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Guideline on good pharmacovigilance practices (GVP)

Module XVI – Risk minimisation measures (Rev 3)

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*Note: Draft Revision 3 released for public consultation versus Revision 2 included the following:

- Changes to XVI.A. to clarify the role of risk minimisation for risk management planning and for the impact on the risk-benefit balance of medicinal products, and the role of effectiveness evaluation of risk minimisation measures, and to delete/merge concepts already included in other sections of the Module;
- Addition of XVI.B.2. to give more guidance about the criteria for applying/requesting additional risk minimisation measures;
- Changes to XVI.B.3.1. with a new classification for educational materials;
- Changes to XVI.B.3.4. regarding the concept of controlled access systems and examples illustrating the requirements;
- Addition of XVI.B.4. to clarify the role of risk communication, dissemination and implementation as a relevant part of any additional risk minimisation activity;

- Changes to XVI.B.5. to give more guidance on criteria and methods for risk minimisation evaluation; emphasis has been given on the concept of risk minimisation evaluation, which includes an iterative planned and prospective approach with integrated measurement of different elements and regulatory follow-up;
- Changes to XVI.B.5.4. to give more guidance on risk minimisation evaluation parameters (e.g. implementation, behavioural changes, outcomes), including suitable study designs and data collection methods;
- Addition of XVI.B.7. to provide recommendations on additional risk minimisation measures within the lifecycle of the product;
- Changes to XVI.C.3. to give more details on the role of healthcare professionals and patients and to clarify possible strategies for their early engagement and role in risk minimisation development, dissemination and evaluation;
- Deletion of Appendix I on survey methodologies and integration of this guidance in Addendum II of this Module.

** Note: Final Revision 3 versus draft Revision 3 released for public consultation includes the following in response to the consultation:

- Elaboration of the legal basis of RMM and clarifications in the introductory A-part, including reference to implementation science approaches;
- Clarification in the introductory A-part that as technology advances, the potential of supporting risk minimisation through digital applications may be considered, without any further guidance in this Module while an EMA reflection paper on digital support to risk minimisation is under development;
- Clarifications and additions of definitions in a new Terminology section A.1., including clarifications to distinguish between RMM messages and tools;
- Clarifications of the relationship between routine and additional RMM tools and the resulting applicability of the guidance in this Module for both these RMM categories;
- Revised structure of the B-part with overview tables on RMM tools while clarified details on the tools are provided in new Appendices;
- Elaboration on the iterative and non-promotional nature of RMM and RMM objectives, on the implementation pathway and on stakeholder engagement in section B.1.;
- Clarification that a direct healthcare professional communication is a safety communication tool in section B.4.2.1. with reference to GVP Module XV;
- Renaming of risk awareness forms as risk awareness dialogue form/aid in section B.2.3.1. with clarifications in Appendix 2, and deletion of follow-up risk awareness forms as an additional RMM tool;
- Deletion of demonstration kit as an additional RMM tool;
- Revised guidance on risk minimisation control tools and programmes replacing draft guidance on controlled access programmes in section B.2.;
- Transfer of draft guidance on 'pregnancy prevention programmes' to the applicable Addendum to GVP M XVI (under finalisation);
- Clarified and tabulated points to consider for requiring and selecting aRMM tools in section B.3., allowing for risk minimisation measures that are specific to the medicinal product, the risk, the patient population and the healthcare context;
- Emphasised guidance on the development and dissemination planning of RMM materials in section B.4.;
- Clarifications on the naming of RMM materials in section B.4., C.2.2., C.3.1. and Appendix 2;
- Clarifications and tabulated presentation of guidance on RMM effectiveness evaluation studies in section B.5.;
- Integration of guidance on the regulatory follow-up of RMM effectiveness evaluation studies from draft section B.5. in emphasised guidance on adapting RMM in section B.6.;
- Clarifications on quality management in section B.7.;
- Clarifications on the requirements for including RMM and RMM effectiveness evaluation studies in the marketing authorisation, the risk management plan and periodic safety update reports in section C.1.;
- Clarifications in the responsibilities of the EU marketing authorisation holder and the EU regulatory network in sections C.2. and C.3.;
- Integration of guidance on the coordination of RMM effectiveness evaluation for medicinal products containing the same active substance in section C.2.2.;
- Integration of guidance on stakeholder engagement from the draft C-part in sections B.1.4., C.3.1. and C.3.2.2.;
- Updates on transparency in section C.4.;
- Integration of previous Addendum I on approval of RMM materials by competent authorities in Member States; and
- Overall structural, presentational and editorial improvements.

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XVI.A. Introduction

A marketing authorisation for a medicinal product in the EU may be granted subject to taking certain measures for ensuring its safe use to be included in the risk management system [based on DIR Art 21a and REG Art 9(4)(ca)]. These measures support keeping the risk-benefit balance of a medicinal product (see GVP Annex 1) positive, which is a prerequisite for granting and maintaining its marketing authorisation. A risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions [DIR Art 1(28b)], and is described in the risk management plan (RMP) of the product [DIR Art 1(28c)] (see GVP Module V). The objectives of ensuring the safe use of the medicinal product and minimising risks, including their adverse health outcomes, are facilitated by risk minimisation measures (RMM).

In terms of tools, RMM are categorised into routine and additional RMM. The summary of product characteristics (SmPC) is the fundamental routine RMM tool, where the risk and intended actions for risk minimisation are described. This forms the basis for other routine RMM and, where required, additional RMM. Additional RMM tools are meant to emphasise the information on the risk and the intended actions for risk minimisation and to support and/or control the adherence to the intended actions.

For the purpose of RMM, the marketing authorisation holder shall evaluate all information scientifically, consider options for risk minimisation and prevention, and take appropriate measures as necessary [DIR Art 104(2)]. Likewise, the competent authorities in Member States shall evaluate all information scientifically, consider the options and take regulatory action concerning the marketing authorisation as necessary [DIR Art 101(2)], and the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) shall provide recommendations relating to risk management systems [based on REG Art 56(1)(aa)]. Further, the marketing authorisation holder [DIR Art 104(3)(c) and (d)] as well as the competent authorities in Member States and the Agency [based on DIR Art 107h(1)(a), REG Art 28a(1)(a) and REG Art 56(1)(aa)] shall monitor the outcomes of RMM contained in the RMP or any other conditions or restrictions with regard to the safe and effective use of the medicinal product.

Planning for developing, implementing and evaluating RMM should begin early during the development phase of the medicinal product, as part of the proactive risk management system to be set up by the applicants for a marketing authorisation, to whom the guidance for marketing authorisation holders in this Module is applicable too.

It is recognised that risk minimisation is an evolving area for which new approaches and methods will emerge. Implementing RMM in healthcare for patient safety requires approaches from the implementation sciences as well as engagement across different stakeholders for patient-centred healthcare. As technology advances, the potential of supporting risk minimisation through digital applications may be considered.

The terminology for this GVP Module is presented in XVI.A.. XVI.B. provides the principles and tools of RMM, points to consider for their selection as well as guidance for their development, implementation and evaluation, with a view to an overall risk-proportionate and consistent approach to risk

minimisation. XVI.C. describes the related responsibilities of marketing authorisation holders and competent authorities of the EU regulatory network. The Module also reflects on the engagement with healthcare professional and patient representatives.

This GVP Module should be read together with the Addenda of GVP Module XVI and other GVP Modules as referenced, the CHMP Guideline on Safety and Efficacy Follow-up – Risk management of Advanced Therapy Medicinal Products[1], the PRAC Good Practice Guide on Risk Minimisation and Prevention of Medication Errors[2], the EMA Guidance on Post-Authorisation Safety Studies[3] and the EMA Post-Authorisation Guidance[4]. Marketing authorisation holders should also follow guidance in place in Member States.

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 as amended is referenced as 'DIR', Regulation (EC) No 726/2004 as amended as 'REG' and the Commission Implementing Regulation (EU) No 520/2012 as amended as "IR".

XVI.A.1. Terminology

Definitions are presented in GVP Annex 1, including the following developed for this Module:

XVI.A.1.1. Risk minimisation measure

'Risk minimisation measure' (RMM) is defined, for the purpose of this GVP Module, as an intervention intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicinal product, or to reduce their severity or impact on the patient should an adverse reaction occur.

The term 'RMM' is an umbrella term covering the following terms referred to in the legislation: 'measures for ensuring the safe use of a medicinal product to be included in its risk management system', 'measures to prevent or minimise the risks associated with the medicinal product', 'interventions designed to prevent or minimise risks relating to a medicinal product', 'risk minimisation activities relevant to the risk-benefit assessment', 'regulatory action following consideration of options for risk minimisation and prevention', and 'other conditions or restrictions with regard to the safe and effective use of a medicinal product'.

Conceptually, a RMM consists of two components:

- ***RMM messages:*** the key information (i.e. not the full wording) about the risk and the actions intended to be taken by the healthcare professional or the patient for minimising the risk; and
- ***RMM tool:*** the tool by which the RMM messages are disseminated and adherence to the intended actions for risk minimisation is supported and/or controlled, belonging either to the category of routine or additional RMM tools (see XVI.B.2.).

[1] ema.europa.eu
[2] ema.europa.eu
[3] https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass
[4] ema.europa.eu/en/human-regulatory-overview/post-authorisation

RMM messages can be verbally explicit or non-verbal implicit (e.g. a restricted pack size as a RMM tool may imply e.g. the message that overdose is a specific risk to be avoided or that medical supervision of the treatment with this medicinal product is required; also a risk minimisation control programme, e.g. a traceability system or healthcare facility accreditation required for using a given medicinal product, carry implicit messages for the target audience); however, there will always be verbal messages at least in the product information and, if applicable, in further RMM materials.

For a specific medicinal product, a ***RMM material*** is the final individual RMM with its full wording in the local language(s) as approved by the competent authorities.

XVI.A.1.2. Patient

'Patient' is defined, for the purpose of this GVP Module, as an individual using or considering the use of a medicinal product (including (healthy) individuals using vaccines and other medicinal products not intended to treat or alleviate a disease) as well as the embryo/foetus/child who may be adversely affected by a medicinal product at conception, in utero or through breastfeeding, and an individual who may be adversely affected through occupational, accidental or illegal[5] exposure to a medicinal product.

For the ease of reading, the term also includes parents, other carers, as well as patient and consumer representatives and organisations, as they may also be target populations of RMM (see XVI.A.1.4.).

XVI.A.1.3. Healthcare professionals

'Healthcare professionals' are defined, for the purposes of this GVP Module, as persons providing professional healthcare[6] to individual patients.

For the ease of reading, the term also includes healthcare professional representatives and organisations (including learned societies and clinical guideline working groups), as they may be target populations of RMM (see XVI.A.1.4.).

For the purpose of this GVP Module, the term 'healthcare professional' does not include those who are qualified as a healthcare professional but work as employees of a marketing authorisation holder or a competent authority.

XVI.A.1.4. Target population (risk minimisation measure)

'Target population (risk minimisation measure)' is defined, for the purposes of this GVP Module, as the group of individuals who are intended to either receive given RMM materials, be aware of the RMM messages and take the actions intended for risk minimisation, or to provide for systems in healthcare settings supporting that intended actions are taken.

[5] See GVP Annex I for the definition of 'Misuse of a medicinal product for illegal purposes'.
[6] More comprehensively, the following definition of health professional applies: a doctor of medicine, a nurse responsible for general care, a dental practitioner, a midwife or a pharmacist within the meaning of Directive 2005/36/EC, or another professional exercising activities in the healthcare sector which are restricted to a regulated profession as defined in Article 3(1)(a) of Directive 2005/36/EC, or a person considered to be a health professional according to the legislation of the Member State of treatment (see Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare)

When using this term, the definitions of patients (see XVI.A.1.2.) and healthcare professionals (see XVI.A.1.3.) apply, and subgroups of these populations may be specified further, where applicable.

For the ease of reading, the term is abbreviated to target population (for definitions of 'target population' for the purposes of other GVP Modules, see GVP Annex I).

XVI.B. Structures and processes

XVI.B.1. Principles of risk minimisation

XVI.B.1.1. Risk minimisation within the benefit-risk management cycle of the medicinal product

The pharmacovigilance activities for identifying and assessing risks as well as implementing and evaluating RMM for a medicinal product, as performed by marketing authorisation holders (see XVI.C.2.) and the competent authorities (see XVI.C.3.), start with the medicinal product development in the pre-authorisation phase and continue iteratively throughout the post-authorisation phase.

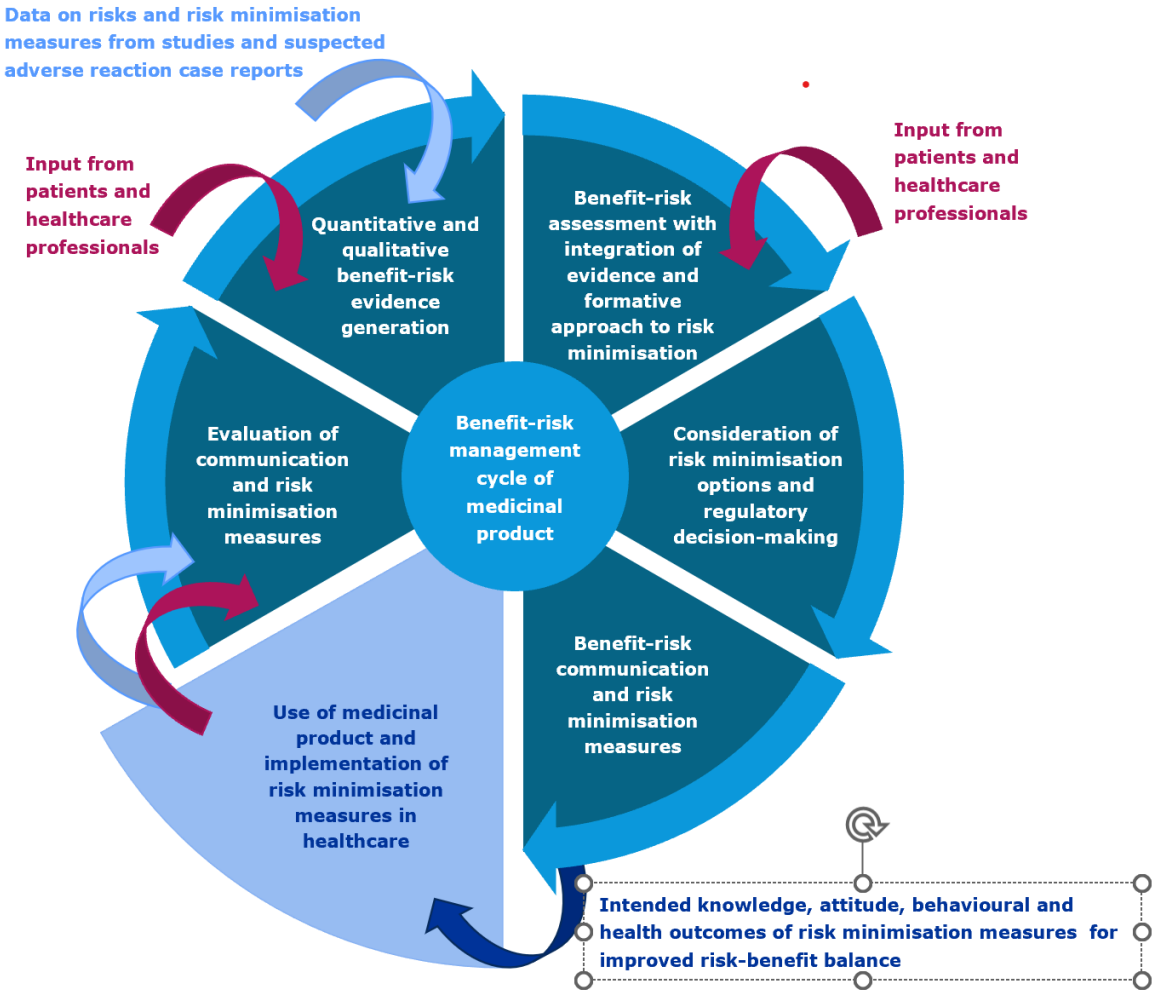

Figure XVI.1.: Benefit-risk management cycle of the medicinal product[7]

[7] Further developed from Bahri P, Morales DR, Inoubli A, Dogné JM, Straus SMJM. Proposals for engaging patients and healthcare professionals in risk minimisation from an analysis of stakeholder input to the EU valproate assessment using the novel analysing

At the time of granting the marketing authorisation of the medicinal product, a RMP is put in place to describe the pharmacovigilance activities for data collection and the RMM. In the post-authorisation phase, new information on existing risks or RMM may emerge or new risks may be identified, which may require new or adapted RMM or RMM dissemination plans to maintain or improve the positive risk-benefit balance of the medicinal product. This process can be depicted as a learning cycle (see Figure XVI.1.), as part of quality management of pharmacovigilance (see XVI.B.7.).

Within this cyclic process, collecting formative data (see XVI.B.1.3.) and input from patients and healthcare professionals (see XVI.B.1.4.) and evaluating RMM effectiveness (see XVI.B.5.) may support evidence-based decisions for requiring and selecting (see XVI.B.3.) or adapting (see XVI.B.6.) RMM, as well as for developing RMM materials and dissemination plans (see XVI.B.4.).

XVI.B.1.2. Intended outcomes of risk minimisation measures

RMM should have clearly defined intended outcomes in terms of:

- Reaching the target populations;
- Knowledge adoption and attitude formation[8] in the target populations and their taking of the intended actions for risk minimisation; and
- Health outcomes in terms of reduced occurrence or severity of adverse reactions or the reduced adverse impact of such reactions on patient or public health.

XVI.B.1.3. Implementation pathway of risk minimisation measures

The intended outcomes of RMM (see XVI.B.1.2.) are achieved along an implementation pathway (see Figure XVI.2.). This pathway distinguishes between:

- Regulatory implementation, which refers to the inclusion of the RMM in the marketing authorisation of the medicinal product (see XVI.C.1.) and the approval of the RMM materials by the competent authorities (see XVI.C.3.2.);
- Dissemination of the RMM, which includes making the product information available and disseminating additional RMM materials to the target populations; and
- Implementation of the RMM in healthcare, which also includes further dissemination of RMM materials from the healthcare professional initially receiving the RMM materials within the healthcare setting and/or to patients, knowledge adoption, attitude formation and actions taken by healthcare professionals and patients as intended for risk minimisation.

While the regulatory implementation of RMM lies within the remit of competent authorities, the development and dissemination of RMM to the target populations fall under the responsibility of the marketing authorisation holders, who are subject to regulatory oversight and inspections (see GVP Module III). Additionally, competent authorities may disseminate information on RMM as part of their

stakeholder safety engagement tool (ASSET). Drug Saf. 2021; 44: 193-209, epub 30 Oct 2020 (developed from [Radawski C, Morrato E, Hornbuckle K, Bahri P, Smith M, Juhaeri J, Mol P, Levitan B, Huang H-Y, Coplan P, Li H, on behalf of the ISPE BRACE SIG. Benefit-risk assessment, communication and evaluation (BRACE) throughout the life cycle of therapeutic products: overall perspective and role of the pharmacoepidemiologist. Pharmacoepidemiol Drug Saf. 2015; 24: 1233-1240.].

[8] Within cognitive processes, forming an attitude as a state of readiness is vital for applying knowledge and taking action (see Fazio RH. Attitudes as object-evaluation associations of varying strength. Soc Cogn. 2007; 25: 603-637.)

legal obligations for safety communication (see GVP Module XV). Generally speaking, dissemination also covers the dissemination of the RMM messages through other channels, e.g. the scientific or general media, which lie outside regulatory oversight, but may be used in the context of wider engagement with healthcare professionals and patients (see XVI B.1.4.) and dissemination planning (see XVI.B.4.2.).

Further dissemination of RMM materials from healthcare professionals to patients may in some instances be an intended action for risk minimisation. Also, wider dissemination of RMM materials or messages within healthcare systems may be necessary to achieve full implementation of RMM. The full implementation of RMM in healthcare takes place through the systems providing healthcare for individual patients. How the intended actions for risk minimisation are integrated in healthcare processes or patient routines will depend on the healthcare settings where the medicinal product is prescribed, dispensed and administered and/or the patient environments, circumstances and care processes.

Within the proactive approach to risk minimisation, implementability refers to the expected opportunities of RMM being implemented effectively in terms of achieving the intended outcomes (see XVI.B.1.2.) and avoiding the potential for unintended outcomes (see B.5.1.), based on evaluative and/or formative evidence on RMM effectiveness and context (see XVI.B.1.1.) and input from patients and healthcare professionals (see XVI.B.1.4.). It is relevant to gain a contextual understanding of the use of the medicine, disease management and overall clinical context, healthcare settings and processes, typical patient environments, circumstances and care processes, health information diffusion, existing knowledge, attitudes and behaviours in target populations, how RMM tools and the intended actions for risk minimisation could be integrated into the given processes, and individual and system factors, which may be enablers or barriers to RMM effectiveness. Both evaluative and formative evidence generation uses the methods described in GVP Module XVI Addendum II.

Figure XVI.2.: Implementation pathway of risk minimisation measures for medicinal products

XVI.B.1.4. Engagement of patients and healthcare professionals in risk minimisation

Engagement across all stakeholders is considered crucial for achieving full implementation (see XVI.B.1.3.) and effectiveness of RMM. Given this shared responsibility, inclusive and appropriate interactions between competent authorities, marketing authorisation holders, healthcare professionals and patients in accordance with their respective roles and responsibilities are important and should be

encouraged. For marketing authorisation holders, such interactions should be separate from promotional activities (see XVI.B.1.5.).

Where additional RMM tools are considered, patient and healthcare professional representatives may be approached in particular to:

- Provide input on RMM options regarding e.g. the tools, messages, target populations, ethical acceptability and implementability (see XVI.B.1.3.) to support regulatory decisions on RMM (see XVI.B.3. and XVI.B.6.);
- Contribute to the development of RMM materials, e.g. through user-testing of RMM materials, and provide input on dissemination plans (see XVI.B.4.);
- Support the dissemination via multiple channels, including those outside the regulatory oversight, to address the media preferences of the target populations and to support the implementation of RMM in healthcare (see XVI.B.1.3.);
- Provide input on and participate in the evaluation of RMM effectiveness (see XVI.B.5.).

XVI.B.1.5. Non-promotional nature of risk minimisation and personal data protection

Any visualisations in the package leaflet or labelling of the packaging shall exclude any element of a promotional nature [DIR Art 62]. Likewise, any RMM material should not contain or be combined with any promotional elements, either direct or veiled, and follow locally applicable policies. Also studies evaluating RMM effectiveness should not contain any promotional element and be separate from any promotional activity, and non-interventional post-authorisation safety studies (PASS) shall not be performed where the act of conducting the study promotes the use of a medicinal product [DIR Art 107m(3)] (see GVP Module VIII).

Any contact information of healthcare professionals or patients which may possibly be gathered through RMM-related activities, including stakeholder engagement (see XVI.B.1.4.), must not be used for any other, including promotional, activities and must be handled in accordance with 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.

In the context of RMM, the invented name of the medicinal product is not considered a promotional element, but should be used as rarely as possible (see XVI.B.4.1.1.).

The marketing authorisation holder`s and/or the product`s logo should generally be avoided; however, if suggested to appear for a given reason, it/they should appear only once in each RMM material and not be larger than the heading font size.

XVI.B.2. Categories and tools of risk minimisation measures

XVI.B.2.1. Categories of risk minimisation measures and their relationship

In terms of the tool, RMM can be categorised into routine (see XVI.B.2.2.) and additional (see XVI.B.2.3.) RMM.

The SmPC is the fundamental routine RMM tool, where the risk of the medicinal product and the intended actions for risk minimisation are described. As such the SmPC forms the basis for the descriptions of the risk and the intended actions in the package leaflet and for other routine RMM and, where required, additional RMM.

Where applicable, the SmPC should mention that additional RMM materials exist for a specific risk and may include information where they can be accessed. If an additional RMM material is targeted at patients, the package leaflet should contain information on the availability of this material and may include accessibility information too.

Additional RMM tools are meant to emphasise the information on the risk and the intended actions for risk minimisation contained in the SmPC and to support and/or control the adherence to the intended actions.

XVI.B.2.2. Tools of routine risk minimisation measures

Routine RMM tools are those which apply to every medicinal product; an exception are visual enhancements and special warnings/information on precautions on the packaging which are routine RMM tools that are not needed for every medicinal product and have to be specifically included in the marketing authorisation if required (see XVI.C.1.1.).

Routine RMM tools include those listed in Table XVI.1. and are detailed in XVI.Appendix 1.

Further, the pharmaceutical form or formulation of a medicinal product may play an important role in minimising the risk, e.g. in minimising the risk of incorrect dosing or administration, misuse or abuse.

Table XVI.1.: Routine risk minimisation measure tools

Routine RMM tools
Summary of product characteristics (SmPC)[9]
Package leaflet (PL)[10]
Labelling of immediate and outer packaging[11]
Pack size
Classification of the medicinal product (legal status)

[9] In rare situations, the SmPC may include a boxed warning in bold font type (see XVI.App1.1.1.).
[10] In rare situations, the PL may include symbols, pictograms and/or warnings on dark background (see XVI.App1.2.1.).
[11] In rare situations, the labelling may include special warnings, information on precautions and/or pictograms (see XVI.App1.3.1.).

XVI.B.2.3. Tools of additional risk minimisation measures

A variety of additional RMM tools are available for use on their own or in combination. Two additional RMM tools can also be merged into one RMM material as part of tailoring where this is relevant to the target population (see XVI.B.4.1.).

Additional RMM tools are sub-categorised as follows:

- Educational/Safety advice tools; and
- Risk minimisation control tools.

Other tools can become additional RMM tools if they meet the definition of RMM (see XVI.A.1.1.).

XVI.B.2.3.1. Educational/Safety advice tools

Educational tools, or synonymously safety advice tools, target either patients or healthcare professionals with the RMM messages and are meant to support adherence to the intended actions for risk minimisation. Educational/Safety advice tools for healthcare professionals may also be intended to support the dialogue with the patient about the risks and intended actions for risk minimisation.

Educational/Safety advice tools include those listed in Table XVI.2. and are detailed in XVI.Appendix 2.

Table XVI.2.: Educational/Safety advice tools

Educational/Safety advice tools
Guides for risk minimisation for patients or healthcare professionals
Healthcare professional checklist for risk minimisation
Risk awareness dialogue form/aid
Patient card
Patient diary for risk minimisation

XVI.B.2.3.2. Risk minimisation control tools

Control of adherence to the intended actions for risk minimisation may be facilitated by additional RMM tools which aim at ensuring the necessary healthcare support to patients for using the medicinal product safely, the prevention of diversion of the medicinal product and/or the traceability of the medicinal product. Such risk minimisation control tools are intended for application in one or more healthcare settings, depending on whether the required control concerns the step(s) of prescribing, distribution, dispensing and/or administration of the medicinal product and where these steps occur in the given healthcare system.

Risk minimisation control tools include those listed in Table XVI.3..

In practice, each risk minimisation control tool may need, for its implementation, several RMM materials (e.g. for healthcare qualification as a tool, materials for training and qualification and a qualification certificate form will be needed; or for traceability, a set of forms will be needed for completion by the different distribution points; or for documented information exchange as a tool, forms will be needed to be completed by different healthcare professionals).

Table XVI.3.: Risk minimisation control tools

Risk minimisation control tools
Healthcare professional qualification which is required for the prescribing, dispensing and/or administration of the medicinal product, and/or for the supervision of the administration by the patient
Healthcare facility accreditation of the available equipment and qualified healthcare professionals which is required for using the medicinal product at this facility
Traceability system which is to be completed at dispatch of the medicinal product from the manufacturing site, all distribution points and the healthcare facility where the medicinal product is dispensed or administered
System for documented exchange of patient information (e.g. results of medical tests) which one healthcare professional is required to receive from another healthcare professional
Check of patient certificates of medical interventions which is required for the prescribing or dispensing of the medicinal product

XVI.B.3. Requiring and selecting tools of additional risk minimisation measures

For the purpose of risk minimisation, all information shall be evaluated scientifically, options for risk minimisation be considered and appropriate RMM be taken as necessary [based on DIR Art 104(2) and DIR Art 101(2)].

Careful consideration should be given to whether the intended RMM outcomes (see XVI.B.1.2.) could be achieved with routine RMM tools alone. Most risks will be sufficiently addressed by routine RMM tools (see XVI.B.2.2.). Additional RMM tools (see B.2.3.) should be required only if they are considered necessary for keeping the risk-benefit balance of the medicinal product positive. Generally, additional RMM tools address important identified or important potential risks (see GVP Annex I).

In determining whether additional RMM tools are necessary and selecting the respective tool(s), marketing authorisation holders and competent authorities should consider the points in Table XVI.4. and use past and formative evidence (see XVI.B.1.1.) as well as input that may be sought from patients and healthcare professionals (see XVI.B.1.4.). Applying these points to consider should lead to selecting and developing RMM that are specific to the given medicinal product, the risk, the patient population and the healthcare context.

Selecting several educational/safety advice tools may be warranted for reaching as many as possible among the target population.

Specifically for medicinal products which may adversely affect the embryo/foetus/child at conception, in utero or through breastfeeding, routine and additional RMM tools can be combined to prevent adverse pregnancy outcomes (see GVP Module XVI Addendum I).

Each risk needs to be considered individually, but an additional RMM material may address more than one risk.

Table XVI.4.: Points to consider for requiring additional risk minimisation measures and selecting tools

Points to consider for requiring additional RMM and selecting tools
Seriousness (see GVP Annex I), severity and other characteristics of the risk

Points to consider for requiring additional RMM and selecting tools
Intended actions to be taken by healthcare professionals and patients during each step of processes in healthcare settings or at home, considering the need for immediate and/or long-term actions within disease management and the overall clinical context
Indication, contraindications, dosing and scheduling, duration of treatment, route of administration/ pharmaceutical form and the potential of errors in handling and administration of the medicinal product
Patient target population for the RMM, the medical condition to be treated and its impact on patients, the typical patient environments, circumstances and care processes, and likely scenarios where patients use the medicinal product and related information needs
Healthcare professional target population for the RMM, the typical healthcare settings and processes, and likely scenarios where the medicinal product is used and related information needs
Possible burden of the RMM on the patient and the healthcare system in relation to the risk, taking into account risk-proportionality (see XVI.A.)
Implementability of the RMM with its anticipated effectiveness in terms of achieving the intended outcomes of the RMM and avoiding the potential for unintended outcomes (see XVI.B.1.3.)

XVI.B.3.1. Risk minimisation control programmes

A risk minimisation control programme applies risk minimisation control tools (see XVI.B.2.3.2.) in addition to routine RMM tools (which may include, if applicable, e.g. pack size restrictions (see XVI.App.1.4.) or specific requirements for the legal status (see XVI.App.1.5.)) and educational/safety advice tools (see XVI.B.2.3.1.).

Such a programme should be considered in rare situations where a serious risk may have a specifically severe impact on the patient and/or public health, which is considered not to be effectively minimised by routine RMM together with educational/safety advice tools alone. These situations may include e.g. risks with possible severe impact for the embryo/foetus/child due to adverse effects of a medicinal product at conception, in utero or through breastfeeding (see GVP Module XVI Addendum I), risks associated with misuse or abuse of a medicinal product with possible severe impact on patient and public health, and risks with advanced therapy medicinal products (ATMPs) that may require specific traceability.

XVI.B.4. Developing materials and dissemination plans for additional risk minimisation measures

Additional RMM, the related materials and dissemination plans need to be developed for implementation at national level (see XCI.C.3.1.). To improve implementability and support the implementation of RMM, the development of the materials and the plan may consider, where available input from patient and healthcare professional representatives (see XVI.B.1.2.) and formative evidence on RMM effectiveness and context (see XVI.B.1.3.). RMM materials and activities for their development should be non-promotional (see XVI.B.1.5.).

XVI.B.4.1. Tailoring of materials to target populations

A target population (see XVI.A.1.4.) should be defined for each additional RMM tool required for a medicinal product. RMM materials should be tailored to the target populations, to facilitate the achievement of the intended outcomes (see XVI.B.1.2.). The tailoring should take into account how the

RMM materials can support that the actions intended for risk minimisation are taken in the given healthcare system and settings and the typical patient environments, in particular through integration of the intended actions in healthcare processes and home routines. Tailoring in terms of adequacy, comprehensibility of language and usability as well as user-friendliness of the RMM material (see XVI.B.4.1.2.) is specifically relevant for special populations using medicinal products, and the guidance in the communication sections in the Product- or Population-Specific Considerations chapters of GVP are applicable for additional RMM materials.

For additional RMM materials targeted at patients, the guidance provided in the Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[12] should be followed as far as applicable by analogy.

XVI.B.4.1.1. Information items in the materials

The information in additional RMM materials should follow the principles of safety communication (see GVP Module XV) and contain the following tailored information items:

- Name of the RMM tool (see XVI.B.2.) as the heading of the additional RMM material;
- Name of the medicinal product as part of the heading, i.e. the invented name and, in brackets, the name of active substance (for a material which refers to more than one medicinal product, see XVI.C.2.2.); in the subsequent text of the material, the invented name should be used as rarely as possible;
- Statements clearly summarising the nature of the risk and specifying the actions to be taken by healthcare professionals or patients to minimise the risk and use the product safely (where warranted, additional RMM materials may elaborate and contextualise the actions for risk minimisation described in the routine RMM materials or present their RMM messages in a different way by using tables, graphics or other visualisations and enhancements);
- Reference to the SmPC or the package leaflet with a reminder to carefully read the SmPC or package leaflet (this may also contain a reference to the SmPC or package leaflet on the website of the competent authority as applicable);
- Statement explaining that the RMM material fulfils the conditions of the marketing authorisation and has been approved by the competent authority, including the version number and the date of its approval in the format "<month> <year>" on the first and/or last page.

National tailoring of RMM materials (see XVI.C.3.1.) may require further information items.

XVI.B.4.1.2. User-testing

Marketing authorisation holders are encouraged where possible or may be required where considered necessary by the competent authority, to user-test draft additional RMM materials with patient and/or healthcare professionals in local contexts (see XVI.B.1.4.). Such user-testing should investigate the materials' adequacy (e.g. for the target populations' settings and their circumstances),

[12] health.ec.europa.eu

comprehensibility and usability (so that diverse patients/healthcare professionals can correctly understand the risk information and identify the actions to be taken for risk minimisation), as well as their user-friendliness (e.g. colours, font type/size, typography, layout, bullet points, summary and table of contents in the case of longer guides for risk minimisation).

Methods for user-testing should build on those established in the areas of e.g. health literacy, risk perception and communication, patient preferences, human factors and implementation sciences. These include testing of draft materials in survey, focus group and scenario-based study designs.

Any interaction with patients or healthcare professionals in this context must not be of any promotional nature to any extent or include any promotional element see (see XVI.B.1.5.).

XVI.B.4.2. Dissemination plans

Dissemination is a crucial step to be optimised along the implementation pathway of RMM (see XVI.B.1.3.), to reach the defined target populations with the RMM materials in their respective healthcare settings and environments. Therefore, marketing authorisation holders should develop and submit plans for the dissemination of additional RMM for approval by competent authorities at national level. These dissemination plans should specify the RMM materials, the target populations, timeframes of (re)dissemination, and, if applicable, the use of supportive dissemination channels for the RMM messages, e.g. healthcare professional or patient organisations, scientific journals and conferences, clinical guidelines, point-of-care aids and training activities (see XVI.B.1.3.).

The timeframes of (re)dissemination should ensure the timely and continuous availability of (amended) RMM materials at healthcare and patient level as a prerequisite of sustainable RMM effectiveness. In the case of long-term treatment, processes for periodically repeated delivery of educational/safety advice materials to a patient may be necessary.

If amendments to additional RMM materials or new RMM have been agreed (see XVI.B.6.), a national dissemination plan to replace the existing with the amended materials at the level of the target populations or to disseminate new RMM should be established by the marketing authorisation holder, agreed with the competent authority at national level and be implemented accordingly.

For the content and format of dissemination plans and supportive communication interventions, templates (see GVP Annex II) and guidance on safety communication (see GVP Module XV) may be applicable as such or by analogy.

XVI.B.4.2.1. Direct healthcare professional communications

A direct healthcare professional communication (DHPC) is a safety communication tool (see GVP Annex I) and may be required to support the dissemination of additional RMM and the implementation of the intended actions for risk minimisation in healthcare, in particular when launching a new or amended additional RMM for a medicinal product. If such DHPC is required, it should be included in the RMM dissemination plan (see XVI.B.4.2.) and the guidance on DHPCs in GVP Module XV should be followed.

XVI.B.5. Evaluating the effectiveness of risk minimisation measures

Evaluating the effectiveness of RMM refers to monitoring outcomes (see XVI.A.1.) of routine and additional RMM of a medicinal product. If for a medicinal product no additional RMM are required in the RMP, studies evaluating RMM effectiveness are not mandatory and outcomes of routine RMM are generally monitored through routine pharmacovigilance activities (see GVP Module V) unless agreed otherwise with the competent authority.

XVI.B.5.1. Scope of studies evaluating risk minimisation measures

Any study relating to an authorised medicinal product conducted with the aim of evaluating the effectiveness of RMM is a post-authorisation safety study (PASS) [DIR Art 1 (15)]. For these studies the guidance in GVP Module VIII should be followed in addition to the guidance in this GVP Module and in GVP Module XVI Addendum II on methods for RMM effectiveness evaluation.

Studies evaluating the effectiveness of RMM should be requested by the competent authority for RMM aimed at minimising risks of major patient and public health importance, considering the nature, seriousness and severity of the risk, the magnitude of population exposure and the amount of public concern.

The study objectives should be defined in relation to the intended outcomes of the RMM (see XVI.B.1.2. and XVI.B.5.3.) and consider possible variations in RMM implementation between countries.

Such studies should be designed to provide evidence enabling an evaluation of whether adaptations to the RMM are warranted, including whether additional RMM materials may be discontinued (see XVI.B.6.).

The discussion of the results of an RMM effectiveness evaluation should consider that national variations in RMM implementation and simultaneous events such as changes in clinical guidelines or reimbursement policies and events impacting healthcare (e.g. a pandemic) or media attention may influence the outcomes of RMM.

In certain situations, RMM may lead to unintended consequences, possibly counteracting the effectiveness of RMM. Therefore, evaluating other outcomes beyond the intended ones (see XVI.B.1.2.) may be appropriate upon request by the competent authority. Such unintended outcomes include, but are not limited to, undue burden of RMM on the patient, healthcare professional or healthcare system and unintended changes in using medicinal products (see Table XVI.5.).

Table XVI.5.: Examples of outcomes of risk minimisation measures in terms of medicinal product use

	Intended outcomes	Unintended outcomes
Switching	RMM recommends that patients are switched to alternative treatment	Patients are switched to a treatment that has a less favourable safety profile for them
Spill-over effect	RMM recommends that the medicine is no longer used in a certain patient population and patients are switched to alternative treatment	The medicine is withheld in a patient population that is not targeted by the RMM and for whom the medicine has a positive risk-benefit balance

	Intended outcomes	Unintended outcomes
Non-treatment	The medicine is no longer authorised and used in an indication as the benefit is no longer considered to outweigh the risks	No alternative treatment is used even though an alternative is available to treat patients with this indication
Lack of adherence to treatment	N/A	Treatment with the medicine is not adhered to by the patient
Additional prescribing	RMM recommends the use of a medicine in the target population in combination with another medical intervention (e.g. as preventive measure)	RMM no longer recommends the use of a medicine in a population, but treatment is continued in combination with another medicine (e.g. to treat adverse reactions)

XVI.B.5.2. Schedule and documentation of studies evaluating risk minimisation measures

Details of how RMM effectiveness will be evaluated should be included in the RMP (see XVI.C.1.2.).

For a specific RMM, several factors will determine the appropriate timepoints for evaluation, including time since launch or implementation of the RMM (see XVI.B.1.3.), estimated magnitude of exposure, seriousness and severity of the risk and the design of the proposed studies evaluating RMM effectiveness. The following timepoints should be considered by marketing authorisation holders for establishing and agreeing schedules with competent authorities:

- After regulatory implementation an initial evaluation of RMM, e.g. within 12-24 months to allow the possibility of necessary changes in healthcare; and
- Within 4 years of regulatory implementation the overall effectiveness evaluation of the RMM (see XVI.B.5.3.), which, where applicable, can also inform the evaluation of the renewal of a marketing authorisation.

The submissions for studies evaluating RMM effectiveness that fall under PASS category 1 or 3 are to be submitted according to guidance in GVP Modules V and VIII, the EMA Guidance on Post-Authorisation Safety Studies[13] and the EMA Post-Authorisation Guidance[14].

Results of any RMM effectiveness evaluation activity should be included in the periodic safety update reports (PSURs) (see XVI.C.1.3.), including a discussion on the need for RMM adaptations (see XVI.B.5.4. and XVI.B.6.).

XVI.B.5.3. Objectives and approaches of studies evaluating risk minimisation measures

In accordance with the scope of RMM effectiveness evaluation (see XVI.B.5.1.), the study objectives include investigating the:

- Extent to which the RMM has been disseminated to the target population(s) as planned (see XVI.B.4.); and,

[13] https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass
[14] ema.europa.eu/en/human-regulatory-overview/post-authorisation

- Extent to which the RMM has led to the intended knowledge and behaviours in the target population(s), or whether other behavioural outcomes have occurred; and
- Extent, as measurable, to which the intended health outcomes have been achieved within relevant timeframes, or whether other health outcomes have occurred.

Study objectives may differentiate between studying the RMM messages and the individual RMM tool(s) (see XVI.A.1.1.).

Different approaches to data collection and analysis may be applied to investigating each step of the RMM implementation process (see XVI.B.1.3. and Figure XVI.3.), as appropriate.

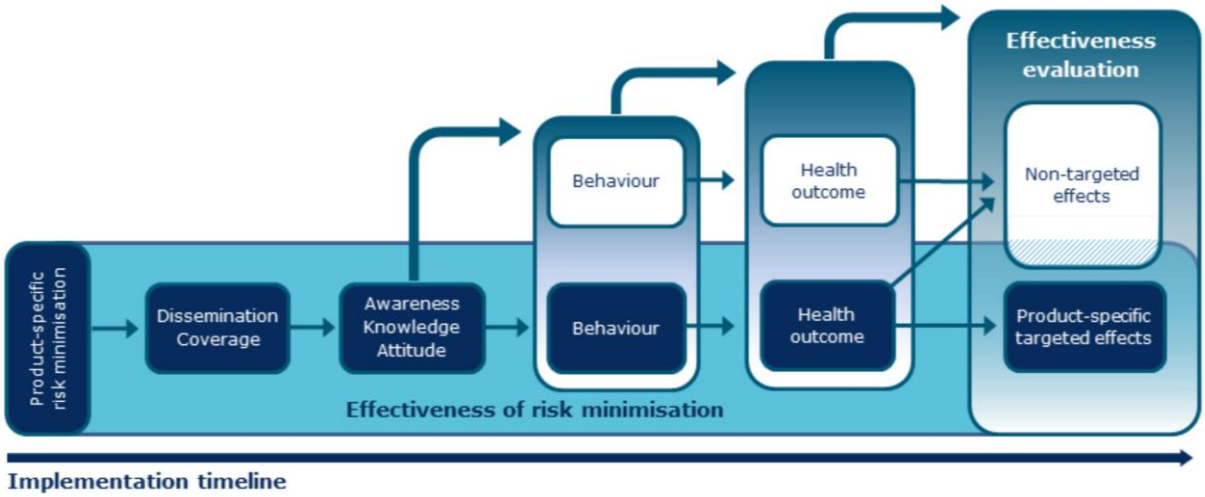

Figure XVI.3.: Approach to evaluating the effectiveness of risk minimisation measures
Note: This approach includes measuring *medicinal product-specific targeted effects* (intended outcomes) and, as appropriate, relevant *non-targeted effects* (unintended outcomes) associated with the use of the concerned (blue boxes) and other medicinal products (white boxes).

Measurements and indicators of RMM effectiveness (see XVI.B.5.4.) should be defined in the study protocol; the choice of indicators for success should be duly justified. Marketing authorisation holders and competent authorities may agree on indicators of success to be included in the RMP (see XVI.C.1.2.). Depending on the study objectives, a combination of qualitative and quantitative research methods is recommended. Figure XVI.5. provides an overview of qualitative and quantitative research outcomes that may evaluate the different steps of the implementation process of RMM. Using quantitative measurements (e.g. prescription levels, medicines utilisation patterns, health outcomes) for evaluating the effectiveness of RMM is particularly important and should be considered, where feasible. Qualitative research may be useful for informing the objectives and the conduct of quantitative research, e.g. with regards to the target populations, healthcare or patient home settings and the context of medicines use, and for understanding the reasons for success or failure of RMM (e.g. lack of intended knowledge or behaviour). Such findings may be relevant when regulatory actions for adapting RMM are considered (see XVI.B.5.4. and XVI.B.6.).

The methodological approach should be risk-proportionate and provide results that are meaningful for further regulatory decision-making without placing undue burden on healthcare systems or patients.

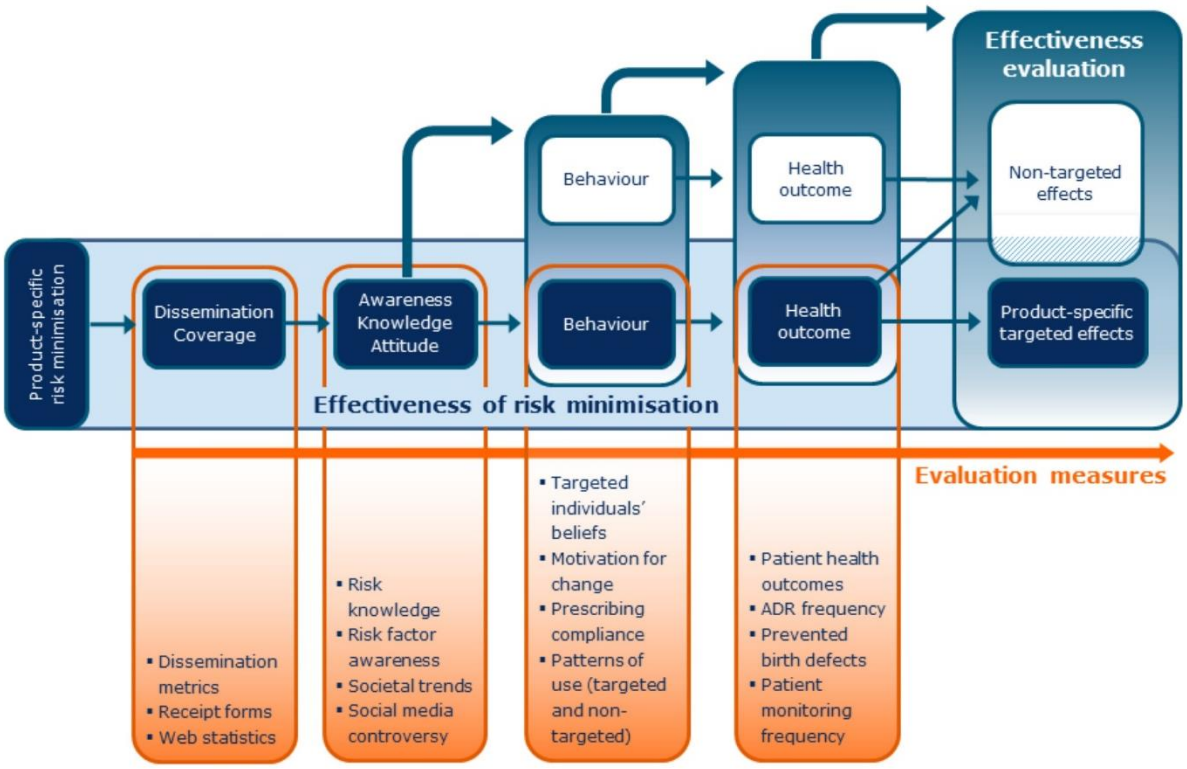

Figure XVI.5.: Approach to effectiveness evaluation of risk minimisation measures with examples of quantitative and qualitative research findings at each implementation step for measuring medicinal *product-specific targeted effects* (intended outcomes) and, as appropriate, relevant *non-targeted effects* (unintended outcomes) associated with the use of the concerned (blue boxes) and other medicinal products (white boxes)

XVI.B.5.3.1. Dissemination and knowledge outcomes

Each stage from dissemination of information on RMM to knowledge adoption by the target populations should be considered during RMM effectiveness evaluation (see Figure XVI.3.).

Dissemination methods and individual perceptions of RMM influence the knowledge of the target population about the risk and the intended actions for risk minimisation. Quantitative measurements of the stages of the risk communication process of dissemination and perception may help to understand the dissemination and knowledge adoption and identify ineffective dissemination processes/barriers and knowledge gaps. When used in combination with quantitative research, qualitative measures of the communication process may help to understand factors influencing risk perception and knowledge adoption, including enablers and barriers. Knowledge may be assessed through qualitative research methods involving e.g. semi-guided interviews and/or focus groups, or through quantitative surveys (see GVP Module XVI Addendum II).

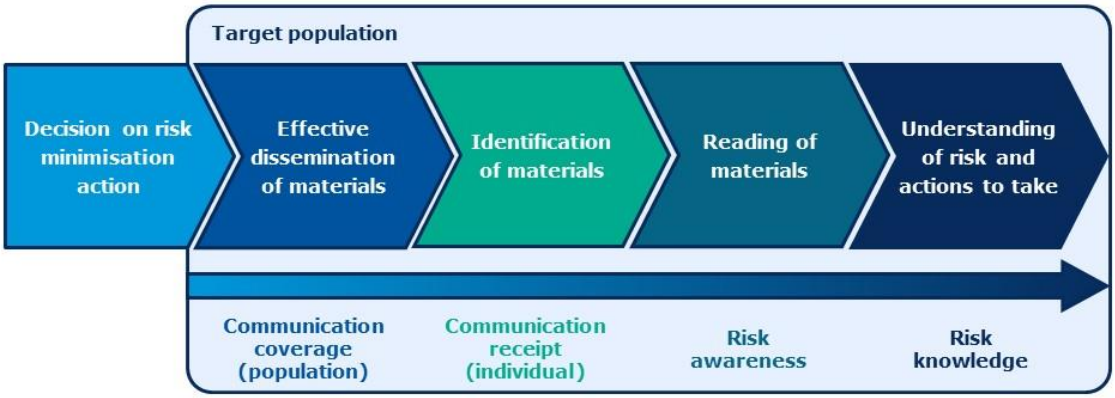

Figure XVI.4.: Pathway of the risk communication process from dissemination to adoption of the knowledge intended by risk minimisation measures

Examples of quantitative measurements and qualitative findings to address RMM dissemination and knowledge-related study objectives are provided in Table XVI.6..

Table XVI.6.: Examples of quantitative measurements and qualitative findings addressing dissemination of risk minimisation measures and knowledge intended by the measures

Quantitative measurements for dissemination and knowledge outcomes
Proportion of target population for which RMM dissemination has been completed over time (in total and e.g. by RMM tool, country or type of healthcare professional)
Download total/webpage view frequency of RMM materials provided on the web, taking into account appropriate denominators depending on the context of the RMM
Proportion of healthcare professionals and patients aware of the RMM and using the educational tools and other sources of information (e.g. information from learned societies)
Level of awareness, comprehension, recall of information and knowledge of healthcare professionals and patients concerning the RMM tool and its messages
Qualitative findings for dissemination and knowledge outcomes
Attitudes (see XVI B.1.3.) 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 (e.g. some healthcare professionals and/or patients are not convinced that there should be a contraindication)
Identification of environmental factors of healthcare systems and patient setting impacting on RMM implementation, e.g. available resources and constraints in clinical pathways and time for dissemination
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 (e.g. social media)

XVI.B.5.3.2. Behavioural outcomes

RMM should be evaluated with a view to achieving the intended actions for risk minimisation and other behaviours in medicines use. Factors that may be enablers or barriers for adopted knowledge to result in intended actions are illustrated in Figure XVI.6.. These enablers and barriers may impact on the feasibility of the RMM in practice.

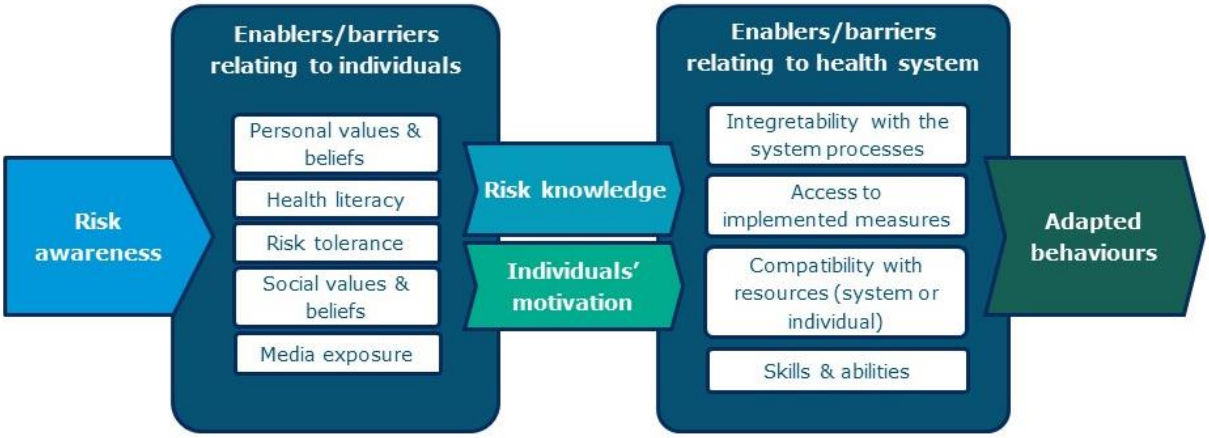

Figure XVI.6.: Pathway from risk awareness to risk minimising actions including enablers and barriers of intended behaviours

Intended actions for risk minimisation and other behaviours 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, or study the extent of the impact of enablers or barriers identified through qualitative research.

Examples of quantitative measurements and qualitative findings to address behavioural outcomes of RMM are provided in Table XVI.7..

Table XVI.7.: Examples of quantitative measurements and qualitative findings addressing behavioural outcomes of risk minimisation measures

Quantitative measurements for behavioural outcomes
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 test) prior, during or after the exposure to a medicinal product
Proportion of co-prescribing of one or more interacting medicinal products
Proportion of (potential) dosing errors
Quantification of 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 RMM and related attitudes)
Extent to which the medicine user was able to perform and maintain the desired behaviour over time (e.g. no prescription in specific contraindications)
Frequency of requests from healthcare professionals for refills of educational materials or other RMM tools as proxies of RMM tool utilisation
Patient-reported outcome measures (PROM) and patient-reported experience measures (PREM) complementing clinical outcome assessments (e.g. of biomarkers, morbidity, or survival data) may be considered where validated health measurement instruments are available
Qualitative findings for behavioural outcomes
Awareness of the intended action for risk minimisation as a prerequisite for the intended behaviour (e.g. a new contraindication is not known by some healthcare professionals and/or patients)
Attitude towards the intended action for risk minimisation as a prerequisite for the intended behaviour (e.g. some healthcare professionals and/or patients are not convinced that there should be a contraindication)

Quantitative measurements for behavioural outcomes
Use of alternative treatments (e.g. despite the contraindication, some patients still need treatment)
Difficulties in implementing RMM in relation to healthcare system (e.g. limited access to diagnostic tools)

XVI.B.5.3.3. Health outcomes

Monitoring and investigating measurable health outcomes evaluates whether implemented RMM have achieved the intended patient and public health impact and avoided adverse health outcomes. Changes in health outcomes may only be partially influenced by RMM. Other factors including changes in clinical guidelines or healthcare practices (e.g. therapeutic monitoring) need to be considered. These factors should be identified and assessed where possible as part of RMM effectiveness evaluations.

Examples of quantitative measurements to address health outcomes-related study objectives are provided in Table XVI.8..

Table XVI.8.: Examples of quantitative measurements addressing health outcomes of risk minimisation measures

Quantitative measurements for health outcomes
Incidence rate or cumulative incidence of an adverse reaction, including stratification by severity to determine changes in severity
Incidence rate or cumulative incidence of pregnancies during treatment under the conditions of a risk minimisation control programme designed to prevent adverse pregnancy outcomes
Incidence rate or cumulative incidence of health outcomes of interest, including surrogate endpoints if actual endpoints cannot be measured

XVI.B.5.4. Interpretation of the results of studies evaluating effectiveness of risk minimisation measures

The interpretation of the results of studies evaluating the effectiveness of RMM should support evidence-based decisions as to whether adaptations to RMM are warranted, including whether additional RMM tools may be discontinued. In some instances, important unintended outcomes of RMM (see Table XVI.5.) may warrant regulatory follow-up action (see XVI.B.6.).

National tailoring of RMM agreed at EU level (see XVI.C.3.1.) should be considered in the interpretation of results.

Indicators for success should be determined a priori and specifically for the given RMM. Threshold values may be defined by using e.g. baseline or historical data, expected frequency in similar populations or of similar risks where feasible. Table XVI.9. includes a list of factors for consideration when determining success (or failure) of RMM. The therapeutic/clinical context, local specificities (e.g. clinical guidelines) but also other dimensions (e.g. ethical or societal acceptability) based on e.g. input from patient and healthcare professional organisations (see XVI.B.1.4.) should be taken into account as appropriate.

Where the results of RMM effectiveness studies indicate that e.g. a pre-defined threshold has been met, this suggests that the intended outcomes of the RMM for a specific medicinal product have been achieved. On the other hand, failure to meet a pre-defined threshold may require further investigation

to obtain a clear understanding of the reasons that could help explain the failure (e.g. qualitative research, see XVI.Add.II.2.1. and XVI.Add.II.3.1.) and may form the basis to initiate appropriate regulatory action as needed.

Table XVI.9.: Factors for consideration when determining success or failure of risk minimisation measure effectiveness

Factors for consideration when determining success or failure of RMM effectiveness	
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) • Comorbidities • Pregnant women • Frailty • Possibility of taking an informed decision (e.g. access to package leaflet, need for urgent treatment, patients with different chronic disease)
Risk	• Seriousness of the risk (see GVP Annex I) • 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	• Variability between populations and countries (e.g. national adaptations to implementation of RMM agreed at EU level) • 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 companies, case law, other technological areas)

XVI.B.6. Adapting risk minimisation measures within the benefit-risk management cycle of the medicinal product

Within the benefit-risk management cycle for a medicinal product (see XVI.B.1.1.) in the post-authorisation phase, it may be necessary to adapt existing RMM, i.e. to:

- Amend existing RMM in terms of e.g. the risk information, intended clinical action, target populations, tool, design of materials or dissemination plan;
- Discontinue one or more of the existing additional RMM; or
- Introduce new RMM.

When considering adapting existing RMM, marketing authorisation holders and competent authorities should apply the points to consider in Table XVI.4. and Table XVI.10..

Table XVI.10.: Points to consider for adapting existing risk minimisation measures

Points to consider for adapting existing RMM
Evolving knowledge on the safety profile of the medicinal product and related updates to the RMP and/or product information (see XVI.C.1.)
Changes to the marketing authorisation of the medicinal product, e.g. expansions to a new indication or patient population, or a new pharmaceutical form or dosing schedule
Evidence derived from RMM effectiveness evaluation studies conducted by marketing authorisation holders or others (see XVI.B.5.), the robustness of the methods and study conduct and the overall conclusiveness of their results
Representativeness of the responders of the study population of an RMM effectiveness evaluation study, the characteristics of those who have not contributed to achieving an RMM effectiveness threshold, and considerations regarding in how far the results can be extrapolated to the non-responders of the study population
Need for continued dissemination of additional RMM materials for maintaining a positive risk-benefit balance of the medicinal product in all patient populations and addressing the need for advice of patients and healthcare professionals
Changes in healthcare processes and other relevant contextual factors
Adverse unintended outcomes of the RMM
Worldwide experience with RMM

Engagement with patient and healthcare professional representatives (see XVI.B.1.4.) may support the considerations for adapting existing RMM, the development of amended or new RMM materials and/or dissemination plans (see XVI.B.4.) and the implementation of adapted RMM in healthcare (see XVI.B.1.3.).

Any proposal for adapting RMM for a medicinal product should be accompanied by a rationale and the underlying evidence or other relevant information. The marketing authorisation and the RMP, if the medicinal product has a RMP, should be updated with the agreed RMM adaptations (see XVI.C.1.).

If amendments to additional RMM materials have been agreed, a national dissemination plan should be implemented (see XVI.B.4.2.).

XVI.B.6.1. Impact of adapted risk minimisation measures on requiring studies evaluating their effectiveness

Adaptations to the RMM (see XVI.B.6.) or inconclusive results of studies evaluating RMM effectiveness (see XVI.B.5.4.) may require a new study to evaluate existing, amended or new RMM or the impact of discontinuing a RMM material (see XVI. B.5.).

The RMP is to be updated accordingly (see XVI.C.1.2.).

XVI.B.7. Quality systems for risk minimisation

Marketing authorisation holders and competent authorities should apply all their requirements for the quality management of pharmacovigilance systems, including the quality improvement cycle, the principles for good pharmacovigilance practices and the requirements for pharmacovigilance record management, (see GVP Module I) to all RMM-related processes and documents.

Marketing authorisation holders shall have specific quality system procedures and processes in place to ensure:

- Examination of options for risk minimisation and prevention [IR Art 11(1)(a)];
- Taking, by the marketing authorisation holder, of appropriate measures [IR Art 11(1)(a)]; and
- Effective communication with the competent authorities on new risks or changed risks, the risk management system and RMM [IR Art 11(1)(e)].

For this purpose, marketing authorisation holders should also:

- Establish and follow processes to ensure that RMM materials meet the quality requirements and are subject to version control (see XVI.B.4.1.);
- Establish and follow processes to ensure that the RMM are disseminated to healthcare professionals and patients according to the dissemination plan (see XVI.B.4.2.), and to keep records of the dissemination process and outcomes (e.g. records of receipt of RMM materials at healthcare sites);
- Establish and follow processes to ensure compliance, at the level of the marketing authorisation holder, with the tools of a risk minimisation control programme and to keep records thereof; and
- Follow the quality requirements for RMPs (see GVP Module V) and PASS (see GVP Module VIII).

A description of the process, data handling and records for the performance of continuous monitoring of the risk-benefit balance of the medicinal product, the monitoring result and the decision-making process for taking appropriate measures, and the monitoring of RMM outcomes shall be included in the pharmacovigilance system master file (PSMF) [IR Art 2(4)(a)-(b)], to be maintained by the marketing authorisation holder [DIR Art 104(3)(b)] (see GVP Module II).

XVI.C. Operation of the EU network

XVI.C.1. Required risk minimisation measures and their evaluation as part of the marketing authorisation in the EU and related documents

XVI.C.1.1. Marketing authorisation, including the product information

In the EU, the marketing authorisation of a medicinal product includes the product information (i.e. the SmPC, package leaflet and labelling of the immediate and outer packaging), the specification of the legal status and the pack size, and, if required, a request for a visual reminder and/or a special warning/information for precaution on the product information as routine RMM (see XVI.B.2.2.), as well as, if required, a listing of the required additional RMM tools and a brief summary of the RMM messages (see XVI.A.1.1.) at the level of detail appropriate for the given medicinal product and risk. Therefore, RMM form an obligation on the marketing authorisation holder in the EU.

When RMM are adapted (see XVI.B.6.), the marketing authorisation is to be updated accordingly.

The specific additional requirements for reflecting a patient card in the marketing authorisation are provided in XVI.App2.5..

XVI.C.1.2. Risk management plan

The required RMM and the activities for their effectiveness evaluation should be included in the risk management plan (RMP) (see GVP Module V) of the medicinal product, which is part of its EU marketing authorisation (see XVI.C.1.1.).

The RMP part V should include the risk minimisation plan, describing, for each safety concern in the safety specification of the RMP, the RMM tools (see XVI.B.2.) with their most important intended outcomes (see XVI.B.1.2.) and the justification for each tool, and describing the development and planning activities for RMM implementation (see XVI.B.4.). It should also include a brief summary of the results of the studies evaluating RMM effectiveness as the justification for adaptations to RMM (see XVI.B.6.). Any adaptation to RMM should be accompanied by a rationale and the underlying evidence or other relevant information (for the content of the RMP part V for a biosimilar, hybrid or generic medicinal product where the marketed reference medicinal product does not have any aRMM, see XVI.C.2.2.).

RMP annex 6 should include a listing of the required additional RMM tools and their messages (see XVI.A.1.1.) at the level of detail appropriate for the given medicinal product and risk (RMM key elements).

The RMP part III on the pharmacovigilance plan and RMP part V should include a description of the activities for evaluating the effectiveness of RMM. Protocols and milestones for RMM effectiveness studies should be included in the RMP part III. Marketing authorisation holders and competent authorities may agree on indicators of success to be included in the RMP (see XVI.B.5.).

The RMP should be kept updated with adaptations to RMM (see XVI.B.6.) and new studies required for evaluating RMM effectiveness (see XVI.B.6.1.).

XVI.C.1.3. Periodic safety update report

The periodic safety update report (PSUR) shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment [IR Art 34(3)].

Therefore, the PSUR should include in its sub-section "Effectiveness of risk minimisation (if applicable)" and the applicable sections of the PSUR EU regional appendix (see GVP Module VII) updates on the implementation (including the development and dissemination) of RMM, the results of the studies evaluating RMM effectiveness, applying the guidance in XVI.B.5., and a discussion on the possible need to adapt the RMM (see XVI.B.6.) and/or the activities required to evaluate the RMM effectiveness (see XVI.B.6.1.).

XVI.C.2. Responsibilities of the applicant/marketing authorisation holder in the EU

The RMM in the marketing authorisation pose an obligation on the marketing authorisation holder in the EU (see XVI.C.1.1.), and the marketing authorisation holder shall by means of its pharmacovigilance system evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary [DIR Art 104(2)].

The applicant for a marketing authorisation shall submit the application accompanied by the RMP [DIR Art 8(3)(iaa)]. The RMP shall describe the risk management system [DIR Art 1(28c)] and also contain a documentation of the RMM, including an assessment of their effectiveness [IR Art 30(1)(c), DIR Art 1(28b)]. The marketing authorisation holder shall operate the risk management system, monitor the outcome of RMM which are contained in the RMP and/or laid down as conditions of the marketing authorisation (pursuant to DIR Art 21a, 22 or 22a), and update the risk management system [DIR Art 104(3)(c)-(e)] (see (see XVI.C.1.2.).

Therefore, when proposing initial or adapted RMM, the applicant/marketing authorisation holder should follow the guidance in XVI.B.1, XVI.B.2., XVI.B.3. and XVI.B.6..

The marketing authorisation holder should develop the required additional RMM materials and a dissemination plan following the guidance in XVI.B.4., addressing the needs for national tailoring (see XVI.C.3.1.), and submit to the competent authorities in Member States the draft materials in the official language(s) as required by the respective Member State and the draft national dissemination plan (see XVI.C.2.1.). For a risk minimisation control programme (see XVI.B.2.3.2.), the marketing authorisation holder should discuss the development, dissemination and maintenance of the RMM and the RMM materials required for the programme with the competent authorities in Member States. The marketing authorisation holder should inform the competent authorities in Member States about any important changes or issues which impact on the previously agreed dissemination plan, together with an updated plan addressing the encountered changes or issues. If amendments to additional RMM materials have been agreed (see XVI.B.6.), a national dissemination plan to replace the existing with the amended materials at the level of the target populations should be submitted by the marketing authorisation holder to the competent authorities for agreement.

The additional RMM materials should have been approved by the competent authorities in Member States before dissemination by the marketing authorisation holder in accordance with the agreed national dissemination plan. If the medicinal product is not placed on the market in a Member State, dissemination of the materials in that Member State is usually not required, but this should be discussed with the competent authority of each Member State as the materials may still be needed, e.g. for imported medicinal product for named patient use.

For the evaluation of RMM effectiveness, the marketing authorisation holder should follow the guidance in XVI.B.5. and XVI.B.6.1.. When requested, the draft protocols of the studies in the RMP for evaluating RMM effectiveness should be submitted by the marketing authorisation holder for regulatory assessment. The process for submission of the study results depends on the study category and should follow the guidance in GVP Modules V and VIII, the EMA Guidance on Post-Authorisation Safety Studies[15] and the EMA Post-Authorisation Guidance[16]. The results of any assessments of RMM effectiveness shall be contained in the PSUR [IR Art 34(3)], to be submitted by the marketing authorisation holder for the medicinal product [DIR Art 107b, REG Art 28 (2)] (see XVI.C.1.3.).

[15] https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/post-authorisation-safety-studies-pass
[16] ema.europa.eu/en/human-regulatory-overview/post-authorisation

If the marketing authorisation holder becomes aware of information regarding the risk and/or the RMM that may impact the risk-benefit balance and/or the RMM of the medicinal product in a way that may constitute an emerging safety issue (ESI), this should be reported as an ESI (see GVP Module IX).

For further specific operations in the EU, the marketing authorisation holder should follow other applicable guidance in XVI.C., and for specific operations in Member States additionally the national guidance in Member States where such guidance is available.

Overall, the marketing authorisation holder should follow the guidance on the principles for risk minimisation in XVI.B.1., in particular regarding the non-promotional nature of the RMM as well as their studies evaluating RMM effectiveness (see XVI.B.1.5.). For the quality systems requirements, the marketing authorisation holder should follow the guidance in XVI.B.7..

XVI.C.2.1. Submission of materials and dissemination plan for additional risk minimisation measures to the competent authorities in Member States

Draft additional RMM materials should be submitted by the marketing authorisation holder to the competent authorities in Member States for approval after the conclusion of the regulatory procedure through which the additional RMM has been required or amended, together with the draft national dissemination plan for agreement.

If no other national requirements apply, the submission should contain the following:

- Cover letter and/or national request form including the following information:
  - the contact details of the marketing authorisation holder and, if applicable, another organisation to which it has subcontracted the submission (with the names and e-mail addresses of the contact persons);
  - the regulatory procedure which has led to the additional RMM materials being submitted with supportive documents (e.g. PRAC recommendation, CHMP opinion, CMDh position, European Commission decision with relevant annexes, national competent authority opinion, approved RMP)
  - the applicable SmPC text;
- Draft additional RMM materials in a common open text-processing electronic format in the official language(s) required by the respective Member State;
- Sample of the intended layout of the additional RMM materials, including where applicable, tables, graphics or other visualisations and enhancements;
- Results from user-testing of draft additional RMM materials, where applicable; and
- Draft national dissemination plan.

If the submission concerns an amendment of an existing RMM material, the changes to the material should be highlighted.

XVI.C.2.2. Coordination of activities for risk minimisation measures across medicinal products containing the same active substance

The marketing authorisation holder for a biosimilar, hybrid or generic medicinal product should have in place the same RMM as required for the marketed reference medicinal product, unless requested otherwise by the competent authorities.

When the marketed reference medicinal product does not have additional RMM, a statement that the safety information in the product information of the biosimilar, hybrid or generic medicinal product is aligned with the reference product is sufficient for the RMP part V.

Where additional RMM materials for a generic, biosimilar or a hybrid medicinal product are identical to the user-tested materials for the reference product, no further user-testing is needed for the generic, biosimilar or hybrid product, unless testing in a not yet tested language is requested by the competent authorities. The marketing authorisation holder for a biosimilar, hybrid or generic medicinal product should develop and agree with the competent authorities national dissemination plans for the RMM materials applicable to their product (see XVI.B.4.2.).

When several medicinal products containing the same active substance, such as generic, biosimilar and hybrid products, have been authorised and require the same additional RMM, their marketing authorisation holders are encouraged to collaborate for fulfilling the responsibilities applicable to each individual marketing authorisation holder (see XVI.C.2.) through coordination of a consistent approach to developing, disseminating, evaluating and adapting RMM materials. Without prejudice to the originality of the format of a RMM material, it is in the interest of patient safety that RMM materials disseminated by different marketing authorisation holders for the same active substance should be kept consistent and as similar as possible, to avoid confusion in the target population.

When a common additional RMM material is developed for more than one medicinal product containing the same active substance, the material may refer only to the name of active substance, and not to all invented names of the concerned medicinal products. Where additional RMM are fully identical with the one for the marketed reference product, there is usually no need for the marketing authorisation holder of the generic, biosimilar or hybrid product to conduct a study evaluating RMM effectiveness for their product, if such a study is already ongoing for the reference product. However, if a considerable proportion of medicines use is expected to possibly be contributed by (a) generic, biosimilar or hybrid product(s), the respective marketing authorisation holder(s) may be requested to conduct a study evaluating RMM effectiveness.

Where a study evaluating RMM effectiveness is conducted jointly by several marketing authorisation holders for their products containing the same active substance or covers otherwise more than one medicinal product containing the same active substance, data collection may be independent of the (invented) names of the medicinal products (e.g. based on the anatomical-therapeutic-chemical (ATC) code of the active substance[17]).

Where the marketing authorisation holder for a generic, biosimilar or hybrid medicinal product is not required to conduct a study to evaluate RMM effectiveness, updates on the dissemination of the

[17] https://www.who.int/tools/atc-ddd-toolkit/atc-classification

additional RMM materials by the marketing authorisation holder and results from RMM effectiveness evaluations through routine pharmacovigilance activities should still be included in the PSURs for the concerned product (see XVI.C.1.3.).

XVI.C.3. Responsibilities of the EU regulatory network

XVI.C.3.1. Competent authorities in Member States

The general role of the competent authorities in Member States for pharmacovigilance in the EU is described in GVP Module I and for risk management in particular in GVP Module V.

Regarding risk minimisation activities, Member States shall by means of their competent authority's pharmacovigilance system evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning marketing authorisations as necessary [DIR Art 101(2)].

For medicinal products authorised nationally by competent authorities in Member States, including those authorised through the mutual recognition procedure or the decentralised procedure, the competent authorities in Member States may impose in the marketing authorisation (see XVI.C.1.1.) an obligation on the marketing authorisation holder to describe and operate a risk management system in the RMP (see XVI.C.1.2.) [DIR Art 104a(2)] and shall monitor the outcome of RMM and assess updates to the risk management system [DIR Art 107h(1)(a) and (b)]. For products authorised nationally through the mutual recognition procedure or the decentralised procedure, the competent authority in a Member State may require additional RMM only for this Member State.

For nationally authorised products subject to a safety-related EU referral procedure, the European Commission may adopt a decision addressed to Member States for the implementation of conditions or restrictions of the marketing authorisation, such as RMM, to be adhered to by the competent authorities in Member States [DIR Art 107k(2) and Art 33 and 34].

For medicines authorised by the European Commission through the centralised procedure, the European Commission may adopt a decision addressed to Member States for the implementation of conditions or restrictions of the marketing authorisation [DIR Art 127a], such as RMM, to be adhered to by the competent authorities in Member States. For centrally authorised products, the competent authorities in Member States shall collaborate with the Agency to monitor the outcomes of RMM and assess updates to the risk management system [based on REG Art 28a(1)(a) and (b)] (see XVI.C.3.2.).

Irrespective of the route of marketing authorisation, the competent authorities in Member States are responsible for the approval of nationally tailored additional RMM materials and the agreement of the national RMM dissemination plans (see XVI.B.4.) and should therefore ensure prompt consideration of the respective submissions by marketing authorisation holders (see XVI.C.2.1.).

Because of the specifics and differences of the healthcare systems in Member States and of how particular risk(s) are managed within these systems, some RMM may need to be implemented differently in Member States. As the implementation of additional RMM takes place at national level,

Member States may tailor the required conditions and restrictions for risk minimisation to their national legal requirements and local healthcare systems. The national tailoring of RMM materials should address the specifics of the healthcare systems in Member States, e.g. applicable subgroups of the target population, naming of the RMM tool and full wording of the RMM material in the official language(s), additional information items, design and formatting, dissemination, with a view to best support the implementation of the RMM in healthcare. Member States may also have specific requirements for using educational/safety advice materials to document healthcare processes, including confirmations through signatures of the healthcare professional or the patient. Especially for risk minimisation control programmes, the competent authorities in Member States should determine and discuss with the marketing authorisation holder how the applicable RMM tools can be implemented in healthcare and which RMM materials are needed for these tools in accordance with the nationally established processes for training and qualification of healthcare professionals, accreditation of healthcare facilities, healthcare documentation and information exchange, and traceability. Risk minimisation control programmes can be supported in their implementation in healthcare by national healthcare processes, e.g. restrictions in amount of medicinal product allowed per prescription or in the validity length of a prescription.

Competent authorities in Member States are encouraged to, as needed, appropriate and possible, seek input from healthcare professional and patient representatives (see XVI.B.1.4.), request from the marketing authorisation holder user-testing of additional RMM materials in the respective official language(s), and consider results from user-testing of RMM when requested from and/or submitted by the marketing authorisation holder. Interactions between the competent authorities in Member States and stakeholders responsible for implementation of RMM in healthcare (see XVI.B.1.3.) are desirable; in particular for risk minimisation control programmes such interactions may be needed to determine how their RMM tools may be best integrated in healthcare processes and which RMM materials are needed to implement the tools. Member States should verify the independence of the representatives for impartial advice, in particular the independence from marketing authorisation holders.

For the purpose of risk minimisation, the competent authorities in Member States should follow the guidance in XVI.B. and XVI.C., including the guidance on transparency in XVI.C.4..

XVI.C.3.2. The European Medicines Agency

The general role of the Agency for pharmacovigilance in the EU is described in GVP Module I and for risk management in particular in GVP Module V.

For medicinal products authorised by the European Commission through the centralised procedure, the Agency conducts the assessments, including on RMM which are to be included in the marketing authorisation (see XVI.C.1.1.) and the RMP (see XVI.C.1.2.). The imposition of such obligations shall be duly justified, notified in writing and shall include the timeframe for submission of the RMP [REG Art 21(2)] (see GVP Module V). Further, the Agency shall, in collaboration with the Member States, monitor the outcomes of RMM and assess updates to the risk management system for centrally authorised products [REG Art 28a(1)(a) and (b)].

For medicinal products authorised nationally by competent authorities in Member States, including those authorised through the mutual recognition procedure or the decentralised procedure (see XVI.C.3.1.), the Agency supports the applicable procedures relevant to RMM activities at EU level.

For nationally authorised products subject to a safety-related EU referral procedure, the Agency conducts these procedures in accordance with the legislation and guidance on Referral procedures: human medicines[18].

The Agency fulfils its legal obligations through the procedures of its Committees, for safety of medicinal products in particular the Committee for Medicinal Products for Human Use (CHMP)[19] and the PRAC (see XVI.3.1.1.), and through supporting the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh)[20] (see GVP Module I).

For the purpose of risk minimisation, the Agency should follow the guidance in XVI.B. and XVI.C., including the guidance on transparency in XVI.C.4..

XVI.C.3.2.1. The Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment Committee (PRAC) (see GVP Module I) shall be responsible for providing recommendations to the CHMP and the CMDh on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems and shall be responsible for monitoring the effectiveness of those risk management systems [REG Art 56(1)(aa)], which includes the RMM and the RMM effectiveness evaluation studies.

Therefore, the PRAC should provide assessments of risks and consider the need for RMM applying the guidance in XVI.B.1., XVI.B.2., XVI.B.3. and XVI.B.6., and if they recommend RMM, specify the tools and messages (see XVI.A.1.1.) in the PRAC recommendation. The PRAC recommendation may also relate to the development and dissemination of additional RMM materials, including the need for a DHPC (see XVI.B.4.2.1.).

Further, the PRAC recommendation may include studies to be requested from the marketing authorisation holder for evaluating RMM effectiveness. The PRAC should assess as appropriate the protocols and results of these studies for regulatory follow-up, taking into account the guidance in XVI.B.5. and XVI.B.6. and other available guidance.

To improve regulatory decision-making on RMM, the PRAC has adopted a strategy for measuring the impact of pharmacovigilance activities[21].

XVI.C.3.2.2. Engagement with patients and healthcare professionals at EU level

The PRAC engages with patient and healthcare professional representatives to support its decision-making on risk minimisation (see XVI.B.1.4.).

[18] ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines
[19] ema.europa.eu
[20] hma.eu/human-medicines/cmdh/about-cmdh.html
[21] ema.europa.eu/en/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities_en.pdf

For their medicinal product assessments, the PRAC therefore involves its members representing patients and healthcare professionals in discussing options for RMM and their implementability for anticipated RMM effectiveness (see XVI.B.1.3.) and considers further involvement of patient and healthcare professional representatives as needed, appropriate and possible for the assessment through the ways and forums established by EMA's frameworks for engaging with partners and networks[22]. These ways and forums include written consultations, scientific advisory groups, ad hoc expert groups and public hearings (see Rules of Procedure on the Organisation and Conduct of Public Hearings at the Pharmacovigilance Risk Assessment Committee[23]).

The PRAC may also seek their input on general matters relevant to implementing RMM in healthcare from its members representing patients and healthcare professionals and further representatives from eligible organisations belonging to EMA's partners and networks.

XVI.C.4. Transparency

The Agency shall make public the agendas and minutes from each meeting of the CHMP, the PRAC and the CMDh (see XVI.C.3.) as regards pharmacovigilance activities [REG Art 26(1)(b)], which includes activities on RMM.

For centrally authorised products, the Agency has legal obligations [DIR Art 21(3), DIR Art 21(4), DIR Art 106(a), DIR Art 106(b), DIR Art 106(c), REG Art 13, REG Art 26(1)(c), REG Art 26(1)(j), REG Art 57(2), IR Art 31(1)] to make public the European public assessment report (EPAR), the conditions of the marketing authorisation, which includes RMM, together with any deadlines for the fulfilment of those conditions, the SmPC, the package leaflet, the information on the outer and inner packaging, and information on the RMP including information on any additional RMM. Further, the Agency has transparency obligations for medicinal products subject to an EU referral procedure [REG Art 26(1)(i)]. To fulfil the obligations, the Agency follows the EMA Publication Policy "What we publish on medicines, and when"[24].

For nationally authorised products, the competent authorities of Member States shall make public assessment reports, conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions, the SmPC, the package leaflet, the information on the outer and inner packaging and a summary of the RMP with specific focus on RMM [DIR Art 21(3), DIR Art 21(4), Art 106(a), Art 106(b), DIR Art 106(c), IR Art 31(1)].

To promote public health, it is encouraged that the Agency and the competent authorities in Member States make available via their websites details on additional RMM materials.

Guidance on transparency applicable to RMPs, PSURs and PASS are likewise relevant for RMM (see GVP Module V, GVP Module VII and GVP Module VIII).

[22] ema.europa.eu/en/partners-networks
[23] www.ema.europa.eu/en/documents/regulatory-procedural-guideline/rules-procedure-organisation-and-conduct-public-hearings-pharmacovigilance-risk-assessment-committee-prac_en.pdf
[24] ema.europa.eu

XVI. Appendix 1: Tools of routine risk minimisation measures

XVI.App1.1. Summary of product characteristics

According to the legislation [DIR Art 8(3)(j), DIR Art 11, REG Art 6(1)] and the Guideline on Summary of Product Characteristics[25], the summary of product characteristics (SmPC) (see GVP Annex I) presents information relevant to RMM in:

- SmPC section 4.8 'Undesirable Effects': Information on adverse reactions, including information characterising the reaction which may be useful to prevent, monitor or manage its occurrence;
- SmPC section 4.4 'Special Warnings and Precautions for Use': Warnings and actions to be taken to avoid specific possible adverse reactions or to be taken if a specific reaction occurs or, if deemed necessary, actions to be taken as a precaution for potential risks;
- SmPC section 4.6 'Fertility, Pregnancy and Lactation': Information on risks of the medicinal product impacting on fertility, pregnancy and lactation, including risks for the embryo/foetus/child due to adverse effects at conception, in utero or through breastfeeding, and actions to be taken to avoid or minimise these risks;
- SmPC sections 4.1 'Therapeutic Indications', 4.2 'Posology and Method of Administration', 4.3 'Contraindications', 4.5 'Interaction with Other Medicinal Products and Other Forms of Interaction', 4.7 'Effects on Ability to Drive and Use Machines' and 4.9' Overdose': Safe use advice regarding indications, dosing and administration, contraindications, interactions, ability to drive and use machines, and overdose.

For medicinal products with additional RMM materials, according to the Guideline on Summary of Product Characteristics[26] and supplementary Guidance on Frequently Asked Questions on SmPC Section 4.4[27], the SmPC section 4.4. should describe the intended actions for risk minimisation and should include a statement on the educational/safety advice materials addressed to healthcare professionals or patients which clearly and succinctly explains the purpose (e.g. "to be handed out to the patient") and scope of the materials. Other SmPC sections may also refer to these materials if necessary.

XVI.App1.1.1. Boxed warning in bold font type

The SmPC section 4.4 may, in exceptional cases, include especially important safety information in bold type within a box (see Guideline on Summary of Product Characteristics[28]).

XVI.App1.2. Package leaflet

According to the legislation [DIR Art 8(3)(j), DIR Art 59, REG Art 6(1)] and the Template for the Package Leaflet[29], the package leaflet (PL) (see GVP Annex I) presents information relevant to RMM for the patient in accordance with the SmPC (see XVI.B.2.1.1.) in:

- PL section 4 'Possible Side Effects': Information on adverse reactions that may occur due to the medicinal product;
- PL sections 2 'What you need to know before you <take/use> <name of medicinal product>' and 3 'How to <take/use> <name of medicinal product>: Safe use advice regarding dosing and

[25] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[26] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[27] EMA; SmPC training presentation – Section 4.4 (rev 1); link: Section 4.4 Special warning and precautions for use (europa.eu)
[28] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[29] ema.europa.eu

administration, contraindications, interactions, ability to drive and use machines, overdose, warnings and actions to be taken to avoid specific possible adverse reactions or to be taken if specific reactions occur and, if deemed necessary, actions to be taken as a precaution for potential risks, and information on risks of the medicinal product impacting on fertility, pregnancy and lactation, including risks for the embryo/foetus/child due to adverse effects at conception, in utero or during breastfeeding, and actions to be taken to avoid or minimise these risks.

The Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[30] and the Guideline on the Packaging Information of Medicinal Products for Human Use Authorised by the Union[31] applies to the PL.

XVI.App1.2.1. Symbols and pictograms

The Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[32] includes guidance on the use of symbols and pictograms to support text in the PL in ways useful to the patient [DIR Art 62], provided the size of the graphic provides for easy legibility and the meaning of the symbol is clear beyond any doubt. Evidence may be required to ensure that their meaning is generally understood and not misleading or confusing.

XVI.App1.2.2. Warnings on dark background

The Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[33] includes guidance for particular warnings applying light text on dark background in the PL.

XVI.App1.3. Labelling of immediate and outer packaging

The labelling (see GVP Annex I) of all medicinal products contains a warning that the medicinal product must be stored out of the reach and sight of children [DIR Art 54(f)].

The Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[34] and the Template for the Labelling of the Immediate and Outer Packaging[35]applies to labelling.

XVI.App1.3.1. Special warnings and information on precautions

According to the legislation [DIR Art 8(3)(j), DIR Art 54, REG Art 6(1)] and the Template for the Labelling of the Immediate and Outer Packaging[36], the labelling may contain a special warning if this is necessary for the medicinal product [DIR Art 54(g)] and, where appropriate, information on specific precautions for the disposal of unused medicinal product or waste derived from a medicinal product [DIR Art 54(j)].

XVI.App1.3.2. Pictograms

According to the Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[37], pictograms may be presented in the labelling if accepted for the medicinal product in accordance with Article 62 of Directive 2001/83/EC and where space on the packaging permits, provided they do not interfere with the legibility of the mandatory information in the labelling.

[30] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[31] European Commission; https://health.ec.europa.eu/system/files/2023-09/2018_packaging_guidelines_en_1.pdf
[32] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[33] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[34] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[35] www.ema.europa.eu
[36] www.ema.europa.eu
[37] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf

XVI.App1.4. Pack size

The pack size of the medicinal product should be appropriate to the usual treatment duration. A small pack size can be useful if overdose or diversion is a risk to minimise. Depending on the number of dosage units in the pack of a prescription-only medicine (see XVI.App1.5.), the exposure will be limited and the patient will need to see a healthcare professional at the interval corresponding to the pack size and dosing if a new prescription is necessary, thus increasing the opportunity for therapeutic monitoring and reducing the length of time a patient will be without medication review. Where the SmPC requires therapeutic monitoring or medication review at specified intervals, the adaptation of the pack size to the corresponding prescribing interval may support the effective implementation of this RMM.

XVI.App1.5. Classification of the medicinal product (legal status)

When a marketing authorisation is granted, the competent authorities shall specify the classification of the medicinal product (legal status) into a medicinal product subject to medical prescription (see XVI.App.1.5.1.), or a medicinal product not subject to medical prescription [DIR Art 70(1)]. When new facts are brought to their attention, the competent authorities shall examine and, as appropriate, amend the classification of a medicinal product [DIR Art 74].

The competent authorities may provide sub-categories, including subject to special medical prescription (see XVI.App.1.5.2.) and subject to restricted medical prescription (see XVI.App.1.5.3.) [DIR Art 70(2)]. If a competent authority does not designate medicinal products into sub-categories, it shall nevertheless take into account the criteria in determining whether any medicinal product shall be classified as a prescription-only medicine [DIR Art 71(5)]. For centrally authorised products, the Guideline on Legal Status for the Supply to the Patient of Centrally Authorised Medicinal Products[38] applies. Where the Commission Decision granting a marketing authorisation requires the legal status of a medicinal product to be subject to special and/or restricted medical prescription, Member States must find suitable ways to allow marketing authorisation holders of centrally authorised products to fulfil all the conditions laid down in the Commission Decision.

A competent authority may waive application above criteria for sub-categories of the legal status of a medicinal product, having regard to the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging and/or other circumstances of use which it has specified [DIR Art 71(4)].

XVI.App1.5.1. Subject to medical prescription

Medicinal products shall be subject to medical prescription where:

- The medicinal product is likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision; or
- The medicinal product is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health; or
- The medicinal product contains (a) substance(s) or preparations thereof, the activity and/or adverse reactions of which require further investigation; or
- The medicinal product is normally prescribed to be administered parenterally [DIR Art 71(1)].

[38] www.ema.europa.eu

XVI.App1.5.2. Subject to special medical prescription

When considering classification of a medicinal product as subject to special medical prescription, the following shall be taken account:

- The medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions; or
- The medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes; or
- The medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure [DIR Art 71(2)].

XVI.App1.5.3. Subject to restricted medical prescription

This legal status can be used to control who may initiate treatment, prescribe the medicinal product and the setting in which the medicinal product can be used.

When considering classification of a medicinal product as subject to restricted medical prescription, the following shall be taken into account:

- The medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment; or
- The medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere; or
- The medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment [DIR Art 71(3)].

XVI. Appendix 2: Educational/Safety advice tools

XVI.App2.1. Guides for risk minimisation for patients or healthcare professionals

A guide for risk minimisation may be intended to support the patient or healthcare professional by:

- Enhancing awareness of a specific risk of the medicinal product, risk factors and the actions for risk minimisation, including early recognition and management of adverse reactions during or after treatment;
- Guiding therapeutic decisions in applicable patients and supporting counselling of patients and shared therapeutic decision-making;
- Preparing and administering the medicinal product correctly; and/or
- Discussing the actions for risk minimisation between the healthcare professional and the patient, in particular when handing out the patient guide.

Specifically, guides for patients may:

- Advise the patient to inform the prescriber about a medical condition or concomitant medication before initiating treatment; or to not attempt self-treatment of signs or symptoms of a possible adverse reaction and/or stop treatment without consulting the healthcare professional, but to seek medical attention; and/or
- Provide guidance on the preparation or administration of the medicinal product where these processes are complex, e.g. in the case of a patient/caregiver-administered infusion at home.

For tailoring RMM materials (see XVI.B.4.1.), the purpose of the guide (e.g. "For the safe administration of the product") may be specified in a sub-heading of the guide, below the name of the RMM tool as the main heading (see XVI.B.4.1.1.).

XVI.App2.2. Healthcare professional checklist for risk minimisation

A healthcare professional checklist for risk minimisation may be intended to support the healthcare professional in:

- Checking and recording before first or repeat prescribing or dispensing (which may include patient counselling by a pharmacist for a medicinal product not subject to medical prescription) whether the medicinal product is (still) appropriate for a given patient by checking whether e.g. contraindications, interacting concomitant medication or risk factors for adverse reactions are present in the patient (which may require conducting a medical test), whether the patient has received the necessary vaccination(s) before start of treatment with the medicinal product, and/or whether signs or symptoms of adverse reactions have emerged during treatment;
- Avoiding medication errors by e.g. selecting the pharmaceutical form, strength and dosing of the medicinal product which are appropriate for the patient and the indication; and/or
- Advising the patient about the risk and the intended actions for risk minimisation and, if applicable,handing out to the patient educational materials.

In contrast to guides for risk minimisation (see XVI.App2.1.), 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.

For tailoring RMM materials (see XVI.B.4.1.), the purpose of the checklist (e.g. "For correct dosing of the product") may be specified in a sub-heading of the checklist, below the name of the RMM tool as the main heading (see XVI.B.4.1.1.). The tailoring may also include presenting the checklist in a poster format for use in healthcare facilities.

XVI.App2.3. Risk awareness dialogue form/aid

A risk awareness dialogue form, or synonymously risk awareness dialogue aid, may be intended to support the prescribing healthcare professional in:

- Ensuring that all necessary information on the risks and the actions for risk minimisation are conveyed and discussed with the patient in the context of shared therapeutic decision-making and, if needed, at repeat prescribing in the case where e.g. the patient risk factors or situation may change over time (a paper version of the form should be handed over to the patient to take home);
- Ensuring that other RMM materials are applied and handed over to the patient if applicable; and/or
- Documenting in the patient's health record that the patient has been made aware of the risk(s) during the discussion with the prescribing healthcare professional and understands the risk and actions to take for risk minimisation if such documentation is required in local healthcare systems.

Risk awareness dialogue forms/aids should clearly state that the patient does not waive any rights by acknowledging the risks. For clarity, risk awareness dialogue forms/aids 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. Also, risk awareness dialogue forms/aids are not informed consent forms as possibly required in local healthcare systems for specific medical procedures/treatments.

XVI.App2.4. Patient card

A patient card may be intended to be carried by the patient at all times to:

- Facilitate (during the hand-over of the card to the patient or the raising awareness of the patient about the card, and/or the personalisation of the card by adding the patient's name on a dedicated field) that the healthcare professional informs the patient at the intended point of care, e.g. during prescribing or dispensing, about the risk and the intended actions for risk minimisation;
- Remind the patient of the risks and the actions to minimise them during treatment, including, if applicable, to inform healthcare professionals that this medicinal product is used and to seek (urgent) medical attention if signs and symptoms of a possible adverse reaction occur;
- Note as a reminder, if applicable, in a dedicated field on the card the dates for regular medication reviews or conducting tests, or for removing the related medical device, and/or the results of a test; and/or
- Inform healthcare professionals during emergency care that the patient is using this medicinal product, possibly with contact details of the prescribing healthcare professional noted in a dedicated field on the card.

The card may carry an instruction for the patient "Carry with you at all times", and as appropriate for the given intended actions for risk minimisation, the card may carry further instructions, e.g. "Show to your healthcare professional before starting a new treatment" or "Keep easily accessible for emergency care".

For tailoring RMM materials (see XVI.B.4.1.), the purpose of the patient card (e.g. addressing patients using the medicinal product for a specific indication or belonging to a specific sex or age group) may be specified in a sub-heading of the patient card, below the name of the RMM tool as the main heading (see XVI.B.4.1.1.).

In the rare cases where a risk has different intended actions for risk minimisation for different patient groups, one patient card may address all concerned patient groups or more than one patient card for the same medicinal product may be appropriate.

For its purpose, a patient card should have the following features:

- Format: single or folded (one-fold or Z-fold) card which is independent of the PL (i.e. not as a tear-off part of the PL);
- Size: at minimum the size of half a credit card and at maximum the size of a credit card, to fit inside a pocket/wallet/card holder (if more space is needed, folds can be used, see above);
- Material: carton of durable thickness and possibly laminated, to sustain wear and tear over time;
- Design: striking (e.g. clean layout, shapes and/or colours), to be visible and immediately identifiable as important, and notably different from the PL (i.e. not resembling a PL);
- Writable fields: a field for the patient's name and, if applicable, for the prescriber's name and contact details;
- Multiple language versions if applicable: can be bundled, but it should be obvious for the patient how to take out from the bundle a complete card in the preferred language.

A patient card can be placed inside the package, be affixed to the outer side of the package as finished by the manufacturer, or be separate from the package. Cards placed inside the package or affixed to the outer side of the package should usually be preferred. Cards separate from the package may (additionally) be needed for hand-over to the patient, e.g. when the given medicinal product may be used in a setting where one package is used for more than one patient, or when the intended action for risk minimisation involves the prescriber handing over the patient card as part of a risk minimisation control programme.

Cards placed inside the package or affixed to the outer side of the package are considered part of the product information and hence their text should be included in the respective part of the marketing authorisation.

In the case when an existing patient card inside the package or affixed to the package outside is amended or newly required in the post-authorisation phase, the marketing authorisation holder should provide dissemination plan proposals to the competent authorities in Member States for interim

measures to be provided as long as packages without the up-to-date patient card are in distribution (see XVI.B.4.2.).

XVI.App2.5. Patient diary for risk minimisation

A patient diary for risk minimisation may be intended to support the patient in:

- Recording specific information in situations where it is considered important that, when using the medicinal product, such information is regularly exchanged between the patient and the healthcare professional for the purpose of risk minimisation, e.g. dates and results of tests at (other) healthcare facilities or at home needed to identify emerging risk factors, or signs and symptoms indicative of a possible adverse reaction;
- Administering the medicinal product at the prescribed dose and time intervals through recording the dose and dates of administration in situations where it is considered that specific potential for medication errors exist; and/or
- Seeking immediate medical attention should the recorded information indicate that a risk factor, adverse reaction or medication error may have emerged.

Where an adverse reaction on the basis of the patient's entries in the diary is suspected, the healthcare professional or patient should report this by using the applicable spontaneous reporting system.