Identifying (Dis-)agreement Between Models for Evaluation of Effectiveness of Risk Minimization Measures (RMMs)

Maria Angeles Natividad Sancho[1]

[1]Thermo Fisher Scientific, Paris, France

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Background

- Evaluating the effectiveness of risk minimization measures (RMMs) via postauthorization safety studies (PASS) is an integral part of pharmacovigilance in Europe and an evolving field for which significant methodological gaps remain.
- The model proposed by regulators to attest success of RMMs includes (1) **process indicators** to measure the degree of prescribers' awareness of the RMMs and knowledge of the key safety and clinical management information they contain, and (2) **outcome indicators** to measure clinical results achieved after implementation of the RMMs.

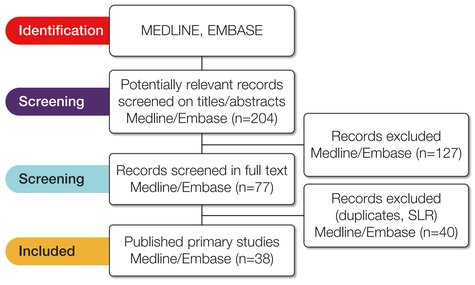
Objectives

- No previous published review has quantitatively analyzed how often these two indicators are used together to assess the effectiveness of RMMs and whether studies assessing both indicators concurrently show conflicting versus complementary results.

Methods

- A structured review of the literature was conducted in December 2025 in Embase and MEDLINE. The search was based on explicit keywords and eligibility criteria and used a search strategy that was developed in consultation with a research librarian. The goal was to summarize the methodology used to assess the effectiveness of RMMs, results, and author-reported limitations.
- Peer-reviewed, full-text original research articles indexed in MEDLINE and Embase were included if they (1) evaluated risk minimization, (2) reported effectiveness measures, (3) were performed in EU countries, (4) were English-language, and (5) were published between 2012 and December 15, 2025. Titles, abstracts, and full texts of the potentially relevant articles were screened by a single researcher to identify those that met the eligibility criteria. Data of interest were extracted from eligible publications into a bespoke spreadsheet (**Figure 1**).
- We also reviewed data from PASS protocols and reports registered in the Heads of Medicines Agencies-EMA Catalogue for real-world data sources up to December 2025 to extract additional information not presented in the published manuscripts.[1]

Figure 1. Study Search and Screening Flow Diagram



Abbreviations: SLR = systematic literature review

Results

Survey-only Studies Assessing Process Indicators

- Of the 38 studies evaluating RMM effectiveness, 19 (50%) were survey-only studies assessing process indicators (**Figure 2**). Of these, 58% (11/19) involved administration of a questionnaire to healthcare professionals (HCPs) only, 11% (2/19) to patients only, and 32% (6/19) to both HCPs and patients (**Figure 3**).
- A total of 65% of the surveys provided information for all three process indicators (i.e., awareness and usage of the risk minimization tools, theoretical knowledge, and behavior); 81% provided information on awareness and theoretical knowledge only.
- Because of the limitations inherent to surveys, RMM effectiveness could not be inferred from process indicators in 5/19 (26%) of the surveys, and results generalizability was limited in all surveys (**Table 1**).

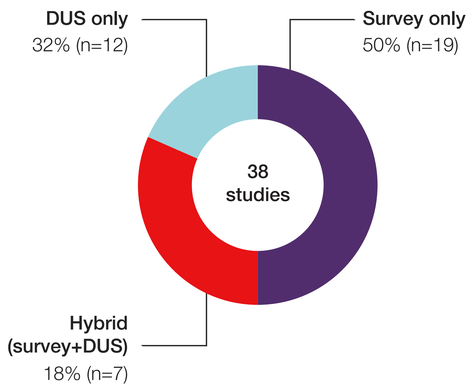
Database-only Studies Assessing Outcome Indicators

- Twelve of 38 studies (32%) assessed outcome indicators, including drug utilization (prescribing practice, occurrence of off-label use, and medication errors) and frequency and/or severity of relevant adverse reactions (**Figure 2**). Methods used to assess outcome indicators included retrospective cohort studies using various electronic healthcare databases (6/12; 50%), retrospective medical chart reviews (2/12; 17%), and studies using data from existing patient registries (3/12; 25%) (**Figure 3**).
- Data interpretation was challenged by limitations common to studies assessing outcome indicators via secondary data (**Table 2**), but prospective studies were not an option because of the length of time needed to obtain results.

Hybrid Studies

- Only seven of 38 studies (18%) evaluating RMM effectiveness measured both outcome and process indicators (i.e., hybrid studies), despite this being the option recommended by regulators (**Figures 2** and **3**).
- Five of the seven hybrid studies (71%) showed conflicting results (findings disagreed, contradicted, or showed discrepancies) between process and outcome indicators involving varying degrees of deviation.
- In addition, five of the seven hybrid studies (71%) concluded that in order to more fully appreciate the effectiveness of RMMs, it is important to consider the results of process indicators from surveys and outcome indicators from secondary database analyses together to form a more complete picture.
- This was accomplished in one of the seven (14%) hybrid studies, in which survey responses were able to be correlated with clinical and safety outcomes in the same patients, thus bridging the gap of linking process indicators with outcomes.
- Despite the advantages, the incorporation of outcome indicators in the assessment of effectiveness of RMMs has decreased in recent years (**Figure 4**).

Figure 2. Type of Study Assessing the Effectiveness of RMMs



Abbreviations: DUS = drug utilization study; RMM = risk minimization measure

Table 1. Challenges Associated With Surveys Assessing the Effectiveness of RMMs

Challenge	Consequence
Reliance on self-reported data and susceptibility to social desirability biases	Overestimation of awareness of and adherence to measures
Self selection of respondents into the survey due to use of a convenience sample	Increased risk of selective inclusion of participants who were more aware or knowledgeable, which could overestimate process indicators
Low survey response rates	Limited generalizability of results
Reliance on respondent recall when participants had to remember when and from whom they had heard about the RMMs	Limited survey data accuracy
Lack of a comparator group or baseline data	Difficulty to quantify the impact of the RMM on respondents' knowledge and behavior

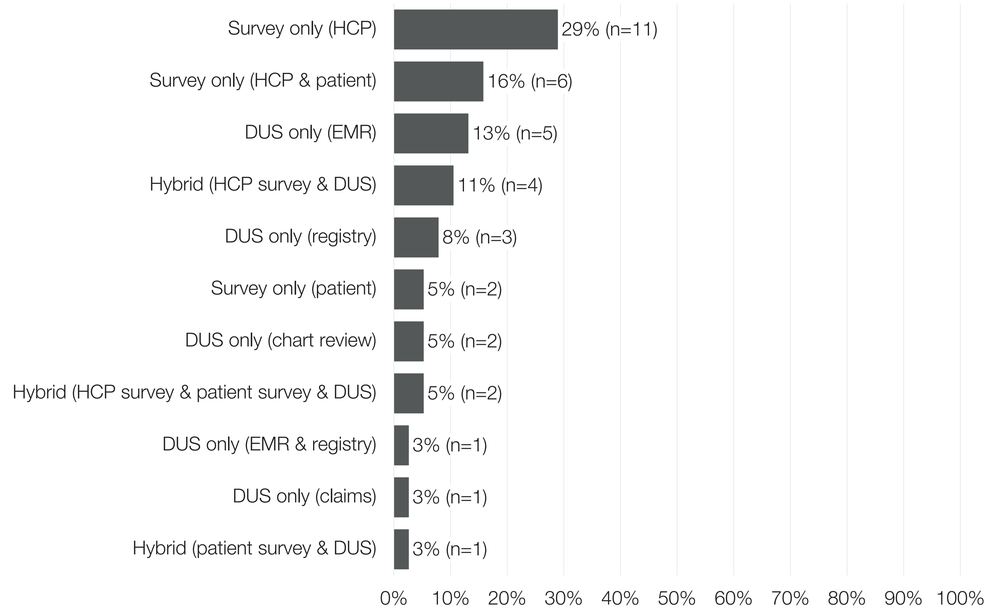
Abbreviations: RMM = risk minimization measure

Table 2. Challenges Associated With Database Studies Assessing the Effectiveness of RMMs

Challenge	Consequence
Missing or incomplete data elements of interest (e.g., treatment, patient clinical features)	Underestimation of the prevalence of off-label use, medication error, and clinical/safety events
Suboptimal validity of diagnosis codes and quality of available secondary data sources	Over- or underestimation of the prevalence of events being measured

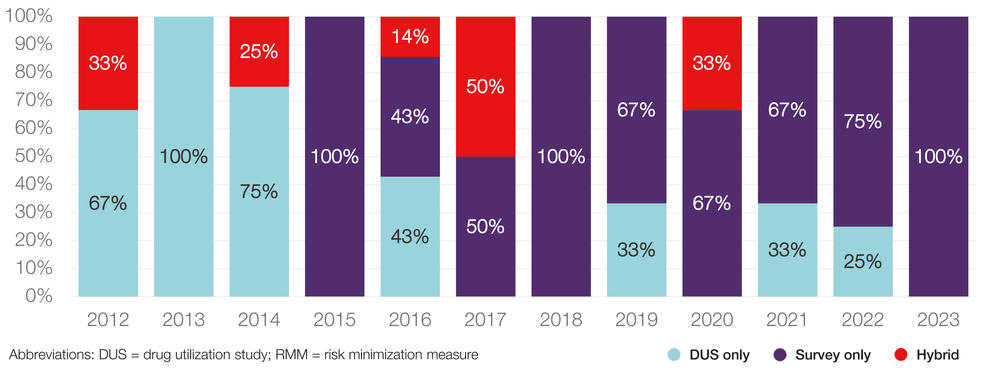
Abbreviations: RMM = risk minimization measure

Figure 3. Type of Study (Data Source) Assessing the Effectivess of RMMs



Abbreviations: DUS = drug utilization study; EMR = electronic medical record; HCP = healthcare professional; RMM = risk minimization measure

Figure 4. Trends Over Time on Type of Studies Assessing the Effectiveness of RMMs



Abbreviations: DUS = drug utilization study; RMM = risk minimization measure

Conclusions

- Surveys remain key to the evaluation of process indicators assessing the implementation of RMMs (e.g., distribution, receipt, usage, and knowledge of key risk messages contained in the RMM materials). However, these surveys are negatively affected by operational challenges and methodological limitations, such as selection and reporting biases.
- Database studies (e.g., drug utilization studies) suffer from limitations of secondary data sources, but provide a complementary method to increase robustness of survey data (e.g., objective assessment of prescribing behavior).
- Only a quarter of studies assessing the effectiveness of RMM use a hybrid design that leverages secondary data to supplement surveys. Further development of this hybrid method and the logistics of correlating survey data with secondary data is warranted.

References

1. European Medicines Agency. Catalogue of RWD studies. https://catalogues.ema.europa.eu/catalogue-rwd-studies

Disclosures

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