26 July 2024
EMA/419982/2019

Guideline on good pharmacovigilance practices (GVP)

Module XVI Addendum II – Methods for evaluating effectiveness of risk minimisation measures

Draft Addendum II of GVP Module XVI finalised by the Agency in collaboration with Member States	18 November 2020
Draft Addendum II of GVP Module XVI agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	7 January 2021
Draft Addendum II of GVP Module XVI adopted by Executive Director	1 February 2021
Release for public consultation	3 February 2021
End of consultation (deadline for comments)	28 April 2021
Revised Addendum II of GVP Module XVI finalised by the Agency in collaboration with Member States	4 July 2024
Revised Addendum II of GVP Module XVI agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	22 July 2024
Revised Addendum II of GVP Module XVI adopted by Executive Director as final*	26 July 2024
Date for coming into effect*	6 August 2024

* The revised final guidance is applicable to new applications for marketing authorisation, new risk minimisation measures and new studies evaluating risk minimisation measures for authorised medicinal products but not immediately applicable to existing risk minimisation measures and ongoing activities regarding risk minimisation measures; however, where existing risk minimisation measures are amended, the revised guidance should be taken into account and applied if this is considered likely to increase the effectiveness of the risk minimisation measure without jeopardising its familiarity for patients and healthcare professionals using the concerned medicinal product.

* Note: The final versus the draft version released for public consultation includes the following in response to the consultation:

- Emphasis on the importance of a mixed methods approach to evaluate RMM outcomes in XVI.Add.II.1.;
- Clarification of the importance of appropriate sampling strategies to ensure representativeness in XVI.Add.II.2.1. and 3.2.;
- Addition of patient-reported outcome measures (PROM) and patient-reported experience measures (PREM) as primary data collected through surveys in XVI.Add.II.2.2.;
- Clarification of the role of spontaneous reporting systems for RMM effectiveness evaluation in XVI.Add.II.2.7.;
- Clarification of considerations to ensure that the objectives of RMM effectiveness studies are feasible in XVI.Add.II.2.8.;
- Addition of references on human factors as enablers and barriers to RMM implementation in XVI.Add.II.3.1.;
- Further clarifications on the limitations of survey methodologies and how these can be overcome in XVI.Add.II.3.2.;
- Updates from the RIMES-SE reporting standard and clarification on its use in XVI.Add.II.4.2.;
- Overall revised structure.

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XVI.Add.II.1. Introduction

This Addendum to GVP Module XVI provides additional guidance to be followed by marketing authorisation holders and competent authorities on data sources and methods for monitoring outcomes of risk minimisation measures (RMM) in line with the guidance on RMM effectiveness evaluation in GVP Module XVI. Depending on the intended outcomes of RMM, studies evaluating RMM effectiveness may integrate different qualitative and quantitative measurements and research approaches (including mixed methods) to evaluate outcomes of RMM described in GVP Module XVI. Dissemination, risk knowledge, behavioural and health outcomes may be considered, and in this respect the guidance on objectives of RMM effectiveness studies in GVP Module XVI should be followed. The Addendum also provides guidance on the reporting of the results of RMM effectiveness studies.

The ENCePP Guide on Methodological Standards in Pharmacoepidemiology[1] should be considered for further methodological guidance, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology[2] may provide additional guidance.

XVI.Add.II.2. Data sources

Depending on the context and objectives of RMM effectiveness evaluation, primary data may be specifically generated to evaluate effectiveness, or secondary (pre-existing) data originally collected for other purposes may be used. Applying qualitative, survey or pharmacoepidemiological methods (see XVI.Add.II.3.) requires different data sources. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology[3] provides further guidance on approaches to data collection.

For pharmacoepidemiological studies, relevant information on clinical actions including prescribing behaviour and health outcomes may be extracted from routinely collected data in electronic healthcare databases of (electronic) medical records, registries, or administrative claims records, for secondary data analyses (1–3). Suitable electronic healthcare databases are described in the literature (4) or may be identified from the HMA-EMA Catalogue of Real-World Data Sources[4], which is a publicly available tool. Medical records do not usually capture whether the prescribed medicine has actually been taken, a limitation which applies to all secondary healthcare data collected for a different purpose, as well as for administrative claims data (see XVI.Add.II.2.5.).

Databases of spontaneous reports of suspected adverse reactions are a further source for pharmacoepidemiological studies.

[1] https://encepp.europa.eu/encepp-tools/methodological-guide_en
[2] https://www.pharmacoepi.org/resources/policies/guidelines-08027/
[3] https://encepp.europa.eu/encepp-tools/methodological-guide_en
[4] https://catalogues.ema.europa.eu/

XVI.Add.II.2.1. Data sources for qualitative research

Common data sources for qualitative research in healthcare are interviews, focus groups and different existing types of documentations (e.g. media reports or clinical guidelines). These data sources may contain information about cognitive processes and experiences of patients and healthcare professionals that provide in-depth understanding of the reasons for RMM achieving (or not) the intended outcomes.

The type of documentation to use as data source for understanding perception and information needs in certain patient or healthcare professional populations may be determined by their media preferences. Preferences for e.g. news, social or scientific media can be identified through qualitative or quantitative media research.

The recruitment of participants in focus groups or interviews, and the selection of documentation is aimed at saturation of data, i.e. all viewpoints, experiences, and suggestions prevalent in the concerned patient or healthcare professional population(s) are collected and the collated data provide for a robust understanding of the cognitive processes and experiences that are typical in the population of interest. This includes covering less common views or needs of sub-populations of patients and healthcare professionals. Therefore, diverse participants should be selected to provide in-depth insights. Appropriate sampling is a key requirement to obtain relevant information and to minimise bias. The sampling strategy's target is relevance and representativeness of the information to be collected, and various strategies can be applied: representative sampling in relation to certain criteria describing the population of interest, oversampling of specific subpopulations or complete sampling to include all concerned people within a defined region or timeframe, or step-by-step sampling to identify all themes or investigate emerging themes more in depth (5–7). Alternatively, purposive sampling is a non-random method where researchers use their expertise to identify and select participants who provide information-rich cases, making best use of available resources (8). However, where the sampling strategy leads to non-representative sampling, the results need to be interpreted in a qualitative setting, i.e. they cannot be interpreted like the results of a representative study. Finally, the appropriate sampling strategy should be adapted to the diversity of the patient or healthcare professional population of interest and recruit also those who may be less proactive to participate in such research.

Data collection through interviews or focus groups should preferably use open questions and can be conducted with variable degrees of structure, depending on the study objective and the available evidence on the topic to be studied (9–11). Studies should be conducted to standards that avoid response bias, e.g. where questionnaires or semi-structured interview guides are used, these should be validated, and interviewers should be experienced.

XVI.Add.II.2.2. Surveys

Surveys are a method to collect primary data from a sample of a population and typically apply a standardised questionnaire through in-person interviews or options for self-reporting with postal

mailings or electronic communication (e.g. open-source web applications). These may be supported by audio computer-assisted self-interviewing (A-CASI) tools or interactive voice response systems (IVRS). The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics, and the type of information to be collected.

For a healthcare professional survey, participants may be recruited from web panels and member lists of professional or learned societies. For patient recruitment, prescribers or pharmacists may be best placed to identify patients in the relevant clinical setting, and existing web panels as well as e.g. member lists of patient organisations may be considered.

Validated health measurement instruments (e.g. self-reported questionnaires or diaries running on interfaces such as hand-held devices or computers) may collect patient-reported outcome measures (PROM) and patient-reported experience measures (PREM).

XVI.Add.II.2.3. Registries

Patient or disease registries as defined in the Guideline on Registry-Based Studies[5] may play an important role for evaluating the effectiveness of RMM by monitoring the use of medicines or health services, thus collecting data relevant to determine behavioural or health outcomes. Behaviours relevant to RMM include e.g. changes in prescribing patterns, usage of diagnostic tests identifying risk factors for adverse reactions or attending teratogenic risk counselling. Registries may be beneficial for collecting data for specific populations such as patients with rare diseases, patients who require highly specialised healthcare interventions, or pregnant women. Some registries collect additional information, such as lifestyle factors, smoking, alcohol use, nutrition, and weight, which may be risk factors for certain adverse reactions and therefore be useful for RMM effectiveness evaluation.

The financial and administrative burden and time effort for setting up tailor-made registries may limit their use solely for RMM effectiveness evaluation and access to existing registries for secondary data analysis may be preferable. Important limitations to be considered are voluntary patient enrolment which may affect accrual rates and introduce selection bias, data quality issues or missing data (12,13).

A registry-based evaluation of the effectiveness of RMM should follow the Guideline on Registry-Based Studies[6].

XVI.Add.II.2.4. Medical records

Electronic medical records may be considered for effectiveness evaluation of RMM in primary care (general practitioner and community services) and/or secondary care (hospitals and specialists) (4) for their rich clinical details such as diagnoses, procedures, laboratory values and health

[5] https://www.ema.europa.eu/en/guideline-registry-based-studies-scientific-guideline
[6] https://www.ema.europa.eu/en/guideline-registry-based-studies-scientific-guideline

outcomes. Medical records are a suitable source for measuring changes in prescribing behaviour, but the feasibility of obtaining and measuring health outcomes in electronic medical records largely depends on the type of outcome, the seriousness of the adverse event and coding practices, e.g. for laboratory test results.

Where relevant outcome variables are not routinely collected, complementary primary data collection may be considered, although this solicited approach may introduce different types of bias depending on the methodology.

XVI.Add.II.2.5. Administrative claims

Administrative claims data are generated by healthcare systems for insurance purposes and cover the entire population or a subset of insured patients. Claims data usually capture information from all healthcare professionals for insured patients and are normally well suited for drug utilisation studies as they record prescriptions at the time of dispensing, i.e. they record that the patient has obtained the medicine.

Different reimbursement policies between countries and policy changes over time may impact the data source's suitability for evaluating RMM effectiveness. A major limitation of administrative claims data is that information not relevant for billing purposes is not documented, such as laboratory values, results of imaging and other diagnostic procedures, prescriptions not submitted or not eligible for reimbursement, and self-medication.

XVI.Add.II.2.6. Healthcare record linkage

Healthcare record linkage systems bring together information from multiple data sources at the level of individual patients, expanding data that is not captured in the initial data source. For example, dispensing data may be linked to cancer- or other registries. Data linkage is regulated at national level to ensure ethical standards and data protection regulation[7] are adhered to which may restrict record linkage.

XVI.Add.II.2.7. Spontaneous reporting systems

Interpreting data from spontaneous reporting systems of suspected adverse reactions for the purpose of RMM effectiveness evaluation needs to consider:

- General underreporting of suspected adverse reactions;
- Increased risk awareness due to the RMM or other sources of information (e.g. national information campaign) possibly leading to increased reporting;
- Weber effect, which describes a frequently seen decline in reporting once an adverse reaction of a medicinal product becomes well-known (14); and

[7] Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation)

- Lack of precise data on the exposure to medicinal products for calculating reporting rates.

Therefore, only comparing trends in spontaneous reporting of suspected adverse reactions for the medicinal product or product class of interest with products used as therapeutic alternatives is not considered adequate for demonstrating RMM effectiveness. However, comparing reporting rates of a specific suspected adverse reaction over time may be useful for RMM evaluation in specific situations. An example of such situation is where the continued spontaneous reporting of a serious adverse reaction with a specifically severe outcome (e.g. adverse pregnancy outcome) supports the evidence from non-interventional studies which indicates that the RMM may not be effective (see XVI.Add.II.3.3.). Spontaneous reporting may also be useful to identify risk factors for adverse reactions in relation to how medicines are used, e.g. in the context of medication errors. Despite limitations, monitoring trends of spontaneous reporting rates for specific suspected adverse reaction over time (e.g. in annual reports) maybe useful and can under certain circumstances be agreed with the competent authority, e.g. in situations where non-interventional studies are not feasible.

XVI.Add.II.2.8. Factors influencing the choice of data source(s)

The choice of data source(s) for RMM effectiveness studies should be determined by the following factors to ensure study objectives are feasible:

- Scope and research question: Good understanding of eligible data sources to verify whether key variables and information required to answer the research question are available for secondary use of routinely collected healthcare data, given that this data collection was not designed to answer the research question. The data source's strengths and limitations should be considered in the study design.
- Accessibility of data sources: Access and conditions for collaboration with data source owners should be clarified.
- Information on exposure and outcome: The validity of information on exposure and outcome data should be verified.
- Availability and timeliness: Pre-existing healthcare data is more likely to be readily available for analysis compared to primary data collection, and timelines for the entire process from data delivery to availability of secondary use data including lag times should be considered. Also, the periodicity of refresh of the database over time may be a limitation. Low exposure in the period following product launch in healthcare may pose challenges to recruitment of study participants in primary data collection, and to detect e.g. changes in prescribing trends based on secondary use data.
- Prevalence of outcomes of interest: Routinely collected data tends to have large sample sizes which may be relevant for rare exposures and rare outcomes.
- Observation period: For detecting changes over time or delayed effects of RMM, data must be collected over a sufficiently long period of time to ensure RMM dissemination and

implementation at healthcare level has happened. As the complete medical history may not be available in databases, the extent of left and/or right truncation should be considered, e.g. if no information is available outside of the respective insurance period in the case of claims data.

- Representativeness of the study population: The representativeness of the study population for the entire population should be assessed. For example, where claims databases are used, the population with a specific health insurance may be inherently different to the entire population, which may introduce bias. Survey studies are prone to selection bias that may affect the generalisability of results. The approach to RMM effectiveness evaluation includes evaluating intended outcomes of RMM and, as appropriate, unintended outcomes associated with the use of the concerned and other medicinal products (see GVP Module XVI, Figure XVI.3). Where unintended outcomes are evaluated, the study population should preferably not be limited to the population targeted by the RMM for the concerned medicinal product and expanded to include populations where unintended outcomes (see GVP Module XVI, Table XVI.5) may be expected.
- Completeness of the data: The amount of missing or incomplete variables should be considered where data was initially collected for a purpose different from the research question, e.g. indication of medicines use, co-morbidities, co-medication, patient monitoring, smoking, diet, body mass index or family history of disease.

The ENCePP Guide on Methodological Standards in Pharmacoepidemiology[8] provides further guidance on assessing study feasibility.

XVI.Add.II.3. Research methods

Figure XVI.Add.II.1. shows relevant methods and study designs for evaluating the effectiveness of RMM, considering each step of the RMM implementation pathway. Effectiveness evaluation includes measuring intended outcomes of RMM (i.e. product-specific targeted effects) and as appropriate, other relevant outcomes (i.e. non-targeted effects) associated with the use of the concerned and other medicinal products that may counteract the effectiveness of RMM under evaluation (see GVP Module XVI, Figure XVI.3.).

Implementation metrics are useful to determine the extent of RMM implementation as planned and depend on the nature of the RMM. Measures of dissemination and receipt of information and RMM materials are used to ascertain delivery to and receipt by the target audience. Quantitative methods may be applied to assess the implementation and impact of RMM at each implementation step. Qualitative methods assess the context of RMM effectiveness and help determining enablers and barriers in terms of user acceptance and integration of RMM in healthcare systems.

[8] https://encepp.europa.eu/encepp-tools/methodological-guide_en

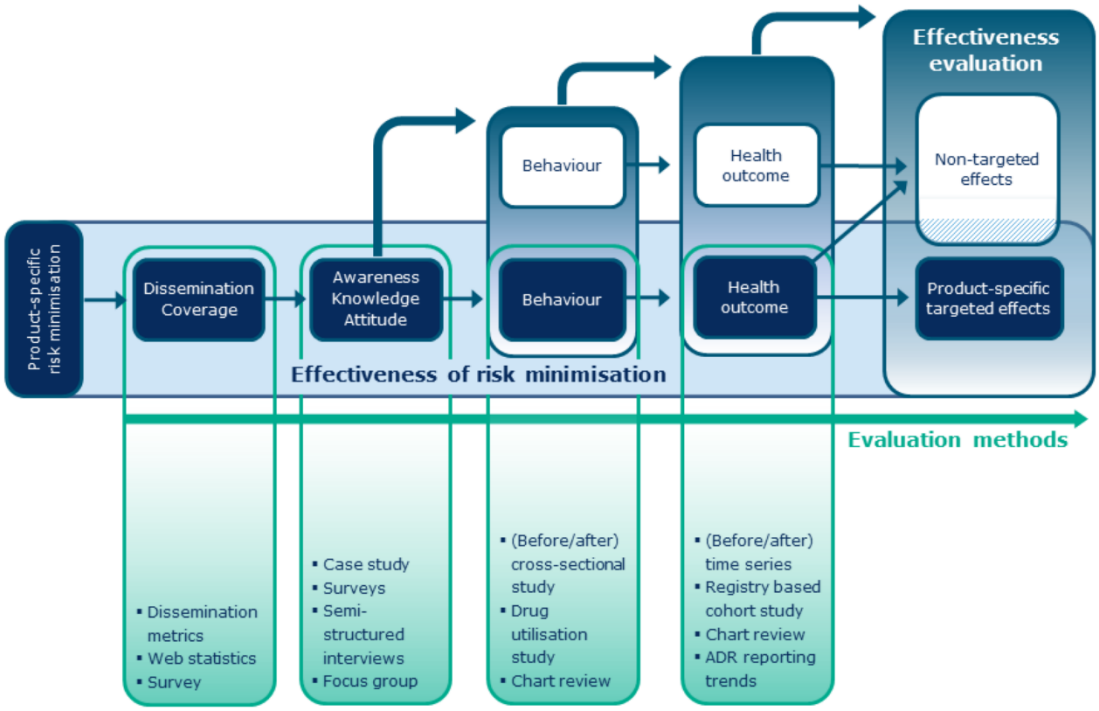

Figure XVI.Add.II.1: Approach to RMM effectiveness evaluation showing examples of quantitative and qualitative methods at each step of the RMM implementation pathway
Note: Medicinal product-specific targeted effects and, as appropriate, relevant non-targeted effects associated with the use of the concerned (blue boxes) and other medicinal products (white boxes) may be measured.

XVI.Add.II.3.1. Qualitative methods

Qualitative research plays a distinctive role in evaluating healthcare interventions (15), especially on issues not yet well understood (9,10). It can study cognitive processes and experiences in their natural setting, such as knowledge, risk awareness, trust, reasoning processes and attitudes about medicines, communication needs and preferences, and experiences of using medicines in real life. Factors that may be enablers and barriers for implementing RMM in healthcare and achieving behavioural change can be identified through qualitative research. These factors include those relating to the interaction between humans and systems elements, as investigated by human factors discipline for enhancing safety and reducing adverse incidences and human error (16–18)[9].

Qualitative studies may generate concepts or hypothesis to be further investigated through quantitative research and inform protocols, sampling strategies and measurement tools for quantitative studies. Qualitative studies may also explore explanations and reasons for results from quantitative research (19) and identify reasons other than the RMM leading to the outcomes of interest.

[9] Human factors research methods include human factors failure modes and effects analysis (FMEA), perception/cognition/action (PCA) analysis, root cause analysis (RCA) and fault tree analysis (FTA) and are frequently used to evaluate the risk of medication errors in line with the PRAC Good Practice Guide on Risk Minimisation and Prevention of Medication Errors (accessible at ema.europa.eu).

Among the various possible study designs (20), the following are well-established and particularly relevant for evaluating RMM:

- Interpretative phenomenological study: Investigates a phenomenon in the real-world context (21), e.g. the cognitive process or experience of patients and healthcare professionals with disease, medicines use and RMM, including related media behaviours, communication needs and preferences (22).
- Grounded theory study: Aims at developing concepts that are grounded in the data and subsequently formulates - through an iterative and comparative process - a well-grounded theory on a cognitive process or experience, e.g. to explore existing knowledge and beliefs in context of health communication (6,23–25).
- Mixed methods study: Combines qualitative with quantitative methods to benefit from the strengths of each, typically using multiple data sources, perspectives and data analysis methods, for example in an approach called triangulation (5–7).
- Case study: Intends to gain an in-depth understanding of a unique event in its complexity, applying qualitative, quantitative or mixed methods data and analysis, e.g. for understanding experiences of patients and healthcare professionals with RMM for a specific medicinal product, a specific RMM tool or RMM implementation in specific healthcare settings (26,27).
- Action research study: Evaluates ongoing implementation of an action in a participatory approach (6,28), e.g. the implementation of a RMM in healthcare with active research participation of patients and healthcare professionals.

Qualitative studies should be designed for rigour, and tools for assessing their quality are encouraged to be used, in order for the studies to serve as evidence for evaluation and decision-making on RMM (10,19,29,30).

XVI.Add.II.3.2. Survey methods

A survey may be conducted to evaluate dissemination of RMM tools, risk knowledge and behavioural outcomes, provided adequate survey methodology is applied.

Sampling and recruitment of survey participants should ensure that the study population is similar to and hence representative of the target population and avoid selection bias due to dissimilarity in one or several relevant aspects. For example, where marketing authorisation holders rely on prescribers to recruit patients, efforts should be made to mitigate the potential for selection bias introduced by e.g. another source for recruiting patients. Selection bias may also occur if web-based survey technology that excludes participants less familiar with internet technology is used.

Bias may be minimised by selecting the optimal sampling frame, accounting for the expected response rate, age, sex, geographical distribution, and additional characteristics of the study population, and by achieving similar response rates across diverse participants to minimise non-response bias. As response rates in health surveys are generally low, continuous sampling may be

necessary until the pre-defined sample size has been met, and additional measures that improve response rates (31) may be considered.

Bias may also be minimised by assuring that the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g. by oversampling a small but important subgroup). For example, in a physician survey, the sampling strategy should consider whether a general random sample would be sufficient, or if the sampling frame should be stratified by key characteristics such as specialty, type of practice (e.g. general practitioner, specialist or hospital care). In a patient survey, characteristics such as socio-economic status and education, medical condition(s), and chronic versus acute use of medicines should be considered for optimising the sampling frame.

The recruitment strategy should also consider that accurate and complete data collection is achieved. Efforts should be made to document the proportion of non-responders and their characteristics to evaluate potential effects on the representativeness of the sample.

Surveys often collect and analyse self-reported data, thus introducing misclassification of exposure or recall bias when participants do not remember previous events or experiences accurately or omit details. Respondents may also improve or modify an aspect of their reported behaviour in response to their awareness of being surveyed.

The data collection instrument should be designed to avoid desired-response-bias (e.g. multiple-choice response options with obvious desired response), to cover all relevant aspects of the RMM and to be able to identify different levels of risk knowledge and attitude. For data collection instruments to be considered reliable the following principles should be adhered:

- Pre-testing and validation: Testing the draft instrument in samples of participants that should be similar to the study population identifies questions that are poorly understood, ambiguous, or produce invalid responses. Pre-tests should be carried out using the same procedures that will be used when applying the data collection instrument to the study population.
- Content validity: Items or variables included in the data collection instrument should capture all aspects related to end-users' risk knowledge and attitudes relevant to the RMM. It is also important that the items or variables are clear and unambiguous and that questions pertaining directly to the implemented regulatory action are avoided (e.g. "do you know that product X is contraindicated for disease Y?") and non-leading questions are used.
- Construct validity: Items or variables in the data collection instrument should be developed in a way that they are likely to accurately measure (at different degrees) end-users' risk knowledge and attitudes relevant to the RMM.

Surveys may be analysed quantitatively including:

- Descriptive statistics, such as:
    - Response rate (i.e. proportion of participants who responded of the total number of invited participants);

- Rate of incomplete responses among responding participants;
- Pooled proportion of participants responding correctly to the questions;
- Stratification by selected characteristics such as RMM target population (e.g. healthcare professional or specialist, patient, carer), geographic region, receipt, and type of RMM;

- Comparison of responder and non-responder characteristics (if data is available);
- Comparison of responders and overall RMM target population characteristics;
- Comparison of characteristics of responders with correct and incorrect answers.

Information collected as free text may also be analysed qualitatively, e.g. using thematic content analysis techniques by identifying common recurrent themes or topics.

To obtain valid survey results, a weight may have to be attached to each respondent considering the following:

- Differences in selection, e.g. if certain subgroups were over-sampled;
- Differences in response rates between sub-groups;
- Differences of responders compared to target population (e.g. healthcare speciality, volume of prescribing);
- Clustering.

Variations among healthcare settings in Member States may pose challenges to implementing survey studies in several Member States due to time constrains for determining and complying with national ethical and data protection requirements. Therefore, early feasibility assessment is paramount in the successful implementation of a survey. National (or regional) requirements for providing incentives to survey participants also need to be accounted for.

There may be also data protection requirements when healthcare professionals are contacted based on a prescriber list of a marketing authorisation holder.

Although survey studies aimed at evaluating risk knowledge and attitudes do not attempt to collect patient health-related information, patients who complete the survey are likely to have received the medicinal product revealing their condition/disease. Therefore, unless the patient response is completely anonymous, data protection regulation applies, and informed consent must be provided.

Survey studies must follow the provisions of the legislation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, as laid down in Regulation (EU) 2016/679 (General Data Protection Regulation) and Regulation (EU) 2018/1725 of the European Parliament and of the Council and require approval(s) by the relevant body(ies) in Member States.

XVI.Add.II.3.3. Pharmacoepidemiological methods

Outcomes of RMM may investigated with non-interventional methods that measure how medicinal products are prescribed, dispensed, or used over time, by means of electronic health records, medical chart abstraction or claims data (see XVI.Add.II.2). Detecting changes in adverse reaction reporting, despite known limitations, may contribute to this investigation (see XVI.Add.II.2.7.).

Since RMM are generally implemented in the entire target population, the identification of a control group may not always be possible and the comparison against suitable reference values should be considered (see GVP Module XVI).

For marketed medicinal products, quantitative measures (see GVP Module XVI) should be estimated in the same study population before and after the RMM intervention, with pre-intervention information acting as a surrogate control (i.e. quasi-experimental designs). However, in absence of pre-intervention information (e.g. for medicinal products with RMM at the time of initial marketing authorisation), any effect of the RMM estimated at (a) time point(s) after implementation can only be evaluated against a predefined reference value (i.e. literature review, historical data, expected frequency in general population, outcome frequency in pre-authorisation clinical trials) taking into account all possible limitations (32) (see GVP Module XVI). The selection of a reference value should be justified.

Whilst appropriate to describe the population for understanding generalisability of observed outcomes, simple descriptive approaches do not determine whether statistically significant changes have occurred (3,33).

XVI.Add.II.3.3.1. Single time point cross-sectional study

The guidance on cross-sectional study designs in GVP Module VIII applies. Cross-sectional studies can only measure an association between exposure and outcome at a single point in time. Therefore, the method is commonly used to monitor indicators of RMM implementation and to complement other studies investigating e.g. patterns of medicines use.

XVI.Add.II.3.3.2. Before-after cross-sectional study

A before-after cross-sectional study is defined as an evaluation at one point in time before and one point in time after the RMM dissemination to healthcare systems (accounting for the implementation timeframe). Including a control can strengthen this design (3); however, careful consideration should be given to whether a suitable control can be identified, e.g. healthcare professionals not targeted by the RMM to control for general prescribing trends. When uncontrolled, baseline trends are ignored, potentially leading to RMM outcomes being estimated incorrectly.

When a RMM is put in place at the time of initial marketing authorisation, the comparison of an outcome frequency indicator obtained after the RMM against a predefined reference value would be acceptable (see GVP Module XVI).

XVI.Add.II.3.3.3. Before-after time series analysis

Time series analysis has commonly been used to evaluate the effectiveness of RMM and should be considered whenever feasible as one of the more robust approaches (3). A time series analysis spanning the date of RMM dissemination to healthcare systems (e.g. interrupted segmented regression analysis) accounts for secular trends and can provide statistical evidence about whether observed changes are significant.

Time series analysis is well suited to study changes in outcomes that are expected to occur relatively quickly following RMM, such as changing prescribing rates. Time series analysis can be used to estimate the immediate change in outcome after the RMM, the change in trend in the outcome over time compared to before, and the effects at specific time points following the RMM. The Cochrane Effective Practice and Organisation of Care (EPOC) Resources for Review Authors on Interrupted Time Series (ITS) Analysis[10] provides further information on the utility of time series regression (34).

Time series analysis requires that enough data points are collected before and after the RMM. The power to undertake a time series analysis depends upon the sample size, the effect size, the prevalence of exposure, the number of data points and their balance before and after the intervention time period (35). Long time periods may also be affected by changes in trends unrelated to the RMM that can violate model assumptions and introduce confounding when evaluating RMM.

Like the before-after cross-sectional design, including a control can strengthen this design by minimising potential confounding.

Factors such as autocorrelation, seasonality and non-stationarity should be checked when conducting time series analysis and may require more complicated modelling approaches if detected or considered likely to occur (36). Interventions associated with major immediate changes (e.g. product withdrawals) may be evaluated without regression modelling, but they risk producing spurious results when the changes are more subtle or multiple confounders are present (3).

Time series analysis also requires that the time point of RMM dissemination to healthcare systems (accounting for the implementation timeframe) is known prior to the analysis. When this is not the case (e.g. during a phased roll out of a regulatory action), more complex modelling techniques and data-driven time series approaches such as Joinpoint regression analysis could be considered (37). There are literature examples of time series analysis using a control (38), estimating effects twelve months after the intervention (33), dealing with autocorrelation and seasonality (39), and using Joinpoint regression (40).

[10] https://epoc.cochrane.org/

XVI.Add.II.3.3.4. Cohort study

The cohort study design may be useful to establish the base population for the conduct of drug utilisation studies to assess behavioural and health outcomes (see GVP Module XVI) or to perform aetiological studies (see GVP Module VIII).

Cohort studies are in particular suitable to examine RMM aimed at preventing adverse pregnancy outcomes (41) or other effects on health outcomes, or medicines use in populations targeted by the RMM (42). Modelling the effect of RMM on health outcomes may require more complex study designs. In aetiological studies, propensity score methodology may be used, e.g. to measure the reduction in stroke with warnings on the use of antipsychotics (43).

XVI.Add.II.4. Reporting on RMM effectiveness studies

XVI.Add.II.4.1. Study registration

All non-interventional studies evaluating the effectiveness of RMM should be *a priori* registered in the HMA-EMA Catalogue of Real-World Data Studies[11]. As for all non-interventional post-authorisation safety studies (PASS), the requirements for study reports, reporting of adverse reactions/events and data relevant to the risk-benefit balance of the studied medicinal product apply and should be reported by the organisation responsible for the conduct of the study in line with the requirements of GVP Module VIII.

XVI.Add.II.4.2. Checklist for harmonised reporting of study results

Established reporting standards such as the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement[12] may have limited effects on the reporting quality of studies evaluating RMM effectiveness (while being appropriate for other purposes). This is because these standards focus on single study designs without addressing the underlying rationale and critical factors relevant to the implementation of health interventions such as RMM in healthcare contexts. The recent Reporting Recommendations Intended for Pharmaceutical Risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE)[13], tailored to study designs frequently used for RMM evaluation (42), should be used to standardise reporting of the results of such studies. Reporting items have been derived from the RIMES-SE standard for reporting results of RMM effectiveness studies (see Table XVI.App.II.1., RIMES-SE items are marked by #), to facilitate the completion of the final report in the format described in GVP Module VIII.

[11] https://catalogues.ema.europa.eu/
[12] https://www.strobe-statement.org/
[13] https://www.equator-network.org/reporting-guidelines/the-reporting-recommendations-intended-for-pharmaceutical-risk-minimization-evaluation-studies-standards-for-reporting-of-implementation-studies-extension-rimes-se/

Table XVI.Add.II.1.: Additional reporting items for RMM effectiveness PASS

PASS report section	Additional reporting items
6. Rationale and background	Regulatory action and its implementation in terms of: - Goals and objectives of the RMM[#], in particular the intended clinical actions - Implementation timetable - Underpinning dissemination- and implementation-relevant theory(ies), model, framework or pilot work and description of the expected pathway for effectiveness of the action[#] - Target population(s) (e.g. individual recipient(s), healthcare facilities(s)) and their key characteristics (e.g. geography, disease condition, age, sex, ethnicity, socioeconomic status, personnel/medical speciality)[#] - Regulatory action/communication/RMM tool selection[#] and development, including pilot testing[#] and formative evaluation - Stakeholder engagement (e.g. of patient and healthcare professional representatives) in the development of RMM and communication[#] - Context of implementation (e.g. social, economic, healthcare, cultural issues and sensitivities, local languages, enablers and barriers that might influence implementation)[#] - Implicated healthcare facilities (e.g. number, type, and location(s))[#] - Organisations responsible for implementing the RMM along the implementation pathway[#] - Dissemination channels[#], including rationale for why specific channels were selected - Degree to which RMM were disseminated completely to all target populations and implemented as intended (degree of fidelity), and description of any adaptations reported, including at local level[#] - Outcome measurements, including for knowledge-, behaviour- and health-related outcomes, how to assess them, including data sources and the pre-determined thresholds of success[#]
11.4 Generali-sability	Discussion of whether the results demonstrate the intended effect across the target population(s) and patients[#]
12. Other information	Degree to which the regulatory action/RMM was integrated in healthcare, policy, practice and/or research implications, and likely sustainability of the effectiveness of the RMM[#] Contextual changes which may have affected effectiveness of the RMM, including any enablers and barriers of effectiveness[#] Processes incurred as a result of implementation as compared to previous usual care[#]

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