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2 EMA/204715/2012 Rev 3\* - **Draft for public consultation**

3 **Guideline on good pharmacovigilance practices (GVP)**  
4 **Module XVI – Risk minimisation measures: selection of tools and**  
5 **effectiveness indicators (Rev 3)**

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

7 \*Note: Revision 3 includes the following:

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

25

See websites for contact details

European Medicines Agency [www.ema.europa.eu](http://www.ema.europa.eu)  
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## 69 **XVI.A. Introduction**

70 Risk management includes the identification, characterisation (including quantification), prevention and  
71 minimisation of risks. Risk management systems consist of pharmacovigilance activities and  
72 interventions relating to individual medicinal products for this purpose, including the assessment of the  
73 effectiveness of those activities and interventions, in accordance with Article 1(28b) of Directive  
74 2001/83/EC. The objectives of risk minimisation are achieved through the implementation of risk  
75 minimisation measures (RMM) required by the competent authorities and generation of evidence that  
76 these measures are effective.

77 Effective RMM and the assessment of their effectiveness should be in place for medicinal products in  
78 accordance with Articles 8(3)(iaa), 21a, 101(2), 104(2), 104(3), 104a and 107h(1) of Directive  
79 2001/83/EC, Articles 9(4), 14a, 21 and 28a of Regulation (EC) No 726/2004 and Articles 2(4b),  
80 11(1a), 11(1e), 30, 31(1) and 34(3) of the Commission Implementing Regulation 520/2012 which  
81 specifically include provisions for monitoring the outcome of RMM for both marketing authorisation  
82 holders and competent authorities. Monitoring RMM outcomes refers to adherence to RMM by  
83 healthcare professionals and patients and achieving the objectives of RMM. Monitoring and amending  
84 RMM, if warranted, aim at ensuring that the benefits of a particular medicinal product continue to  
85 exceed the risks by the greatest achievable margin. The assessment of the effectiveness of RMM is  
86 important for risk management with an iterative process of evaluation, correction and re-evaluation of  
87 RMM, which is integral to the lifecycle benefit-risk assessment of medicinal products.

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

93 **XVI.B.** describes criteria for selection, development, implementation and co-ordination of RMM, in  
94 particular of additional RMM, and the principles and concepts of the evaluation of RMM effectiveness.

95 **XVI.C.** describes the related roles and responsibilities of marketing authorisation holders and  
96 competent authorities in the setting of the EU regulatory network. It also reflects the contribution of  
97 healthcare professional and patient representatives.

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

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

## 107 **XVI.B. Structures and processes**

### 108 ***XVI.B.1. Definition and principles of risk minimisation measures***

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

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

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

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

133 Additional RMM should be completely separated from promotional activities.

### 134 ***XVI.B.2. Criteria for requiring additional risk minimisation measures***

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

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<sup>1</sup> 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](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196981.pdf).

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

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

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

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

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

166 Additional RMM can be categorised into the following categories:

- 167 • Educational materials;
- 168 • Direct healthcare professional communications (DHPCs);
- 169 • Pregnancy prevention programmes (PPPs);
- 170 • Controlled access programmes.

### 171 **XVI.B.3.1. Educational materials**

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

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

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

186 An educational material should contain the following information elements:

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

201 Further guidance on educational materials in [GVP XVI Addendum I](#) should be followed.

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

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

205 Typical objectives of such guides include to:

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

215 Other objectives of patient guides may be:

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

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

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

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

### 231 ***XVI.B.3.1.b. Healthcare professional checklists for risk minimisation***

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

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

239 Typical objectives of checklists include to:

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

#### 260 **XVI.B.3.1.c. Risk awareness forms**

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

267 Typical objectives of such forms include to:

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

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

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

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

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

#### 294 ***XVI.B.3.1.d. Demonstration kits***

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

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

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

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

#### 310 ***XVI.B.3.1.e. Patient diaries for risk minimisation***

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

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

315 Typical objectives of such diaries include to:

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

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

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

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

#### 338 **XVI.B.3.1.f. Patient cards**

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

344 Objectives of patient cards include to:

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

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

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

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

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

373 Patient cards should be designed so they can be:

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

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

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

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

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

- 396 • Patient card inside or affixed to the outer packaging:

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

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

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

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

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

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

### 426 **XVI.B.3.2. Direct healthcare professional communications**

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

### 432 **XVI.B.3.3. Pregnancy prevention programmes**

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

436 The typical objectives of a PPP are to:

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

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

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

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

457 **XVI.B.3.4. Controlled access programmes**

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

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

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

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

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

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

477 **XVI.B.3.4.b. Centre accreditation systems**

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

481 This may be required in specific situations such as for ATMPs or complex administration procedures.

482 Centre accreditation should be organised according to nationally established procedures applicable and  
483 be complemented with adequate training of healthcare professionals as agreed with the competent  
484 authorities.

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

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

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<sup>2</sup> 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.

<sup>3</sup> 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.

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

#### 490 ***XVI.B.3.4.d. Dispensing forms***

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

495 Agreement with the competent authority at national level is required.

#### 496 ***XVI.B.4. Dissemination plans***

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

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

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

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

#### 514 ***XVI.B.5. Effectiveness evaluation of risk minimisation measures***

##### 515 ***XVI.B.5.1. Principles for effectiveness evaluation***

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

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

527 **Principle 1: Focussed evaluation**

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

531 **Principle 2: Regular evaluation**

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

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

544 **Principle 3: Evaluation of intended and unintended outcomes**

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

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

557

558

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

	<b>Intended</b>	<b>Unintended</b>
<b>Switching</b>	RMM recommends that patients are switched to alternative therapy	Patients are switched to a treatment that has a less favourable safety profile
<b>Spill-over effect</b>	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
<b>Non-treatment</b>	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
<b>Lack of adherence</b>	N/A	RMM is not adhered to in the target population
<b>Additional prescribing</b>	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

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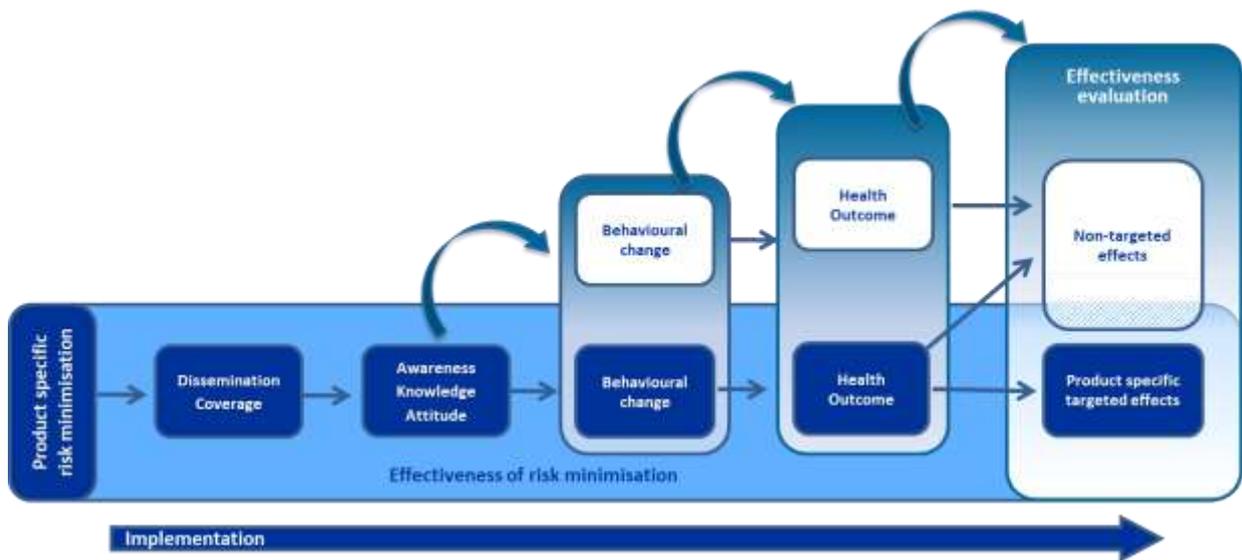
561 RMM effectiveness evaluation should consider that simultaneous events such as changes in clinical  
 562 guidelines, reimbursement policies, and media attention may influence the outcome of a regulatory  
 563 action and make establishing a causal relationship between a regulatory action and its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

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

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

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

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



576

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

580

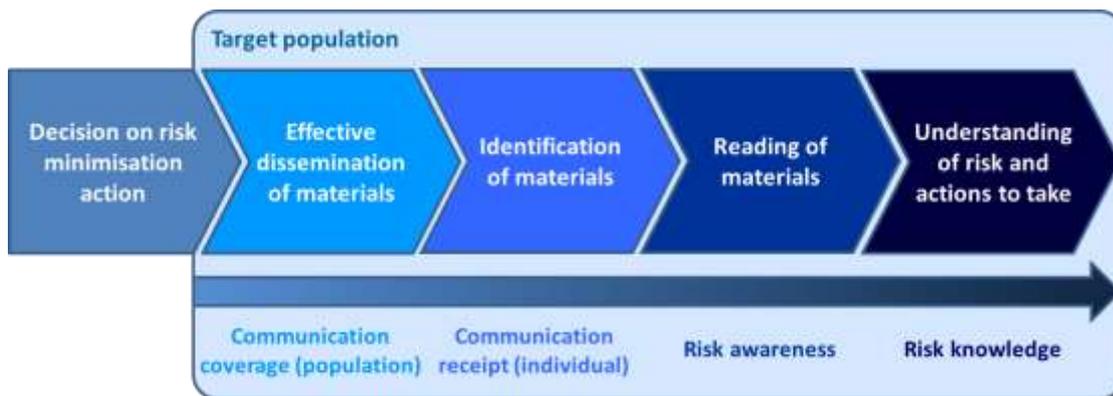
581 Depending on the scope of the effectiveness evaluation, a combination of research methods may be  
 582 useful, and the objectives should be defined in the evaluation strategy in relation to the desired health  
 583 outcomes of RMM. Marketing authorisation applicants/holders and competent authorities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

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

595 **XVI.B.5.2.1. Dissemination and risk knowledge**

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

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



603

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

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606 **Quantitative measurements:**

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

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

615 **Qualitative findings:**

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

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

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

627 **XVI.B.5.2.2. Behavioural changes**

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

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

635 **Quantitative measurements:**

636 Examples of quantitative measurements of behavioural changes are:

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

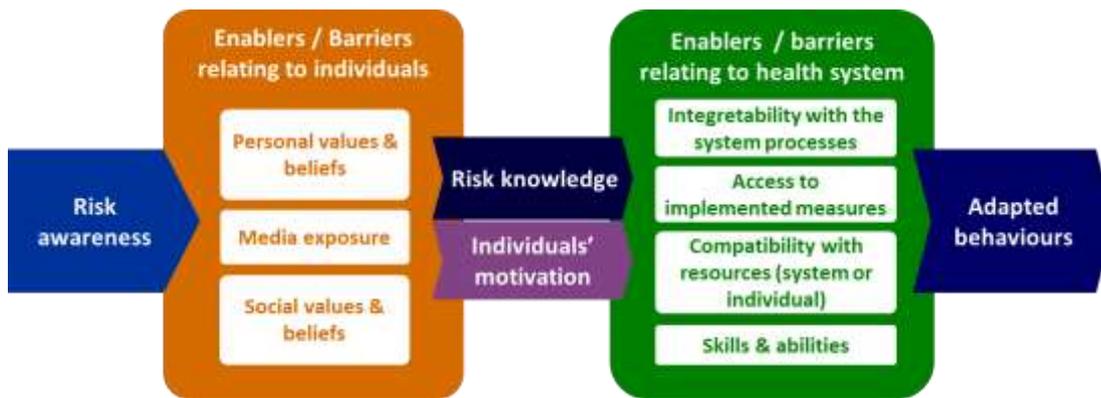
648 Behavioural changes may be evaluated through prescribing-, dispensing- and other drug utilisation  
649 studies, making use of data from electronic healthcare databases or medical records and possibly  
650 applying record linkage between different medical and/or demographic data, or through surveys.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

655 **Qualitative findings:**

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

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

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

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669 **XVI.B.5.2.3. Health outcomes**

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

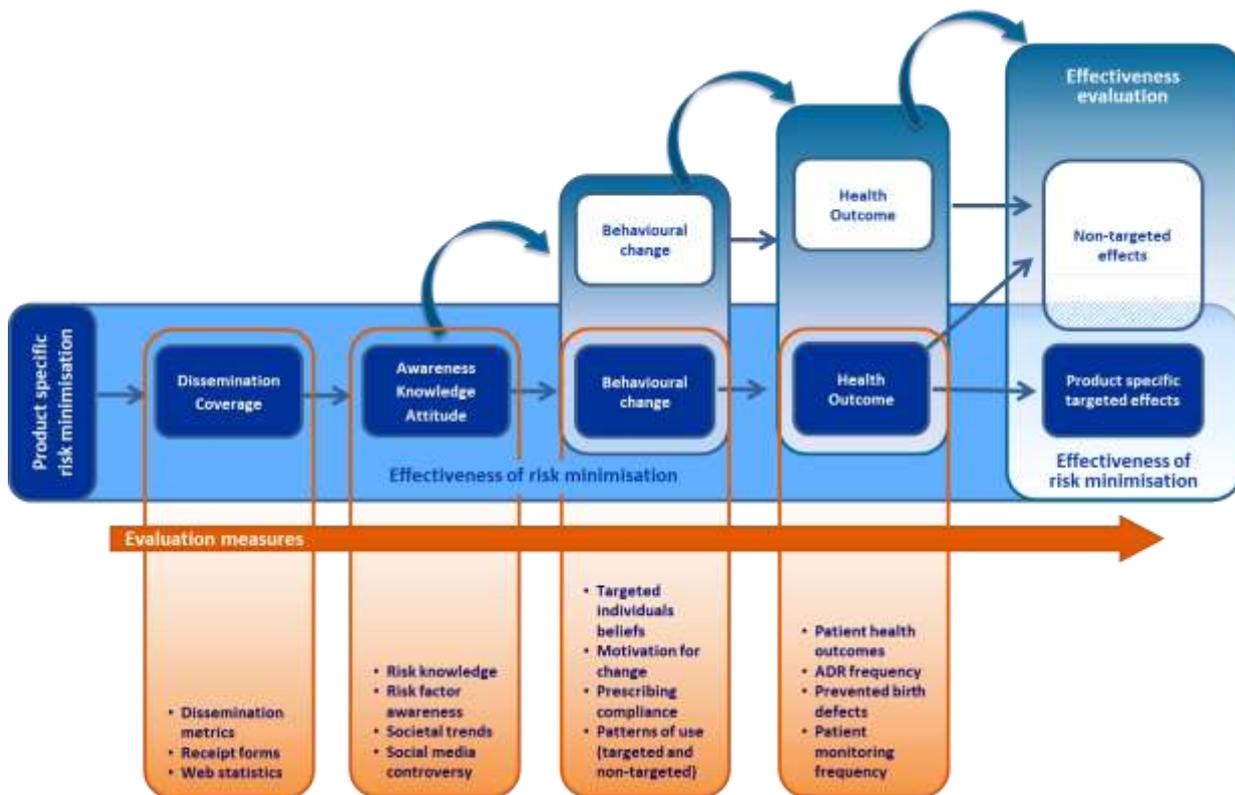
672 **Quantitative measurements:**

673 Examples of quantitative measurements of health outcomes are:

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

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

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



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

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

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

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

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

Criteria	
<b>Therapeutic need</b>	<ul style="list-style-type: none"> <li>• Seriousness of the indication (e.g. life-threatening condition, serious consequences on the quality of life, natural evolution of the disease)</li> <li>• Access to therapeutic alternatives</li> </ul>
<b>Population at risk</b>	<ul style="list-style-type: none"> <li>• Size of the population</li> <li>• Age-group at risk (e.g. children, older patients)</li> <li>• Pregnant women</li> <li>• Frailty</li> <li>• Possibility of taking an informed decision (e.g. access to PL, need for urgent treatment, patients with different chronic disease)</li> </ul>
<b>Risk</b>	<ul style="list-style-type: none"> <li>• Seriousness of the risk (e.g. life-threatening, hospitalisation, reversibility, impact on quality of life)</li> <li>• Novelty of the risk</li> <li>• Risk incidence</li> <li>• Proportion of the risk that can be avoided (risk reduction)</li> <li>• Absolute increase of the risk</li> </ul>
<b>Technical possibilities</b>	<ul style="list-style-type: none"> <li>• Is the level of knowledge to develop a threshold sufficient?</li> </ul>
<b>Acceptability</b>	<ul style="list-style-type: none"> <li>• Benefit-risk balance prior to the new information</li> <li>• Variability between populations</li> <li>• Regulatory acceptability (e.g. previous regulatory decisions for similar risks or medicinal products)</li> <li>• Engagement with concerned patients/carers and healthcare professionals</li> <li>• Level of public interest</li> <li>• Risk level accepted by society (e.g. insurance company, case law, from other technological areas)</li> </ul>

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

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

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

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

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

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

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

### 734 ***XVI.B.7. Additional risk minimisation measures in the lifecycle of the*** 735 ***product***

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

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

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

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

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

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

### 763 **XVI.B.8. Quality systems of risk minimisation measures**

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

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

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

### 774 **XVI.C. Operation of the EU network**

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

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

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

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

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

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

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

### 808 **XVI.C.1.1. The European Medicines Agency**

809 The Agency shall, in collaboration with the Member States, monitor the outcome of RMM contained in  
810 RMP and of conditions referred to in Directive 2001/83/EC (Articles 8(3)(iaa), 21a, 101(2), 104(2),  
811 104(3), 104a and 107h (1)) and Regulation (EC) No 726/2004 (Articles 9(4), 14a, 21, 28a). In  
812 monitoring the outcome of RMM, the Agency should support the Pharmacovigilance Risk Assessment  
813 Committee (PRAC) in its scientific assessment of outcomes of additional RMM, through the integration  
814 of data provided by Member State resources and research activities.

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

#### 816 **XVI.C.1.1.1. The Pharmacovigilance Risk Assessment Committee**

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

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

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

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<sup>4</sup> [https://www.ema.europa.eu/en/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities\\_en.pdf](https://www.ema.europa.eu/en/documents/other/prac-strategy-measuring-impact-pharmacovigilance-activities_en.pdf)

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

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

### 831 **XVI.C.1.2. Competent authorities in Member States**

832 The competent authorities in Member States are responsible for the oversight at national level of the  
833 development and dissemination of additional RMM imposed as a condition of the marketing  
834 authorisation for the safe and effective use of a medicinal product in the EU, irrespective of the route  
835 of marketing authorisation. Articles 104(3)(d) and Article 107h(1) of Directive 2001/83/EC and Article  
836 28a of Regulation (EC) No 726/2004 specifically include provisions for monitoring the outcome of RMM  
837 for both marketing authorisation holders and competent authorities. For centrally authorised products  
838 and nationally authorised products referred to PRAC, key elements will be agreed at EU level and need  
839 to be implemented in a coordinated manner across Member States. However, finalisation and  
840 dissemination of the RMM are agreed with competent authorities in Member States. Furthermore, they  
841 shall, in collaboration with the Agency, monitor the outcome of RMM contained in RMPs and of the  
842 conditions referred to in Articles 21a, 22 or 22a of Directive 2001/83/EC [DIR Art 107h(1)(a)].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 912 ***XVI.C.3. Collaboration with healthcare professional and patient*** 913 ***organisations***

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

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

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

### 933 ***XVI.C.4. Impact of risk minimisation measures effectiveness evaluations on*** 934 ***risk management plans and periodic safety update reports in the EU***

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

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

### 943 ***XVI.C.5. Transparency***

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

946 For centrally authorised products, the Agency shall make public:

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

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

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

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

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