Limitations Reported in Evaluating Effectiveness of Risk Minimization Measures in the EU during 2018–2021: A Qualitative Analysis of Industry-Sponsored Post-Authorization Safety Studies

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Marketing-authorization holders evaluate the effectiveness of risk minimization measures (RMM) for medicines through the conduct of post-authorization safety studies (PASS). Earlier studies show that concluding on RMM effectiveness is challenging. The aim of this study was to describe reported limitations associated with RMM effectiveness assessments of industry-sponsored PASS that did not render a conclusion. We conducted a thematic analysis of study limitations extracted from assessment reports and study reports finalized by the Pharmacovigilance Risk Assessment Committee between 2018 and 2021. In 39 (61.0%) of the PASS a conclusion on RMM effectiveness was drawn, where 25 (39.0%) PASS was inconclusive. Most PASS had a cross-sectional design with surveys as primary data sources (73.4% and 65.6% respectively). Four main themes emerged: (i) survey-specific limitations, (ii) limitations specifically related to secondary use of data, (iii) general limitations related to study design, and (iv) limitations not related to study design. In general, frequently reported limitations were survey-related, such as selection bias or information bias. Interestingly, well-known study limitations related to secondary use of data such as missing or misclassification of data were more often presented in inconclusive compared with conclusive PASS. Given that about 40% of PASS did not allow a conclusion on RMM effectiveness, our results suggest prioritization for strategies to mitigate limitations related to the secondary use of data at the protocol stage, for example, through feasibility assessments. Although many databases may have incomplete registration of some variables, feasibility testing prior to conducting a PASS could contribute to meeting study objectives and concluding on RMM effectiveness.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Effectiveness of risk minimization measures (RMM) is evaluated in post-authorization safety studies (PASS). A previous review demonstrated that approximately four out of 10 PASS evaluating RMM do not render a conclusion due to methodological and other limitations.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Which common methodological limitations prevent concluding on RMM effectiveness and preempt PASS to add to regulatory decision-making as they should?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ RMM effectiveness PASS often use survey design, hence common limitations found in our thematic analysis were inherent to surveys. Interestingly, in inconclusive PASS limitations related to the secondary use of data were frequently presented. These include missing data and misclassification of data.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Assessing the feasibility of study objectives prior to study conduct including strategies to mitigate common methodological limitations related to survey studies and secondary use of data will increase the added value of RMM effectiveness PASS for regulatory decision-making.

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Risk minimization measures (RMM) put in place by marketing-authorization holders (MAHs) are an example of a pharmacovigilance activity aiming to ensure safe and effective use of medicinal products throughout their life cycle.[1] The introduction of the so-called "routine RMM" is mandatory for all medical products under the remit of the European Medicines Agency (EMA), which includes the summary of product characteristics (SmPC), the patient information leaflet, and product labeling. Additional RMM can be required when routine RMM alone cannot sufficiently manage risks associated with a specific medical product, examples include educational materials for health care professionals (HCPs) and/or patients/caregivers, controlled access programs, controlled distribution programs, pregnancy prevention programs (PPPs), and direct healthcare professional communications (DHPCs).[2] Key elements of RMM, such as the RMM messages and tools, are agreed upon at the European Union (EU) level. However, due to national legislation, differences in implementation may occur between EU countries as the final RMM materials are approved by the national competent authorities.[2]

The pharmacovigilance risk assessment committee (PRAC) of the EMA has a strategy in place to measure the impact of pharmacovigilance activities, that is, the PRAC impact strategy.[3] One key activity area of this strategy is focused on effectiveness evaluations of RMM. Since the amendment of the pharmacovigilance legislation in 2012, MAHs are required to evaluate the effectiveness of RMM in post-authorization safety studies (PASS), which are in turn assessed by PRAC.[4,5] In a previous study, we reviewed industry-sponsored PASS evaluating RMM effectiveness assessed by PRAC between 2016 and 2021. A main finding from this previous work was that a large proportion of the PASS was inconclusive, which means that results did not render a conclusion on the effectiveness of the RMM. Specifically, 4 out of 10 of the included PASS assessed during this period were inconclusive.[6] Potential reasons have been reported in previous studies, indicating that inadequate study design is a common issue in PASS. This could result in the PASS not being able to provide sufficient evidence to conclude on RMM effectiveness. Other potential flaws include improper data collection (e.g., recruitment issues resulting in unrepresentative survey results) and lack of comparators or insufficient study outcomes.[7,8] This previous work demonstrates that PASS evaluating RMM effectiveness requires resources from MAHs, national competent authorities (NCAs) as well as the EMA, making it a complex system with many factors affecting outcomes. Completely avoiding PASS rendering no conclusion about RMM effectiveness may be difficult, but insights into methodological limitations presented by MAH's in their PASS reports is an important starting point to (re)define mitigation strategies. Furthermore, it is important to better understand why PASS do not render a conclusion on RMM effectiveness to inform regulatory decision makers and to try to improve outcomes of pharmacovigilance processes and impact activities.

This current article presents results from a follow-up from a study we published in 2022 which reported on characteristics of industry-sponsored PASS that measured the effectiveness of RMMs.[6] In this qualitative study, we aim to describe (methodological) limitations presented in PASS and to compare limitations presented in conclusive and inconclusive PASS.

METHODS

Data sources and eligibility

We conducted this analysis on a subset of PASS included in the cohort of our all industry-sponsored PASS evaluating the effectiveness of routine and/or additional RMMs with PRAC assessment finalized between 1st of January 2016 and 31st of December 2021.[6] In short, data sources used to retrieve information about these PASS included PRAC assessment reports and MAH study reports, which were retrieved from non-public EMA databases (i.e., Documents Records Electronic Archive Management System (DREAM) and the European Review System (EURS) for electronic Common Technical Documents (eCTDs)). All PASS with PRAC assessment finalized between 2018 and 2021 were considered eligible for this current analysis. More extensive information on data sources and eligibility criteria for the cohort are presented in Grupstra et al.[6]

Study outcome

The primary outcome of this study was to identify methodological and other limitations reported in the PRAC assessment report of RMM effectiveness PASS. These were identified through several steps: First, all text from the assessment report section covering PRAC's overall conclusion on RMM effectiveness, sections explicitly dedicated to study limitations, and text from the MAHs study report covering study limitations was extracted and copied in an MS Word file per individual PASS. Next, an initial coding framework representing limitations that the authors expected to be reported in the PASS was constructed by R.J.G. with input from experts from EMA and Utrecht University (V.S., T.G., H.G.) (**Figure S1**). This coding framework was used to code the extracted text from the PASS (R.J.G.). An example from text presenting a study limitation as extracted from a PASS assessment report is as follows: "Information bias also needs to be considered as a limitation of this study, as the respondents could consult the HCP Guide while responding to the survey." Extracted text was deductively coded and the coding framework was adjusted accordingly, following the principles of thematic analysis.[9] The finalized coding framework was used to consecutively recode data from conclusive and inconclusive PASS to allow for comparison of reported limitations between the two groups.

Extraction of PASS characteristics

The following characteristics of the included PASS were collected: year of PRAC outcome, PASS design (cohort study, case-control study, cross-sectional study, time series), type of data collection (primary, secondary, both), type of RMM (routine, additional, both). Data were collected from the validated data set of the 2023 study.[6]

Data analysis

Descriptive statistics were used to report on extracted PASS characteristics (see 'Extraction of PASS characteristics'). Thematic analysis of text extracted from the PASS was conducted using NVivo 12 Pro, QSR International (Burlington, MA, USA). For validation purposes and in line with the principles of thematic analysis, identified code categories were iteratively reviewed among the researchers (R.J.G., H.G.) and aggregated into (sub-) themes.[9] Final (sub-)themes were discussed until a consensus was reached by the entire research team (R.J.G., H.G, T.G.).

RESULTS

Cohort of PASS

Text from 64 PASS concerning 52 medicinal products for which the PRAC finalized the final assessment in 2018–2021

was included in the thematic analysis (Table S1). In 39 (61.0%) of the PASS, a conclusion on RMM effectiveness was drawn, whereas 25 (39.0%) PASS did not render a conclusion on RMM effectiveness (referred to as "inconclusive PASS"). Most PASS had a cross-sectional study design (73.4%), followed by a cohort study (32.8%), time series (3.1%), and case-control study (1.6%). As 7 (10.9%) PASS used a mixed methods approach, the above-presented percentages for types of study design combined exceed 100%. The sole use of primary data collection was most common in the included PASS (65.6%) followed by secondary use of data (25.0%) and a combination of primary and secondary use of data (9.4%). The majority of PASS evaluated additional RMM (57.8%), whereas less PASS evaluated a combination of routine and additional RMM (32.8%) or routine RMM only (9.4%).

Identified themes

The thematic analysis resulted in a coding framework consisting of four main themes with various subthemes, that is, (i) survey-specific limitations, (ii) limitations specifically related to secondary use of data, (iii) general limitations related to study design, and (iv) limitations not related to study design. Each of these themes is presented below, whereafter limitations identified in conclusive and inconclusive PASS are compared (Table 1).

Limitations related to survey study design. The first out of four themes identified concerned limitations related specifically to surveys as a study design. Many reports acknowledged that representativeness issues are inevitable when conducting (voluntary) surveys as the number of participants is bound to quantitative limitations and due to various types of bias, that is convenience sample bias, non-response bias, participation bias, selection bias either by the researchers or by HCP's helping with recruitment, and self-selection bias. In some PASS imbalanced country distribution of subjects was also listed as a limitation as well as a small number of survey participants. Various causes for the latter were identified: (i) limited availability of eligible patients, for example, in case of rare diseases, (ii) burdensome (i.e., lengthy or complicated) surveys, (iii) lack of monetary compensation for survey completion, (iv) participants ignorance of participation value, (v) COVID-19 pandemic-related low response rates, and (vi) data protection policies. The risk of information bias in survey-collected data was also often reported, particularly in surveys for which participation is voluntary. Inherent information bias included response bias, recall (or memorization) bias, social desirability bias, and survival (or intervention) bias. Chance of cheating by subjects, for example, when participants use educational materials while remotely conducting an online survey, survey fatigue and the chance of patient's illness affecting the trustworthiness of their answers (e.g., in the case of patients with cognitive impairments) were also discussed in some PASS reports. Flaws in survey question design were also regularly mentioned. These range from translational issues with survey questions set out in multiple countries to phrasing errors in survey questions preventing adequate assessment of collected data. Related to this, the logistics of survey distribution were also sometimes presented as limiting, as well as RMM distribution-related issues. The cross-sectional character of survey studies was also presented as a limiting interpretation of PASS results as results are based on a single point-in-time estimate, albeit infrequently.

Limitations related to the secondary use of data. One commonly presented limitation related to the secondary use of data concerns non-generalizability of data in the chosen database, due to selection bias within the chosen database or because of small samples in the database. Measurement bias was also presented as a limitation, either caused by missing data, inaccurate data entries, or misclassification of data. Missing data may occur when variables of interest are not captured in the database, or not consistently included in the database for example, due to switches in database management, or because of non-compliance or underreporting by those entering data. Inaccurate data entries can happen due to lack of precision as different physicians use different data entry methods. When databases do not record, for example, intended duration of a treatment, this can be estimated, but this could result in misclassification of defining drug exposure. The retrospective nature of the secondary use of data was sometimes also presented as limiting PASS results, for instance due to history bias.

General challenges related to study design. Various types of analytical limitations were reported that include the occurrence of confounding data, flaws in the calculation of scores, conduct of solely unadjusted analyses, use of unmatched groups, and lack of a powerful analytical approach.

Additionally, timing-related issues of PASS were common. Either the starting point of a PASS, or delays of conducting the PASS, and the length, or follow-up period of the PASS were appointed as restricting. One PASS report stated, for example, how delays caused enrollment issues. Another report stated how short data collection periods disenable proper assessment. General issues related to the availability of any type of data were also presented as limiting. There might be a lack of comparable data, or the desired data might not be available to the researchers. The use of a flawed effectiveness measure was presented as a limiting interpretation of study outcomes, albeit infrequently.

Limitations not related to study design. The final theme covers limitations that are not directly related to general aspects of study design. Several PASS reports stated that the obtained results might not be entirely attributable to the RMM in question. An example from one of the PASS: "earlier warnings that took place in Europe (prior to the [RMM] changes in 2008) (...) may have already influenced safer prescribing of [drug] among clinicians." Other examples provided in Good Pharmacovigilance Practices (GVP) Module XVI on Risk Minimization Measures (Rev. 3) include simultaneous events, such as changes in clinical guidelines, reimbursement policies, or events impacting healthcare (e.g., a pandemic) that make establishing a causal relationship between a specific RMM and its outcomes challenging.[2]

Various PASS reports also stated that limited patient exposure to a drug for instance due to unavailability and thereby their exposure to the RMM under evaluation may be a restricting factor for assessment of study results.

Table 1 Overview of identified themes and subthemes with comparison of number of times limitations under the subthemes were observed in conclusive vs. inconclusive PASS. 24 inconclusive and 39 conclusive PASS included, denominators defined accordingly.

Subtheme	Specific limitation as example (if applicable)	Conclusive PASS, *n* (%)	Inconclusive PASS, *n* (%)
Theme: Limitations related to survey study design			
Representativeness of subjects limitations	Convenience sample used/sample not random (cluster sampling bias)	5 (12.8)	1 (4.0)
	Selection bias (by researchers)[a]	11 (28.2)	12 (48.0)
	Self-selection bias	11 (28.2)	7 (28.0)
	Selection bias by HCPs	4 (10.3)	1 (4.0)
	Participation bias	23 (59.0)	18 (72.0)
	Quantitative limitation	4 (10.3)	2 (8.0)
	Non-response bias	11 (28.2)	4 (16.0)
	Imbalanced country inclusion and/or distribution	13 (33.3)	7 (28.0)
Limitations related to number of subjects	(Undefined) low response rate (limited availability of participants)	19 (48.7)	9 (36.0)
	Low monetary compensation	2 (5.1)	0 (0.0)
	Lack of understanding of importance of participation	1 (2.6)	0 (0.0)
	Lack of mandate from regulatory bodies/recruitment issues related to data protection and/or policies	5 (12.8)	4 (16.7)
	Surveys too burdensome to complete	1 (2.6)	0 (0.0)
	Limited use of product, therefore limited participants	4 (10.3)	3 (12.5)
	COVID-related low response rate	0 (0.0)	1 (4.2)
	Subjects failed to (correctly) complete survey, therefore responses less usable	2 (5.1)	3 (12.5)
Information bias in survey-collected data	Response bias	7 (17.9)	1 (4.0)
	Recall/memorization bias	11 (28.2)	8 (32.0)
	Social desirability bias	6 (15.4)	4 (16.0)
	Intervention bias/survival bias	1 (2.6)	1 (4.0)
	Subjects affected by illness (hence unable to provide trustworthy data)	3 (7.7)	0 (0.0)
	Due to 'cheating' by participants (e.g., using RMM educational materials while doing online survey)	4 (10.3)	0 (0.0)
	Other information bias	2 (5.1)	3 (12.0)
	Due to survey fatigue (which lessens the quality of provided answers)	1 (2.6)	0 (0.0)
Flaws in design of survey questions/content	Translation issues	1 (2.6)	1 (4.0)
	Flaws in formulation of survey questions	5 (12.8)	6 (24.0)
	Study feasibility not performed	2 (5.1)	0 (0.0)
Logistical limitations of survey conduct	Insufficient distribution of survey	2 (5.1)	0 (0.0)
RMM distribution-related issues		3 (7.7)	4 (16.0)
Cross-sectional design of survey as limitation		2 (5.1)	0 (0.0)
Theme: Limitations related to secondary use of data			
Data generalisability issues in database	Selection bias in database	6 (15.4)	10 (40.0)
	Small sample in database	6 (15.4)	8 (32.0)
Measurement bias/information bias in secondary data source	Lack of precision as different physicians use different methods to enter data in database	1 (2.6)	1 (4.0)
	Due to underreporting by physicians/participants	1 (2.6)	2 (8.0)
	Missing data (e.g., due to insufficient recording or underreporting)	0 (0.0)	12 (48.0)

(Continued)

Table 1 (Continued)

Subtheme	Specific limitation as example (if applicable)	Conclusive PASS, *n* (%)	Inconclusive PASS, *n* (%)
	Information bias in database due to policy or guideline changes	1 (2.6)	0 (0.0)
	Misclassification of data	0 (0.0)	4 (16.0)
	Low quality of data due to data entry errors	3 (7.7)	5 (20.0)
Retrospective nature of secondary data source as limitation	E.g., history bias	0 (0.0)	1 (4.0)
	Other	2 (5.1)	4 (16.0)
Theme: general challenges related to study design			
Analytical flaws	Confounding data	6 (15.4)	1 (4.0)
	Flaws in calculation of scores	1 (2.6)	2 (8.0)
	Unadjusted analyses only	1 (2.6)	1 (4.0)
	Unmatched groups	1 (2.6)	1 (4.0)
	Lack of powerful analytical approach	3 (7.7)	3 (12.0)
Limitations of selected timeframe	Wrong/unideal start of study	5 (12.8)	3 (12.0)
	Delays encountered	1 (2.6)	0 (0.0)
	Wrong/limiting study period length (too long or too short)	5 (12.8)	6 (24.0)
Data availability issues (therefore limited interpretation options)	Data source needed not available or challenging to have access to	1 (2.6)	3 (12.0)
	Lack of comparable data (e.g., no data from prior to RMM initiation)	1 (2.6)	5 (20.0)
Flawed or wrong effectiveness measure(s)		0 (0.0)	1 (4.0)
Theme: limitations not related to study design			
Impact not solely linked to RMM		1 (2.6)	3 (12.0)
Patient/participant exposure to RMM/drug is limited		5 (12.8)	7 (28.0)

HCP, healthcare professional; PASS, post-authorization safety study; RMM, risk minimization measures.
[a]Selection bias by researchers due to them selecting study participants.

Comparison of conclusive and inconclusive PASS

Some limitations were frequently reported in inconclusive PASS reports, but not presented in any of the conclusive PASS in our cohort. For example, missing data and misclassification of data were presented as limitations in 48.0% and 16.0% of inconclusive PASS while these were never explicitly discussed in any of the assessment or study reports of conclusive PASS in this cohort (**Table 1**). Other limitations that were more commonly reported in inconclusive compared with conclusive PASS include participation bias, selection bias in the database, and small sample in the database (72.0%, 40.0%, and 32.0% vs. 59.0%, 15.4%, and 15.4%, respectively). In contrast, (undefined) low survey response rate (48.7%), response bias (17.9%), and information bias in survey-collected data such as "cheating by participants" and "'subjects affected by illness" (10.3% and 7.7%, respectively) were more frequently discussed for conclusive PASS compared with inconclusive PASS (36.0%, 4.0%, 0.0%, and 0.0%, respectively).

DISCUSSION

This analysis demonstrates that the assessment of RMM effectiveness can be impacted by a broad range of limitations. Three out of four main themes in our finalized coding framework relate to study design, that is, survey studies, studies using secondary data sources, or general design limitations such as analytical flaws. Most of the PASS included in this thematic analysis had a survey design, hence a foreseeable large proportion of reported PASS limitations identified from PRAC assessment reports and MAH study reports were inherent to survey studies. Common limitations under this theme in both conclusive and inconclusive PASS are well-known and have been frequently reported in the literature. These included issues with the representativeness of study subjects, for example, due to participation bias or selection bias, issues caused by information bias in survey data, for example, due to recall bias or social desirability bias, and recruitment issues.[10,11] These survey-related limitations can be hard to bypass,[12] but GVP Module XVI (Rev. 3) provides guidance to overcome some of these,[2] and multiple strategies to minimize their impact are presented in the literature. These include, among others, the usage of weighting adjustments to mitigate the influence of selection bias,[13] mixing recruitment strategies to enlarge the study population,[11] and minimization of the impact of information biases like social desirability bias through the usage of external (e.g., verify answers with reports from friends or family) or internal validation

(e.g., verify answers through comparison with other data collection methods such as laboratory results).[14]

The limitations that we identified in our study, have been acknowledged in several studies that have been conducted to assess the impact of RMMs, both in the EU and beyond. For instance, survey-related limitations such as selection bias and representativeness issues were presented by Lysen et al. in 2023 and by Buhl et al. in 2024.[15,16] Issues such as non-generalizability of data in the chosen database, measurement bias, and missing data encountered in studies using secondary data sources have been presented by Hedenmalm et al. in 2019, by Plueschke et al. in 2022, and by Morales et al. in 2020, respectively.[17–19] Similar limitastions were also presented in a 2021 review of studies investigating the impact of RMMs in the United States Food and Drug Administration setting.[20]

Compared with conclusive PASS from our cohort, limitations related to the use of secondary data were more often presented in inconclusive PASS. As in the ideal situation, any PASS should be conclusive to add value to regulatory decision-making, this result suggests prioritization of mitigation of such limitations, for instance, by providing regulatory guidance. Apart from EMA initiatives that have already been initiated to aid the identification of suitable data sources, for example, the EMA Meta-data catalog,[21] additional mitigation strategies could be considered. A starting point could be to implement external validation studies to identify the misclassification of data, for instance, by combining the use of primary secondary data in mixed methods PASS. Already in 2018, it was suggested to utilize self-reported data, for example, through survey conduct, to identify erroneous values in data sources or to help deal with missing data.[22] GVP Module XVI (Rev. 3) presents mixed methods approaches as potential tools to help overcome common study limitations and to aid the conclusiveness of PASS evaluating RMM effectiveness.[2] Our results align with this and demonstrate that some PASS require a different approach to mitigate methodological limitations, which may be achieved by implementing mixed methodologies.

Furthermore, our analysis suggests that issues rendering a PASS using secondary data sources inconclusive could have been anticipated by appropriate feasibility assessment, for instance, by exploring the size of the target population and completeness of the data before choosing a database. GVP Module XVI (Rev. 3) lists more factors that should be considered in order to ensure that data sources chosen for evaluating RMM effectiveness are feasible. These include verifying if the information required to answer the research question is available and accessible, checking the validity of the information, and timeliness of data.[2] The importance of these was reflected in the limitations presented in our cohort. The specific limitation of lack of feasibility assessment was even explicitly mentioned in one of the analyzed PASS. Examples from literature show that feasibility assessments have aided PASS in utilizing secondary data sources and demonstrate how up-front feasibility assessment contributes to the endorsement of study objectives in general.[23,24] Furthermore, the literature already states that feasibility assessment through survey testing prior to study initiation may also enhance the mitigation of survey limitations.[25] MAHs are currently strongly recommended, but not obliged to comment on feasibility of their PASS design as this is not mandatory from GVP VIII.[5,26,27] According to draft GVP Module XVI (Rev. 3), RMM objectives should be clearly defined in line with the intended behavior and health outcomes, and these RMM objectives should guide the definition of study objectives of PASS evaluating RMM effectiveness.[2] Together with the fact that lack of feasibility testing was explicitly presented as a survey limitation in PASS from our cohort albeit infrequently, our results could be used as a reference to make it mandatory to perform feasibility investigations before launching any (RMM effectiveness) PASS and to draft a template list of minimum required information within feasibility investigation.

Limitations

We only included free text from specific sections dedicated to the limitations of the PASS, but sometimes, those sections contained no or only limited information. It is important to acknowledge existing differences between pharmacovigilance assessors in terms of what is written down in an assessment report and what is not. In this study, we were bound to what was explicitly presented in assessment reports, but it is possible that further study limitations were discussed verbally in PRAC plenary meetings. Furthermore, differentiation between PASS documentation may exist based on the outcomes, for instance, conclusive PASS may be less prone to elaborate on study limitations as the study was successful in rendering a conclusion. We believe, however, that this is a minor limitation as our main interest was to elucidate what limitations cause a PASS to be inconclusive. We acknowledge that different scenarios may render a PASS evaluating RMM effectiveness inconclusive, for example, the PASS was completed without obtaining results that allowed a conclusion on RMM effectiveness, or other methodological study limitations that may or may not be sufficiently addressed.

CONCLUSION

In conclusion, we found that in terms of limitations explicitly presented in MAH PASS reports and PRAC assessment reports rendering a PASS inconclusive, limitations related to secondary use of data were more common in inconclusive PASS compared with conclusive PASS in our cohort. Development of guidance for mitigation strategies of such limitations should be prioritized. Although not all limitations can be avoided, one approach that could be considered involves a mandatory feasibility assessment of study protocols prior to PASS conduct to avoid common methodological limitations up-front. To aid this, guidance for systematic conduct of feasibility assessments prior to study conduct should also be developed. Furthermore, rigorous review of protocols for RMM effectiveness PASS including the feasibility of study objectives and a priori definition of appropriate indicators for RMM effectiveness are recommended.

SUPPORTING INFORMATION

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

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AUTHOR CONTRIBUTIONS
R.J.G. and H.G. wrote the manuscript; all authors designed the research; R.J.G. performed the research; Grupstra 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.

ETHICS STATEMENT
This research project did not involve human subjects, hence there has not been an Institutional Review Board review of the study.

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