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Guideline on good pharmacovigilance practices (GVP)

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

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

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

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

* The revised final guidance is applicable to new applications for marketing authorisation, new risk minimisation measures and new

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

*Note: 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 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 tools and messages;
- Clarifications of the relationship between routine and additional RMM tools and 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.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)]. As such, these measures support keeping the risk-benefit balance of a medicinal product positive, which is a prerequisite for granting and maintaining its marketing authorisation. ~~Risk management includes the identification, characterisation (including quantification), prevention and minimisation of risks.~~ A r~~R~~isk management system~~s~~ is~~consist~~ 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).~~of pharmacovigilance activities and interventions relating to individual medicinal products for this purpose, including the assessment of the effectiveness of those activities and interventions, in accordance with Article 1(28b) of Directive 2001/83/EC~~. The objectives of ensuring the safe use of the medicinal product and minimising risk~~s~~, including their adverse health outcomes, ~~minimisation~~ are ~~achieved through~~supported~~facilitated by~~ ~~the implementation of~~ risk minimisation measures (RMM) ~~required by the competent authorities and~~ the generation of evidence ~~that these~~ RMM~~measures are effective.~~

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 options for risk minimisation and prevention 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 and RMM [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 and evaluating RMM should already begin early during the development phase of the medicinal product, as part of the 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 risk minimisation is an evolving area for which new methods will emerge. Implementing RMM in healthcare requires approaches from the implementation and behavioural sciences concerned with improving patient-centred healthcare. This requires engagement across stakeholders for patient safety. As technology advances, the potential of supporting risk minimisation through digital applications may be considered.

~~Effective RMM and the assessment of their effectiveness should be in place for medicinal products in accordance with Articles 8(3)(iaa), 21a, 101(2), 104(2), 104(3), 104a, 107h(1) of Directive 2001/83/EC, Articles 9(4), 14a, 21 and 28a of Regulation (EC) No 726/2004 and Articles 2(4b),~~

~~11(1a), 11(1e), 30, 31(1) and 34(3) of the Commission Implementing Regulation 520/2012 which specifically include provisions for monitoring the outcome of RMM for both marketing authorisation holders and competent authorities. Monitoring RMM outcomes refers to adherence to RMM by healthcare professionals and patients and achieving the objectives of RMM. Monitoring and amending RMM, if warranted, aim at ensuring that the benefits of a particular medicinal product continue to exceed the risks by the greatest achievable margin. The assessment of the effectiveness of RMM is important for risk management with an iterative process of evaluation, correction and re-evaluation of RMM, which is integral to the lifecycle benefit-risk assessment of medicinal products.~~

The terminology for this GVP Module is provided in XVI.A.. XVI.B. provides~~describes~~ the principles and tools of RMM, ~~criteria~~ points to consider for their selection as well as guidance for their ~~,~~ development, implementation and ~~co-ordination of RMM, in particular of additional RMM,~~ ~~and the principles and concepts of~~ the evaluation ~~of RMM effectiveness~~, with a view to an overall risk-proportionate and consistent approach to risk minimisation. XVI.C. describes the related roles and responsibilities of marketing authorisation holders and competent authorities in the setting of the EU regulatory network and~~. It also~~ reflects on the engagement with~~contribution of~~ healthcare professional and patient representatives within appropriate frameworks.

This GVP Module should be read together with the Addenda of GVP Module XVI and other GVP Modules as referenced, ~~GVP Module V on risk management systems as documented through risk management plans (RMPs) and on details of routine RMM, GVP odule VII on eriodic afety pdate eports (PSUR), GVP Module VIII on post-authorisation safety studies (PASS), GVP Module XV on safety communication~~, the CHMP Guideline on Safety and Efficacy Follow-up – Risk management of Advanced Therapy Medicinal Products[1], the ~~This includes preventing or reducing the occurrence of adverse reactions due to medication errors (see~~ PRAC Good Practice Guide on Risk Minimisation and Prevention of Medication Errors[2]~~)~~ and the EMA Post-Authorisation Guidance[3]~~.~~ ~~and the Addenda of this GVP Module as referenced~~. Marketing authorisation holders should also take into consideration guidance ~~specifications and any specific processes that are already~~ in place in Member States and follow their requirements.

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 ~~on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC~~as amended as "IR".

XVI.A.1. Terminology

Definitions are provided in GVP Annex 1, including the following specifically relevant for this Module:

[1] www.ema.europa.eu
[2] www.ema.europa.eu
[3] www.ema.europa.eu/en/human-regulatory-overview/post-authorisation

XVI.A.1.1. Risk minimisation measure

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

The term 'RMM' is an umbrella term covering the following terms also 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'.

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 the RMM-intended actions are supported for their further implementation (see XVI.B.1.2.3.), belonging either to the category of routine or additional RMM tools (see XVI.B.2.).

The RMM for a specific medicinal product are referred to as:

RMM material: the final individual RMM with its full wording, as approved by the competent authorities; and

RMM set: all routine and additional RMM materials addressing a given risk of the medicinal product.

XVI.A.1.2. Patient

'P~~p~~atient' ~~in this guidance~~ is defined, for the purpose of this GVP Module, as ~~covers~~ individuals ~~patients more generally consumers subjects~~ 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 ~~It also~~ the embryo/foetus/child who may be adversely affected ~~exposed to~~ by a medicinal product at conception, in utero or through breastfeeding (including by delayed and/or life-long adverse effects), ~~(unborn) child in the case of~~as may ~~, exposure during pregnancy~~ and individuals ~~may~~ who may be adversely affected through occupational, accidental, or illegal[4] exposure to a medicinal product.

For the ease of reading of this GVP Module, the term 'patient' also includes parents, ~~and~~ other carers, as well as ~~and~~ patient and consumer representatives and organisations, who may be target audiences of RMM in their role to support patients.

[4] See GVP Annex I for the definition of 'Misuse of a medicinal product for illegal purposes'

XVI.A.1.3. Healthcare professionals

'Healthcare professionals' are defined, for the purposes of this GVP Module, as persons providing professional healthcare, such as physicians, dentists, pharmacists and nurses.

For the ease of reading of this GVP Module, the term 'healthcare professionals' also includes healthcare professional representatives and organisations, and learned societies, who may be target audiences of RMM in their role to support healthcare professionals.

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 receive the tools and messages of a given RMM tool or material.

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 population groups may be specified further for a given RMM RMM tool or materials.

For the ease of reading of this GVP Module, the term 'Target population (risk minimisation measure)' is usually 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. ~~Definition and p~~Principles of risk minimisation

~~RMM are interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur (see GVP Annex I). This includes preventing or reducing the occurrence of adverse reactions due to medication errors (see PRAC Good Practice Guide on Risk Minimisation and Prevention of Medication Errors[5]).~~ ~~For all medicinal products, risk minimisation is generally addressed by routine RMM. These include the provision of information and recommendations in the summary of product characteristics (SmPC) and the package leaflet (PL), the labelling on the immediate or outer packaging of a medicine, pack size appropriate to the usual treatment duration and a risk appropriate legal status of the product (e.g. prescription only medicine) (see GVP Module V). For some important risks, however, routine RMM might not be sufficient, and it might be necessary to implement additional RMM.~~

~~The risk benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimising benefits, both through patient selection and treatment management (e.g. specific dosing regimen, relevant testing, patient follow up). RMM should therefore support the optimal~~

~~[5] Pharmacovigilance Risk Assessment Committee. Good practice guide on risk minimisation and prevention of medication errors (EMA/606103/2014). London: EMA; 18 November 2015. Accessible at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196981.pdf.~~

~~use of a medicinal product in clinical practice with the principal goal of providing the right medicine at the right dose and at the right time to the right patient and with the right information and monitoring.~~

The following principles of risk minimisation should be followed by marketing authorisation holders and competent authorities:

XVI.B.1.1. Iterative approach to 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, as performed by marketing authorisation holders and competent authorities, are iterative, starting with the medicine product development in the pre-authorisation phase and continuing throughout the post-authorisation phase. In the post-authorisation phase, new data as well as input from patients and healthcare professionals (see XVI.B.1.3.) on the risks and the effectiveness of RMM may emerge and impact on the risk-benefit balance of the medicinal product, possibly requiring adaptations to the existing RMM ~~a~~ . Within this cycle, formative gathering of evidence and input from patients and healthcare professionals for regulatory decision-making on requiring or adapting RMM (see XVI.B.3. and XVI.B.6.) and~~,~~ for developing RMM materials and dissemination plans (see XVI.B.4.) alternate with the evaluation of RMM effectiveness (see XVI.B.5.)~~.~~

This iterative process can be depicted as a learning ~~-~~cycle for keeping the risk-benefit balance of medicinal products positive and improving it (see Figure XVI.1.), ~~-~~as part of quality management of pharmacovigilance for patient and public health (see XVI.B.7.).

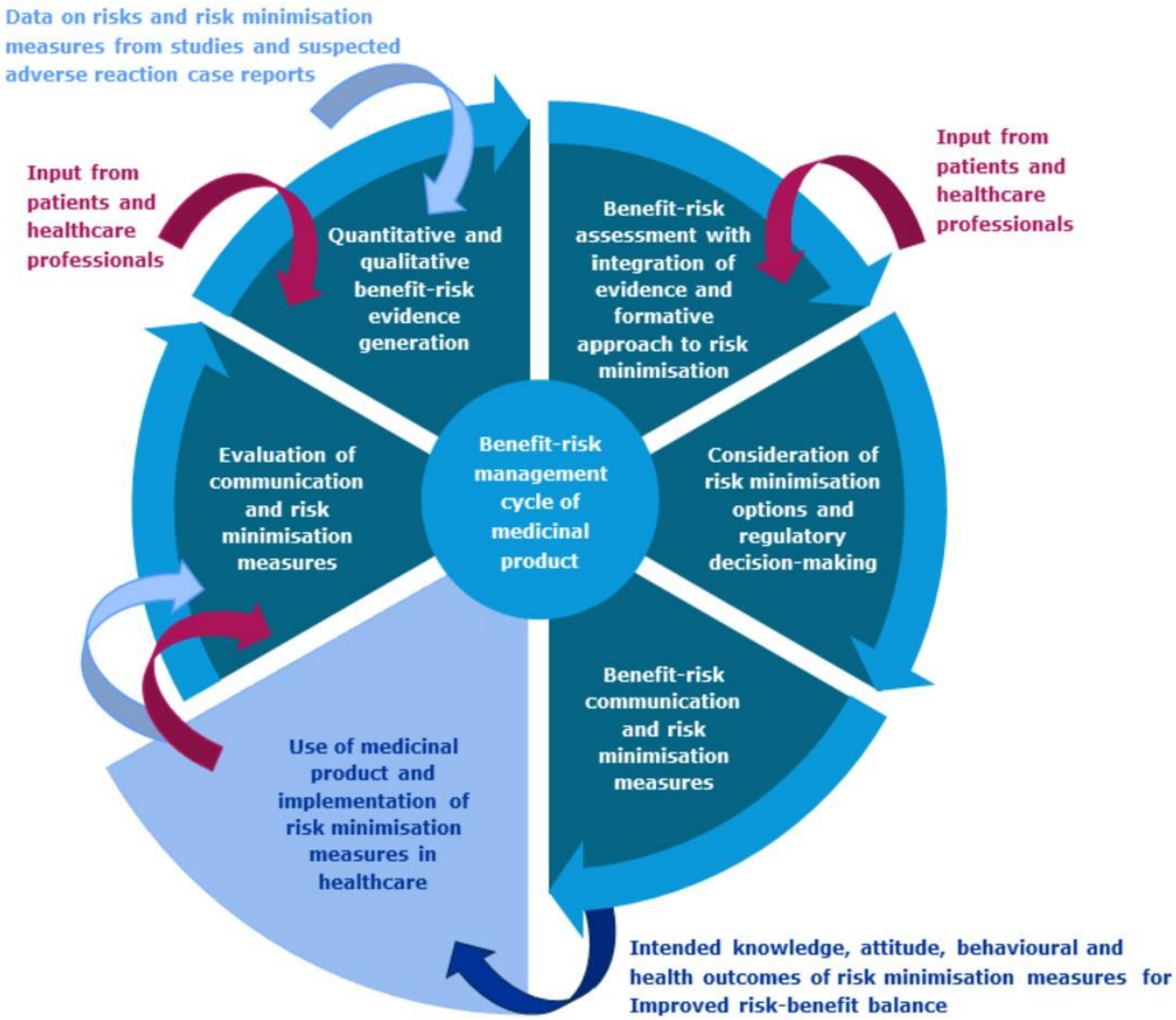

Figure XVI.1.: Benefit-risk management cycle of the medicinal product[6]

XVI.B.1.2. Intended outcomes as specific objectives of risk minimisation measures

To achieve the overall objectives of ensuring the safe use of a medicinal product and minimising its risks, RMM should have clearly defined specific objectives, i.e. intended outcomes, including:

- Reaching the target audiences through dissemination of RMM materials;
- Knowledge adoption, attitude formation and behavioural changes in audiences for the actions described in the RMM messages;
- Integration of RMM materials establishing a risk management control programme in healthcare processes;

[6] 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 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.]

- Health outcomes in terms of reduced occurrence or severity of adverse reactions or their impact on patient or public health.

Within cognitive processes, forming an attitude as a state of readiness is vital for applying knowledge and takinge action[7].

~~Behaviours of healthcare professionals and patients, or actions, typically intended by RMM relate to:~~

- ~~Initiating treatment with the medicinal product in accordance with the authorised indications and taking into account contraindications, interactions and risk factors for adverse reactions the patient may have;~~
- ~~Conducting tests before initiating treatment with the medicinal product and tests and/or therapeutic monitoring during treatment;~~
- ~~Appropriate dosing and correct administration of the medicinal product;~~
- ~~Discontinuing the medicinal product when the patient has achieved the treatment goal, does not respond to the medicinal product or experiences signs and symptoms of a possible adverse reaction;~~
- ~~Using other than previously used medicinal products to reduce interactions or using additional medicinal products to reduce the occurrence or severity of an adverse reaction;~~
- ~~Correct handling of the medicinal product or its preparation for administration; and~~
- ~~S.eeking medical attention in the case of signs or symptoms of a possible adverse reaction.~~

XVI.B.1.3. Implementation pathway of risk minimisation measures – regulatory implementation, dissemination and implementation in heathcare

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 through which the RMM tools and messages become part of the terms of the marketing authorisation for a medicinal product (including in its product information and RMP (see XVI.C.1.)) and the RMM materials are approved by the competent authorities~~,~~;
- Dissemination of RMM materials by marketing authorisation holders to the target audiences; and
- Implementation of RMM in healthcare, which manifest in onward dissemination of RMM materials to targeted healthcare professionals and patients, the intended knowledge adoption of the RMM messages and attitude formation in healthcare professionals and patients, and changes towards the RMM-intended actions in the behaviours of healthcare professionals and patients during the concerned processes of healthcare or using the medicinal product at home.

While the regulatory implementation lies within the remit of competent authorities, the development and initial dissemination of RMM materials falls under the responsibility of marketing authorisation holders under regulatory oversight. Additionally, competent authorities may disseminate information on RMM as part of their legal obligations for safety communication (see GVP Module XV). Onward

[7] ~~Fazio RH. Attitudes as object-evalution associations of varying strength. Soc Cogn. 2007; 25: 603-637.~~

dissemination of RMM materials (disseminated from marketing authorisation holders to healthcare professionals) to patients may be demanded from healthcare professionals as an RMM-intended action, and wider dissemination of RMM within healthcare systems may also be necessary to achieve full implementation of RMM in healthcare. In general, dissemination covers not only the dissemination of RMM materials to the target audiences, but also the dissemination of the RMM messages via other channels-, e.g. the scientific or general media, which lie outside regulatory oversight and may be used in the framework of stakeholder engagement (see XVI. B.1.4. and XVI.B.4.).

The implementation of RMM in healthcare falls under the responsibility of healthcare systems for safe and effective patient-centred care. How the RMM are -implemented in healthcare processes will depend on the settings where the medicinal product is prescribed, dispensed and administered. Within the proactive approach to risk minimisation, implementability refers to the expected opportunities of RMM being implemented effectively (which includes avoiding adverse outcomes), based, as available, on past or formative evidence on RMM effectiveness (see XVI.B.1.1.) and input from patients and healthcare professionals (see XVI.B.1.4.), in particular on enabling or disabling factors to RMM effectiveness taking into account the context of the typical healthcare and patient home settings and likely scenarios in which the medicinal product is used and how the additional RMM tools and RMM-intended actions could be integrated in the processes in healthcare and at home. While past evidence is generated from RMM effectiveness evaluations (see XVI.B.5.), formative evidence in particular relates to use of medicines, processes of healthcare and health information diffusion, and existing knowledge, attitudes and behaviours in audiences for RMM, gained from (available) quantitative, qualitative and mixed methods research applying similar methods as used for RMM effectiveness evaluation (see GVP Module XVI Addendum II).

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

XVI.B.1.4. Stakeholder engagement- in risk minimisation

Engagement across stakeholders is considered crucial for achieving full implementation of RMM in healthcare and the intended positive patient and public health outcomes (see XVI.B.1.3.). Given these shared responsibilities, marketing authorisation holders and competent authorities should have appropriate processes in place which allow for inclusive engagement of stakeholders. For marketing authorisation holders, these processes shall be separate from promotional activities (see XVI.B.1.5.).

Within these frameworks, patient and healthcare professional representatives should be encouraged to engage in risk minimisation, in particular to:

- Provide input on RMM options in terms of tools, messages and target audiences and~~,~~ implementability (see XVI.B.1.3.) for regulatory decision-making on RMM (see XVI.B.3.), in particular based on insights on current risk awareness, disease management and healthcare systems, including the processes and system/individual factors which impact on the likelihood of effectiveness of RMM options;
- Contribute to the development of RMM materials, e.g. designing/tailoring to target audiences, user-testing, input to consultations prior to approval of RMM materials, ~~-~~and to the planning for implementation of RMM in healthcare (see XVI.B.4.);
- Advise on and support the dissemination of RMM via multiple channels, in particular those that exist outside the regulatory oversight and address the media preferences of the target audiences, (see XVI.B.1.3. and XVI.B.4.) and advise on and support the full implementation of RMM in healthcare (see XVI.B.1.3.);
- Advise on and participate in the evaluation of RMM effectiveness (see XVI.B.5.).

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

~~Additional RMM should be completely separated from promotional activities.~~

XVI.B.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, a~~A~~dditional RMM materials should ~~be completely separated from~~ not contain any promotional elements~~activities~~ ~~, -~~ either direct or veiled and in accordance with locally applicable policies.

Likewise, studies evaluating RMM effectiveness should not contain any promotional element and be separate from any promotional activity, as non-interventional post-authorisation safety studies 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 for stakeholder engagement (see XVI.B.1.4.) must not be used for any other, including promotional, activities and must be handled in accordance with Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data.

In the context of RMM, the invented name of the medicinl product is not considered a promotional element.

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

The RMM tools belong either to the main category of routine (see XVI.B.2.2.) or additional (see XVI.B.2.3.) RMM.

XVI.B.2.1. Relationship between routine and additional risk minimisation measures

The RMM messages, i.e. the risk information and the intended action to be taken by the healthcare professional or the patient for minimising the risk (see XVI.A.1.1.), are described in the summary of product characteristics (SmPC) as the fundamental routine RMM tool and form the basis for the messages in other routine and, where required, additional RMM tools (see XVI.B.3.).

Additional RMM are hence meant to- emphasise the messages in routine RMM and may elaborate and contextualise the actions for risk minimisation described in the routine RMM tools or present the information in a different way by using tables, graphics or other visualisations and enhancements.

The SmPC (see XVI.App1.1.) and/or the package leaflet, depending on the target audience of the RMM materials~~,~~ should mention if additional RMM materials exists for a specific risk and may include information where they can be accessed.

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

~~For all medicinal products, risk minimisation is generally addressed by routine RMM. These include the provision of information and recommendations in the summary of product characteristics (SmPC) and the package leaflet (PL), the labelling on the immediate or outer packaging of a medicine, pack size appropriate to the usual treatment duration and a risk-appropriate legal status of the product (e.g. prescription-only medicine) (see GVP Module V).~~

Routine ~~risk minimisation activities~~RMM tools are those which apply to every medicinal product -as part of the marketing authorisation. However, a visual reminder (e.g. symbols, pictograms, visually enhanced warnings) and special warnings/information on precaitions on the packaging are -routine RMM tools which are not needed for every medicinal product, and if needed, have to be specifically requested in the marketing authorisation.

Routine RMM tools include those listed in Table XVI.1. and are detailed in XVI.Appendix.1.. Further, the formulation itself may play an important role in minimising the risk of a medicinal product, e.g. in minimising the risk of incorrect dosing or administration, misuse or abuse of the medicinal product.

Table XVI.1.: Routine risk minimisation measure tools

Routine RMM tools
Summary of product characteristics (SmPC) (including boxed warnings in bold font type)

Routine RMM tools
Package leaflet (PL) for the patient in accordance with the SmPC (including symbols, ~~and~~ pictograms and warnings on dark background)
Labelling of immediate and outer packaging (including special warnings, information on precautions and pictograms)
Pack size
Classification (legal status) of the medicinal product

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

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

A variety of tools of additional RMM are ~~currently~~ available for use on their own or in combination, or two additional RMM tools can also be merged into one RMM material as part of audience tailoring (see XVI.B.4.1.)~~ed manner as additional RMM. As digital technology advances, the potential of electronic dissemination, such as through electronic medical records or web- and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to paper-based materials~~.

Additional RMM tools ~~are~~ ~~can be~~ sub-categorised as ~~into the~~ follow~~sing categories~~:

- Educational/Safety advice tools~~materials~~; and
- ~~Direct healthcare professional communications (DHPCs);~~
- ~~Pregnancy prevention programmes (PPPs);~~
- Risk minimisation c~~C~~ontrol~~led access programme~~ tools~~s~~.

Other sub-categories or tools are not excluded to become additional RMM tools if they meet the definition of RMM (see XVI.A.1.1.).

Risk minimisation control programmes usually apply their specific tools in combination to educational/safety advice tools.

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

A direct healthcare professional communication (DHPC) may be required to support a set of routine and additional RMM materials of a medicinal product, as this safety communication tool (see GVP Module XV and GVP Annex I) may support the implementation of RMM-intended actions (see XVI.B.4.2.1.).

XVI.B.2.3.1. Educational/Safety advice tool ~~material~~s

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

Educational tools, or synonymously safety advice tools, are targeted at either patients or healthcare professionals, whereby those targeted at healthcare professionals may also be intended to support the dialogue between the patient and the healthcare professional in healthcare about the risks and actions intended by RMM.

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

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

Table XVI.2.: Educational/Safety advice tools

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

~~**XVI.B.3.1.a f.**~~

~~XVI.B.3.2. Direct healthcare professional communications~~

~~XVI.B.3.3. Pregnancy prevention programmes~~

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

~~The typical objectives of a PPP are to:~~

- ~~Avoid that female patients are pregnant when starting the treatment; and~~
- ~~Avoid that female patients become pregnant during and, if relevant, for a specific period after stopping treatment;~~

- ~~Avoid, if applicable, that a male patient father a child during and, if relevant, for a specified period after stopping treatment.~~

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

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

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

XVI.B.2.3.24. Risk minimisation cControlled access programme tools

A risk minimisation controlled access programme includes educational/safety advice tools required for the medicinal product and further one~~is a tool~~ or more~~set of~~ additional RMM tools to control the adherence to the intended actions for risk minimisation through ensuring the necessary healthcare support to patients, preventing diversion of the medicinal product and/or providing for traceability of the medicinal product. ~~that seeks to control access to a medicinal product beyond the level of control as specified in the SmPCapplied to medicinal products by means of routine RMM (see XVI.A.).~~ These programmes may also include pack size restrictions (see XVI.App.1.4.).

Risk minimisation control tools are intended for application by one or more healthcare settings, depending on whether the required control concerns the steps of prescribing, distribution, dispensing and/or administration of the medicinal product.

~~It may restrict the time period of validity of a prescription[8] or the maximum amount to be prescribed in a single prescription, or require a visual reminder[9] as part of the labelling of the outer packaging. Controlled access programmes should be considered and applied only in exceptional situations of an important safety concern with a severe impact on the patient or a significant public health impact, taking into account the nature of the risk and the likelihood that this risk cannot be managed by other RMM.~~

~~[8] Some medicines might require immediate dispensing as soon as prescribed. In those cases, the applicants should agree with the competent authorities on how best to achieve this objective.~~
~~[9] Visual reminders aim to highlight important information either in the packaging or the PL. These can take many forms depending on the local specifications. For example, some visual reminders can be presented as pictograms, whereas others can be presented as boxed warnings and use different colours to highlight information.~~

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

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

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. training materials and certificates of qualification, or forms to be completed by different healthcare professionals for information exchange, or by different distribution points for traceability.

Table XVI.3.: Risk minimisation control tools

Risk minimisation control tools
Healthcare professional qualification required for the prescribing, dispensing and/or~~,~~ ~~administration~~ of the medicinal product, and/or the supervision of the administration by the patient
Healthcare facility accreditation of the available equipment and qualified healthcare professionals required for using the medicinal product at this facility
Traceability system 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 exchange of patient information (e.g. results of medical tests) one healthcare professional is required to receive from the other healthcare professional for completing the RMM-intended action for the medicinal product
Check of patient certificates of medical interventions~~-~~ required for the prescribing or dispensing of the medicinal product

~~***XVI.B.3.4.a. c.***~~

XVI.B.3~~2~~. ~~Criteria for~~ R~~r~~equiring 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)(d) and DIR Art 101(2)].

Most safety concerns will be ~~are~~ sufficiently addressed by routine RMM (see XVI.B.2.2.) ~~(see GVP Module V)~~. Careful consideration should be given to whether the intended~~the~~ RMM~~risk minimisation~~ outcomes ~~objectives~~ (see XVI.B.1.2.) could be achieved~~reached~~ with routine RMM tools~~measures~~ alone. ~~, and o~~Only if ~~when not this in not considered sufficient and~~ it is considered necessary for keeping the risk-benefit balance of the medicinal product positive, ~~it should be considered which~~ additional ~~measure(s)~~RMM tool(s) (see B.2.3.) should be required~~is (are) the most appropriate~~.

Generally, a~~A~~dditional RMM ~~should~~ address~~focus on important safety concerns~~ important identified or important potential risks (see GVP Annex I).

Each ~~safety concern~~risk needs to be considered individually, ~~and the selection of RMM should take into account:A safety concern may be addressed by using more than one ,~~ but an individual additional RMM~~, and~~ materials~~one RMM~~ may address more than one risk~~safety concern~~.

In determining whether additional RMM tools are necessaryneeded and selecting thewhich measures tool(s) would be most effective, marketing authorisation applicants/holders and competent authorities should consider take into account the points in Table XVI.4. and:: :

- Consider the target population, frequency, seriousness, severity, context of use, possible impact and preventability of the risk for which the additional RMM is meant to be developed ;
- Consider the need fo advice to healthcare professionals for appropriate patient selection and excluding patient exposure when treatment is indicated, which patients to exclude from treatment where the use of the medicinal product is contraindicated, patient monitoring patients during treatment to either detectprevent adverse reactions or early detection or prevent them and management of adverse reactions;
- Assess the potential for effectiveness of the additional RMM, as anticipated based on past and formative evidence (see XVI.B.1.1.) or input that may be sought from patient and healthcare professional representatives (see XVI.B.1.4.). , including the burden the RMM may impose on the healthcare system and possible unintended effects;
- Consider the intended behavioural changes of healthcare professionals and patients during each step of the treatment process.; and
- Select the RMM tools that are expected to be:
  - risk-proportionate and effective in timely manner in minimising the risk;
  - practical and not too burdensome for patients or the healthcare system.

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

The selection of RMM and determining whether only routine or also additional RMM are necessary should be based on the characterisation of the safety concerns in the safety specifications of the RMP (see GVP Module V).

Combining educational/safety advice tools may address the different preferences of the target audiences for receiving the RMM messages in complimentary manner.

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 identified or potential risk severity and frequency of the adverse reaction(s)
Preventability and the Kind of clinical immediate and long-term actions- able required intended to minimise the risk
Indication/restriction of indication,- contraindications, dosing and scheduling, duration of treatment-, route of administration/pharmaceutical form of the medicinal product, the potential of errors in its handling and

Points to consider for requiring additional RMM and selecting tools
administration, and the medical condition to be treated overall, including the impact of the medical condition on the patient
, the Patient target population for the RMM, their typical state of health and circumstance, and healthcare/home setting, the healthcare setting and likely scenarios where they use the medicinal for the use of the product
Healthcare professional target population for the RMM, and the typical healthcare settings and for the use of the productclinical context, and likely scenarios where the medicinal product is used of use
Intended behavioural changes of healthcare professionals and patients during each step of processes in healthcare or at home and related nNeeds for advice to healthcare professionals
Possibleimpact and burden of the risk and 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 (see XVI.B.1.3.) with its aAnticipated Possible effectiveness in achieving the intended outcomes of the RMM (see XVI.B.1.2.) and avoiding the potential for unintended outcomes effects of the RMM (see B.5.1.)

he selection of RMM

XVI.B.3.1. Risk minimisation control programmes

A risk minimisation cControlled access programmes applying specific tools (see XVI.B.2.3.2.) should be considered and applied only in exceptional rare situations where a serious risk may have a specifically of an important risksafety concern with a severe impact on the patient and/or or the (unborn) child exposed in utero, or a significant public health, which is considered not to be effectively minimised by routine RMM together with educational/safety advice tools alone. impact, taking into account the nature of the risk and the likelihood that this risk cannot be managed by other RMM.

This includes 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 (including with delayed and/or life-long adverse effects), 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.

This tool could also be considered for products controlled under the respective national legislations to prevent misuse and abuse of medicines. For products that need to be prepared for a specific patient (i.e. advanced therapy medicinal products (ATMPs)), further RMM may be needed for ensuring an adequate distribution, storage, preparation, handling and use of the product. This may be required in specific situations such as for ATMPs or complex administration procedures.

XVI.B.4. Developing materials and planning the dissemination of additional risk minimisation measures plans

XVI.B.4.1. Tailoring of materials to target audiences and local healthcare systems, and user-testing

Educational To facilitate achieving the intended knowledge adoption, attitude formation and behavioural outcomes of the RMM in the given healthcare and patient settings, material have also to be tailored to the various national healthcare systems where they should be used and a target audience (see XVI.A.1.4.) should be defined for each additional RMM tool, and the additional RMM materials should be tailoredbe adapted to these target audiences. This should take into account how the

materials can support the intended behavioural changes in the given healthcare and patient settings through integration of the RMM-intended actions in processes in healthcare and at home.

~~When developing educational materials,~~ Marketing authorisation holders are~~it is~~ therefore encouraged, where possible, or may be required where considered necessary by the competent authority, to user-test draft additional RMM materials ~~engage~~ with healthcare professional~~s~~ and patient representatives in local contexts (see XVI.B.1.4.). ~~and user-test proposed materials for~~ Such user-testing should investigate the materials' adequacy (e.g. for the audiences' settings and their circumstances), 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, ~~readability, accessibility, and~~ as well as their user-friendliness ~~of formats~~ (e.g. colours, font type/size, typography, layout).

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

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[10] should be followed as far as applicable by analogy.

~~as well as of channels in the target population.~~

XVI.B.4.1.1. Information items in the materials

The information in RMM materials should follow the principles of safety communication (see GVP Module XV) are generally applicable.

An ~~educational~~ additional RMM material should contain the following information items~~elements~~:

- Name of the RMM tool (see XVI.B.2.) as the heading of the RMM material as applicable;
- ~~Up-to-date, objective, unambiguous and C~~clear ~~s~~Statements clearly summarising the nature of ~~the safety concern(s) and~~ the risk and outlining the specific actions to be taken by healthcare professionals or patients ~~in order~~ to minimise the risk and use the product safely (where warranted,~~,~~ ~~information~~ the messages of routine RMM may be elaborated and contextualised, or ~~can~~ be presented~~provided in more detail or~~ in a different way ~~than in the SmPC/PL e.g.~~ by using ~~by the use of~~ tables, graphics or other visualisations and enhancements (see XVI.B.2.1.)~~flow charts or illustrations))~~ ;
- ~~Guidance for the specific actions, e.g. on the prescribing, including indication/contraindication/ patient selection, treatment duration, diagnostic testing, therapeutic monitoring, product handling, preparation for administration, administration, switching to another treatment, or when to seek medical attention in the case of signs or symptoms indicating a possible adverse reaction;~~

[10] https://health.ec.europa.eu

- Reference to the SmPC or the package leaflet ~~PL~~ with a reminder to carefully read the SmPC or package leaflet ~~whenever possible; in the case of digital educational materials, these could refer to the SmPC or PL through a hyperlink; and~~;
- ~~A sS~~Statement explaining that the~~is~~ RMM ~~educational~~ material fulfills ~~is part of~~ the conditions of the marketing authorisation and has been approved by the ~~respective~~ competent authority, including the version date/number and date of approval/last ;

  review of the RMM matarial.~~.~~

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

National tailoring to of RMM materials may require further information items.

XVI.B.4.2. Dissemination plans

With the aim to reach the defined target audiences of RMM in their respective settings, dissemination is a crucial step to be optimised along the implementation pathway of RMM (see XVI.B.1.3.). Therefore, m~~M~~arketing authorisation holders should submit plans for the dissemination of additional RMM materials ~~to healthcare professionals and patients~~ for approval~~agreement~~ by competent authorities at national level. The plans should specify ~~list~~ the RMM tools (see XVI.B.3.), the target audiences~~, the audience-tailored formats and contents, the dissemination channels (e.g. paper, printable documents, audio, video), use of electronic features (e.g. email, mail, QR codes, hyperlinks or references), targeted outcomes,~~ , timeframes of (re)dissemination~~, for ensuring continuous availability of materials~~, and, if applicable, the use of supportive dissemination channels , ~~communication interventions strategies (~~e.g.~~ through~~ scientific journals, healthcare professional~~learned societies,~~ or patient organisations and their conferences, clinical guidelines, point-of-care tools and training activities (see XVI.B.1.2.)~~.~~.

The timeframes of~~for~~ (re)dissemination should ensure the continuous availability of (amended) RMM materials at healthcare and patient level as a prerequisite of ~~consider the needed~~ sustainability of RMM effectiveness over time~~, both within healthcare professional communities and for individual healthcare professionals and patients~~. The knowledge adoption, attitude formation and behavioural changes of healthcare professional may require repeated RMM using various tools (see XVI.B.6.). In the case of long-term treatment,~~-~~ processes for periodically repeated delivery of educational/safety advice materials to a patient may be necessary. ~~Periodic provision of the materials locally is systemically considered at competent authority level at time of implementation. The knowledge adoption, and behavioural change of healthcare professional may require repeated RMM interventions in various formats.~~

For the content and format of dissemination plans and supportive communication interventions, ~~the DHPC communication plan~~ templates (see GVP Annex II) and guidance on safety communication (see GVP Module XV) may be applicable~~, a for the planning of the dissemination of the RMM and supportive communication interventions~~.

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

XVI.B.4.23.1.2. 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 materials and the implementation of RMM-intended actions in healthcare, in particular when launching a new or amended RMM set for a medicinal product. If such DHPC is required, it should be included in the RMM dissemination plan and the guidance on DHPCs in GVP Module XV should be followed.

~~A direct healthcare professional communication (DHPC) is a safety communication tool (see GVP Annex I) that may also serve as an additional RMM.~~

~~It is to be considered in situations where it is deemed important that all relevant healthcare professionals in the given jurisdiction are timely informed of a risk and actions to take for risk minimisation.~~

~~Guidance on DHPCs in GVP Module XV should be followed, and the DHPC and DHPC communication plan templates (see GVP Annex II) should be used~~.

XVI.B.5. Evaluating the eEffectiveness ~~evaluation~~ of risk minimisation measures

Monitoring RMM outcomes refers to evaluating the effectiveness of routine and additional RMM. Where no additional RMM are required in the RMP, RMM effectiveness studies are not mandatory and outcomes of routine RMM are generally monitored through routine pharmacovigilance activities unless otherwise agreed with the competent authority.

~~post-authorisation safety study()RMM .~~

XVI.B.5.1. Scope of studies evaluating risk minimisation measures ~~Principles for effectiveness evaluation~~

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.

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

~~Any study measuring the effectiveness of RMM is a PASS [DIR Art 1 (15)] and the guidance for conducting a PASS in GVP Module VIII should be followed for studies evaluating the effectiveness of RMM in addition to the specific guidance in XVI.B.5.. The guidance on methods for effectiveness~~

~~evaluation in GVP Module XVI – Addendum II should be followed and protocols for qualitative studies be included in the pharmacovigilance plan of the RMP (see GVP Module V).~~

~~Principle 1: Focussed evaluation~~

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

~~Principle 2: Regular evaluation~~

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

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

~~Principle 3: Evaluation of intended and unintended outcomes~~

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

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

Studies evaluating the e~~E~~ffectiveness ~~evaluation~~ of RMM should be requested by the competent authority for RMM aim~~ing~~ed ~~to~~at minimis~~e~~ing~~mitigating~~ risks of major patient and public health importance, considering the nature, seriousness and severity ~~and seriousness~~ of the risk, the magnitude of population exposure and the amount of public concern.

The design of such studies should provide evidence enabling evaluation of whether adaptations to RMM are warranted, including whether additional RMM may be discontinued (see XVI.B.6).

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

RMM effectiveness evaluation should consider that simultaneous events such as changes in clinical guidelines, reimbursement policies, events impacting healthcare (e.g. a pandemic), national variation in RMM implementation and media attention may influence the outcome of RMM and make establishing a causal relationship between a specific RMM and its outcomes challenging.

In certain situations, RMM may lead to unintended consequences, possibly counteracting the effectiveness of RMM, and other outcomes of RMM beyond the intended ones (see XVI.B.1.2) may be appropriate for ~~investigation~~evaluation upon request of the competent authority. Such unintended outcomes include e.g.~~, for example,~~ undue burden of RMM on the patient, healthcare professional or healthcare system. Other examples are shown in Table XVI.5~~.~~.

Table XVI.5.: Outcomes of risk minimisation measures ~~RMM~~ on 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
Spill-over effect	RMM recommends that the~~-~~ medicine is no longer used in a certain patient population and patients are switched to alternative treatment	Medicine is withheld in a patient population that is not targeted by the RMM and where the medicine has a positive benefit/risk profile
Non-treatment	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).

~~Monitoring RMM outcomes is intended to evaluate the effectiveness of RMM and may include both routine (see XVI.B.1.) and additional RMM (see XVI.B.3.) removed~~

~~is~~

Effectiveness evaluation of RMM should focus on RMM of major patient and public health importance, taking into account the nature, severity and seriousness of the risk, the magnitude of population exposure and the amount of public concern. where measures in addition to routine RMM are required.

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

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

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

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

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

Principle 1: Focussed evaluation

Principle 2: Regular evaluation

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

Details of how RMM effectiveness will be measured should be included in the RMP. Protocols and milestones for qualitative and quantitative RMM effectiveness studies should be included in the pharmacovigilance plan, and the results should be considered for updating the risk minimisation plan of the RMP (see XVI.C.1.2 ~~and GVP Module V~~). For a specific RMM several factors will determine the appropriate timepoints, including time since launch or implementation of the RMM, estimated magnitude of exposure, ~~seriousness~~seriousness, and severity ~~and seriousness~~ of the risk(s) and the design of the proposed studies evaluating RMM effectiveness.

The following timepoints should be considered by marketing authorisation holders for setting and agreeing timetables with competent authorities:

- After regulatory implementation (see XVI.B.1.3.) an initial evaluation of RMM e.g. within 12-24 months), to allow the possibility of necessary ~~amendments~~changes in healthcare;
- ~~,~~Within 4 years of implementation, to assess the overall effectiveness of the RMM (see XVI.B.5.3.), and where applicable to inform the evaluation of the renewal of a marketing authorisation.

Unless requested otherwise, results of RMM effectiveness evaluation should be submitted with the periodic safety update reports (PSURs) (see XVI.C.1.3.~~GVP Module VII~~), including a discussion on~~-~~ the need for RMM amendments (see XVI.B.5.3. and XVI.B.6.).

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

~~and protocols for qualitative studies be included in the pharmacovigilance plan of the RMP (see GVP Module V).~~

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

- ~~After initial implementation of a risk minimisation programme (e.g. within 12-18 months), in order to allow the possibility of necessary amendments;~~

- ~~Within 3 years of initial implementation of a risk minimisation programme to potentially add further elements to the risk minimisation programme (see XVI.B.5.3.); and~~
- ~~Within 5 years to assess the overall effectiveness of the risk minimisation programme (see XVI.B.5.3.) or in time for the evaluation of the renewal of a marketing authorisation;~~

~~Principle 3: Evaluation of intended and unintended outcomes~~

XVI.B.5.3~~2~~. Objectives and approaches of studies evaluating risk minimisation measures~~to effectiveness evaluation~~

In accordance with XVI.B.5.1. objectives of RMM effectiveness evaluation may include investigating e.g. the:

- Eextent of the RMM that has been delivered to the target population as planned;
- Extent the RMM has led to the intended knowledge and behaviour in the target population, or whether other outcomes have occurred; and
- Extent the RMM-intended health outcomes have been achieved within relevant timeframes, or whether other health outcomes have occurred.

Study objectives may differentiate between the RMM message, i.e. the knowledge on the risk information and the actions intended by the RMM, and the individual or set of RMM tool(s).

Different approaches to data collection and analysis as appropriate may be applied for each step of the RMM implementation process (see XVI.B.1.3. and Figure XVI.3.). Measurements and indicators of RMM effectiveness (see XVI.B.5.4.) should be defined in the study protocol.

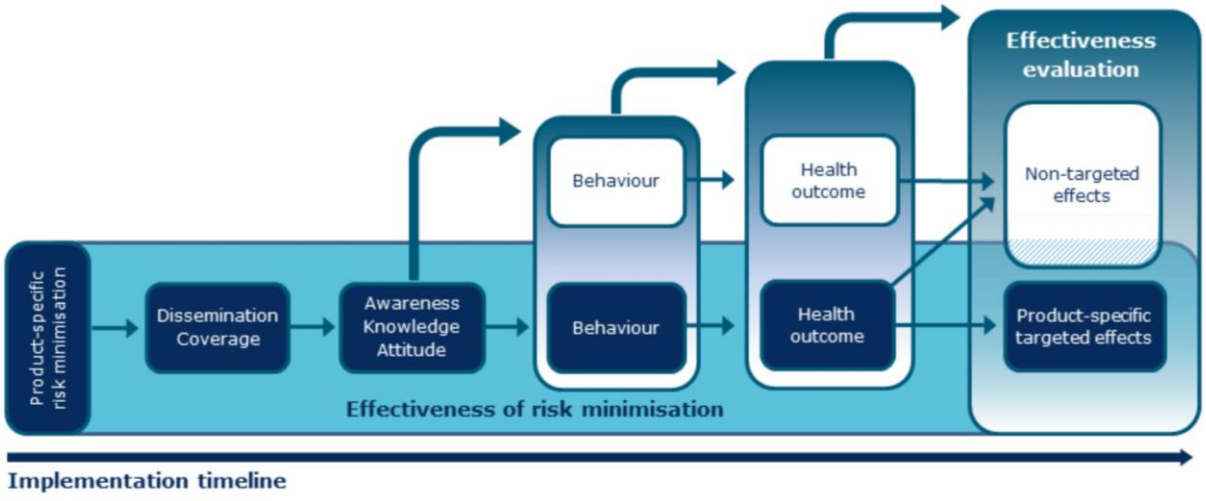

Figure XVI.3.: A~~The~~ approach to evaluating the effectiveness ~~evaluation~~ of risk minimisation measures

Note: This approach includes measuring medicinal *product-specific targeted effects* and, as appropriate, relevant *non-targeted effects* associated with the use of the concerned (blue boxes) and other medicinal products (white boxes).

Depending on the study objectives, a combination of qualitative and quantitative research methods may be appropriate. The scope and objectives should be defined in relation to the desired health outcomes of RMM. Marketing authorisation holders and competent authorities may agree on indicators of success to be included in the risk minimisation plan of the RMP (see XVI.C.1.2). Using quantitative measurements (e.g. prescription levels or medicines utilisation patterns, health outcomes) for evaluating the effectiveness of RMM where feasible is particularly important and should be considered when deciding on RMM. Qualitative research may be useful for informing the objectives of quantitative research and understanding the reasons for success or failure of RMM (e.g. lack of intended knowledge or behaviours), and such findings may be relevant when regulatory actions for adapting~~amending~~ RMM are considered (see XVI.B.5.4. and XVI.B.6.).

The evaluation strategy should consider that methods are risk-proportionate and provide accurate results that are meaningful for further regulatory decision-making without placing undue burden on healthcare systems or patients.~~In accordance with the principles in XVI.B.5.1. the objectives of effectiveness evaluation are to investigate:~~

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

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

~~**Figure XVI.21.: The approach to effectiveness evaluation of risk minimisation includes measuring medicinal *product-specific targeted effects* and, as appropriate, relevant *non-targeted effects* associated with the use of the concerned and other medicinal products**~~

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

~~The evaluation strategy should consider which methods are proportionate and likely to provide accurate results that are meaningful for further regulatory decision-making without placing undue~~

~~burden on healthcare systems or patients. The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed.~~

XVI.B.5.~~3~~2.1. Dissemination and ~~risk~~ knowledge outcomes

Each stage from dissemination of information on RMM to ~~risk~~ knowledge adoption should be ~~optimised~~ and considered during RMM evaluation (see Figure XVI.3.).

Dissemination methods and individual perception of RMM information influence the knowledge of risks and RMM. Quantitative measurements of the stages of the communication process may help to identify barriers to dissemination and knowledge adoption, ineffective dissemination processes and knowledge gaps. When used in combination with quantitative research, qualitative measures of the risk communication process may help to understand factors influencing risk perception and knowledge adoption. Risk 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).

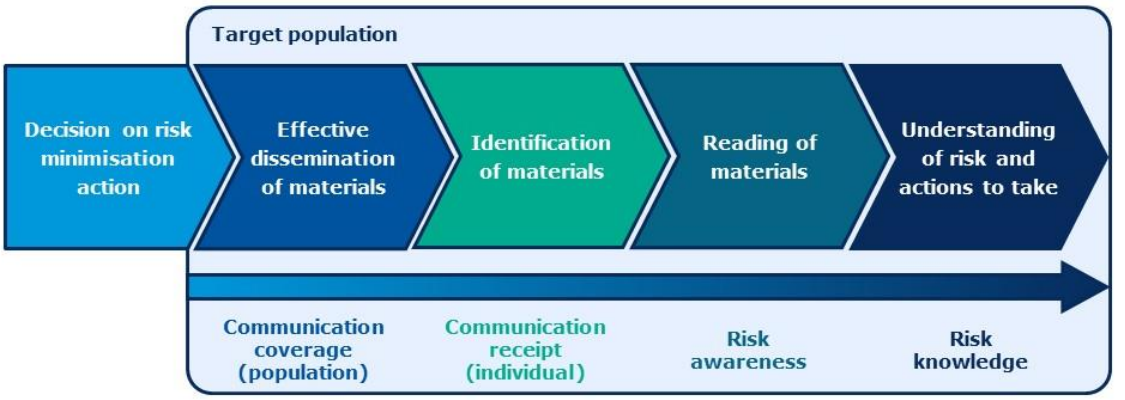

Figure XVI.4.: Pathway of the risk communication process from ~~RMM~~ dissemination ~~of risk minimisation measures~~ to adoption of the ~~risk~~knowledge intended by the risk minimisation ~~measures~~measures.~~.~~

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

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

Quantitative measurements
Proportion of target population for which RMM tool dissemination has been completed over time (in total and e.g. by RMM tool, country, or type of healthcare professional)~~;~~
Download total/webpage view frequency if web based RMM tools are provided, 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 learnt societies)~~;~~

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;
Level of comprehension, recall of information and knowledge of healthcare professionals and patients concerning the RMM tool and its messages;
Qualitative findings
Attitudes about the RMM in terms of e.g. perceived feasibility, acceptability, usability, opinion, motivations, confidence to apply the tool correctly (self-efficacy) and that RMM will be effective in controlling the risk;
Identification of environmental factors of healthcare systems and patient life impacting on RMM implementation, e.g. available resources and constraints in clinical pathways and time;
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);

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

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

~~***Quantitative measurements:***~~

~~Examples of quantitative measurements of dissemination and knowledge adoption are:~~

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

~~***Qualitative findings:***~~

~~Examples of outputs of qualitative research into knowledge adoption are:~~

- ~~Understanding of attitudes about the RMM in terms of e.g. perceived feasibility, acceptability, usability, opinion, motivations, confidence to apply the tool correctly (self-efficacy) and that RMM will be effective in controlling the risk;~~
- ~~Identification of environmental factors of healthcare systems and patient life impacting on RMM implementation, e.g. resource issues, time constraints;~~

~~• Identification of information-related factors influencing knowledge uptake in patients and healthcare professionals, particularly prior information awareness and knowledge of the receiver and communication on the risk from other (preferred) sources.~~

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

XVI.B.5.~~3~~2. Behavioural ~~changes~~ outcomes

RMM should be evaluated with a view to achieving the intended actions and behaviours in medicines use. ~~patient~~ Factors that may be enablers or barriers for ~~acquired risk~~ adopted knowledge to result in intended actions and behaviours are illustrated in Figure XVI.5.. These enablers and barriers may impact on the feasibility of the RMM in practice.

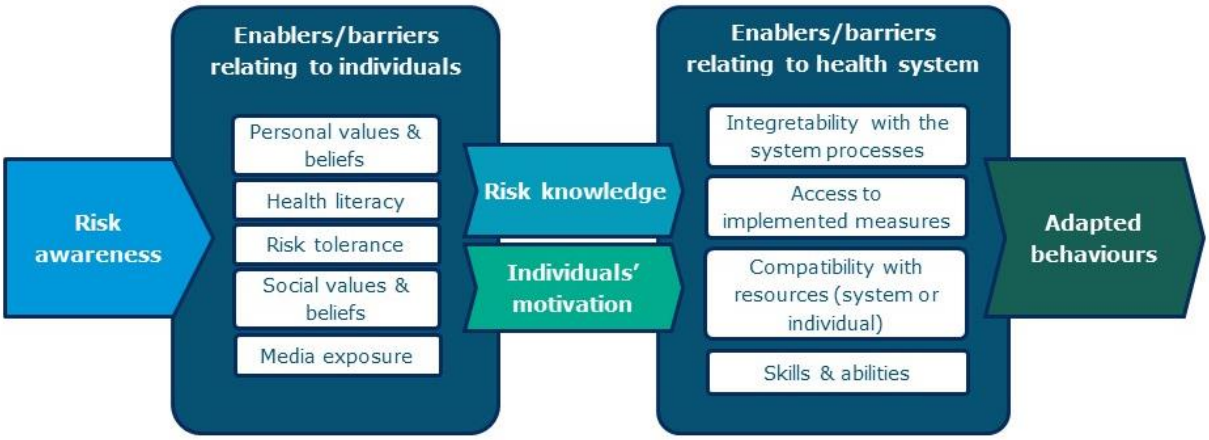

Figure XVI.5.: Pathway from risk awareness to risk minimising behaviours including enablers and barriers of behavioural change~~.~~

RMM-intended actions 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 (e.g. healthcare environment factors, availability of resources and processes, access to alternative treatment, healthcare professionals' and patients' perception of RMM and related attitudes).

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

Table XVI.7.: Examples of quantitative measurements and qualitative findings addressing behavioural outcomes~~.~~

Quantitative measurements
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~~;~~

Quantitative measurements
Quantification of enablers or barriers for intended behavioural changes (e.g. healthcare environment, availability of resources, access to alternative treatment, perception of a RMM and 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
Awareness (e.g. a new contraindication is not known by some healthcare professionals and/or patients)~~;~~
Attitude (e.g. some healthcare professionals and/or patients are not convinced that there should be a contraindication)~~;~~
Alternative treatments (e.g. despite the contraindication, some patients still need treatment)~~;~~
Difficulties in implementing RMM in relation to healthcare system (e.g. limited access to diagnostic tools)~~;~~

~~Based on achieving knowledge on risks and RMM in patients and healthcare professionals, RMM should be developed and evaluated with a view to achieving changes towards intended behaviours of medicines use. Therefore, implementation of RMM in healthcare needs to be feasible and targeted healthcare professionals and patients need to engage and comply with the measures in healthcare and daily routines. Factors that may be enablers or barriers for acquired risk knowledge to result in intended behavioural changes are illustrated in Figure XVI.3.. These enablers and barriers of behavioural change may impact on the feasibility of the RMM in practice. D**igital tools designed to elicit behavioural changes** proactively (e.g. app reminders for tablet intake) not only support RMM implementation but also allow collecting data on behavioural changes in real time (e.g. recording laboratory results, confirming digital educational material receipt, completed patient diary etc.).~~

~~***Quantitative measurements:***~~

~~Examples of quantitative measurements of behavioural changes are:~~

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

- ~~Frequency of requests from healthcare professionals for refills of educational materials or other RMM tools as proxies of RMM tool utilisation.~~

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

~~Qualitative findings:~~

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

- ~~Awareness (e.g. a new contraindication is not known by some healthcare professionals and/or patients);~~

- ~~Attitude (e.g. some healthcare professionals and/or patients are not convinced that there should be a contraindication);~~

- ~~Alternative treatments (e.g. despite the contraindication, some patients still need treatment);~~

~~Difficulties in implementing RMM (e.g. due to lack of diagnostic tools).~~

XVI.B.5.~~3~~2.3. Health outcomes

Monitoring and investigating measurable health outcomes ~~are means to~~ evaluate~~s~~ 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 regulatory actions aimed at minimising risks. 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 outcome objectives are provided in Table XVI.8..

Table XVI.8.: Examples of quantitative measurements addressing health outcomes~~:~~

Quantitative measurements
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~~:~~

Figure XVI.6. provides an overview of qualitative and quantitative research outcomes that may evaluate the different stages of the implementation process of RMM.

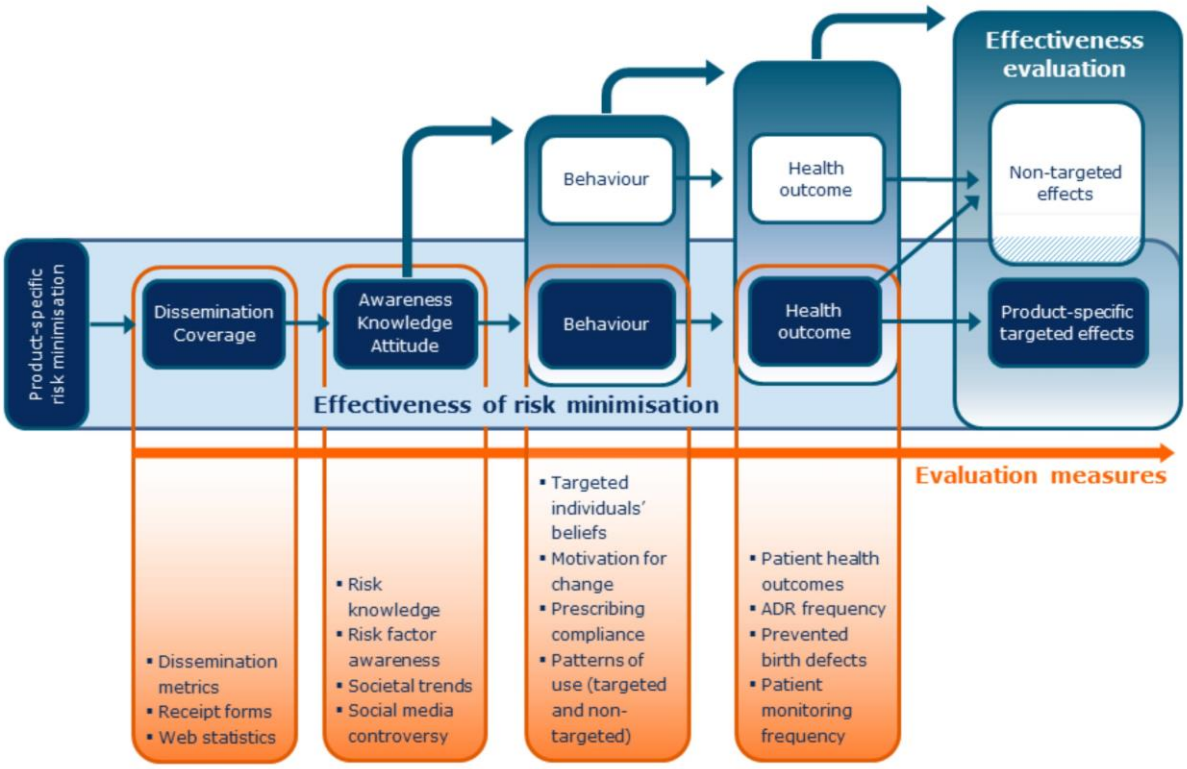

Figure XVI.6.: Approach to effectiveness evaluation of risk minimisation measures ~~RMM~~with ~~showing~~ examples of quantitative and qualitative research outcomes at each implementation step for measuring medicinal *product-specific targeted effects* and, as appropriate, relevant *non-targeted effects* associated with the use of the concerned (blue boxes) and other medicinal products (white boxes)

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

~~Quantitative measurements:~~

~~Examples of quantitative measurements of health outcomes are:~~

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

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

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

XVI.B.5.~~43~~. ~~Assessment~~ Interpretation of the results of studies ~~of~~ evaluating the effectiveness of risk minimisation measures ~~and regulatory follow-up~~

The design of studies evaluating the effectiveness of RMM should provide evidence to determine whether adaptations~~amendments~~ to RMM are warranted, including whether ~~or~~ 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 ~~adaptations~~ to implementing RMM agreed at EU level should be considered in the interpretation of results~~ across Member States~~.

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

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

Factors for consideration	
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?

Factors for consideration	
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)

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 requires 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.~~2.~~1. and XVI.Add.II.3.1.).

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

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

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

~~Criteria~~	
~~**Therapeutic need**~~	~~• Seriousness of the indication (e.g. life-threatening condition, serious consequences on the quality of life, natural evolution of the disease)~~ ~~• Access to therapeutic alternatives~~
~~**Population at risk**~~	~~• Size of the population~~ ~~• Age group at risk (e.g. children, older patients)~~ ~~• Pregnant women~~ ~~• Frailty~~

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

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

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

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

XVI.B.6~~7~~. Amending, discontinuing and introducing a~~A~~dditional risk minimisation measures within the benefit-risk~~life~~ management cycle of the medicinal product

As part of the benefit-risk management cycle for a medicinal product (see XVI.B.1.1.) in the post-authorisation phase ~~lifecycle approach~~, it may be ~~is also~~ necessary to ~~continuously~~ adapt its ~~additional~~ RMM set for improvement, i.e. to:

- Amend existing RMM materials in terms of e.g. the risk information, intended clinical action, target audiences, design or dissemination plan (see XVI.B.4.);
- Discontinue one or more of the existing additional RMM materials; or
- Introduce (a) new RMM tool(s).

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

Table XVI.10.: Points to consider for adapting a set of risk minimisation measures

Points to consider for adapting a RMM set
Evolving knowledge on the safety profile of the medicinal product and related updates to the RMP and/or product information (see XVI.C.1.1.)
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, if applicable, 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 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 RMM
Worlwide experience with RMM

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

~~over time and consider their maintenance as appropriate.~~

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

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

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

~~.~~

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

Any proposal for adapting RMM for a medicinal product ~~for reclassification or discontinuation~~ should ~~always~~ be accompanied by a ~~thorough discussion with a due justification~~ rationale and the underlying evidence or other relevant information.~~about whether the implemented additional RMM needs to be updated (e.g. strengthening of the wording), enhanced (e.g. introduction of further additional RMM), changed (e.g. patient card instead of prescriber checklist), or discontinued~~. ~~.~~The marketing authorisation and the RMP, if the medicinal product has a ~~The~~ RMP, should be updated with the agreed RMM adaptations~~accordingly~~ (see XVI.C.1.2.).

If amendments to additional RMM materials have been agreed, a national dissemination plan (see XVI.B.4.) to replace the existing with the amended materials at the level of the target audiences should be established and implemented by the marketing authorisation holder.

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

Adaptations to RMM (see XVI.B.6.), as well as 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 in the context of the adapted RMM set for the medicinal product (see XVI. B.5.). The RMP requires being updated accordingly (see XVI.C.1.2.).

XVI.B.~~7~~8. Quality systems ~~of~~or risk minimisation ~~measures~~

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 (see XVI.4.1. and XVI.4.2.) and are subject to version control;
- Establish and follow processes to ensure that the RMM materials are disseminated to healthcare professionals and patients according to the dissemination plan (see XVI.B.4.3.), and to keep

records of the dissemination process and outcomes (e.g. records of receipt of RMM materials at healthcare sites); ~~and~~

- Establish and follow processes to ensure compliance, at the level of the marketing authorisation holder, with the tools of a risk minimisation control programme ~~n~~and to keep records thereof; ~~.~~
- Follow the quality requirements for RMPs (see GVP Module V) and PASS (see GVP Module VIII);
- Apply the quality improvement cycle and the principles for good pharmacovigilance practices (see GVP Module I) to RMM-related processes;
- Apply the requirements for pharmacovigilance record management (see GVP Module I) to all RMM-related processes and documents; and
- Describe the RMM-related processes and their quality management in the pharmacovigilance system master file (PSMF) (see GVP Module II).

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

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

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

The competent authorities should apply all their requirements for the quality management of pharmacovigilance systems (see GVP Module I) to their RMM-related processes and documents.

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

In the EU, ~~The Annex IID of~~ the marketing authorisation of a medicinal product ~~authorised in the EU~~ includes ~~outlines~~ the ~~key elements of any additional~~ 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 (see XVI.B.2.3.) with their messages (see XVI.A.1.1.). ~~,~~ ~~are~~imposed ~~on the marketing authorisation, as a condition for the safe and effective use of a medicinal product. These additional RMM~~ Therefore, ~~the~~ RMM form an obligation on the marketing authorisation

holder in the EU. ~~For a centrally authorised product,~~ W~~w~~hen the RMM are adapted (see XVI.B.6.), the marketing authorisation is to be updated, following the EMA Post-Authorisation Guidance[11] for centrally authorised product or the applicable guidance in Member States for nationally authorised products.

For a medicinal product subject to an EU referral procedure~~-~~, the Commission Decision on the referral includes the required RMM tools and their key messages imposed on the marketing authorisation holder, while adaptations of RMM required thereafter are included in the updated national marketing authorisations.

The specific requirements for reflecting a patient card in the marketing authorisation are provided in XVI.App2.4..

XVI.C.1.2. Risk management plan

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

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 intended outcomes (see XVI.B.1.2.) and the justification for each tool, and describing the planning and implementation activities for the RMM. It should also include a summary of the results of the studies evaluating RMM effectiveness as the justification for adaptations to RMM.

RMP annex 6 should include the RMM key elements (see XVI.A.1.1.) if RMM tools beyond the SmPC and PL are required.

RMP part III on the pharmacovigilance plan and RMP part V on the risk minimisation plan should include a description of ~~,~~the activities for evaluating the effectiveness of RMM, in particular in relation to their intended outcomes.

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

XVI.C.1.3. Periodic safety update report

The 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 (see GVP Module VII) should include the updates on the development and dissemination of RMM and 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 set (see XVI.B.6.), and/or the activities required to evaluate the RMM effectiveness (see XVI.B.6.1.).

[11] www.ema.europa.eu/en/human-regulatory-overview/post-authorisation

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

~~PSURs and updates of the RMP should include a summary evaluation of the outcomes of specific RMM in the EU. In the RMP, the focus should be on how this informs risk minimisation and pharmacovigilance planning. In the PSUR, there should also be an evaluation of how the implemented measures impact the safety profile and risk-benefit balance of the product. In general, the focus should be on information which has emerged during the reporting period or since dissemination of the most recent RMM in the EU. Where there is parallel submission of a PSUR and an RMP update to the competent authorities of the EU regulatory network, the use of a common content module should be considered (see GVP Modules V and VII). For the evaluation, the guidance in XVI.B.5. applies.~~

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

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

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

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

~~To continuously improve regulatory decision-making on RMM, the Pharmacovigilance Risk Assessment Committee (PRAC) (see XVI.C.1.1.1.) adopted a strategy for measuring the impact of pharmacovigilance activities[12] that includes the effectiveness evaluation of RMM (see XVI.B.5.). The guidance on RMM effectiveness evaluation resulting from this strategic work is provided in GVP Module XVI – Addendum II and should be followed too.~~

~~[12] https://www.ema.europa.eu/en/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities_en.pdf~~

XVI.C.2. Roles and responsibilities for the applicant/marketing authorisation holder in the EU

The RMM pose an obligation on the marketing authorisation holder (see XVI.C.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 in the EU shall submit the application accompanied by the RMP which the applicant will introduce for the medicinal product [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(28c)]. The applicant/marketing authorisation holder in the EU should include RMM in the RMP in accordance with the guidance in XVI.C.1.. In 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 RMM materials and a dissemination plan following the guidance in XVI.B.4. 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 dissemination plan for agreement. For establishing and maintaining the tools required a risk minimisation control programme (see XVI.B.2.3.2.), the marketing authorisation holder should discuss the development and dissemination of the RMM required for the programme with the competent authorities in Member States. The final additional RMM materials should be approved by the competent authorities in Member States before dissemination in accordance with the national dissemination timetable agreed with the competent authorities in Member States in the dissemination plan.

The marketing authorisation holder shall operate a risk management system for each medicinal product, monitor the outcome of RMM which are contained in the RMP 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)]. 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 results of assessments of RMM effectiveness (i.e. of studies evaluating 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)]. Therefore, the marketing authorisation holder should follow the guidance in XVI.B.5. and XVI.C.1. .

The marketing authorisation holder should inform the competent authorities in Member States ~~provide information regarding the status of dissemination of additional RMM as agreed with the competent authorities in Member States and keep them informed of~~ about any important changes or issues which impact on the previously agreed dissemination plan, together with an updated plan ~~to~~ addressing the encountered changes or issues.

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

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.).

Further, for specific operations in the EU, the marketing authorisation holder should follow the guidance in XVI.C., and for specific operations in Member States additionally ~~The marketing authorisation holder should follow~~ national guidance~~ Module and agree the appropriate terms with the competent authority~~ in~~ each~~ Member State~~s where such guidance is available~~.

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 PSMF [IR Art 2(4)(a)-(b)], to be maintained by the marketing authorisation holder [DIR Art 104(3)(b)] (see GVP Module II). For the quality systems requirements, the marketing authorisation holder should follow the guidance in XVI.B.7..

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

~~Regarding RMM, the marketing authorisation applicant/holder in the EU should therefore follow the guidance in XVI.B. and further guidance in XVI.C. addressed to the marketing authorisation holder as well asnd as referenced. document RMM in the RMP (see GVP Module V).~~

~~The marketing authorisation applicant/holder should plan for developing and evaluating RMM early during the development phase of the medicinal product andis encouraged to discuss these plans for RMM with the competent authorities, and should also discuss with the competent authorities in Member States as soon as early as is feasible, e.g. when it seems likely that additional RMM materialsspecific risk minimisation activities maywill need to be adaptations ed to the different healthcare systems in place in the different Member States. The RMM adopted in the RMP should be agreed with the national competent authorities before dissemination in accordance with the timetable agreed by national competent authorities. In the development and dissemination of web-based tools, marketing authorisation applicants/holders should follow the requirements of each Member State, with particular consideration of potential issues linked to accessibility, recognisability, responsibility, and privacy and data protection.~~

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

~~User-testing of materials for risk minimisation in the local languages is recommended.~~

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

~~The marketing authorisation holder shall monitor the outcome of RMM which are contained in the RMP or which are laid down as conditions of the marketing authorisation pursuant to Articles 21a, 22 or 22a of DIR [DIR Art 104(3)(d)] and should therefore follow the guidance on RMM effectiveness evaluation in XVI.B.5.. The marketing authorisation holder should report the findings of the evaluation when updating the RMP (see GVP Module V) and in the periodic safety update report (PSUR) (see GVP Module VII) with a view whether the RMM ensure the positive risk-benefit balance of the product or adjustments to the RMM or other regulatory action is needed (see XVI.C.4., VII.B.5.16.5. and VII.C.5.5.). If the marketing authorisation holder becomes aware of information regarding RMM that may impact the benefit-risk balance of the medicinal product, this should be reported as an emerging safety issue.~~

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

XVI.~~BC.6~~2.2.~~.~~ Coordination of activities for ~~risk minimisation measures effectiveness evaluation~~ across medicinal products containing the same active substance

The ~~Applicants~~marketing authorisation holder for a biosimilar, hybrid or~~and~~ generic medicinal product should ~~in principle~~ implement the same RMM materials~~in terms of content and dissemination~~ as required for the reference medicinal product, unless requested otherwise by the competent authorities. ~~(see XVI.C.1.1.1.).~~ Where for a generic, biosimilar or a hybrid medicinal product additional RMM materials identical to the user-tested materials in place for the reference product are being implemented, no second user-testing for the generic, biosimilar or hybrid product is needed, unless testing in a not yet tested language is requested by the competent auhorities. The marketing authorisation holder for a biosimilar, hybrid or generic medicinal product should develop and agree with the competent authorities a dissemination plan for the RMM materials (see XVI.B.4.2.)

Additional RMM for generic, biosimilar or hybrid products may be required in some circumstances beyond those of the reference medicinal product (e.g. different formulation or route of administration).

When~~If~~ several medicinal products~~, including generics, biosimilars or hybrids,~~ containing the same active substance, such as generic, biosimilar and hybrid products, ~~-~~have been authorised and require additional RMM, their marketing authorisation holders are encouraged

to collaborate for fulfilling their responsibilities (see XVI.C.2.) through coordination of a ~~there should be a~~ consistent approach to developing, disseminating, evaluating and adapting RMM materials. ~~planning the evaluation of RMM, overseen by the competent authorities, to ensure that the RMM~~

~~effectiveness can be achieved for each individual product as well as for all products collectively (see XVI.B.2.).~~

When a common RMM material is developed for~~ever~~ more than one medicinal product containing~~s~~ the same active substance~~,~~ ~~and the same messages of the patient card apply to all these products, it is recommended that marketing authorisation holders collaborate on designing and disseminating a~~ the material may~~single patient card~~ refer~~ring~~ only to the name of active substance, and not to all~~any~~ invented name~~s~~ of the~~a~~ concerned medicinal product~~s~~.

~~However, w~~Where RMM for a generic, biosimilar or hybrid medicinal product are fully identical with the marketed~~originator/~~reference product,~~ ~~there is usually no need to request the marketing authorisation holder of the generic, biosimilar or hybrid product to conduct a study evaluating~~e~~ RMM effectiveness for their product. ~~(~~unless requested ~~periodic dissemination measures (see XVI.B.5.2.1. are agreed otherwise~~ in the RMP of this product, in particular if there is uncertainty that ~~). This applies under the assumption that~~ the RMM evaluation strategy ~~requested~~ for the reference product will be able to gather sufficient data, or if a considerable proportion of medicines use is expected to possibly be contributed by ~~. For example, if the introduction of~~ (a) generic, biosimilar or hybrid product(s) ~~reduces exposure to the reference product, the data underpinning the RMM evaluation for the reference product may become insufficient, and competent authorities may also request RMM evaluations for the generic, biosimilar or hybrid product(s)~~.

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

Where the marketing authorisation holder for a generic, biosimilar or hybrid medicinalvproduct is not required to conduct a study to evaluate RMM effectiveness, updates on the dissemination of RMM should still be included in the PSURs for the concerned product (see XVI.C.1.3.).

~~In all cases, the MAH for a generic, biosimilar or hybrid product should agree with the relevant competent authorities their proposals for the pharmacovigilance plan and for risk minimisation.~~

XVI.C.3~~1~~. Roles and responsibilities within the EU regulatory network

XVI.C.3~~1~~.1~~2~~. 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.

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~~Art~~, 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.).

~~Overall, ir competent authority's~~

Irrespective of the route of marketing authorisation, t~~T~~he competent authorities in Member States are responsible for ~~the oversight at national level of the development and dissemination of additional RMM imposed as a condition of the marketing authorisation~~ the approval of nationally tailored additional RMM materials ~~in the official language(s) of the respective Member State~~ and the agreement of the national RMM dissemination plans (see XVI.B.4.) and should ensure ~~for the safe and effective use of a medicinal product in the EU~~, ~~irrespective of the route of marketing authorisation. Articles 104(3)(d) and Article 107h(1) of Directive 2001/83/EC and Article 28a of Regulation (EC) No 726/2004 specifically include provisions for monitoring the outcome of RMM for both marketing authorisation holders and competent authorities. For centrally authorised products and nationally authorised products referred to PRAC, key elements will be agreed at EU level and need to be implemented in a coordinated manner across Member States. However, finalisation and dissemination of the RMM are agreed with competent authorities in Member States~~. ~~Furthermore, they shall, in collaboration with the Agency, monitor the outcome of RMM contained in RMPs and of the conditions referred to in Articles 21a, 22 or 22a of Directive 2001/83/EC [DIR Art 107h(1)(a)].~~

~~For those RMM introduced after the initial marketing authorisation, the competent authorities in Member States should ensure~~ prompt consideration ~~and agreement of the RMM with~~of the respective submissions by ~~the~~ marketing authorisation holders (see XVI.C.2.1.). ~~They should agree the final content, format and media of the RMM tools, including printed materials, web-based platforms and other audio-video media, availability of materials, as well as the timetable of (re-)dissemination by the marketing authorisation applicant/holder before a product is introduced to their market or at any time thereafter as needed (see GVP Module XVI – Addendum I~~).

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

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

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

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 may have specific requirements for using educational/safety advice materials for documenting healthcare processes, including confirmations by signatures of the healthcare professional or patient. Especially, for risk minimisation control programmes the ~~Such programmes should be adapted to local healthcare settings in agreements with~~ competent authorities in Member States should determine and discuss with the marketing authorisation holder how the applicable RMM tools should be implemented in healthcare and which RMM materials are needed for these tools in ~~.~~ ~~Centre accreditation should be organised~~ accordance~~ing to~~ with the nationally established processes for training and qualification of healthcare professionals, accreditation of healthcare facilities, healthcare documentation and information exchange, and traceability. ~~procedures and be complemented with adequate training of healthcare professionals as agreed with the competent authorities.~~ Risk minimisation control programmes can be locally supported in their implementation in healthcare with national adaptations, e.g. restricted amount of medicinal product per prescription, or restricted validity length of a prescription.

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

~~Whenever there are d~~Deviations from RMM key elements ~~-~~ agreed at EU level~~, this should be duly~~ may sometimes be needed in a Member State, to account for specific situations of the healthcare system and are subject to justification and agreement between~~ed by~~ the competent authority in the Member State and the marketing authorisation holder~~., as applicable, for example:~~

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

Competent authorities in Member States are encouraged to seek input from healthcare professional and patient representatives (see XVI.B.1.4.) as needed, appropriate and possible, and to consider results from user-testing of RMM when requested from and/or submitted by the marketing authorisation holder. Especially, for risk minimisation control programmes interactions between the competent authorities in Member States and stakeholders responsible for integrating these in healthcare processes may be needed. For the engagement with healthcare professional and patient representatives, competent authorities in Member States should have frameworks in place which verify the independence of the representatives for impartial advice, in particular the independence from marketing authorisation holders. User-testing of materials for risk minimisation in the local languages is encouraged.

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..

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

XVI.C.3~~1~~.2~~1~~. 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 may be imposed to address important identified or important potential risks and 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 nationally authorised products subject to a safety-related referral procedure, the Agency conducts these referral procedures in accordance the legislation and guidance on Referral procedures: human medicines[13].

For medicinal products authorised nationally, including those authorised through the mutual recognition procedure or the decentralised procedure, which are under the responsibility of the competent authorities in Member States (see XVI.C.3.1.), the Agency supports the applicable procedures at EU level (see XVI.C.3.1.1.).

[13] www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/referral-procedures-human-medicines

The Agency fulfils its legal mandate through the procedures of its Committee for Medicinal Products for Human Use (CHMP)[14] and its ~~The Agency shall, in collaboration with the Member States, monitor the outcome of RMM contained in RMP and of conditions referred to in Directive 2001/83/EC (Articles 8(3)(iaa), 21a, 101(2), 104(2), 104(3), 104a and 107h (1)) and Regulation (EC) No 726/2004 (Articles 9(4), 14a, 21, 28a). In monitoring the outcome of RMM, the Agency should support the~~ Pharmacovigilance Risk Assessment Committee (PRAC) (see XVI.3.1.1.), and ~~in its scientific assessment of outcomes of additional RMM, through the integration of data provided by Member State resources and research activities. , and~~ through supportings the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh)[15].

For the purpose of risk minimisation, the Agency should follow the guidance in XVI.B. and XVI.C.~~The guidance on transparency requirements in XVI.C.5. applies~~.

XVI.C.~~3~~1.~~2~~1.1. The Pharmacovigilance Risk Assessment Committee

The PRAC (see GVP Module I)~~C~~ 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 ~~evaluate the need for RMM and their outcome, including additional RMM,~~ and if they recommend RMM~~-~~, ~~make recommendations regarding the~~ specify the tools and messages (see XVI.A.1.1.) in the PRAC recommendation~~elements of the necessary regulatory action to the Committee for Medicinal Products for Human Use (CHMP) for centrally authorised products or the Coordination Group – Human (CMDh) for nationally authorised products referred to PRAC~~. The PRAC recommendation may also relate to the development (see XVI.B.4.1.) and dissemination (see XVI.B.4.2.) of additional RMM materials, including the need for a DHPC (see XVI.B.4.2.1.).

Further, the PRAC recommendation should include~~-~~ studies to be requested from the marketing authorisation holder for evaluating RMM effectiveness (see XVI.B.5.).~~In order to respect the diversity of the different healthcare systems in Member States, some key elements will be specific for only some Member States (e.g. an activity is specifically linked to the healthcare system of one Member State), but these should still be included in the RMP agreed at EU level~~. ~~To facilitate alignment between generic, hybrid or biosimilar products, the PRAC may as appropriate give advice on the key elements that should be implemented for all concerned products (as conditions of their marketing authorisation) and, on agreement, may make these general requirements publicly available to facilitate implementation at national level.~~ The PRAC should assess ~~as appropriate~~ the protocols and results of

[14] www.ema.europa.eu
[15] https://www.hma.eu/human-medicines/cmdh/about-cmdh.html

these studies ~~PASS which aim to evaluate the effectiveness of RMM~~ for regulatory follow-up in accordance with the guidance in XVI.B.5. and XVI.B.6.~~and GVP Module VIII~~.

~~-~~To continuously improve regulatory decision-making on RMM, the PRAC adopted a strategy for measuring the impact of pharmacovigilance activities[16], which includes the effectiveness evaluation of RMM (see XVI.B.5.).

XVI.C.3.~~2~~.2. Stakeholder engagement framework

The PRAC engages with patient and healthcare professional representatives to support PRAC decision-making on risk minimisation (see XVI.B.1.4.). Therefore, the PRAC involves its members representing patient and healthcare professionals in discussing options for RMM and their implementability for anticipated RMM effectiveness (see XVI.B.1.3.) and may also seek their insights on general matters relevant to implementing RMM in healthcare; and the PRAC considers further forums for engaging with patient and healthcare professional representatives established by EMA within its frameworks for engaging with partners and networks[17], which includes 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[18]).

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

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

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

- ~~Current awareness, understanding and management of the potential risks of the medicine;~~
- ~~Effectiveness, appropriateness and feasibility of having additional RMM in place;~~
- ~~Most efficient risk minimisation tools and appropriate and feasible dissemination processes in relation to target audience(s) and channels;~~

[16] www.ema.europa.eu/en/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities_en.pdf
[17] https://www.ema.europa.eu/en/partners-networks
[18] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/rules-procedure-organisation-and-conduct-public-hearings-pharmacovigilance-risk-assessment-committee-prac_en.pdf

- ~~Support for healthcare professional and patient organisations by means of e.g. clinical guidelines, patient guides made available by healthcare systems or patient organisations, articles in scientific journals and conferences; and~~
- ~~Other practical suggestions for improvement.~~

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

~~PSURs and updates of the RMP should include a summary evaluation of the outcomes of specific RMM in the EU. In the RMP, the focus should be on how this informs risk minimisation and pharmacovigilance planning. In the PSUR, there should also be an evaluation of how the implemented measures impact the safety profile and risk-benefit balance of the product. In general, the focus should be on information which has emerged during the reporting period or since dissemination of the most recent RMM in the EU. Where there is parallel submission of a PSUR and an RMP update to the competent authorities of the EU regulatory network, the use of a common content module should be considered (see GVP Modules V and VII). For the evaluation, the guidance in XVI.B.5. applies.~~

XVI.C.4. Transparency

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

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)], and this includes activities on RMM.

For a centrally authorised product~~s~~, the Agency shall make public~~:~~

~~Summary of the RMP [REG Art 26(1)(c)], with specific focus on risk minimisation activities described therein [IR Art 31.1];~~

the European public assessment report (EPAR)~~,~~ ~~that includes~~ the~~any~~ 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 information on the RMP ~~,~~ including~~such as~~ information on any additional RMM [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)].~~:~~ Further the Agency has transparency obligations for medicinal products subject to an EU referral procedure. To fulfil their transparency requirements, the Agency follows the EMA publication policy "What we publish on medicines, and when"[19].

~~SmPCs and PLs [REG Art 57]; and~~

[19] ema.europa.eu

- ~~Conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions [REG Art 13].~~

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

~~P~~public assessment report~~s~~, ~~-~~conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions, ~~this shall include a summary written in a manner that is understandable to the public~~, the SmPC, the package leaflet, the information on the outer and inner packaging and a summary of the RMP [DIR Art 21(3), DIR Art 21(4), Art 106(a)~~,~~];

~~SmPCs and PLs~~ [~~DIR Art 21(3),~~ Art 106(b)];

- ~~Conditions of the marketing authorisation together with any deadlines for the fulfilment of those conditions [DIR Art 21(3)]; and~~

~~Summary of the RMP~~ [DIR Art 106(c)], with specific focus on risk minimisation activities described therein [IR Art 31.1].

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

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

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

XVI.Appendix ~~.~~1: Tools of routine minimisation measures

XVI.App~~.~~1.1. 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[20], the SmPC (see GVP Annex I) presents information relevant to RMM in:

- SmPC section 4.8 'Undesirable Effects': Information on adverse reactions that may occur due to the medicinal product and 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 ~~with~~ adverse effects at conception, in utero or through breastfeeding (including delayed and/or life-long adverse effects), 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.

According to the Guideline on Summary of Product Characteristics[21]), the SmPC section 4.4. for medicinal products with additional RMM materials should include a statement on the educational/safety advice materials addressed to healthcare professionals or patients which clearly and succinctly explains the purpose and scope of the materials, with a reminder to healthcare professionals to be aware of the materials and to inform the patients of the materials targeted to patients. Other SmPC sections may also refer to these materials.

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

The SmPC may, in exceptional cases, include especially important safety information in bold type within a box (see Guideline on Summary of Product Characteristics[22]).

XVI.App~~.~~1.2. Package leaflet (including symbols and pictograms)

According to the legislation [DIR Art 8(3)(j), DIR Art 59, REG Art 6(1)] and the Template for the Package Leaflet[23] (PL), the 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 administration, contraindications, interactions, ability to drive and use machines, overdose,

[20] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[21] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[22] European Commission; https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf
[23] www.ema.europa.eu

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 (including delayed and/or life-long adverse effects), 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[24] applies to PLs.

XVI.App1.2.1. Symbols and pictograms

The Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use[25] 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[26] includes guidance for particular warnings 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[27] and the Template for the Labelling of the Immediate and Outer Packaging[28]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[29], 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 or waste derived from a medicinal products or waste derived [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[30], 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.

[24] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[25] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[26] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[27] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf
[28] www.ema.europa.eu
[29] www.ema.europa.eu
[30] European Commission; https://health.ec.europa.eu/system/files/2016-11/2009_01_12_readability_guideline_final_en_0.pdf

XVI.App.1.4. 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.B.2.1.5.) , 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 ~~is~~ 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.App.1.5. Classification of the medicinal product (legal status)

~~and a risk appropriate legal status of the product (e.g. prescription only medicine)~~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 70(4)].

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[31] 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 holder 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.App.1.5.1. 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)].

[31] www.ema.europa.~~eu~~

XVI.App.1.5.2. 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.App.1.5.3. 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.~~App.~~2.~~B.3.~~1.~~a.~~ Guides for patients or healthcare professionals for risk minimisation

A patient or healthcare professional guide for risk minimisation is intended to support~~a tool that highlights information and the specific actions to take for risk minimisation (see XVI.B.1.)~~ the patient or ~~o~~ healthcare professional in~~s or patients~~.

~~Typical objectives of such guides include to:~~

- Enhanc~~e~~ing awareness of ~~(~~a~~)~~ specific risk~~(s)~~ of the ~~associated with a~~ medicinal product, ~~and~~ (possible) risk factors, and the actions for risk minimisation, including early recognition and management of adverse reactions during or after treatment;
- Gui~~e~~ding therapeutic decision-making in applicable patients ~~selection~~ and supporting patient counselling and shared therapeutic decision-making;
- Preparing and administering the medicinal product correctly; and/or
- ~~Instruct on the prevention, early recognition and timely management of adverse reactions during or after the treatment, including details of enhanced monitoring requirements to aid in the early recognition of certain adverse reactions; or~~
- Discussing ~~Encourage that~~ the actions for risk minimisation between with ~~recommendations in patient guides are discussed by~~ the healthcare professional and the patient, in particular when handing out the patient guide ~~when handing out the guide to ensure that the risks and RMM (e.g. need for a diagnostic test, advice on how to prevent medication errors) of the medicine are understood~~.

~~Other objectives of~~ Specifically, patient guides may advise ~~be~~:

~~Ask~~ the patient to inform the prescriber ~~physician~~ about ~~the presence of any/a~~ a ~~specific~~ medical condition or concomitant medication before initiating treatment, where such condition or medication is a risk factor; ~~with this medicinal product is initiated;~~

~~Instruct the patient~~ to not attempt ~~to~~ self-treatment of signs or symptoms of a possible~~specific~~ adverse reactions or stop treatment without consulting the~~a relevant~~ healthcare professional, but to seek medical attention; or

~~P~~rovide 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~~s~~ at home.

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

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

~~Other terms or publication formats, such as 'brochure', 'sheet', 'patient leaflet', 'slide decks', 'posters', 'dosing guides' or 'induction graphs' should be avoided as synonyms for educational material, and only the term 'guide' should be used to ensure consistency and clarity of the requirements and application~~

~~of RMM in practice. It is preferable not to add qualifiers to describe the content (e.g. 'administration guide').~~

For tailoring RMM materials to target audiences (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~~B.3.1.b~~. Healthcare professional checklist~~s~~ for risk minimisation

A healthcare professional checklist for risk minimisation is intended to support the healthcare professional in~~a tool that lists actions aiming to support the prescriber or dispenser to~~;

~~check and record the presence or absence of certain clinical circumstances for risk minimisation. It is to be considered in situations where the safe and effective use of a medicinal product involves complex approaches and decision-making regarding the diagnosis, treatment, prescribing or dispensing, or when the treatment carries a high risk of medication errors.~~

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

~~Typical objectives of checklists include to:~~

- ~~Facilitate determining~~ 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 ~~before or during treatment, e.g~~. by checking whether~~for~~ e.g. contraindications (including e.g. pregnancy), ~~recommendations of use, warnings, concomitant~~ interacting concomitant medication~~inc(s)~~ or risk factors for adverse reactions are present in the patient, which may require conducting a medical test as a RMM-intended action, ~~or certain tests parameters~~, whether the ~~;~~

~~Ensure any~~ the patient has received the necessary vaccinations before start of treatment with the medicinal product, or whether signs or symptoms of adverse reactions have emerged during treatment ~~start~~;

- ~~~~

- ~~Exclude pregnancy before/during treatment, by c~~Conducting ~~a recording the results of a pregnancy test before/during treatment and prescribing or dispensing of the medicinal product only in the absence of pregnancy recording the pregnancy testing results when pregnancy is a contraindication for the product;,~~

- ~~support counselling on the need to avoid pregnancy and therefore use of contraception and support advice in the case of becoming pregnant during treatment~~;

- ~~Therapeutic monitoring by checking whether the patient's conditions or medical test results have changed or signs or symptoms of adverse reactions have emerged for considering whether the medicinal product is still appropriate for the patient;~~

- ~~Inform about the risk of~~ Avoiding medication errors~~ and how to avoid them,~~ by e.g.~~ by paying attention to~~ selecting the ~~right~~ pharmaceutical form~~ulation~~,~~ checking the~~ strength and dosing of the medicinal product ~~or~~ which are appropriate for the patient is and the ~~dosing against the~~ indication or advising the patient regarding the potential of medication errors; and/or

  ~~Assist in determining the correct amount of product that can be prescribed or dispensed;~~

  ~~Remind the healthcare professional of the need to monitor the patient for specific signs and symptoms, including specific abnormal laboratory findings, in order to identify adverse reactions early;~~

- ~~Prompt the healthcare professional to inform the patient about the importance of returning unused product and not sharing the medicine with others, especially for medicines with high risks for other persons or the environment;~~

- ~~Prompt informing~~ Informing the patient about~~-~~RMM-intended actions, e.g. for correctly administering the medicinal product at home or of the importance of not donating blood during treatment~~while taking the medicine~~, or reminding the healthcare professional to discuss the risks and the RMM for the medicinal product with the patient, possibly applying other RMM materials.~~; or~~

- ~~Inform about the need to apply risk awareness forms (see XVI.B.3.1.c.).~~

In contrast to guides for risk minimisation (see XVI.App2~~B.3~~.1.~~a.~~), a checklist is presented as a series of questions which can generally be answered in a 'yes'/'no'/'not applicable' manner or with a very short answer.

For tailoring RMM materials to target audiences (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.~~B.~~3~~.1.c~~. Risk awareness dialogue~~-~~ form~~s~~/aid

A risk awareness dialogue form, or synonymously risk awareness dialogue aid, is intended to support the prescribing healthcare professional in: ~~a tool that informs primarily patients, but also physicians, on (a) certain risk(s) of a medicinal product and the need for risk minimisation. It is also meant to support~~

- 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 (e.g. where the patient risk factors or situation may change over time, at repeat prescribing (the patient should receive a paper version of the form from the prescribing healthcare professional to take home);
- Ensuring that other RMM materials are applied and handed over to the patient if applicable; and/or
- D~~d~~ocumenting in the patient's health record that the patient has been made aware of the risk(s) during the~~a~~ discussion with the prescribing healthcare professional~~a physician~~ and understands the risk and actions to take for risk minimisation, if such documentation is required in local healthcare systems~~. It is to be considered in situations where this is essential for using the product~~. ~~The~~

~~patient is meant to receive a paper version (or a printout of an electronic version of the form) from the physician.~~

~~Typical objectives of such forms include to:~~

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

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

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

Risk awareness dialogue forms/aids should clearly state that the patient does not waive any rights by acknowledging the risks. For clarity, risk awareness forms do not transfer the physician's responsibilities when treating a patient to the patient nor do they impact on the patient's rights in relation to the marketing authorisation holder's and healthcare professional's liability. Also, risk awareness dialogue forms/aids are not informed consent forms as may be required in local healthcare systems for some medical procedures/treatments.

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

XVI.App-2.~~B.3.1.f~~4. Patient card~~s~~

A patient card is intended ~~a tool that (a) may include the key safety information on the risk or (b) reminds the patient of (a) certain action(s) to take for risk minimisation or (c) precautions for use, e.g. instruct patients to separate their med from antiacids or calcium supplements to prevent the drug not working as well as it should. It~~ aims to ensure that information regarding the patient's current

~~treatment with the medicinal product and its risks is~~ to be handed over to the patient to carry~~ied~~held it~~by the patient wallet~~ -at all times to: ~~and used as a communication aid with healthcare professionals. It is to be considered in situations where it is essential for risk minimisation that this information is always readily available to the patient and healthcare professionals.~~

~~Objectives of patient cards include to:~~

- Facilitate, during the hand-over and personalisation of the card by adding the patient's name on a dedicated field, that the healthcare professional informs the patient about the risk and the actions to minimise them at the intended point of care, i.e. during prescribing or dispensing;
- Remind the patient~~s~~ of the ~~specific~~ risks and the actions to minimise them~~ir RMM~~ during treatment, including, if applicable, ~~the need~~ to inform healthcare professionals that~~of~~ this medicinal product~~e~~ is used and to seek (urgent) medical attention if signs and symptoms of a possible adverse reaction occur;
- Note in a dedicated field on the card, if applicable, the dates for regular medication reviews or conducting tests, or for removing the related medical device; and/or
- ~~Alert~~ 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. ~~taking a certain medicine, in particular, those who have not prescribed the product but provide other care to the patient, including emergency care.;~~
- ~~Facilitate that the healthcare professional informs the patient about the risk and the actions to be taken for risk minimisation at the intended point of care, i.e. during prescribing or dispensing; or~~
- ~~Provide contact details of the prescribing physician.~~

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

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

- ~~The medicinal product is (potentially) teratogenic and requires use of effective contraception;~~
- ~~Blood donations by the patient are forbidden during treatment and until a certain period has passed after treatment;~~
- ~~Certain signs or symptoms of the adverse reaction require the patient to seek (urgent) medical care;~~
- ~~The treating physician needs to be informed of this medication when prescribing other medicines or planning surgeries;~~
- ~~The device of the medicinal product, e.g. an intrauterine device, should be removed at a specified date;~~
- ~~Regular monitoring or diagnostic testing is required at specified dates (future medical appointments);~~

- ~~There is potential for clinically significant interactions with other therapies and that concomitant treatment with those should be avoided;~~
- ~~The patient on this medicinal product requires additional medication, precautions or other medical procedures to enable necessary surgery or other medical interventions;~~
- ~~There is the need to avoid vaccination with live attenuated vaccines during treatment~~;
- ~~It is recommended to read the PL~~.

As appropriate for the given risk and RMM-intended actions, the card should carry an instruction, e.g. 'Carry with you at all times', 'Show to your healthcare professional before starting a new treatment', and/or 'Keep easily accessible for emergency care'.

For tailoring RMM materials to the target populations (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 actions for risk minimisation for different patient groups, one patient card may address all concerned patient groups or differential patient cards for the medicinal product may be appropriate.

For its purpose, a p~~P~~atient card~~s~~ should have the following features~~be designed :~~ ~~so they can be:~~

- Format: single or folded (one fold or Z-fold) card, and independent from the PL (i.e. not as a tear-off part of the PL);
- ~~Carried by patients easily, therefore their s~~Size: at minimum the size of half a credit card and at maximum the size of a credit card, to ~~should~~ fit inside a pocket/~~a~~ wallet/card holder~~ or a pocket and ideally have the size of a credit card~~ (if more space is needed~~required for content or multilingual requirements~~, folds can be used, see below)~~; however, for simplicity, as few folds as possible should be used)~~;
- Material: carton of durable thickness or possibly be laminated,

  ~~Read and understood easily, therefore, the information provided in the patient card should be focused and concise, kept to the minimum necessary to convey the key message(s); and~~

  ~~Used over a long time, therefore their material should be of sufficient durability~~ to sustain ~~considerable~~ wear and tear over time,~~ e.g.~~ possibly~~be~~ laminated~~ if possible and not be a cut-out or tear-off paper sheet as part of the PL~~;
- Design: striking (e.g. clean layout, shapes and/or colours), to be visible and immediately identifiable as important, and notably different (i.e. not resembling) a PL;
- Writable fields: a field for the patient's name and, if applicable, of the prescriber's name and contact details;
- Multiple language versions: 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 package outside or be separate from the package. Cards placed inside the package or affixed to the package outside should usually be preferred, unless cards separate from the package are needed for handing over to the patient because the medicinal product is often used in a hospital or care home setting without using a package for a specific patient or because the local processes involve repackaging of medicinal products by the pharmacy for e.g. weekly medication schedules of individual patients. Cards placed inside the package or affixed to the package outside become part of the product information and hence their text must be included in the respective part of the marketing authorisation.

~~To respect the limitation in space and the risk minimisation purpose of the card, it is recommended to not include in a patient card information on how to report adverse reactions or the black triangle if applicable to the product (see GVP Module X) (this is considered an exception to the guidance on the black triangle and explanatory statements provided in the GVP XVI – Addendum I and in GVP Module X and this does not affect the obligation to include the relevant text about additional monitoring in other documents such as the SmPC and the PL).~~

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

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

- ~~Patient card inside or affixed to the outer packaging:~~

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

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

  In the case when~~n~~re a~~the~~ patient card inside the package or affixed to the package outside becomes a new additional RMM or when an existing card is amended~~requirement~~ in the post-authorisation phase, the marketing authorisation holder should provide proposals to the competent authorities in

Member States for interim measures as long as packages without or with a previous card are in distribution (see XVI.B.4.2.).~~may need to take interim measures until the new packages with the patient card are or to allow for dispensing existing pharmacy stock of the medicinal product.~~

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

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

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

XVI.App-2.5~~B.3.1.e~~. Patient diary~~ies~~ for risk minimisation

A patient diary for risk minimisation is intended to support the patient in: ~~is a tool that~~

- ~~supports the patient in r~~Recording specific information ~~on the treatment with the medicinal product. It is to be considered~~ in situations where it is ~~considered important essential~~ that, when using the medicinal product, such ~~updated~~ 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; and/or
- 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 when using the medicinal product, specific risks 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.

~~Typical objectives of such diaries include to:~~

- ~~Record dates of administration or dose to avoid medication errors, e.g. in the case of different daily or interval dosing when using the medicinal product in different indications;~~
- ~~Record dates or outcomes of health monitoring and diagnostic tests at home needed to identify risk factors or signs and symptoms of adverse reactions during continuous treatment to facilitate~~

~~monitoring of the patient (e.g. monitoring of blood pressure when taking a medicine with a cardiac risk); or~~

- ~~Record signs and symptoms indicating a possible adverse reaction, in particular during dose adjustments.~~

~~However, information for healthcare professionals regarding a patient diary should remind a healthcare professional who~~Where ~~suspects~~ an adverse reaction on the basis of the patient's entries in the diary is suspected, the healthcare professional or patient should ~~to~~ report this by using the ~~usual~~ spontaneous reporting system~~s~~.

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

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

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

~~*Demonstration kits*~~

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

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

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

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

~~needed to improve the demonstration kit, the device or product information of the actual medicinal product, and initiate the necessary actions.~~

XVI.Appendix.3 Tools of additional minimisation measures – Controlled access programme tools

XVI.App3.1.XVI.B.3.4.a. Controlled prescription and supply systems

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

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

XVI.AppB.3.24.b. Centre accreditation systems

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

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

XVI.AppB.3.24.c. Forms for patient information exchange

Different tools are available to ensure that the pharmacist is informed about legally required test results before the product is dispensed, e.g. pregnancy test. This information exchange can take place via paper forms, connected electronic systems or personal confirmation (e.g. dispensing forms, see XVI.B.3.4.d.).

XVI.B.3.4.d. Dispensing forms

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

Agreement with the competent authority at national level is required.