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Guideline on good pharmacovigilance practices (GVP)

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

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This track-change version identifies the majority of changes introduced to the public consultation version of this document as the Agency's response to the comments received from the public consultation. This track-change version is published for transparency purposes and must not be taken or quoted as the final version.

* For this reason, the timetable above, and in particular the date of coming into effect, apply only the clean version published as final.

For the final version of this document and any future updates, please see the GVP webpage of the Agency's website.

* 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.4.2.;
- Overall revised structure.

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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 meth~~odologie~~s for monitoring outcomes of risk minimisation measures (RMM) in line with the ~~principles for~~guidance on RMM effectiveness evaluation ~~laid down~~ in GVP Module XVI. Depending on the risk minimisation objective, studies evaluating RMM effectiveness may integrate different qualitative ~~quantitative measurements~~ and quantitative ~~qualitative~~ measurements and research approaches (including mixed methods) to evaluate ~~risk minimisation~~ outcomes ~~for individual tools or sets~~ of RMM described in GVP Module XVI. ~~Measures of d~~Dissemination, r~~R~~isk knowledge, behavioural ~~changes~~ and health outcomes may be considered, and in this respect the guidance on objectives of RMM effectiveness ~~evaluation~~ studies in GVP Module XVI should be followed. The Addendum also provides guidance on the reporting of the results of RMM effectiveness studies ~~evaluating the effectiveness of RMM~~.

~~For evaluating RMM comprehensively, the effectiveness at different steps of the implementation pathways should be assessed (see GVP Module XVI), using different suitable methods and primary or secondary data sources. The evaluation should also identify if a theoretical model or framework has been underpinning the RMM design in terms of its envisaged implementation and intended behaviour change.~~

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 should be considered to evaluate effectiveness more comprehensively.~~

~~XVI.Add.II.3. 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].~~

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

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[4] 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 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 HMA-EMA Catalogue of Real-World Data Sources[5], which is a publicly available tool to identify registries and databases for effectiveness evaluation. Medical records do not usually capture whether the prescribed medicine has actually been taken, a limitation which is applicable 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.

~~XVI.Add.II.3.1.~~

~~XVI.Add.II.3.2.~~ XVI.Add.II.2.1. Data sources for qualitative research

Common data sources for qualitative research in healthcare are ~~physician and patient~~ interviews, focus group ~~questionnaire~~s and different existing types of documentations (e.g., media reports or clinical guidelines)~~., as they~~ These data sources may contain information about cognitive processes and experiences of patients and healthcare professionals that provide in-depth understanding of the ~~cause~~sreasons for RMM~~s not~~for achieving (or not) the ~~expected~~intended ~~effectiveness~~outcomes. ~~.~~

The type of documentation to use as data source for understanding perception and information needs in certain patient or healthcare professional populations ~~will~~ 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, ~~or~~ and the selection of documentation is aimed at saturation of data, ~~so that~~i.e., ~~-~~all viewpoints, ~~experiences~~experiences, and suggestions prevalent in the concerned patient or healthcare professional populations are collected and the collated data ~~y~~ provide for a robust understanding of the cognitive processes and experiences that are typical in the population of interest. ~~In addition, patient interviews shouldand~~This includes ~~also~~ covering less common views or needs of sub-populations of patients and healthcare professionals. Therefore, diverse participants should be selected ~~for their ability~~ to

[4] https://encepp.europa.eu/encepp-tools/methodological-guide_en
[5] https://catalogues.ema.europa.eu/

provide in-depth insights. Appropriate sampling is a key requirement to obtain relevant information, and to and minimisingseminimise 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 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 survey. 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. The rationale for the chosen sampling strategy should be discussed in the protocol.

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 expected 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.3.3. 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 sourceopen-source web panels applications). 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, taking into account national ethical and data privacy legislation.

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

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.

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). ~~that complement clinical outcome assessments of biomarkers, morbidity or survival data.~~

~~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. Low exposure in the period following market launch and reimbursement constraints may pose operational challenges to recruitment. Selection bias is introduced where web-based survey technology excludes participants that are less familiar with internet technology.~~

~~XVI.Add.II.3.4.~~ XVI.Add.II.2.3. Registries

~~A patient registry is an organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure. A disease registry is a patient registry whose members are defined by a particular disease or disease-related patient characteristic regardless of exposure to any medicinal product, other treatment, or particular health service ().~~

~~Registries~~ Patient or disease registries as defined in the Guideline on registry-based studies[6] play an important role for evaluating the effectiveness of RMM by monitoring the use of medicines or health services~~, or medical conditions~~, ~~and hence for~~thus ~~evaluating RMM in terms of~~collecting data relevant to determine behavioural ~~changes~~ or health outcomes. Behaviours relevant to RMM include for example changes in prescribing patterns, usage of diagnostic tests identifying risk factors for adverse reactions or ~~attending~~ providing teratogenic risk counselling. Registries may be beneficial for collecting data for specific populations such as patients with rare diseases, patients that require highly specialised healthcare interventions, or pregnant women. Some registries collect additional information, such as lifestyle factors, smoking, alcohol use, ~~nutrition~~nutrition, and weight, which may be risk factors for certain adverse reactions and ~~can hence help~~therefore useful for ~~evaluating adherence to~~ RMM effectiveness evaluation ~~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 may be preferable. Important limitations to be considered are voluntary patient enrolment which may affect~~ing~~ ~~low~~ accrual rates and introduce selection bias, data quality issues or missing data (12,13).

[6] https://www.ema.europa.eu/en/guideline-registry-based-studies ~~https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf~~

A registry-based evaluation of the effectiveness of RMM should follow the ~~EMA~~ Guideline on ~~Registry~~registry-based ~~Studies~~[4] studies[5].

~~XVI.Add.II.3.5.~~ XVI.Add.II.2.4. Medical records

Electronic medical records ~~should~~ may be considered for effectiveness evaluation of RMM ~~to be implemented~~relevant for~~in~~ ~~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 although this solicited approach may introduce different types of bias depending on the methodology. ~~Compared to administrative claims data, m~~Medical records do not capture whether the prescribed medicine has actually been taken, a limitation which is applicable to all secondary healthcare data collected for a different purpose, as ~~also~~well as for administrative claims data ~~dispensed~~ (see XVI.Add.II.2.5.). ~~A limitation is that the actual administration and use of the medicine by patients cannot be verified. which is applicable to all secondary healthcare data collected for a different purpose.~~

~~XVI.Add.II.3.6.~~ XVI.Add.II.2.5. Administrative claims

Administrative claims data are generated by healthcare systems for insurance purposes and cover the entire population ~~of~~ or a subset of insured patients. Claims data usually capture information from all healthcare professionals ~~physicians and care providers~~ for ~~the~~ 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~~, 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~~ RMM 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~~over the counter ~~(OTC) products~~. ~~Furthermore, information on inpatient medication and diagnoses made in hospitals may not be available. Another limitation is the periodicity of refresh of the data over time.~~

~~XVI.Add.II.3.7.~~ 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 ~~that~~ ethical standards and personal data protection regulation[7] are adhered to~~. A limitation are privacy restrictions in Member States that~~which may restrict record linkage.

~~XVI.Add.II.3.8.~~ XVI.Add.II.2.7. Spontaneous report~~s of suspected adverse reactions~~ing systems

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 or other sources of information (e.g., national campaign) 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 (14); and
- ~~iv)~~ the lack of precise data on the exposure to medicinal products for calculating reporting prevalence.

~~-~~Therefore, only comparing trends in spontaneous reporting of events of interest for the targeted medicinal product or product class with alternative products is not considered ~~adequate~~ sufficient for demonstrating ~~that~~ RMM ~~has been effective~~effectiveness. However, comparing ~~of~~ reporting rates of a specific adverse event over time may be useful in specific situations, and ~~the~~ continued spontaneous reporting of a very serious adverse reaction (e.g., adverse pregnancy outcome) despite RMM in combination with evidence from non-interventional studies may ~~be taken as~~provide supportive evidence indicating that the RMM may not be effective ~~in combination with evidence from non-interventional studies~~

(~~see~~see XVI.Add.II.3.3.). ~~In summary, despite mentioned limitations, mMonitoring spontaneous reporting trends over time in annual reports maybe be agreed with the regulatory authority for specific events or medicinal products e.g. when non-interventional studies cannot be conductedare not feasible.~~ 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. ~~A limitation to be accounted for is the~~The heterogeneity of ~~national~~ reporting systems in Member States, ~~e.g.~~e.g., in terms of direct patient reporting infrastructure, ~~and~~ may ~~however result in different~~influence reporting rates ~~between countries~~. ~~In summary, d~~Despite ~~mentioned~~ limitations, monitoring spontaneous reporting trends over time (e.g., in annual reports) maybe useful and can under certain circumstances be agreed with the ~~regulatory~~competent authority for specific adverse events or medicinal products e.g., in situations ~~when~~where non-interventional studies are not feasible.

[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)

~~XVI.Add.II.3.9.~~ XVI.Add.II.2.8. Factors influencing the choice of data source(s)

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

- Scope and research question: Good understanding of eligible data sources to verify whether key variables and information ~~answering~~ required to answer the research question ~~is~~ are available ~~(e.g.~~as secondary use of routinely collected healthcare data were not designed to answer the research question~~). and its~~The data source's strengths and limitations should be considered in the study 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~~ validity of information on exposure and outcome ~~in the data source under consideration~~data 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. Low exposure in the period following product~~market~~ launch in healthcare ~~and reimbursement constraints~~ may pose operational challenges to recruitment. Another limitation ~~is~~may be the periodicity of refresh of the database over time.
- 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. 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. The approach to RMM effectiveness evaluation includes ~~measuring medicinal product-specific targeted effects~~evaluating intended outcomes of RMM and, as appropriate, ~~relevant non-targeted effects~~unintended outcomes associated with the use of the concerned and other medicinal products (see GVP Module XVI, Figure XVI.~~1~~3.). ~~In case of evaluating~~Where ~~non-targeted effects~~unintended outcomes ~~of RMM (see GVP Module XVI, Figure XVI.1.)~~ are evaluated, the study population should preferably not be limited to the

population targeted by the RMM for the concerned ~~product-specific regulatory action~~medicinal product and expanded to include populations where unintended ~~effects~~outcomes ~~of regulatory actions on medicinal product use~~ (see GVP Module XVI, Table XVI.~~1~~5) ~~can~~may be expected ~~(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.

The ENCePP Guide on Methodological Standards in Pharmacoepidemiology ~~(Annex 2)~~[8] provides further guidance on assessing study feasibility.

~~XVI.Add.II.4.~~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~~pathway. Effectiveness evaluation includes measuring intended outcomes of RMM (i.e., ~~medicinal~~ product-specific targeted effects) ~~and,~~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 ~~the risk minimisation measures~~RMM under evaluation (see GVP Module XVI, Figure XVI.~~1~~3.)

~~Dissemination~~Implementation metrics are useful to determine the extent of RMM implementation as planned and depend on the nature of the intervention. Measures of ~~distribution~~dissemination and receipt of information and materials are used to ascertain delivery to and receipt by the target audience. ~~and actual receipt by the target population. Qualitative methods assess the context of RMM effectiveness and help determining enablers and barriers in terms of user acceptance and integration in healthcare systems.~~ Quantitative methods may be applied to assess the implementation and impact of RMM ~~programmes on the target population~~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~~http://www.encepp.eu/standards_and_guidances/documents/GuidanceAnnex2.impact.pdf~~

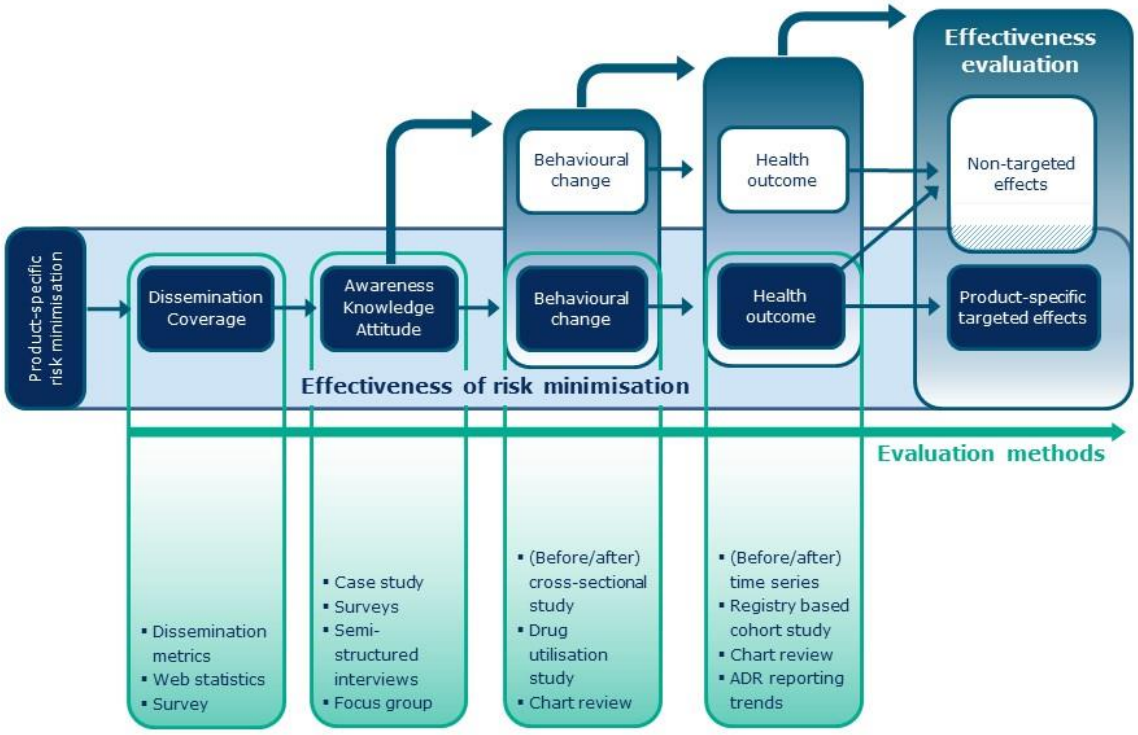

Figure XVI.Add.II.1: Approach to RMM effectiveness evaluation showing examples of quantitative and qualitative methods at each step of the implementation pathway. Medicinal product-specific targeted effects and, as appropriate, relevant non-targeted effects associated with the use of the concerned (blue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

~~XVI.Add.II.4.1.~~ 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. F~~Contextual f~~actors that may be ~~such as~~ e~~E~~nablers and barriers for implementing RMM in healthcare and ~~for~~ achieving behavioural change can~~may~~ 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)~~[Ref 1-4]~~[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 good practice guide on risk minimisation and prevention of medication errors (EMA/606103/2014)~~GPG ME II (ref).~~.

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 ~~risk minimisation measures~~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. ~~of stakeholder input in a public hearing~~ 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.4.2.~~ 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[10]).~~

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 ~~applicants/~~holders rely on ~~prescribing physicians~~prescribers to recruit patients, efforts should be made to mitigate the

~~10~~ ~~https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtmlhttp://www.encepp.eu/standards_and_guidances/documents/GuideMethodRev8.pdf~~

potential for selection bias ~~by e.g. introducing~~introduced by e.g., ~~a~~another source for recruiting ~~the~~ patients. Selection bias may also occur if web-based survey technology that excludes participants ~~that are~~ 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~~distribution, and additional characteristics of the study population, and by achieving similar response rates across diverse participants to ~~avoid~~ minimise non-response bias. ~~Insufficient numbers~~As response rates in health surveys are generally low, continuous sampling may be necessary until the pre-defined sample size has been met, and ~~of survey participants may be mitigated with the appropriate strategy, i.e., sampling is continued until the predefined sample size is met and~~ additional measures that improve response rates (31) may ~~are~~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.~~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.~~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 ~~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.

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. ~~the Hawthorne effect, i.e., R~~respondents may also improve or modify an aspect of their reported behaviour in response to their awareness of being ~~observed.~~surveyed.

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

- Pre-testing and validation: Testing the draft instrument ~~on~~ in samples of participants~~subjects~~ that should be similar to the study population ~~to~~ identifi~~es~~y 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~~cluded in~~ the data collection instrument should capture all aspects related to end-users' risk knowledge and attitudes relevant to~~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?") and non-leading questions are used.

- 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~~ relevant to the RMM ~~tool~~.

Surveys may be analysed quantitatively including~~The following analytical elements should be considered for quantitative surveys exploring risk knowledge~~:

- Descriptive statistics, such as:
  - Response rate (~~i.e.~~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 RMM target population (~~e.g.~~e.g., healthcare professional or specialist, patient, ~~caregiver~~carer), geographic region, receipt and type of RMM ~~tool~~;
- 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.

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

- Differences in selection, ~~e.g.~~e.g., if certain subgroups were over-sampled;
- Differences in response rates between sub-groups;
- Differences of responders compared to target population (~~e.g.~~e.g., healthcare 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 ethical and data protection requirements. Therefore, early feasibility assessment is ~~a key step~~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 ~~privacy considerations~~data protection requirements 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, data protection regulation ~~s to protect patient health information apply~~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~~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.4.3.~~ XVI.Add.II.3.3. Pharmacoepidemilogical ~~Methods~~ methods ~~evaluating behaviour and health outcomes~~

Outcomes of ~~risk minimisation~~RMM may ~~be monitored and evaluated~~ 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 ~~monitoring~~ investigation (see XVI.Add.II.2.7.). ~~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.).~~

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). ~~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.~~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 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 ~~the~~ 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.4.3.1.~~ 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 ~~temporal~~ association~~s~~ 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 ~~on e.g.~~e.g., investigating patterns of medicines use.

~~XVI.Add.II.4.3.2.~~ 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)~~;~~; however, c~~.~~ ~~C~~areful 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 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 ~~post~~ after the RMM ~~intervention~~ against a predefined reference value would be acceptable (see GVP Module XVI).

~~XVI.Add.II.4.3.3.~~ 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~~RMM and should be considered whenever feasible as one of the more robust approaches (3). A time series analysis spanning the date of the RMM ~~a regulatory action~~ (~~e.g.~~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~~ RMM~~regulatory action~~, such as changing prescribing rates. Time series analysis can be used to estimate the immediate change in outcome after the RMM~~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~~RMM. Cochrane Effective Practice and Organisation of Care (EPOC) 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 ~~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 (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 ~~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.~~such as Joinpoint regression analysis~~)~~ could be considered (37). There are literature examples of time series analysis using a control (38), estimating effects 12 months after the ~~regulatory action~~intervention (33), dealing with autocorrelation and seasonality (39), and using Joinpoint regression (40).

~~XVI.Add.II.4.3.4.~~ 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 RMM aimed at preventing adverse pregnancy outcomes ~~pregnancy prevention programmes~~ (41), medicines use in ~~RMM targeted~~ populations targeted by the RMM (42) and effects on health outcomes. Modelling the effect of ~~regulatory actions~~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.4.3.5. Randomised trial**~~

~~A randomised trial may be suitable to evaluate the effectiveness of components of regulatory actions, in particular presentation of 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.5.~~XVI.Add.II.4. Reporting ~~results of~~on RMM effectiveness ~~evaluation~~studies

~~XVI.Add.II.5.1.~~ XVI.Add.II.4.1. Study registration ~~in the EU PAS Register~~

All non-interventional studies ~~evaluating measuring~~evaluating the effectiveness of RMM should be *a priori* registered in the HMA-EMA Catalogue of Real-World Data Studies~~EU PAS Register~~[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.5.2.~~ XVI.Add.II.4.2. Checklist for harmonised reporting of study results

Established reporting standards such as STROBE[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 ~~real-world~~ healthcare contexts. The~~A~~ recent Reporting Recommendations Intended for Pharmaceutical Risk Minimization Evaluation Studies: Standards for Reporting of Implementation Studies Extension (RIMES-SE)[13],~~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~~RMM evaluation (44), ~~can~~ should be used to standardise ~~and improve the~~ reporting ~~from~~ of the results of such studies. Reporting items have been derived from the RIMES-SE standard ~~Statement~~ 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 ~~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 RMM effectiveness ~~study reports~~PASS

[11] https://catalogues.ema.europa.eu/~~http://www.encepp.eu/encepp/studiesDatabase.jsp~~
[12] https://www.strobe-statement.org/ ~~https://strobe-statement.org/index.php?id=strobe-home~~
[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/

PASS report section	Additional reporting items
6. Rationale and background	RDesign of the regulatory action and its implementation in terms of: - Goals and objectives of the action, of the RMM#, in particular the intended clinical actions; - Implementation timetable; - Underlying dissemination- and implementation-relevant theory(ies), model, framework or pilot work and description of the expected pathway for effectiveness of the action#including the expected causal pathway for effectiveness; - Target population(s) (e.g. individual recipient(s), healthcare facilities(s)) and their key characteristics Targeted recipient(s), population/healthcare setting, including key characteristics (e.g.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; - Consideration of cultural issues and sensitivity and adaptation (e.g.e.g., local language, sociocultural values and traditions); - Stakeholder engagement (e.g.e.g., from patient and healthcare professional representatives) in the development of RMM and communication#; Message content; - Context of implementation (e.g. social, economic, healthcare, cultural issues and sensitivities, local languages, enablers and barriers that might influence implementation)# - Dissemination channels #modality, including rationale for why specific modality(ies) 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#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.e.g., number, type and location(s)); -

PASS report section	Additional reporting items
	- ~~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 target population(s) and patients[#]~~targeted diverse recipient(s), population/ healthcare setting~~
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[#] ~~Likelihood of sustainability and discussion of the degree to which the regulatory action was integrated into the delivery setting (e.g.~~e.g., ~~policies or incentives put in place to support implementation maintenance)~~ 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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