1 1 February 2021
2 EMA/419982/2019 - **Draft for public consultation**

3 Guideline on good pharmacovigilance practices (GVP)

4 Module XVI Addendum II – Methods for effectiveness evaluation

Date for coming into effect of first version	1 March 2014
Date for coming into effect of Revision 1	28 April 2014
Date for coming into effect of Revision 2	31 March 2017
Draft Revision 3* finalised by the Agency in collaboration with Member States	18 November 2020
Draft Revision 3 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	7 January 2021
Draft Revision 3 adopted by Executive Director	1 February 2021
Release for public consultation	3 February 2021
End of consultation (deadline for comments)	28 April 2021
Anticipated date for coming into effect after finalisation	Q4 2021/Q1 2022

5
6

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu.

7

8

Table of Contents

XVI.Add.II.1.Introduction 3
XVI.Add.II.2.Data collection 3
XVI.Add.II.2.1. Data sources 3
XVI.Add.II.2.1.1. Qualitative research 3
XVI.Add.II.2.1.2. Surveys 4
XVI.Add.II.2.1.3. Registries 4
XVI.Add.II.2.1.4. Medical records 5
XVI.Add.II.2.1.5. Administrative claims 5
XVI.Add.II.2.1.6. Healthcare record linkage 5
XVI.Add.II.2.1.7. Spontaneous reports of suspected adverse reactions 6
XVI.Add.II.2.2. Factors influencing the choice of data source(s) 6
XVI.Add.II.3.Research methods 7
XVI.Add.II.3.1. Qualitative methods 7
XVI.Add.II.3.2. Survey methods 8
XVI.Add.II.3.3. Methods evaluating behaviour and health outcomes 10
XVI.Add.II.3.3.1. Single time point cross-sectional study 11
XVI.Add.II.3.3.2. Before/after cross-sectional study 11
XVI.Add.II.3.3.3. Before/after time series analysis 11
XVI.Add.II.3.3.4. Cohort study 12
XVI.Add.II.3.3.5. Randomised trial 12
XVI.Add.II.4.Reporting results of effectiveness evaluation 12
XVI.Add.II.4.1. Study registration in the EU PAS Register 12
XVI.Add.II.4.2. Checklist for harmonised reporting of study results 13
References 14

XVI.Add.II.1. Introduction

This Addendum to GVP Module XVI provides additional guidance for marketing authorisation holders and competent authorities on data sources and methodologies for monitoring outcomes of risk minimisation measures (RMM) in line with the principles for RMM effectiveness evaluation laid down in GVP Module XVI. Depending on the risk minimisation objective, studies evaluating RMM effectiveness may integrate different quantitative measurements and qualitative research approaches to evaluate risk minimisation outcomes for individual tools or sets of RMM described in GVP Module XVI. Risk knowledge, behavioural changes and health outcomes may be considered, and in this respect the guidance on objectives of effectiveness evaluation in GVP Module XVI should be followed. The Addendum also provides guidance on the reporting of the results of studies evaluating the effectiveness of RMM.

The ENCePP Guide on Methodological Standards in Pharmacoepidemiology (Annex 2)[1] and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology[2] provide further methodological guidance.

XVI.Add.II.2. Data collection

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. A combination of primary and secondary data sources may be considered to evaluate effectiveness more comprehensively.

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 or administrative claims records, for secondary data analyses (1–3). Suitable electronic healthcare databases are described in the literature (4) or may be identified in the ENCePP Resource Database, which is a publicly available tool to identify registries and databases for effectiveness evaluation[3].

XVI.Add.II.2.1. Data sources

XVI.Add.II.2.1.1. 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), as they may contain information about cognitive processes and experiences of patients and healthcare professionals.

The type of documentation to use as data source for understanding perception and information needs in certain patient or healthcare professional populations will 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, or the selection of documentation is aimed at saturation of data, so that they provide for a robust understanding of the cognitive

[1] http://www.encepp.eu/standards_and_guidances/documents/GuidanceAnnex2.impact.pdf
[2] https://www.pharmacoepi.org/resources/policies/guidelines-08027/
[3] http://www.encepp.eu/encepp/resourcesDatabase.jsp

processes and experiences that are typical in the population of interest, and also cover less common views or needs of sub-populations of patients and healthcare professionals. Therefore, diverse participants should be selected for their ability to provide in-depth insights. Appropriate sampling is a key requirement to obtain relevant information and minimise bias, and to achieve study results of high quality that can provide findings that are applicable to the whole population of interest. The sampling strategy's target is relevance of the information to be collected, and various strategies can be applied: representative sampling in relation to certain criteria describing the population of interest, 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). 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 (8–10). Studies should be conducted to standards that avoid expected-response bias.

XVI.Add.II.2.1.2. 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. web panels). These may be supported by audio computer-assisted self-interviewing (A-CASI) 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 data to be collected.

For a healthcare professional survey, participants may be recruited from web panels and member lists of professional and learned societies. For patient recruitment, the relevant clinical setting and existing web-panels should be considered as well as members of patient organisations.

A survey may be conducted to evaluate dissemination of RMM tools, risk knowledge and behavioural changes provided adequate survey methodology (see XVI.Add.II.3.2.) is applied.

Important limitations to be considered are poor sampling strategies and low response rates that may introduce bias (see XVI.Add.II.3.2.). Surveys often collect and analyse self-reported data, thus introducing misclassification of exposure or the Hawthorne effect, i.e. respondents may improve or modify an aspect of their behaviour in response to their awareness of being observed.

XVI.Add.II.2.1.3. Registries

Patient registries organised systems that collect data and information on a group of people defined by a particular disease or condition, and that serve a pre-determined scientific, clinical and/or public health (policy) purpose (see EMA Guideline on Registry-based Studies[4]).

Registries play an important role for monitoring the use of medicines or health services, or medical conditions, and hence for evaluating RMM in terms of behavioural changes or health outcomes. Behaviours relevant to RMM include for example change 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

[4] https://www.ema.europa.eu

patients with rare diseases, patients that require highly specialised health 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 can hence help evaluating adherence to RMM addressing these risk factors. The financial and administrative burden and time effort for setting up tailor-made registries may limit their use solely for RMM effectiveness evaluation and give preference to acquiring access to existing registries for secondary data analysis. Important limitations to be considered are low accrual rates, data quality issues or missing data (11,12).

A registry-based evaluation of the effectiveness of RMM should follow the EMA Guideline on Registry-based Studies[4].

XVI.Add.II.2.1.4. Medical records

Electronic medical records should be considered for effectiveness evaluation of RMM to be implemented 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 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. Compared to administrative claims data, medical records do not capture whether the prescribed medicine has actually been dispensed (see XVI.Add.II.2.1.5.). A limitation is that the actual administration and use of the medicine by patients cannot be verified.

XVI.Add.II.2.1.5. Administrative claims

Administrative claims data are generated by healthcare systems for insurance purposes and cover the entire or a subset of insured patients. Claims data usually capture information from all physicians and care providers for the insured patient 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, although they cannot record whether the medicine has actually been taken, at which dose and in which way. Different reimbursement policies between countries and policy changes over time may impact the data source's suitability for evaluating the effectiveness of a RMM.

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 eligible for reimbursement and self-medication including over-the-counter (OTC) products. Furthermore, information on inpatient medication and diagnoses made in hospitals may not be available.

XVI.Add.II.2.1.6. 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 to ensure that ethical standards and personal data protection regulation are adhered to.

XVI.Add.II.2.1.7. Spontaneous reports of suspected adverse reactions

Interpreting data from spontaneous reporting of suspected adverse reactions for the purpose of RMM effectiveness evaluation needs to take into account *i)* general underreporting of adverse reactions; *ii)* increased risk awareness due to the RMM possibly leading to increased reporting; *iii)* the Weber effect, which describes a frequently seen decline in reporting once an adverse reaction of a medicinal product becomes well-known; and *iv)* the lack of precise data on the exposure to medicinal products for calculating reporting prevalence. Therefore, comparing trends in spontaneous reporting of events of interest for the targeted medicinal product or product class with alternative products is not considered adequate for demonstrating that RMM has been effective. However, in specific situations, the continued spontaneous reporting of a very serious adverse reaction despite RMM may be taken as supportive evidence indicating that the RMM may not be effective in combination with evidence from non-interventional studies (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.

XVI.Add.II.2.2. Factors influencing the choice of data source(s)

The choice of data source(s) for effectiveness evaluation should be determined by the following factors:

- Scope and research question: Good understanding of eligible data sources to verify whether information answering the research question is available (e.g. secondary use of routinely collected data were not designed to answer the research question) and its strengths and limitations should be considered in the design of studies evaluating effectiveness.
- Accessibility of data sources: Access and conditions for collaboration with data source owners should be clarified.
- Information on exposure and outcome: The reliability of information on exposure and outcome in the data source under consideration should be verified.
- Availability and timeliness: Pre-existing 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 and lag times should be considered.
- 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. As the complete medical and clinical history may not be available in databases, the extent of left and/or right truncation should be considered, for example if no information is available outside of the respective insurance period in 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. In case of evaluating non-targeted effects, the study population should preferably not be limited to the population targeted by the product-specific regulatory action (see GVP Module XVI, Figure XVI.1.).

- 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, for example indication of medicines use, co-morbidities, co-medication, patient monitoring, smoking, diet, body mass index or family history of disease.

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 implementation process.

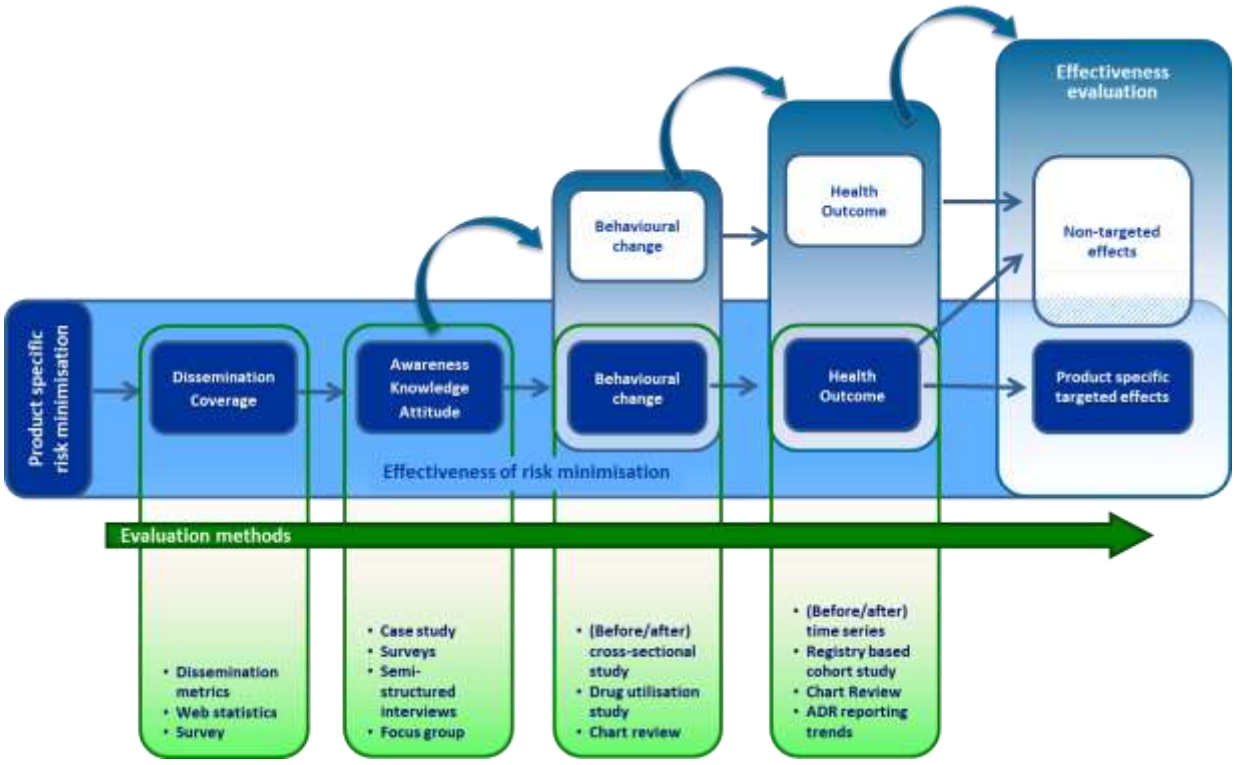

Figure XVI.Add.II.1: Overview of quantitative and qualitative methods for evaluating effectiveness of risk minimisation measures at each step of the implementation process (Note: Effectiveness evaluation includes measuring medicinal product-specific targeted effects and, as appropriate, relevant non-targeted effects associated with the use of the concerned and other medicinal products (see GVP Module XVI, Figure XVI.1.).)

XVI.Add.II.3.1. Qualitative methods

Qualitative research plays a distinctive role in evaluating healthcare interventions (13), especially on issues not yet well understood (8,9). 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. Enablers and barriers for implementing RMM in healthcare and for achieving behavioural change may be identified through qualitative research.

Qualitative studies may generate concepts or hypothesis to be further investigated through quantitative research and inform protocols for quantitative studies. Qualitative studies may also explore explanations and reasons for results from quantitative research (14) and identify reasons other than the RMM leading to the outcomes of interest.

Among the various possible study designs (15), the following are well-established and particularly relevant for evaluating RMM:

- Interpretative phenomenological study: investigates a phenomenon in the real-world context (16), e.g. the cognitive process or experience of patients and healthcare professionals with disease, medicines use and risk minimisation measures, including related media behaviours, communication needs and preferences (17);
- 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 (6,18–20);
- 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 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. of stakeholder input in a public hearing (21,22);
- Action research study: evaluates ongoing implementation of an action in a participatory approach (6,23), 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 (9,14,24,25).

XVI.Add.II.3.2. Survey methods

The design and conduct of a survey study should be considered carefully with a view to minimise potential bias and optimise the generalisability of the results in the target population (see ENCePP Guide on Methodological Standards in Pharmacoepidemiology[5]).

Sampling and recruitment of survey participants should ensure that the study population is similar 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 applicants/holders rely on prescribing physicians to recruit patients, effort should be made to mitigate the potential for selection bias.

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 avoid non-response bias. 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

[5] http://www.encepp.eu/standards_and_guidances/documents/GuideMethodRev8.pdf

education, medical condition(s), chronic versus acute medicines use should be considered for optimising the sampling frame.

The recruitment strategy should also account for chances of achieving accurate and complete data collection. Efforts should be made to document the proportion of non-responders and their characteristics to evaluate potential effects on the representativeness of the sample.

The data collection instrument should be designed so that it avoids desired-response-bias (e.g. obvious multiple-choice response), covers all relevant aspects of the RMM and is able to identify different levels of risk knowledge and attitude. For a data collection instrument to be considered reliable the following principles should be adhered:

- Pre-testing and validation: Testing the draft instrument on samples of subjects should be similar to the study population to identify 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 in the data collection instrument should capture all aspects related to end-users' risk knowledge and attitudes on the RMM tool. It is also important that the items or variables included in the data collection instrument 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?").
- Construct validity: Items or variables in the 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 on the RMM tool.

The following analytical elements should be considered for quantitative surveys exploring risk knowledge:

- 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 proposed questions;
  - Stratification by selected characteristics such as target population (e.g. healthcare professional or specialist, patient, caregiver), geographic region, receipt and type of RMM tool;
- Comparison of responder and non-responder characteristics (if data is available);
- Comparison of responders and overall target population characteristics;
- Comparison of characteristics of responders with correct and incorrect answers.

In order 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. speciality, volume of prescribing);
- Clustering.

Ethical and data privacy requirements in Member States need to be followed. 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 requirements. Therefore, early feasibility assessment is a key step 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 privacy considerations when healthcare professionals are contacted based on a prescriber list of a marketing authorisation applicant/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 the condition/disease they suffer from. Therefore, unless the patient response is completely anonymous, regulations to protect patient health information apply and informed consent must be provided.

Survey studies need to follow the provisions of the legislation on the protection of individuals with regard to the processing of personal data and on free movement of such data, as laid down in Directive 95/46/EC and Regulation (EC) No 45/2001 of the European Parliament and of the Council, and require approval (s) by the relevant body(ies), in Member States including ethical approval.

XVI.Add.II.3.3. Methods evaluating behaviour and health outcomes

Outcomes of risk minimisation may be monitored and evaluated 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.2.1.). Detecting changes in adverse reaction reporting, despite known limitations, may contribute to this monitoring (see XVI.Add.II.2.1.7.). Outcomes of interest and evaluation objectives (see GVP Module XVI) may not be limited to the medicinal product or product class targeted by the regulatory action (see Figure XVI.Add.II.1.).

Where feasible, a control group unexposed to the RMM should be included to ascertain if the observed outcome is attributable to the RMM intervention or to the presence of external factors (e.g. secular trends). 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 can be only estimated against a predefined reference value (i.e. literature review, historical data, expected frequency in general population, outcome frequency in the pre-authorisation clinical trials) taking into account all possible limitations (26) (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 (3,27).

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 temporal associations at a single point in time. Therefore, the method is commonly used to monitor indicators of RMM implementation and to complement other studies on 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 date of the RMM intervention (accounting for the implementation timeframe). When uncontrolled, baseline trends are ignored, potentially leading to RMM outcomes being estimated incorrectly. Including a control can strengthen this design (3). Careful consideration should be given to whether a suitable control can be identified, for example healthcare professionals not targeted by the RMM to control for general prescribing trends.

When RMM is put in place at the time of initial marketing authorisation, the comparison of an outcome frequency indicator obtained post-RMM intervention 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 regulatory actions and should be considered whenever feasible as one of the more robust approaches (3). A time series analysis spanning the date of a regulatory action (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 a regulatory action, such as prescribing rates. Time series analysis can be used to estimate the immediate change in outcome after the regulatory action, the change in trend in the outcome over time compared to before, and the effects at specific time points following the regulatory action. Cochrane Effective Practice and Organisation of Care (EPOC) provides further information on the utility of time series regression (28).

Time series analysis requires that enough data points are collected before and after the RMM intervention. 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 (29). 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 (30). 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 intervention (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 (e.g. Joinpoint analysis) could be considered (31). There are literature examples of time series analysis using a control (32), estimating effects 12 months after the regulatory action (27), dealing with autocorrelation and seasonality (33), and using Joinpoint regression (34).

XVI.Add.II.3.3.4. Cohort study

The cohort study design as defined in GVP Module VIII may be useful to establish the base population for the conduct of drug utilisation studies to assess behavioural changes and health outcomes (see GVP Module XVI) or to perform aetiological studies (see GVP Module VIII). Modelling the effect of regulatory actions on health outcomes may require more complex study designs.

Cohort studies are in particular suitable to examine pregnancy prevention programmes (35), medicines use in RMM targeted populations (36) and effects on health outcomes.

In aetiological studies, propensity score methodology may be used, e.g. to measure the reduction in stroke with warnings on the use of antipsychotics (37).

XVI.Add.II.3.3.5. Randomised trial

A randomised trial may be suitable to evaluate the effectiveness of components of regulatory actions, in particular safety information and dissemination channels. Test groups should be representative of the target population. Stepped wedge cluster trial designs may be considered for a phased role out of the intervention (38). Only a few examples of effectiveness evaluation with this study design exist in line with GVP Module VIII (3).

XVI.Add.II.4. Reporting results of effectiveness evaluation

XVI.Add.II.4.1. Study registration in the EU PAS Register

All non-interventional studies evaluating the effectiveness of RMM should be *a priori* registered in the EU PAS Register[6]. 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.

[6] http://www.encepp.eu/encepp/studiesDatabase.jsp

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

Established reporting standards such as STROBE[7] may have limited effects on the reporting quality of studies evaluating RMM effectiveness. This is because these standards focus on single study designs without addressing the underlying rationale and critical factors relevant to the implementation of RMM in real-world healthcare. A checklist entitled "Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies" (i.e. the "RIMES Statement"), tailored to the study designs frequently used for risk minimisation evaluation (39), can be used to standardise and improve the reporting from such studies. Reporting items have been derived from the RIMES Statement for reporting results of effectiveness studies (see Table XVI.App.II.1.), to facilitate the completion of the final report of an RMM effectiveness study in the format for PASS reports described in GVP Module VIII.

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

PASS report section	Additional reporting items
6. Rationale and background	Design of the regulatory action and its implementation in terms of: - Goals and objectives of the action; - Implementation timetable; - Underlying dissemination- and implementation-relevant theory(ies), including the expected causal pathway for effectiveness; - Targeted recipient(s), population/healthcare setting, including key characteristics (e.g. geography, disease condition, age, sex, ethnicity, socioeconomic status, medical speciality); - Regulatory action/communication/RMM tool selection and development, including pilot testing and formative evaluation; - Consideration of cultural issues and sensitivity and adaptation (e.g. local language, sociocultural values and traditions); - Stakeholder engagement (e.g. from patient and healthcare professional representatives); - Message content; - Dissemination modality, including rationale for why specific modality(ies) were selected; - Success metrics with a priori specification of measures and threshold for determination of intervention success; - Organisations responsible for implementing the regulatory action at the level of authorities and healthcare; - Selection of implementers including their qualifications and training for implementation; - Ecological context of the healthcare settings (e.g. number, type and location(s)); - Fidelity to a formal protocol for implementing the regulatory action and important intentional modifications made to regulatory action or its implementation after commencement, including at local level
11.4 Generali-sability	Discussion of whether the results demonstrate the intended effect across the targeted diverse recipient(s), population/ healthcare setting
12. Other information	Likelihood of sustainability and discussion of the degree to which the regulatory action was integrated into the delivery setting (e.g. policies or incentives put in place to support implementation maintenance)

[7] https://strobe-statement.org/index.php?id=strobe-home

References

1. Vora P, Artime E, Soriano-Gabarró M, Qizilbash N, Singh V, Asiimwe A. A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European Union electronic Register of Post-Authorization Studies. Pharmacoepidemiol Drug Saf [Internet]. 2018 Apr 16 [cited 2018 Apr 19]; Available from: http://doi.wiley.com/10.1002/pds.4434
2. Farcas A, Huruba M, Mogosan C. Study design, process and outcome indicators of post-authorization studies aimed at evaluating the effectiveness of risk minimization measures in the EU PAS Register. Br J Clin Pharmacol. 2019 Mar;85(3):476–91.
3. Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions - Systematic review and methodological considerations: Methods for measuring impact of medicines regulatory interventions. Br J Clin Pharmacol. 2018 Mar;84(3):419–33.
4. Pacurariu A, Plueschke K, McGettigan P, Morales DR, Slattery J, Vogl D, et al. Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation. BMJ Open. 2018 Sep;8(9):e023090.
5. Flick U. An Introduction to Qualitative Research. 3rd ed. London: Sage Publications Ltd.; 2006.
6. Lingard L, Albert M, Levinson W. Grounded theory, mixed methods, and action research. BMJ. 2008 Aug 7;337:a567.
7. Creswell JW, Plano Clark VL. Designing and conducting mixed methods research. 3rd ed. London: Sage Publications Ltd.; 2017.
8. Silvermann David, editor. Qualitative Research. 4th ed. London: Sage Publications Ltd.; 2016.
9. Kuper A, Lingard L, Levinson W. Critically appraising qualitative research. BMJ. 2008 Aug 7;337:a1035.
10. Campbell A, Taylor BJ, McGlade A. Research Design in Social Work: Qualitative and Quantitative Methods Transforming Social Work Practice Series. Learning Matters; 2016.
11. Bouvy JC, Blake K, Slattery J, De Bruin ML, Arlett P, Kurz X. Registries in European post-marketing surveillance: a retrospective analysis of centrally approved products, 2005-2013. Pharmacoepidemiol Drug Saf. 2017 Dec;26(12):1442–50.
12. McGettigan P, Alonso Olmo C, Plueschke K, Castillon M, Nogueras Zondag D, Bahri P, et al. Patient Registries: An Underused Resource for Medicines Evaluation: Operational proposals for increasing the use of patient registries in regulatory assessments. Drug Saf. 2019 Jul 13;
13. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015 Mar 19;350:h1258.
14. Taylor BJ, Killick C, McGlade A. Understanding & Using Research in Social Work [Internet]. 1 Oliver's Yard, 55 City Road London EC1Y 1SP: SAGE Publications, Inc.; 2015 [cited 2020 Apr 22]. Available from: http://sk.sagepub.com/books/understanding-and-using-research-in-social-work
15. Creswell JW. Qualitative Inquiry and Research Design: Choosing Among Five Approaches. 2012th ed. London: Sage Publications Ltd.; 2012.
16. Tindall L. J.A. Smith, P. Flower and M. Larkin (2009), *Interpretative Phenomenological Analysis: Theory, Method and Research*: London: Sage. Qual Res Psychol. 2009 Nov 25;6(4):346–7.
17. Bahri P, Fogd J, Morales D, Kurz X, ADVANCE consortium. Application of real-time global media monitoring and "derived questions" for enhancing communication by regulatory bodies: the case of human papillomavirus vaccines. BMC Med. 2017 02;15(1):91.
18. Charmaz Kathy. Introducing Qualitative Methods series. 2nd ed. London: Sage Publications Ltd; 2014.
19. Newman PA, Seiden DS, Roberts KJ, Kakinami L, Duan N. A small dose of HIV? HIV vaccine mental models and risk communication. Health Educ Behav Off Publ Soc Public Health Educ. 2009 Apr;36(2):321–33.
20. Omedo M, Ogutu M, Awiti A, Musuva R, Muchiri G, Montgomery SP, et al. The effect of a health communication campaign on compliance with mass drug administration for schistosomiasis control in western Kenya--the SCORE project. Am J Trop Med Hyg. 2014 Nov;91(5):982–8.
21. Yin RK. Case Study Research: Design and Methods. 5th ed. London: Sage Publications Ltd.; 2013.
22. Bahri P, Morales DR, Inoubli A, Dogné JM, Straus SMJM. Proposals for engaging patients and healthcare professionals in risk minimisation from an analysis of stakeholder input to the EU valproate assessment using the novel Analysing Stakeholder Safety Engagement Tool (ASSET). Drug Saf. 2020;(accepted).
23. Bradbury H. The SAGE Handbook of Action Research [Internet]. 1 Oliver's Yard, 55 City Road London EC1Y 1SP: SAGE Publications Ltd; 2015 [cited 2020 Apr 7]. Available from: http://methods.sagepub.com/book/the-sage-handbook-of-action-research-3e
24. Taylor BJ, Moorhead SA. The social sciences. In: In Bahri P (ed) Communicating about risks and safe use of medicines: real life and applied research. Singapore: Springer Nature; 2020.
25. Noyes J, Booth A, Cargo M, Flemming K, Harden A, Harris J, Garside R, Hannes K, Pantoja T, Thomas J. Chapter 21: Qualitative evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors) Cochrane Handbook for Systematic Reviews of Interventions version 60 (updated July 2019). Cochrane; 2019.

26. Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures: effectiveness of risk minimisation. Pharmacoepidemiol Drug Saf. 2012 Aug;21(8):896–9.

27. Weatherburn CJ, Guthrie B, Dreischulte T, Morales DR. Impact of medicines regulatory risk communications in the United Kingdom on prescribing and clinical outcomes: systematic review, time series analysis and meta-analysis. Br J Clin Pharmacol. 2019 Aug 29;

28. Cochrane Effective Practice and Organisation of Care (EPOC). Interrupted time series (ITS) analyses. EPOC Resources for review authors, 2017. [Internet]. Available from: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Resources-for-authors2017/interrupted_time_series_analyses.docx

29. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. J Clin Epidemiol. 2011 Nov;64(11):1252–61.

30. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017 01;46(1):348–55.

31. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000 Feb 15;19(3):335–51.

32. Hedenmalm K, Kurz X, Morales D. Effect of withdrawal of fusafungine from the market on prescribing of antibiotics and other alternative treatments in Germany: a pharmacovigilance impact study. Eur J Clin Pharmacol [Internet]. 2019 Mar 5 [cited 2019 Apr 24]; Available from: http://link.springer.com/10.1007/s00228-019-02650-z

33. Hernandez-Santiago V, Marwick CA, Patton A, Davey PG, Donnan PT, Guthrie B. Time series analysis of the impact of an intervention in Tayside, Scotland to reduce primary care broad-spectrum antimicrobial use. J Antimicrob Chemother. 2015 Aug;70(8):2397–404.

34. Hedenmalm K, Blake K, Donegan K, Macia M-A, Gil M, Williams J, et al. A European multicentre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children. Pharmacoepidemiol Drug Saf [Internet]. 2019 Jun 20 [cited 2019 Jul 23]; Available from: http://doi.wiley.com/10.1002/pds.4836

35. Zomerdijk IM, Ruiter R, Houweling LMA, Herings RMC, Sturkenboom MCJM, Straus SMJM, et al. Isotretinoin exposure during pregnancy: a population-based study in The Netherlands. BMJ Open. 2014 Nov 12;4(11):e005602.

36. Morales DR, Morant SV, MacDonald TM, Mackenzie IS, Doney ASF, Mitchell L, et al. Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and The Netherlands. Pharmacoepidemiol Drug Saf [Internet]. 2020 Jan 3 [cited 2020 Jan 28]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4955

37. Sultana J, Fontana A, Giorgianni F, Tillati S, Cricelli C, Pasqua A, et al. Measuring the Effectiveness of Safety Warnings on the Risk of Stroke in Older Antipsychotic Users: A Nationwide Cohort Study in Two Large Electronic Medical Records Databases in the United Kingdom and Italy. Drug Saf [Internet]. 2019 Sep 25 [cited 2019 Oct 8]; Available from: http://link.springer.com/10.1007/s40264-019-00860-z

38. Eccles M, Grimshaw J, Campbell M, Ramsay C. Research designs for studies evaluating the effectiveness of change and improvement strategies. Qual Saf Health Care. 2003 Feb;12(1):47–52.

39. Smith MY, Russell A, Bahri P, Mol PGM, Frise S, Freeman E, et al. The RIMES Statement: A Checklist to Assess the Quality of Studies Evaluating Risk Minimization Programs for Medicinal Products. Drug Saf. 2018 Apr;41(4):389–401.