comparator	70 (75.3)	34 (73.9)	7 (70.0)	29 (78.4)
	Descriptive statistics with significance testing with a comparator	12 (12.9)	7 (15.2)	2 (20.0)	3 (8.1)
	Descriptive statistics with significance testing without a comparator	5 (5.4)	2 (4.4)	0 (0.0)	3 (8.1)
	Regression models	7 (7.5)	5 (10.8)	1 (10.0)	1 (2.7)
	Time series analysis	4 (4.3)	1 (2.2)	1 (10.0)	2 (5.4)
	Thematic analysis	1 (1.1)	1 (2.2)	0 (0.0)	0 (0.0)
Type of RMM	Routine	8 (8.6)	5 (10.8)	1 (10.0)	2 (5.4)
	Additional	58 (62.4)	31 (67.4)	5 (50.0)	22 (59.5)
	Both	27 (29.0)	10 (21.7)	4 (40.0)	13 (35.2)
Type of routine RMM[a]	SmPC	32 (34.4)	12 (80.0)	5 (100.0)	15 (100.0)
	Labeling	4 (4.3)	2 (13.3)	0 (0.0)	2 (13.3)
	Package leaflet	6 (6.5)	2 (13.3)	2 (40.0)	2 (13.3)
	Legal status	2 (2.2)	0 (0.0)	0 (0.0)	2 (13.3)
Type of additional RMM[b]	Educational materials	61 (65.6)	30 (73.2)	6 (66.6)	25 (71.4)
	HCP guide	59 (63.4)	26 (63.4)	8 (88.8)	25 (71.4)
	Patient guide	26 (28.0)	12 (29.3)	5 (55.6)	9 (25.7)
	HCP checklist	9 (9.7)	6 (14.6)	1 (11.1)	2 (5.7)
	Demonstration kit	1 (1.1)	1 (2.4)	0 (0.0)	0 (0.0)
	Patient diary	3 (3.2)	2 (4.8)	0 (0.0)	1 (2.9)
	Patient alert card	24 (25.8)	17 (41.5)	1 (11.1)	6 (17.1)
	Direct DHPC	13 (14.0)	5 (12.2)	1 (11.1)	7 (20.0)
	Pregnancy prevention program	1 (1.1)	1 (2.4)	0 (0.0)	0 (0.0)
	Educational materials + DHPC	13 (14.0)	6 (14.6)	3 (33.3)	4 (12.9)
Regulatory follow-up	None	63 (67.7)	40 (87.0)	2 (20.0)	21 (56.8)
	New PASS	3 (3.2)	1 (2.2)	1 (10.0)	1 (2.7)
	New or revisited RMM	10 (10.8)	1 (2.2)	0 (0.0)	9 (24.3)
	Remove existing RMM	6 (6.5)	2 (4.4)	2 (20.0)	2 (5.4)
	Change to terms of MA	2 (2.2)	2 (4.4)	0 (0.0)	0 (0.0)
	New PASS + new or revisited RMM	6 (6.5)	0 (0.0)	4 (4.4)	2 (5.4)
	Other	3 (3.2)	0 (0.0)	1 (10.0)	2 (5.4)

(Continued)

Table 1 (Continued)

Category	Subcategory	Total, *n* (%) (*n* = 93)	Effective, *n* (%) (*n* = 46)	Ineffective, *n* (%) (*n* = 10)	Inconclusive, *n* (%) (*n* = 37)
Predefined effectiveness criteria		45 (48.4)	20 (43.4)	7 (70.0)	18 (48.6)
	Threshold	30 (32.2)	17 (37.0)	4 (40.0)	9 (24.3)
	Change before-after	2 (2.2)	0 (0.0)	1 (10.0)	1 (2.7)
	Descriptive assessment	12 (12.9)	2 (4.4)	2 (20.0)	8 (21.6)
	Threshold + descriptive assessment	1 (1.1)	1 (2.2)	0 (0.0)	0 (0.0)

Abbreviations: ADR, adverse drug reaction; DHPC, direct healthcare professional communication; EU PAS, European Union electronic Register of Post-Authorisation Studies; HCP, healthcare professional; MA, marketing authorization; PASS, post-authorization safety study; PRAC, Pharmacovigilance Risk Assessment Committee; RMM, risk minimization measure; SmPC, summary of product characteristics.
[a]Totals presented per column (i.e., all PASS *n* = 93; effective PASS *n* = 46; ineffective PASS *n* = 10; and inconclusive PASS *n* = 37), and used as denominator.
[b]Categories are not mutually exclusive, total > 100%. [c]Observed other PASS objective: simulated use scenario comparing different label designs.

in regulatory follow-up (80.0%) when compared to inconclusive PASS (43.2%). Only a few of the effective RMM resulted in regulatory follow-up action (13.0%).

DISCUSSION

This study demonstrates that among all PASS assessed by the PRAC between 2016 and 2021, 4 out of 10 (39.8%) did not allow a conclusion on RMM effectiveness and were therefore deemed inconclusive. The PRAC revisited its strategy to measure the impact of pharmacovigilance activities, highlighting the need to revise GVP Module XVI guidance, which resulted in the public consultation in 2021 of draft revision 3 of GVP Module XVI with a revised conceptual approach to RMM effectiveness evaluation.[10] The methodological guidance provided in the new Addendum II of GVP Module XVI revision 3 is expected to result in improved quality and to increase the amount of conclusive PASS evaluating RMM effectiveness over time. Our results do not reflect this, however, this review only included PASS that were finalized and assessed between 2016 and 2021, and the final GVP XVI revision 3 is yet to be published.[6] Most of the included PASS aimed to measure HCPs' awareness, behavior, and knowledge regarding RMM. Accordingly, common study outcomes included (change in) awareness/knowledge, self-reported behavior, and attitudes; (change in) prescribing/dispensing pattern; and (change in) health outcomes (adverse reactions, morbidity, etc.) in accordance with the EMA's revised guidance in GVP Module XVI.[10] The majority of PASS included in our review used a survey design with primary data collection for the evaluation of RMM effectiveness, a finding in line with an earlier review by Engel *et al*. in which 58% of 189 included PASS protocols and assessments submitted to the PRAC between 2012 and 2015 utilized primary data.[9] According to the International Society for Pharmacoepidemiology (ISPE), surveys are a well-established measure to determine what stakeholders (here, among others, physicians and patients) know or believe,[11] which is reflected in the finding that many of the included PASS were designed as survey studies. However, GVP Module XVI does not advocate surveys as the gold standard for measuring RMM effectiveness; rather, it considers them to be complementary to drug utilization studies or time series studies.[10] Our study revealed that 7.5% of the PASS in our cohort used this mixed-methods approach within the study design (i.e., utilizing both primary data and secondary data analysis), which indicates that the use of mixed-methods is already relatively established in the field. Additionally, this finding creates an incentive to further investigate the opportunities of conducting studies that use primary data collection and secondary data (e.g., drug utilization studies or time series studies in combination with survey studies) in a single PASS evaluating RMM effectiveness as a means to avoid common limitations encountered when conducting either of these two types of study designs. Similar to prior findings from a review assessing PASS between 2011 and 2018,[12] our study showed that the majority of PASS in our cohort evaluated additional RMMs. The most common additional RMMs were educational materials, including HCP guides and patient guides. This is consistent with previous research by Francisca *et al*., who reported that educational materials for HCPs were available for 94% of the 130 products for which they assessed RMMs, and educational materials for patients were available for 55%.[13] To assess the effectiveness of these RMMs, half of the PASS used predefined effectiveness criteria. In particular, the use of a threshold to determine RMM effectiveness was frequently observed. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology states that the successful use of a threshold to determine the effectiveness of RMM is challenging.[14] One reason for this is the difficulty of capturing various levels of effectiveness—that is, in relation to dissemination, knowledge, and behavior or health outcome changes—within a single threshold.[12] Defining a quantifiable threshold for measures, such as awareness and behavioral changes caused by RMMs, is complex because it requires combining process indicators (e.g., the extent to which RMMs have been implemented and whether they are used as expected) with health outcomes (e.g., outcomes of improved patient or public health), which is particularly challenging when PASS data are based on self-reported behavior via surveys.[5] Nearly half of the PASS in our cohort that evaluated RMM as effective utilized predefined effectiveness criteria, whereas

ineffective and inconclusive PASS did so to a lesser extent. It could therefore be argued that the inability to define effectiveness criteria *a priori* makes it difficult to conclude on RMM effectiveness, as this perhaps indicates that the study setting or question was overly complex, making the implementation of predefined effectiveness criteria recommendable. A previous PASS review already stated that thresholds for success should be set *a priori* to help interpret study results[6]; hence, our finding complements this statement. The GVP Module XVI draft revision 3 provides a list of factors to consider when predefining effectiveness criteria and emphasizes that this should be determined on a case-by-case basis,[1] which is supported and reinforced by our findings. Stratification of PASS characteristics by effectiveness evaluation outcome demonstrated limited differences between effective, ineffective, and inconclusive PASS. We observed, for example, a minor difference between PASS using descriptive statistics with a comparator as an analytical method, which was more frequently observed in PASS that led to a conclusion on RMM effectiveness compared to inconclusive PASS (10.0% vs. 2.7%, respectively). This finding implies that the use of a comparator could potentially facilitate the process of drawing conclusions regarding RMM effectiveness. However, given the marginal differences, no stringent conclusion can be drawn.

This study is assessing a comprehensive sample of industry sponsored PASS that evaluate impact of RMMs using EMA data. However, the study was limited to PASS evaluated by the PRAC at the level of the European Union. National procedures were only included in this review if they were subject to PRAC oversight, for instance, if the PASS was conducted in more than one member state or if the national competent authority asked for PRAC advice. Therefore, our cohort of studies might be incomplete with regard to national PASS procedures. Moreover, only PASS procedures assessing final study reports were included, implying that study protocols for these PASS might have been discussed at the PRAC before regulatory and scientific guidance on methods for evaluating RMM effectiveness has been published (e.g., GVP Module XVI and ENCePP Methods Guide).

To conclude, 4 out of every 10 PASS did not render a conclusion by the PRAC. Half of the PASS that evaluated RMM as effective utilized predefined effectiveness criteria, which makes the use of case-by-case effectiveness criteria recommendable. Additionally, our data create an incentive to further investigate the potential impact of applying mixed methodologies in RMM effectiveness PASS to increase the likelihood of conclusive results. Aside from this, only marginal differences were observed between PASS that rendered a conclusion on RMM effectiveness (i.e., either effective or ineffective RMM) and PASS that did not. Therefore, to learn more about factors that might play a role it may be useful to perform an in-depth thematic analysis of those PASS assessments in which no conclusion on RMM effectiveness could be drawn. This may provide more insights into the types of (methodological) limitations within PASS designs that hamper conclusions on RMM effectiveness and could inform regulatory decision makers on how to improve guidance on PASS designs.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.J.G. and H.G. wrote the manuscript. R.J.G., H.G., T.G., and J.S. designed the research. R.J.G., J.S., and V.S. performed the research. R.J.G. and H.G analyzed the data.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the authors are employed/affiliated.

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