1 1 February 2021
2 EMA/204715/2012 Rev 3* - **Draft for public consultation**

3 Guideline on good pharmacovigilance practices (GVP)

4 Module XVI – Risk minimisation measures: selection of tools and
5 effectiveness indicators (Rev 3)

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

6

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu. *We are specifically seeking comments on the need and suggestions for possibly replacing the established term 'controlled access programmes' to avoid confusion with the concepts 'access to medicines' and 'controlled substance'.*

7 *Note: Revision 3 includes the following:

8 - Changes to XVI.A. to clarify the role of risk minimisation for risk management planning and for the impact on the risk-benefit
9 balance of medicinal products, and the role of effectiveness evaluation of risk minimisation measures, and to delete/merge
10 concepts already included in other sections of the Module;
11 - Addition of XVI.B.2. to give more guidance about the criteria for applying/requesting additional risk minimisation measures;
12 - Changes to XVI.B.3.1. with a new classification for educational materials;
13 - Changes to XVI.B.3.4. regarding the concept of controlled access systems and examples illustrating the requirements;
14 - Addition of XVI.B.4. to clarify the role of risk communication, dissemination and implementation as a relevant part of any
15 additional risk minimisation activity;
16 - Changes to XVI.B.5. to give more guidance on criteria and methods for risk minimisation evaluation; emphasis has been given
17 on the concept of risk minimisation evaluation, which includes an iterative planned and prospective approach with integrated
18 measurement of different elements and regulatory follow-up;
19 - Changes to XVI.B.5.4. to give more guidance on risk minimisation evaluation parameters (e.g. implementation, behavioural
20 changes, outcomes), including suitable study designs and data collection methods;
21 - Addition of XVI.B.7. to provide recommendations on additional risk minimisation measures within the lifecycle of the product;
22 - Changes to XVI.C.3. to give more details on the role of healthcare professionals and patients and to clarify possible strategies
23 for their early engagement and role in risk minimisation development, dissemination and evaluation;
24 - Deletion of Appendix I on survey methodologies and integration of this guidance in Addendum II of this Module.

25

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

The European Medicines Agency is an agency of the European Union

Table of contents

XVI.A. Introduction

Risk management includes the identification, characterisation (including quantification), prevention and minimisation of risks. Risk management systems consist of pharmacovigilance activities and interventions relating to individual medicinal products for this purpose, including the assessment of the effectiveness of those activities and interventions, in accordance with Article 1(28b) of Directive 2001/83/EC. The objectives of risk minimisation are achieved through the implementation of risk minimisation measures (RMM) required by the competent authorities and generation of evidence that these measures are effective.

Effective RMM and the assessment of their effectiveness should be in place for medicinal products in accordance with Articles 8(3)(iaa), 21a, 101(2), 104(2), 104(3), 104a and 107h(1) of Directive 2001/83/EC, Articles 9(4), 14a, 21 and 28a of Regulation (EC) No 726/2004 and Articles 2(4b), 11(1a), 11(1e), 30, 31(1) and 34(3) of the Commission Implementing Regulation 520/2012 which specifically include provisions for monitoring the outcome of RMM for both marketing authorisation holders and competent authorities. Monitoring RMM outcomes refers to adherence to RMM by healthcare professionals and patients and achieving the objectives of RMM. Monitoring and amending RMM, if warranted, aim at ensuring that the benefits of a particular medicinal product continue to exceed the risks by the greatest achievable margin. The assessment of the effectiveness of RMM is important for risk management with an iterative process of evaluation, correction and re-evaluation of RMM, which is integral to the lifecycle benefit-risk assessment of medicinal products.

This GVP Module should be read together with GVP Module V on risk management systems as documented through risk management plans (RMPs) and on details of routine RMM, GVP Module VIII on post-authorisation safety studies (PASS), GVP Module XV on safety communication and the Addenda of this GVP Module as referenced. Marketing authorisation holders should also take into consideration specifications and any specific processes that are already in place in Member States.

XVI.B. describes criteria for selection, development, implementation and co-ordination of RMM, in particular of additional RMM, and the principles and concepts of the evaluation of RMM effectiveness. XVI.C. describes the related roles and responsibilities of marketing authorisation holders and competent authorities in the setting of the EU regulatory network. It also reflects the contribution of healthcare professional and patient representatives.

The term 'patient' in this guidance covers patients using or considering the use of a medicine, parents and other carers, and patient and consumer representatives. It also includes the (unborn) child in the case of exposure during pregnancy.

In this GVP Module, all applicable legal requirements are referenced as explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should". Directive 2001/83/EC is referenced as 'DIR', Regulation (EC) No 726/2004 as 'REG' and the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC as "IR".

XVI.B. Structures and processes

XVI.B.1. Definition and principles of risk minimisation measures

RMM are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur (see GVP Annex I). This includes preventing or reducing the occurrence of adverse reactions due to medication errors (see PRAC Good Practice Guide on Risk Minimisation and Prevention of Medication Errors[1]).

For all medicinal products, risk minimisation is generally addressed by routine RMM. These include the provision of information and recommendations in the summary of product characteristics (SmPC) and the package leaflet (PL), the labelling on the immediate or outer packaging of a medicine, pack size appropriate to the usual treatment duration and a risk-appropriate legal status of the product (e.g. prescription-only medicine) (see GVP Module V). For some important risks, however, routine RMM might not be sufficient, and it might be necessary to implement additional RMM.

The risk-benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimising benefits, both through patient selection and treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up). RMM should therefore support the optimal use of a medicinal product in clinical practice with the principal goal of providing the right medicine at the right dose and at the right time to the right patient and with the right information and monitoring.

The selection of RMM and determining whether only routine or also additional RMM are necessary should be based on the characterisation of the safety concerns in the safety specifications of the RMP (see GVP Module V). Each safety concern needs to be considered individually, and the selection of RMM should take into account the seriousness of the identified or potential risk, the severity of the adverse reaction(s), the possible impact of the risk and the RMM on the patient, the preventability and the clinical actions required to minimise the risk as well as the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety concern may be addressed by using more than one RMM, and one RMM may address more than one safety concern.

Additional RMM should be completely separated from promotional activities.

XVI.B.2. Criteria for requiring additional risk minimisation measures

Most safety concerns are sufficiently addressed by routine RMM (see GVP Module V). Careful consideration should be given to whether the risk minimisation objectives could be reached with routine measures, and only when not considered sufficient, it should be considered which additional measure(s) is (are) the most appropriate. Additional RMM should focus on important safety concerns (see GVP Annex I).

[1] Pharmacovigilance Risk Assessment Committee. Good practice guide on risk minimisation and prevention of medication errors (EMA/606103/2014). London: EMA; 18 November 2015. Accessible at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196981.pdf.

In determining whether additional RMM are needed and which measures would be most effective, marketing authorisation applicants/holders and competent authorities should:

- Consider the target population, frequency, seriousness, severity, context of use, possible impact and preventability of the risk for which the additional RMM is meant to be developed;
- Consider the need for advice to healthcare professionals for appropriate patient selection and excluding patient exposure where the use of the medicinal product is contraindicated, patient monitoring during treatment to prevent adverse reactions or early detection and management of adverse reactions;
- Assess the potential for effectiveness of the additional RMM, including the burden the RMM may impose on the system and possible unintended effects;
- Consider the intended behavioural changes of healthcare professionals and patients during each step of the treatment process; and
- Select the RMM tools that are expected to be:
  - risk-proportionate and effective in timely manner in minimising the risk;
  - practical and not too burdensome for patients or the healthcare system.

If several medicinal products, including generics, biosimilars or hybrids, containing the same active substance have been authorised, there should preferably be a consistent approach to developing and disseminating additional RMM coordinated and overseen by the competent authorities. Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination as required for the reference medicinal product (see XVI.C.1.1.1.).

XVI.B.3. Categories and tools of additional risk minimisation measures

A variety of tools are currently available for use on their own or in combined manner as additional RMM. As digital technology advances, the potential of electronic dissemination, such as through web- and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to paper-based materials.

Additional RMM can be categorised into the following categories:

- Educational materials;
- Direct healthcare professional communications (DHPCs);
- Pregnancy prevention programmes (PPPs);
- Controlled access programmes.

XVI.B.3.1. Educational materials

An educational material should have a clearly defined scope and objective and add value beyond the SmPC and PL. Although it should not be a mere repetition of the SmPC/PL content or parts of it, it should not relate to safety issues or measures that are not included in the SmPC and PL. The applicable RMM tools described below (see XVI.B.3.1.a.-f.) can be applied on their own or in combination.

Educational materials may have different target audiences, e.g. healthcare professionals or patients. They should be provided in formats and through channels ensuring that the material is readily accessible to the different sub-groups of the target population(s). Educational materials may be helpful for encouraging discussions between healthcare professionals and patients in relation to the safety concerns(s) and RMM when the objectives of RMM cannot be reached with the SmPC and PL alone.

Educational material should be adapted to the target audience. When developing educational materials, it is therefore encouraged, where possible, to engage with healthcare professionals and patient representatives and user-test proposed materials for readability, accessibility, adequacy and user-friendliness of formats (e.g. colours, font type/size) as well as of channels in the target population.

An educational material should contain the following information elements:

- Up-to-date, objective, unambiguous and clear statements summarising the nature of the safety concern(s) and the risk and outlining the specific actions to be taken by healthcare professionals or patients in order to minimise the risk and use the product safely (where warranted, information can be provided in more detail or in a different way than in the SmPC/PL e.g. by the use of tables, flow charts or illustrations);
- Guidance for the specific actions, e.g. on the prescribing, including indication/contraindication/ patient selection, treatment duration, diagnostic testing, therapeutic monitoring, product handling, preparation for administration, administration, switching to another treatment, or when to seek medical attention in the case of signs or symptoms indicating a possible adverse reaction;
- Reference to the SmPC or the PL whenever possible; in the case of digital educational materials, these could refer to the SmPC or PL through a hyperlink; and
- Statement explaining that this educational material is part of the marketing authorisation and has been approved by the respective competent authority, including the version date/number and date of approval.

Further guidance on educational materials in GVP XVI Addendum I should be followed.

XVI.B.3.1.a. Guides for patients or healthcare professionals for risk minimisation

A patient or healthcare professional guide is a tool that highlights the specific actions to take for risk minimisation (see XVI.B.1.) to healthcare professionals or patients.

Typical objectives of such guides include to:

- Enhance awareness of (a) specific risk(s) associated with a medicinal product and (possible) risk factors;
- Guide patient selection;
- Instruct on the prevention, early recognition and timely management of adverse reactions during or after the treatment, including details of enhanced monitoring requirements to aid in the early recognition of certain adverse reactions; or
- Encourage that recommendations in patient guides are discussed by the healthcare professional and the patient when handing out the guide to ensure that the risks and RMM (e.g. need for a diagnostic test, advice on how to prevent medication errors) of the medicine are understood.

Other objectives of patient guides may be:

- Ask the patient to inform the physician about the presence of any/a specific medical condition or concomitant medication before treatment with this medicinal product is initiated;
- Instruct the patient to not attempt to self-treat signs or symptoms of specific adverse reactions or stop treatment without consulting a relevant healthcare professional; or
- Provide guidance on the preparation or administration of the product where these processes are complex, e.g. in the case of patient/caregiver-administered infusions at home.

Although post-authorisation studies and registries are not considered RMM, healthcare professional guides can be useful for reminding healthcare professionals of an on-going registry/study.

In the description of the tool in the RMP, details on the format (e.g. DIN A4 size or larger), its length (e.g. a short or a comprehensive guide) should be specified.

Other terms or publication formats, such as 'brochure', 'sheet', 'patient leaflet', 'slide decks', 'posters', 'dosing guides' or 'induction graphs' should be avoided as synonyms for educational material, and only the term 'guide' should be used to ensure consistency and clarity of the requirements and application of RMM in practice. It is preferable not to add qualifiers to describe the content (e.g. 'administration guide').

XVI.B.3.1.b. Healthcare professional checklists for risk minimisation

A healthcare professional checklist is a tool that lists actions aiming to support the prescriber or dispenser to check and record the presence or absence of certain clinical circumstances for risk minimisation. It is to be considered in situations where the safe and effective use of a medicinal product involves complex approaches and decision-making regarding the diagnosis, treatment, prescribing or dispensing, or when the treatment carries a high risk of medication errors.

In contrast to guides (see XVI.B.3.1.a.), a checklist is presented as a series of questions which can generally be answered in a 'yes'/'no'/'not applicable' manner or with a very short answer.

Typical objectives of checklists include to:

- Facilitate determining whether the medicinal product is appropriate for a given patient before or during treatment, e.g. by checking for contraindications, recommendations of use, warnings, concomitant medicine(s) or certain test parameters;
- Ensure any necessary vaccinations before treatment start;
- Exclude pregnancy before/during treatment, record pregnancy testing results, support counselling on the need to avoid pregnancy and therefore use of contraception and support advice in the case of becoming pregnant during treatment;
- Inform about the risk of medication errors and how to avoid them, e.g. by paying attention to selecting the right formulation, checking the strength or dosing against the indication or advising the patient regarding the potential of medication errors;
- Assist in determining the correct amount of product that can be prescribed or dispensed;
- Remind the healthcare professional of the need to monitor the patient for specific signs and symptoms, including specific abnormal laboratory findings, in order to identify adverse reactions early;
- Prompt the healthcare professional to inform the patient about the importance of returning unused product and not sharing the medicine with others, especially for medicines with high risks for other persons or the environment;
- Prompt informing the patient about the importance of not donating blood while taking the medicine; or
- Inform about the need to apply risk awareness forms (see XVI.B.3.1.c.).

XVI.B.3.1.c. Risk awareness forms

A risk awareness form is a tool that informs primarily patients, but also physicians, on (a) certain risk(s) of a medicinal product and the need for risk minimisation. It is also meant to support documenting that the patient has been made aware of the risk(s) during a discussion with a physician and understands the risk and actions to take. It is to be considered in situations where this is essential for using the product. The patient is meant to receive a paper version (or a printout of an electronic version of the form) from the physician.

Typical objectives of such forms include to:

- Create awareness of specific serious risks e.g. raise awareness about high teratogenicity before and also during treatment, i.e. at the time of repeated prescriptions;
- Reinforce guides for patients and healthcare professionals (see XVI.B.3.1.a.) regarding specific serious risks to further support that the information on risk minimisation in the guide will be read by the patient and be discussed between the patient and physician; or
- Reinforce healthcare professional checklists (see XVI.B.3.1.c.) regarding specific serious risks through documenting that the actions provided in a checklist have been fulfilled and discussed with the patient.

Given these objectives, this tool is likely to be applicable only for very particular risks.

When in a specific local setting formal documentation of the delivery of information for risk awareness to the patient is required at national level, this can take several forms depending on the healthcare system, ranging from a paper or electronic entry in the patient's medical record to using an electronic or paper risk awareness form with a field for the date when the discussion between the patient and physician took place and e.g. a checkbox for confirmation, or, if required nationally, a signature. The form should be provided by the marketing authorisation holder in formats that are adapted to fulfilling documentation purposes in the record management systems of given healthcare systems, as agreed with the competent authorities.

Risk awareness forms should clearly state that the patient does not waive any rights by acknowledging the risks. For clarity, risk awareness forms do not transfer the physician's responsibilities when treating a patient to the patient nor do they impact on the patient's rights in relation to the marketing authorisation holder's and healthcare professional's liability.

Depending on the seriousness of the risk and taking into account the need for treatment and typical changes in the patient's situation (e.g. change in the medical condition, risk factors, personal situations such as the wish for a child), it could be useful to consider the need for additional follow-up risk awareness forms aiming to renew risk awareness of the patient during treatment adapted to typical patient situations.

XVI.B.3.1.d. Demonstration kits

A demonstration kit is a tool that trains healthcare professionals or supports healthcare professionals in training the patient for administering the medicinal product safely. It is to be considered in situations where the administration procedure is complex.

In addition to written or visual material, such kits may contain demonstration objects, such as dummy or demonstrator injectors or inhalers. Demonstration objects should not contain the active ingredient and be clearly marked with "For demonstration purposes only".

These demonstration kits would typically be supplemented with other aRMM, e.g. guides (see XVI.B.3.1.a.).

Any concern arising from the use of such demonstration kit or indicative of the potential for medication errors when using the medicinal product in real healthcare should be reported to the marketing authorisation holder and, as applicable, to the competent authorities. The marketing authorisation holder should include reporting advice to healthcare professionals and patients in the instructions of the demonstration kits, investigate such reports and notify the competent authorities of any action needed to improve the demonstration kit, the device or product information of the actual medicinal product, and initiate the necessary actions.

XVI.B.3.1.e. Patient diaries for risk minimisation

A patient diary for risk minimisation is a tool that supports the patient in recording specific information on the treatment with the medicinal product. It is to be considered in situations where it is essential

that such updated information is regularly exchanged between the patient and the healthcare professional.

Typical objectives of such diaries include to:

- Record dates of administration or dose to avoid medication errors, e.g. in the case of different daily or interval dosing when using the medicinal product in different indications;
- Record dates or outcomes of health monitoring and diagnostic tests at home needed to identify risk factors or signs and symptoms of adverse reactions during continuous treatment to facilitate monitoring of the patient (e.g. monitoring of blood pressure when taking a medicine with a cardiac risk); or
- Record signs and symptoms indicating a possible adverse reaction, in particular during dose adjustments.

Recording of information for risk minimisation purposes can also occur as part of applying other additional RMM tools, e.g. patients may be asked to record vaccination status, diagnostic test results or dates of product administration on a diary form inside a guide (see XVI.B.3.1.a.) instead of providing it in a stand-alone diary.

Patient diaries for risk minimisation are not primarily meant to be used as a data collection tool by marketing authorisation holders for e.g. PASS. However, information for healthcare professionals regarding a patient diary should remind a healthcare professional who suspects an adverse reaction on the basis of the patient's entries in the diary to report this by using the usual spontaneous reporting systems.

It is to be noted that other patient diaries exist for recording information unrelated to risk minimisation but useful for monitoring the efficacy of the product in an individual patient, changes in the patient's physiology (e.g. blood pressure, menstrual cycle), or changes in the patient's lifestyle. However, those patient diaries are not categorised as educational material for risk minimisation and should not be proposed as part of the RMP.

XVI.B.3.1.f. Patient cards

A patient card is a tool that reminds the patient of (a) certain action(s) to take for risk minimisation or aims to ensure that information regarding the patient's current treatment with the medicinal product and its risks is held by the patient at all times and used as a communication aid with healthcare professionals. It is to be considered in situations where it is essential for risk minimisation that this information is always readily available to the patient and healthcare professionals.

Objectives of patient cards include to:

- Remind patients of specific risks and their RMM during treatment, including, if applicable, the need to inform healthcare professionals of this medicine use;
- Alert healthcare professionals that the patient is taking a certain medicine, in particular, those who have not prescribed the product but provide other care to the patient, including emergency care;

- Facilitate that the healthcare professional informs the patient about the risk and the actions to be taken for risk minimisation at the intended point of care, i.e. during prescribing or dispensing; or
- Provide contact details of the prescribing physician.

Independently of the objective of a given patient card, other terms, such as 'alert card' or 'reminder card', should not be used as synonyms for patient card, and only the term 'patient card' should be used to ensure consistency and clarity of the requirements and application of RMM in practice.

The content of messages in patient cards may for example cover that:

- The medicinal product is (potentially) teratogenic and requires use of effective contraception;
- Blood donations by the patient are forbidden during treatment and until a certain period has passed after treatment;
- Certain signs or symptoms of the adverse reaction require the patient to seek (urgent) medical care;
- The treating physician needs to be informed of this medication when prescribing other medicines or planning surgeries;
- The device of the medicinal product, e.g. an intrauterine device, should be removed at a specified date;
- Regular monitoring or diagnostic testing is required at specified dates (future medical appointments);
- There is potential for clinically significant interactions with other therapies and that concomitant treatment with those should be avoided;
- The patient on this medicinal product requires additional medication, precautions or other medical procedures to enable necessary surgery or other medical interventions;
- There is the need to avoid vaccination with live attenuated vaccines during treatment;
- It is recommended to read the PL.

Patient cards should be designed so they can be:

- Carried by patients easily, therefore their size should fit inside a wallet or a pocket and ideally have the size of a credit card (if more space is required for content or multilingual requirements, folds can be used; however, for simplicity, as few folds as possible should be used);
- Read and understood easily, therefore, the information provided in the patient card should be focused and concise, kept to the minimum necessary to convey the key message(s); and
- Used over a long time, therefore their material should be of sufficient durability to sustain considerable wear and tear, e.g. be laminated and not be a cut-out or tear-off paper sheet as part of the PL.

To respect the limitation in space and the risk minimisation purpose of the card, it is recommended to not include in a patient card information on how to report adverse reactions or the black triangle if

applicable to the product (see GVP Module X) (this is considered an exception to the guidance on the black triangle and explanatory statements provided in the GVP XVI - Addendum I and in GVP Module X and this does not affect the obligation to include the relevant text about additional monitoring in other documents such as the SmPC and the PL).

Patient cards should not be presented to patients as a substitute or a small version of the PL or of other educational materials, should they be required for a given medicinal product.

Applicants/marketing authorisation holders should submit a proposal during initial evaluation for how the patient card will be risk-proportionately disseminated for agreement by the competent authorities; i.e. whether the card will be distributed inside/affixed to the packaging or outside of the packaging box. Marketing authorisation holders should ensure that patient cards are always available to healthcare professionals when handing over the card to the patient at the applicable point of care (e.g. prescribing or dispensing the medicine). Possible dissemination paths include:

- Patient card inside or affixed to the outer packaging:

  Patient cards placed inside or affixed to one of the sides of the outer packaging (e.g. patient card attached to the outer packaging as a flap side with a tear-off section) are considered part of the product labelling (see XVI.C.1.1.2.). Marketing authorisation holders should ensure that no information on the outer packaging is covered by an affixed patient card. A patient card inside the outer packaging or affixed to the outer packaging ensures that the patient always receives a new patient card with every new package and facilitates the information exchange between the patient and a healthcare professional at the time of dispensing. In addition, it will minimise the burden for the healthcare professional in terms of maintaining a stock of stand-alone patient cards.

  It should however be taken into consideration that the medicine packaging may not reach the patient. If so, further measures need to be taken to ensure that the patient receives the patient card, e.g. in the cases where a medicinal product is administered in hospital settings or in emergency care, or where medicines are repacked at the pharmacy for weekly medication schedules of individual patients.

  In the case where the patient card becomes a new requirement in the post-authorisation phase, the marketing authorisation holder may need to take interim measures until the new packages with the patient card are distributed or to allow for dispensing existing pharmacy stock of the medicinal product.

- Stand-alone patient card (separated from the outer or inside packaging):

  If patient cards are provided separately from the packaging, marketing authorisation holders should ensure regular dissemination of a sufficient number of patient cards to healthcare professionals and easy access for healthcare professionals to new stock. In addition, it is recommended to provide healthcare professionals with access to an online request service for additional patient cards and also to online versions of patient cards. Stand-alone patient cards can also facilitate a discussion between the patient and the prescriber independently from the dispensing process of the package.

Whenever more than one medicinal product contains the same active substance and the same messages of the patient card apply to all these products, it is recommended that marketing authorisation holders collaborate on designing and disseminating a single patient card referring only to the name of active substance, and not to any invented name of a medicinal product.

XVI.B.3.2. Direct healthcare professional communications

A direct healthcare professional communication (DHPC) is a safety communication tool (see GVP Annex I) that may also serve as an additional RMM. It is to be considered in situations where it is deemed important that all relevant healthcare professionals in the given jurisdiction are timely informed of a risk and actions to take for risk minimisation. Guidance on DHPCs in GVP Module XV should be followed, and the DHPC and DHPC communication plan templates (see GVP Annex II) should be used.

XVI.B.3.3. Pregnancy prevention programmes

A pregnancy prevention programme (PPP) is a set of tools that aims at minimising exposure to a medicinal product during pregnancy. It is to be considered in situations where the product has teratogenic effects.

The typical objectives of a PPP are to:

- Avoid that female patients are pregnant when starting the treatment; and
- Avoid that female patients become pregnant during and, if relevant, for a specific period after stopping treatment;
- Avoid, if applicable, that a male patient father a child during and, if relevant, for a specified period after stopping treatment.

A PPP combines the use of different RMM tools and the following should be considered for the development of a PPP:

- Educational material tools (see XVI.B.3.1.) to inform healthcare professionals and patients about the teratogenic risk and the required actions to minimise this risk (e.g. guidance on the need to use appropriate contraception, on the time period during which pregnancy is to be avoided after stopping the treatment);
- Controlled access tools (see XVI.B.3.4.) to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescribing or dispensing of the medicinal product;
- Restriction of amount to be prescribed in a single prescription, often to a maximum supply of 30 days; and
- Counselling in the event of the wish for a child, an unplanned pregnancy or evaluation of an adverse pregnancy outcome.

For assessing the effectiveness of a PPP, organising data collection by means of specific forms for reporting a pregnancy, should it occur, may be part of a PPP.

XVI.B.3.4. Controlled access programmes

A controlled access programme is a tool or set of tools that seeks to control access to a medicinal product beyond the level of control applied to medicinal products by means of routine RMM (see XVI.A.). It may restrict the time period of validity of a prescription[2] or the maximum amount to be prescribed in a single prescription, or require a visual reminder[3] as part of the labelling of the outer packaging. Controlled access programmes should be considered and applied only in exceptional situations of an important safety concern with a severe impact on the patient or the (unborn) child exposed in utero, or a significant public health impact, taking into account the nature of the risk and the likelihood that this risk cannot be managed by other RMM.

Such programmes should be adapted to local healthcare settings in agreements with competent authorities.

Tools for controlled access, which can be applied on their own or in combination, include the following:

XVI.B.3.4.a. Controlled prescription and supply systems

A controlled prescription and supply system is a tool that consists of a set of measures ensuring that the distribution of a medicinal product is tracked up to the prescription or dispensing of the product.

Tracking orders and shipments of product from all identified distribution points facilitate traceability of the product. This tool could also be considered for products controlled under the respective national legislations to prevent misuse and abuse of medicines. For products that need to be prepared for a specific patient (i.e. advanced therapy medicinal products (ATMPs)), further RMM may be needed for ensuring an adequate distribution, storage, preparation, handling and use of the product.

XVI.B.3.4.b. Centre accreditation systems

A centre accreditation system is a tool to ensure that a medicinal product is only supplied to healthcare centres with necessary equipment and healthcare professionals specifically trained to administer the product.

This may be required in specific situations such as for ATMPs or complex administration procedures. Centre accreditation should be organised according to nationally established procedures applicable and be complemented with adequate training of healthcare professionals as agreed with the competent authorities.

XVI.B.3.4.c. Forms for patient information exchange between prescriber and dispenser

Different tools are available to ensure that the pharmacist is informed about legally required test results before the product is dispensed, e.g. pregnancy test. This information exchange can take place

[2] Some medicines might require immediate dispensing as soon as prescribed. In those cases, the applicants should agree with the competent authorities on how best to achieve this objective.
[3] Visual reminders aim to highlight important information either in the packaging or the PL. These can take many forms depending on the local specifications. For example, some visual reminders can be presented as pictograms, whereas others can be presented as boxed warnings and use different colours to highlight information.

via paper forms, connected electronic systems or personal confirmation (e.g. dispensing forms, see XVI.B.3.4.d.).

XVI.B.3.4.d. Dispensing forms

A dispensing form is a tool that supports risk minimisation during dispensing. It is to be considered in situations where it is intended to e.g. manage dispensing complex medicines, those requiring certain monitoring or testing within limited time before dispensing or those that require that certain information is transmitted from one healthcare professional to another.

Agreement with the competent authority at national level is required.

XVI.B.4. Dissemination plans

Marketing authorisation holders should submit plans for the dissemination of RMM to healthcare professionals and patients for agreement by competent authorities. The plans should list the RMM tools (see XVI.B.3.), the target audiences, the audience-tailored formats and contents, the dissemination channels (e.g. paper, printable documents, audio, video, web-based, training programmes), use of electronic features (e.g. QR codes, hyperlinks or references), targeted outcomes, timeframes of (re)dissemination for ensuring continuous availability of materials, and supportive communication interventions strategies (e.g. through learned societies or patient organisations).

The timeframes for dissemination should consider the needed sustainability of RMM effectiveness over time, both within healthcare professional communities and for individual healthcare professionals and patients. In the case of long-term treatment, periodically repeated delivery of educational materials to a patient may be necessary. Periodic provision of the materials locally is systemically considered at competent authority level at time of implementation. The knowledge adoption and behavioural change of healthcare professional may require repeated RMM interventions in various formats.

For the content and format of dissemination plans, the DHPC communication plan template (see GVP Annex II) may be applicable for the planning of the dissemination of the RMM and supportive communication interventions.

Supportive information is available in the guidance on safety communication (see GVP Module XV).

XVI.B.5. Effectiveness evaluation of risk minimisation measures

XVI.B.5.1. Principles for effectiveness evaluation

Marketing authorisation holders shall monitor the outcome of RMMs which are contained in the RMP or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a [DIR Art 104 (3) (d)]. Competent authorities shall monitor the outcome of RMM which are contained in RMPs or measures that are laid down as conditions to the marketing authorisations [DIR Art 107h (1), REG Art 28a]. Monitoring RMM outcomes is intended to evaluate the effectiveness of RMM and may include both routine (see XVI.B.1.) and additional RMM (see XVI.B.3.).

Any study measuring the effectiveness of RMM is a PASS [DIR Art 1 (15)] and the guidance for conducting a PASS in GVP Module VIII should be followed for studies evaluating the effectiveness of RMM in addition to the specific guidance in XVI.B.5.. The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed and protocols for qualitative studies be included in the pharmacovigilance plan of the RMP (see GVP Module V).

Principle 1: Focussed evaluation

Effectiveness evaluation of RMM should focus on RMM of major patient and public health importance, taking into account the nature, severity and seriousness of the risk, the magnitude of population exposure and the amount of public concern.

Principle 2: Regular evaluation

Details of how RMM effectiveness will be measured at regular timepoints should be included in the pharmacovigilance plan of the RMP (see GVP Module V). Several factors will determine the appropriate timepoints, including time since launch or implementation of the RMM, estimated magnitude of exposure, severity and seriousness of the risk(s) and the design of the proposed studies evaluating RMM effectiveness. The following timepoints should generally be considered by marketing authorisation applicants/holders for setting timetables:

- After initial implementation of a risk minimisation programme (e.g. within 12-18 months), in order to allow the possibility of necessary amendments;
- Within 3 years of initial implementation of a risk minimisation programme to potentially add further elements to the risk minimisation programme (see XVI.B.5.3.); and
- Within 5 years to assess the overall effectiveness of the risk minimisation programme (see XVI.B.5.3.) or in time for the evaluation of the renewal of a marketing authorisation;

Principle 3: Evaluation of intended and unintended outcomes

RMM objectives should be defined in relation to the targeted dissemination of the RMM as well as targeted changes in knowledge and behaviours or the safe use of medicines by patients, healthcare professionals and organisations providing healthcare. These objectives correspond with the intended outcomes of the RMM and should guide defining the outcomes to be investigated in the evaluation.

As outcomes with a wider impact may occur and unintended consequences may counteract the effectiveness of RMMs, other outcomes of RMM may be investigated where appropriate or upon request of the competent authority (see Table XVI.1.). Unintended outcomes include, for example, undue burden of RMMs on the patient, healthcare professional or healthcare system; decreased prescribing or discontinuation of the medicinal product in patients where the risk-benefit balance remains positive or lack of adherence to prescribed treatment e.g. following risk perceptions amplified by the RMM; switching to another medicinal product with less favourable risk-benefit balance; and spill-over effects due to changes in behaviours beyond the RMM objectives.

559 **Table XVI.1.: Effects of regulatory actions on medicinal product use**

	Intended	Unintended
Switching	RMM recommends that patients are switched to alternative therapy	Patients are switched to a treatment that has a less favourable safety profile
Spill-over effect	RMM recommends that the treatment is no longer used in a certain patient population and patients are switched to alternative therapy	Treatment is withheld in a patient population that is not targeted by the RMM and where the treatment can be used
Non-treatment	RMM no longer recommends the use of a medicine in indications where the therapeutic benefit is no longer considered to outweigh the risks	No alternative medicine is used in some patients of the target population to treat the condition even though alternatives are available
Lack of adherence	N/A	RMM is not adhered to in the target population
Additional prescribing	RMM recommends the use of a medicine in the target population in combination with another therapy (e.g. as preventive measure)	RMM no longer recommends the use of a medicine in the target population, but treatment is continued in combination with another medicine (e.g. to treat adverse reactions) and the recommendation is not adhered to

560

561 RMM effectiveness evaluation should consider that simultaneous events such as changes in clinical
562 guidelines, reimbursement policies, and media attention may influence the outcome of a regulatory
563 action and make establishing a causal relationship between a regulatory action and its outcomes
564 challenging.

565 ## XVI.B.5.2. Objectives and approaches to effectiveness evaluation

566 In accordance with the principles in XVI.B.5.1. the objectives of effectiveness evaluation are to
567 investigate:

568 - To what extent the RMM has been delivered to the target audience as planned;
569 - If the RMM has led to the intended knowledge and behavioural changes in the target audience, or
570 whether other knowledge and behaviour related outcomes have occurred; and
571 - To what extent the RMM objectives have been met in terms of improved population health within
572 relevant timeframes, or whether other health outcomes have occurred.

573 Different approaches to data collection and analysis as appropriate may be applied for each step of the
574 RMM implementation process (see Figure XVI.1.). Measurements and indicators of RMM effectiveness
575 should be defined as part of the study protocol.

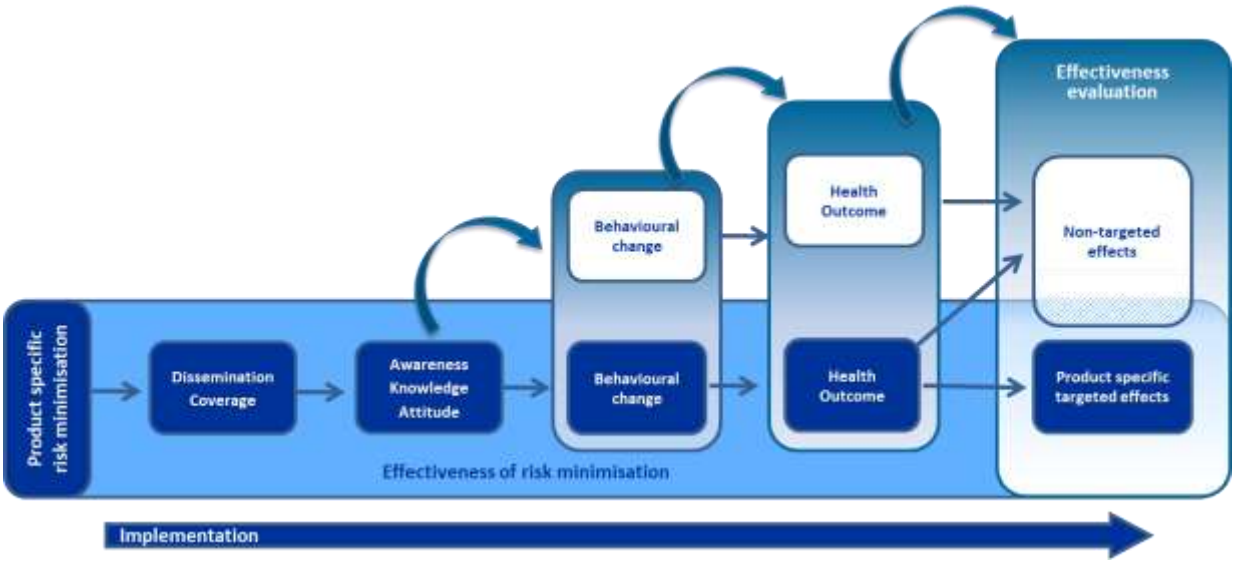

Figure XVI.1.: The approach to effectiveness evaluation of risk minimisation includes measuring medicinal *product-specific targeted effects* and, as appropriate, relevant *non-targeted effects* associated with the use of the concerned and other medicinal products

Depending on the scope of the effectiveness evaluation, a combination of research methods may be useful, and the objectives should be defined in the evaluation strategy in relation to the desired health outcomes of RMM. Marketing authorisation applicants/holders and competent authorities should agree on indicators of success to be included in the evaluation plan. Evaluating the effectiveness of RMM based on quantitative measurements (e.g. prescription or utilisation patterns, health outcomes) is considered particularly important for decision-making on RMM and should be used where feasible. Qualitative research is useful for defining the objectives of quantitative research and understanding the reasons for success or failure of a regulatory action (e.g. observed changes or lack of intended changes in knowledge or behaviours) and its findings may hence be important for considering corrective actions.

The evaluation strategy should consider which methods are proportionate and likely to provide accurate results that are meaningful for further regulatory decision-making without placing undue burden on healthcare systems or patients. The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed.

XVI.B.5.2.1. Dissemination and risk knowledge

Each stage from dissemination of information on RMM to risk knowledge should be optimised and considered during RMM development and evaluation (see Figure XVI.2.).

Dissemination methods and individual perception of RMM information influence the knowledge of risks. Quantitative measurements of the stages of the communication process may help to identify barriers to dissemination and knowledge adoption, ineffective dissemination processes and knowledge gaps. Qualitative research may help to understand factors influencing risk perception and knowledge adoption.

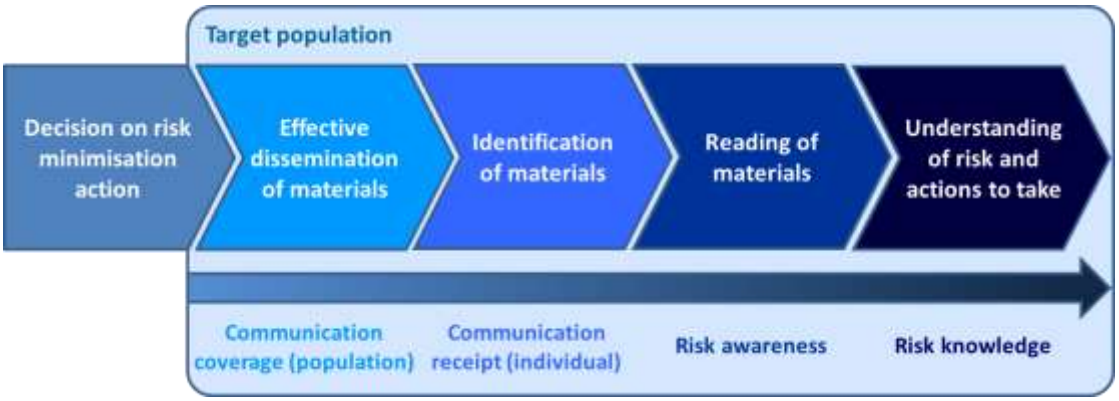

Figure XVI.2.: Pathways of the risk communication process from RMM dissemination to adoption of risk knowledge

Quantitative measurements:

Examples of quantitative measurements of dissemination and knowledge adoption are:

- Proportion of target population for which RMM tool dissemination has been completed over time (in total and e.g. by RMM tool, country or type of healthcare professional) or download total/frequency if electronic tools are provided;
- Proportion of healthcare professionals and patients aware of the RMM and using the educational tools;
- Level of comprehension, recall of information and knowledge of healthcare professionals and patients concerning the RMM tool and its contents.

Qualitative findings:

Examples of outputs of qualitative research into knowledge adoption are:

- Understanding of attitudes about the RMM in terms of e.g. perceived feasibility, acceptability, usability, opinion, motivations, confidence to apply the tool correctly (self-efficacy) and that RMM will be effective in controlling the risk;
- Identification of environmental factors of healthcare systems and patient life impacting on RMM implementation, e.g. resource issues, time constraints;
- Identification of information-related factors influencing knowledge uptake in patients and healthcare professionals, particularly prior information awareness and knowledge of the receiver and communication on the risk from other (preferred) sources.

Risk knowledge may be assessed through qualitative research methods involving case studies, semi-guided interviews and/or focus groups, or through surveys.

XVI.B.5.2.2. Behavioural changes

Based on achieving knowledge on risks and RMM in patients and healthcare professionals, RMM should be developed and evaluated with a view to achieving changes towards intended behaviours of

medicines use. Therefore, implementation of RMM in healthcare needs to be feasible and targeted healthcare professionals and patients need to engage and comply with the measures in healthcare and daily routines. Factors that may be enablers or barriers for acquired risk knowledge to result in intended behavioural changes are illustrated in Figure XVI.3.. These enablers and barriers of behavioural change may impact on the feasibility of the RMM in practice.

Quantitative measurements:

Examples of quantitative measurements of behavioural changes are:

- Proportion of patients exposed to a medicinal product in accordance with the authorised indication;
- Proportion of contraindicated patients exposed to a medicinal product;
- Proportion of patients undergoing recommended diagnostic tests (e.g. laboratory, genetic, instrumental) prior, during or after the exposure to a medicinal product;
- Proportion of co-prescribing of two interacting medicinal products;
- Proportion of potential dosing errors;
- Quantification of enablers or barriers for intended behavioural changes;
- Extent to which the user was able to perform and maintain the desired behaviour over time (e.g. prescribing according to the authorised indications or not prescribing in specific contraindications);
- Frequency of requests from healthcare professionals for refills of educational materials or other RMM tools as proxies of RMM tool utilisation.

Behavioural changes may be evaluated through prescribing-, dispensing- and other drug utilisation studies, making use of data from electronic healthcare databases or medical records and possibly applying record linkage between different medical and/or demographic data, or through surveys. Quantitative data analyses may also identify enablers or barriers for intended behavioural changes (e.g. healthcare environment factors, availability of resources and processes, access to alternative treatment, healthcare professionals' and patients' perception of a regulatory action and related attitudes).

Qualitative findings:

Examples of outputs of qualitative research into behavioral changes include the identification of enablers or barriers in relation to:

- Awareness (e.g. a new contraindication is not known by some healthcare professionals and/or patients);
- Attitude (e.g. some healthcare professionals and/or patients are not convinced that there should be a contraindication);
- Alternative treatments (e.g. despite the contraindication, some patients still need treatment);
- Difficulties in implementing RMM (e.g. due to lack of diagnostic tools).

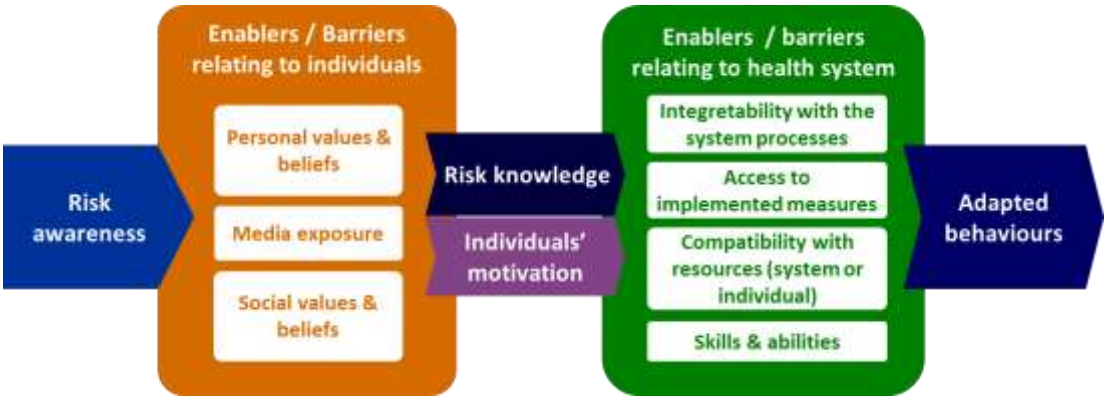

Figure XVI.3.: Pathway from risk awareness to risk minimising behaviours including enablers and barriers of behavioural change

XVI.B.5.2.3. Health outcomes

Monitoring and investigating health outcomes evaluate whether implemented RMM have improved patient and public health.

Quantitative measurements:

Examples of quantitative measurements of health outcomes are:

- Incidence rate or cumulative incidence of an adverse reaction;
- Incidence rate or cumulative incidence of health outcomes of interest, including surrogate endpoints if actual endpoints cannot be measured.

Changes in health outcomes may only be partially influenced by regulatory actions aimed at minimising risks. Other factors including changes in clinical guidelines or healthcare practices (e.g. monitoring) need to be considered. These factors should be identified and assessed where possible as part of RMM evaluations.

Figure XVI.4. provides an overview of qualitative and quantitative research outcomes that may evaluate the different stages of the implementation process of regulatory actions.

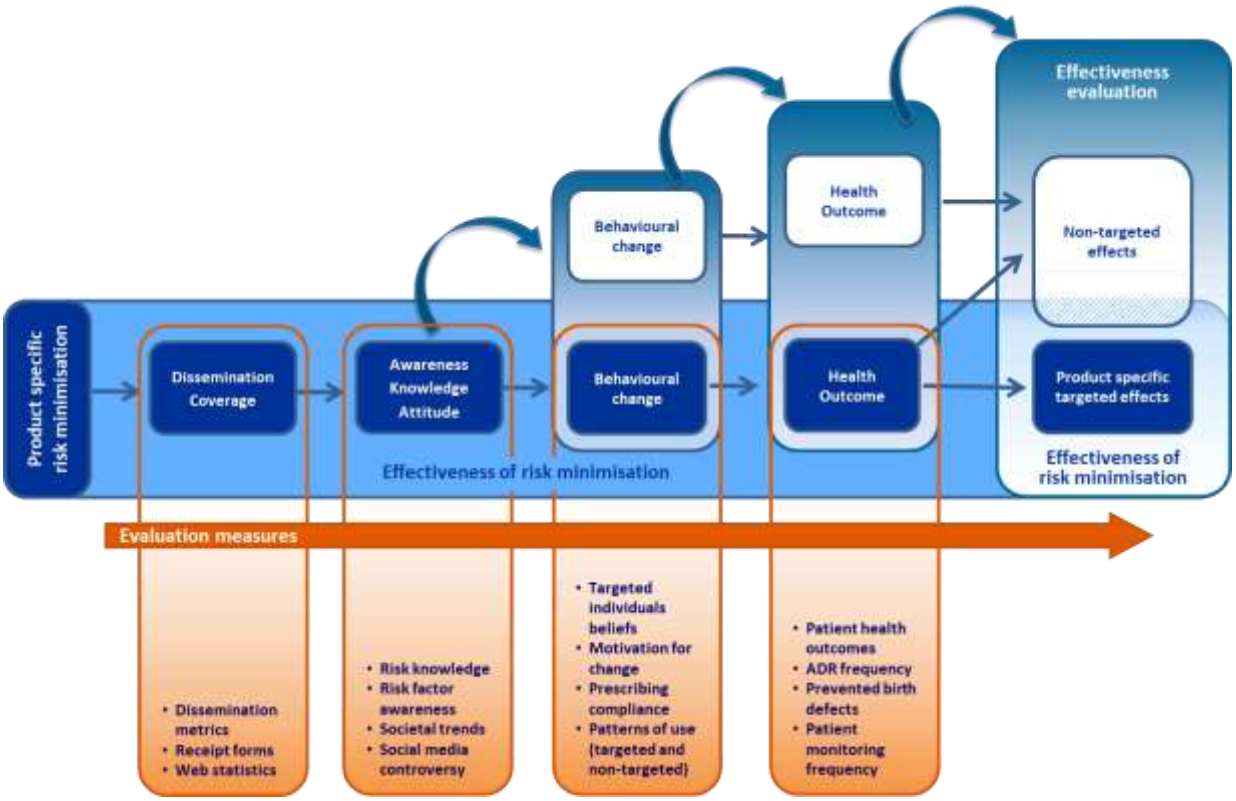

Figure XVI.4.: Approach to effectiveness evaluation of risk minimisation measures showing examples of quantitative and qualitative research outputs at each implementation step

XVI.B.5.3. Assessment of effectiveness and regulatory follow-up

Evaluating the effectiveness of RMM should provide evidence to regulators to determine whether amendments to RMM are warranted, e.g. through amending the SmPC or PL, clarifying risk minimisation advice, or improving or adding RMM tools (see XVI.B.7.). New evidence on the risk may lead to the assessment conclusion that a RMM tool is no longer necessary. This may for example be the case when more information on the risk being less serious accumulates over time in addition to the evidence on the contribution of the RMM to patient health. Alternatively, there may be reassuring information that the advice contained in the RMM has become standard healthcare and is practiced accordingly in which case regulators may conclude to discontinue the RMM. In some instances, important unintended consequences associated with the RMM (see XVI.B.5.1.) will warrant regulatory action to remedy the situation.

Indicators for success or failure should be determined *a priori* and on a case by case basis. Threshold values may be defined by using for example baseline or historical data, expected frequency in comparable populations or of comparable risks. Table XVI.3. includes a list of factors to consider for determining thresholds. The therapeutic context, local specificities (e.g. clinical guidelines) but also other dimensions (e.g. ethical or sociological acceptability) based on input from patient and healthcare professional organisations should be taken into account.

706 **Table XVI.3.: Factors to be considered when determining success or failure of regulatory actions**

Criteria	
Therapeutic need	• Seriousness of the indication (e.g. life-threatening condition, serious consequences on the quality of life, natural evolution of the disease) • Access to therapeutic alternatives
Population at risk	• Size of the population • Age-group at risk (e.g. children, older patients) • Pregnant women • Frailty • Possibility of taking an informed decision (e.g. access to PL, need for urgent treatment, patients with different chronic disease)
Risk	• Seriousness of the risk (e.g. life-threatening, hospitalisation, reversibility, impact on quality of life) • Novelty of the risk • Risk incidence • Proportion of the risk that can be avoided (risk reduction) • Absolute increase of the risk
Technical possibilities	• Is the level of knowledge to develop a threshold sufficient?
Acceptability	• Benefit-risk balance prior to the new information • Variability between populations • Regulatory acceptability (e.g. previous regulatory decisions for similar risks or medicinal products) • Engagement with concerned patients/carers and healthcare professionals • Level of public interest • Risk level accepted by society (e.g. insurance company, case law, from other technological areas)

707 Effectiveness evaluation where results indicate that pre-defined thresholds have been reached confirm
708 that the objectives of the regulatory action for a specific product have been met. On the other hand,
709 failure to reach the pre-defined threshold requires further investigation to obtain a clear understanding
710 of the reasons that could help explain the failure.

711 Corrective action to achieve RMM objectives or prevent unintended consequences may include
712 engaging with stakeholders involved in developing clinical guidelines and setting treatment standards.

713 *XVI.B.6. Coordination of effectiveness evaluation across medicinal products*
714 *containing the same active substance*

715 If several medicinal products, including generics, biosimilars or hybrids, containing the same active
716 substance have been authorised, there should be a consistent approach to planning the evaluation of
717 RMM, overseen by the competent authorities, to ensure that the RMM effectiveness can be achieved for
718 each individual product as well as for all products collectively (see XVI.B.2.).

719 However, where RMM for a generic, biosimilar or hybrid product are fully identical with the
720 originator/reference product, there is usually no need to request the marketing authorisation holder of

the generic, biosimilar or hybrid product to evaluate RMM for their product (unless agreed otherwise in the RMP). This applies under the assumption that the RMM evaluation strategy requested for the reference product will be able to gather sufficient data. For example, if the introduction of a generic, biosimilar or hybrid product(s) reduces exposure to the reference product, the data underpinning the RMM evaluation for the reference product may become insufficient, and competent authorities may also request RMM evaluations for the generic, biosimilar or hybrid product(s).

Where PASS for evaluating RMM effectiveness are required for generic, hybrid and biosimilar products, studies conducted jointly by all marketing authorisation holders (see GVP Module VIII) are encouraged in order to minimise the burden on the healthcare systems. For instance, if a prospective cohort study is instituted, study entry should be independent from the prescription of a product with a specific invented name or provided by a specific marketing authorisation holder. Recording of specific product details may still be important for enabling identification of any new safety hazard with a specific product (e.g. for quality or device defects).

XVI.B.7. Additional risk minimisation measures in the lifecycle of the product

As part of the lifecycle approach, it is also necessary to continuously adapt additional RMM over time and consider their maintenance as appropriate.

RMP for initial marketing authorisations are mainly based on information available from pre-authorisation data, while in some cases, there may be post-authorisation data available if the product has already been authorised elsewhere. Therefore, the information in the RMP at that stage may be incomplete and applicants and regulators might prefer to apply a certain approach at the start of the lifecycle of product and choose to have additional RMM to best address safety concerns that are considered not to be fully mitigated in clinical practice with routine RMM only.

As safety information becomes available with post-authorisation experience, safety concerns (important identified and potential risks and missing information) in the RMP may be reclassified or removed e.g. during the lifecycle of the product, there may be cases where important potential risks that will be further characterised and become important identified risks. With the removal of a risk from the RMP, the need for additional RMM to mitigate this risk becomes obsolete.

There may be a point in time where additional RMM have been implemented in clinical guidance and the healthcare professionals have learned about how to mitigate these risks. In that scenario, a well-known risk is appropriately mitigated and the additional RMM could be discontinued. A regular evaluation for the need of additional RMM is necessary, which should take into account both the effectiveness of the additional RMM and its incorporation in routine clinical practice.

During the lifecycle of the product, the marketing authorisation holder should critically assess whether the materials are still up-to-date with the current knowledge on the safety of the medicinal product. Where applicable, based on experience and effectiveness evaluations since its implementation and considering current clinical practice, the content, format, layout and distribution modality may be revised or optimised. The RMP should be updated accordingly (see GVP Module V).

Any proposal for reclassification or discontinuation should always be accompanied by a thorough discussion with a due justification about whether the implemented additional RMM needs to be updated (e.g. strengthening of the wording), enhanced (e.g. introduction of further additional RMM), changed (e.g. patient card instead of prescriber checklist), or discontinued.

XVI.B.8. Quality systems of risk minimisation measures

In accordance to the quality principles detailed in GVP Module I and quality requirements for RMPs of GVP Module V and PASS in GVP Module VIII, the marketing authorisation holder and its qualified person responsible for pharmacovigilance (QPPV) have specific responsibility for the quality, including medical adequacy and scientific integrity, of RMM tools and the quality of the processes for the timely and complete dissemination of RMM to healthcare professionals and patients. For this purpose, the marketing authorisation holder should keep track and record the dissemination process and outcomes.

The marketing authorisation holder is responsible for updating the RMP, including its section on RMM, when new information becomes available.

The MAH should ensure appropriate version control of the RMM indicating the 'last review'-date and ensure that the RMM in circulation are consistent with the authorised product information.

XVI.C. Operation of the EU network

The Annex IID of the marketing authorisation of a medicinal product authorised in the EU outlines the key elements of any additional RMM imposed on the marketing authorisation as a condition for the safe and effective use of a medicinal product. These additional RMM form an obligation on the marketing authorisation holder in the EU.

For a centrally authorised product, additional RMM become, once adopted by the European Commission through a Commission decision, conditions for the safe and effective use of the product. Because of the specificities of the healthcare systems in Member States and of how particular risks are managed within these systems, some RMM may need to be implemented differently at the level in Member States in accordance with feasibility, and the RMM dissemination by the marketing authorisation holder requires additional agreement with the competent authorities of Member States (see GVP Module XVI - Addendum I). Therefore, for centrally authorised products, Article 127a of Directive 2001/83/EC foresees the option that in addition to the Commission decision on the marketing authorisation a Commission decision may be addressed to Member States, giving them the responsibility for ensuring that specific conditions or restrictions are implemented by the marketing authorisation holder in their territory.

For a product authorised under the mutual recognition or decentralised procedure or via a purely national procedure, additional RMM to be included in the RMP and laid down as conditions of the marketing authorisation as well as their dissemination by the marketing authorisation holder should be agreed by the competent authorities in the reference and concerned Member States.

Further guidance on the principles for educational materials, including the submission of draft educational material(s) by the marketing authorisation applicant/holder to competent authorities in Member States and the assessment of such material(s) by these competent authorities, in particular of the format and content, in GVP Module XVI - Addendum I should be followed.

To allow for flexibility in Member States, given their differences in languages and healthcare systems, synonyms for the term 'educational materials' (e.g. risk minimisation materials or risk information materials) may be used at national level. The marketing authorisation holder should follow national guidance and agree the appropriate terms with the competent authority in each Member State.

To continuously improve regulatory decision-making on RMM, the Pharmacovigilance Risk Assessment Committee (PRAC) (see XVI.C.1.1.1.) adopted a strategy for measuring the impact of pharmacovigilance activities[4] that includes the effectiveness evaluation of RMM (see XVI.B.5.). The guidance on RMM effectiveness evaluation resulting from this strategic work is provided in GVP Module XVI - Addendum II and should be followed too.

XVI.C.1. Roles and responsibilities within the EU regulatory network

XVI.C.1.1. The European Medicines Agency

The Agency shall, in collaboration with the Member States, monitor the outcome of RMM contained in RMP and of conditions referred to in Directive 2001/83/EC (Articles 8(3)(iaa), 21a, 101(2), 104(2), 104(3), 104a and 107h (1)) and Regulation (EC) No 726/2004 (Articles 9(4), 14a, 21, 28a). In monitoring the outcome of RMM, the Agency should support the Pharmacovigilance Risk Assessment Committee (PRAC) in its scientific assessment of outcomes of additional RMM, through the integration of data provided by Member State resources and research activities.

The guidance on transparency requirements in XVI.C.5. applies.

XVI.C.1.1.1. The Pharmacovigilance Risk Assessment Committee

The PRAC should evaluate the need for RMM and their outcome, including additional RMM, and make recommendations regarding the key elements of the necessary regulatory action to the Committee for Medicinal Products for Human Use (CHMP) for centrally authorised products or the Coordination Group – Human (CMDh) for nationally authorised products referred to PRAC.

In order to respect the diversity of the different healthcare systems in Member States, some key elements will be specific for only some Member States (e.g. an activity is specifically linked to the healthcare system of one Member State), but these should still be included in the RMP agreed at EU level.

To facilitate alignment between generic, hybrid or biosimilar products, the PRAC may as appropriate give advice on the key elements that should be implemented for all concerned products (as conditions

[4] https://www.ema.europa.eu/en/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities_en.pdf

of their marketing authorisation) and, on agreement, may make these general requirements publicly available to facilitate implementation at national level.

The PRAC should assess as appropriate protocol and results of PASS which aim to evaluate the effectiveness of RMM in accordance with XVI.B.5. and GVP Module VIII.

XVI.C.1.2. Competent authorities in Member States

The competent authorities in Member States are responsible for the oversight at national level of the development and dissemination of additional RMM imposed as a condition of the marketing authorisation for the safe and effective use of a medicinal product in the EU, irrespective of the route of marketing authorisation. Articles 104(3)(d) and Article 107h(1) of Directive 2001/83/EC and Article 28a of Regulation (EC) No 726/2004 specifically include provisions for monitoring the outcome of RMM for both marketing authorisation holders and competent authorities. For centrally authorised products and nationally authorised products referred to PRAC, key elements will be agreed at EU level and need to be implemented in a coordinated manner across Member States. However, finalisation and dissemination of the RMM are agreed with competent authorities in Member States. Furthermore, they shall, in collaboration with the Agency, monitor the outcome of RMM contained in RMPs and of the conditions referred to in Articles 21a, 22 or 22a of Directive 2001/83/EC [DIR Art 107h(1)(a)].

For those RMM introduced after the initial marketing authorisation, the competent authorities in Member States should ensure prompt consideration and agreement of the RMM with the marketing authorisation holder. They should agree the final content, format and media of the RMM tools, including printed materials, web-based platforms and other audio-video media, availability of materials, as well as the timetable of (re-)dissemination by the marketing authorisation applicant/holder before a product is introduced to their market or at any time thereafter as needed (see GVP Module XVI - Addendum I).

When additional RMM are considered necessary for a generic, biosimilar or hybrid medicinal product based on safety concerns related to the active substance, the RMM for the generic, biosimilar or hybrid product should be aligned with those for the reference medicinal product. Additional RMM for generic, biosimilar or hybrid products may be required in some circumstances beyond those of the reference medicinal product (e.g. different formulation or route of administration).

In addition to the above, for centrally authorised products, further responsibility for ensuring implementation of the RMM in Member States maybe be given to national competent authorities by means of a Commission Decision under Article 127a of Directive 2001/83/EC.

Where patient cards (see XVI.B.3.1.f.) are included in the outer packaging, they are considered as part of the labelling, therefore the full text and the format should be agreed by the relevant competent authority (and the full text is to be included in Annex IIIA of the marketing authorisation for centrally authorised products).

Whenever there are deviations from key elements agreed at EU level, this should be duly justified by the competent authority in the Member State and the marketing authorisation holder, as applicable, for example:

- Contraception is not always prescribed by the same healthcare professional in all Member States; this responsibility may either fall within the remit of e.g. a general practitioner, a gynaecologist or a specialised nurse, or patients may purchase contraceptive products without a prescription;
- Certain medicinal products may in some Member States permitted to be prescribed nurses or pharmacists with or without oversight by a general practitioner.

The guidance on transparency requirements in XVI.C.5. applies.

XVI.C.2. Roles and responsibilities of the marketing authorisation holder or applicant in the EU

The marketing authorisation applicant/holder in the EU is responsible for ensuring compliance with the conditions of the marketing authorisation for their products wherever they are used within the EU. It is the responsibility of the marketing authorisation applicant/holder to implement all conditions or restrictions with regard to the safe and effective use of the product in a particular territory.

Regarding RMM, the marketing authorisation applicant/holder should therefore follow the guidance in XVI.B. and document RMM in the RMP (see GVP Module V).

The marketing authorisation applicant/holder is encouraged to discuss plans for RMM with the competent authorities in Member States as early as is feasible, e.g. when it seems likely that specific risk minimisation activities will need to be adapted to the different healthcare systems in place in the different Member States. The RMM adopted in the RMP should be agreed with the national competent authorities before dissemination in accordance with the timetable agreed by national competent authorities. In the development and dissemination of web-based tools, marketing authorisation applicants/holders should follow the requirements of each Member State, with particular consideration of potential issues linked to accessibility, recognisability, responsibility, and privacy and data protection.

Specifically the implementation of risk awareness forms may vary significantly from one Member State to the other, a therefore a detailed description of the forms and dissemination processes in Member States to be followed by the marketing authorisation holder should be available within the RMP, as agreed with the competent authority(ies) in (the) Member State(s). The same applies to controlled access programmes which should be adapted to local healthcare settings in agreement with the competent authorities in Member States, as the healthcare systems might differ significantly between Member States. User-testing of materials for risk minimisation in the local languages is recommended.

The marketing authorisation holder should provide information regarding the status of dissemination of additional RMM as agreed with the competent authorities in Member States and keep them informed of any changes or issues encountered in dissemination process. Any relevant changes should be agreed with the competent authorities in Member States.

The marketing authorisation holder shall monitor the outcome of RMM which are contained in the RMP or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a of DIR [DIR Art 104(3)(d)] and should therefore follow the guidance on RMM effectiveness evaluation in XVI.B.5.. The marketing authorisation holder should report the findings of the evaluation when updating the RMP (see GVP Module V) and in the periodic safety update report (PSUR) (see GVP

Module VII) with a view whether the RMM ensure the positive risk-benefit balance of the product or adjustments to the RMM or other regulatory action is needed (see XVI.C.4., VII.B.5.16.5. and VII.C.5.5.). If the marketing authorisation holder becomes aware of information regarding RMM that may impact the benefit-risk balance of the medicinal product, this should be reported as an emerging safety issue.

The applicant or marketing authorisation holder should ensure timely communication with the competent authorities for relevant regulatory evaluation and actions, as appropriate (see XVI.C.2. and GVP Modules V and VII).

XVI.C.3. Collaboration with healthcare professional and patient organisations

The contribution from healthcare professionals and patients is of paramount importance for the decision-making of competent authorities, to ensure that RMM are adequate to address the risk and feasible, and do not create an undue burden to patients, healthcare professionals and the overall healthcare systems. Patients' and healthcare professionals' contributions are considered to optimise the development of RMM tools by bringing their real-life experience of disease management and medicines' use into the regulatory assessments. This should also ensure that any RMM is able to overcome the barriers often encountered in the process of their implementation in healthcare due to the characteristics and differences of the healthcare systems.

Where possible, it is encouraged that the Agency, its Committees and competent authorities in Member States, as applicable, engage with healthcare professionals and patient representatives for obtaining their contributions and discussing:

- Current awareness, understanding and management of the potential risks of the medicine;
- Effectiveness, appropriateness and feasibility of having additional RMM in place;
- Most efficient risk minimisation tools and appropriate and feasible dissemination processes in relation to target audience(s) and channels;
- Support for healthcare professional and patient organisations by means of e.g. clinical guidelines, patient guides made available by healthcare systems or patient organisations, articles in scientific journals and conferences; and
- Other practical suggestions for improvement.

XVI.C.4. Impact of risk minimisation measures effectiveness evaluations on risk management plans and periodic safety update reports in the EU

PSURs and updates of the RMP should include a summary evaluation of the outcomes of specific RMM in the EU. In the RMP, the focus should be on how this informs risk minimisation and pharmacovigilance planning. In the PSUR, there should also be an evaluation of how the implemented measures impact the safety profile and risk-benefit balance of the product. In general, the focus should be on information which has emerged during the reporting period or since dissemination of the most recent RMM in the EU. Where there is parallel submission of a PSUR and an RMP update to the

competent authorities of the EU regulatory network, the use of a common content module should be considered (see GVP Modules V and VII). For the evaluation, the guidance in XVI.B.5. applies.

XVI.C.5. Transparency

Procedures should be in place to ensure full transparency of relevant information pertaining to RMM for medicinal products authorised in the EU.

For centrally authorised products, the Agency shall make public:

- Summary of the RMP [REG Art 26(1)(c)], with specific focus on risk minimisation activities described therein [IR Art 31.1];
- European public assessment report (EPAR) that includes any conditions of the marketing authorisation, such as additional RMM [REG Art 26(1)(j)];
- SmPCs and PLs [REG Art 57]; and
- Conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions [REG Art 13].

For centrally and nationally authorised products and by means of the national medicines web-portals, the Member States shall make publicly available at least the following:

- Public assessment report, this shall include a summary written in a manner that is understandable to the public [DIR Art 21(4), Art 106(a)];
- SmPCs and PLs [DIR Art 21(3), Art 106(b)];
- Conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions [DIR Art 21(3)]; and
- Summary of the RMP [DIR Art 106(c)], with specific focus on risk minimisation activities described therein [IR Art 31.1].

To promote public health, it is recommended that the Agency and the competent authorities in Member States make the following additional information available via their websites:

- Details of additional RMM (e.g. electronic copy of RMM tools/materials that are to be disseminated by marketing authorisation holders in print).