RMP Project
Question & Answers Summary List

Introduction & Background

The risk management plan (RMP) is to be submitted as part of the Common Technical Dossier (CTD) submission for registration of medicinal products, as to the European directive.

RMPs are particularly important in the case of novel vaccines (targeting new diseases or produced using novel technology platforms) with no or limited experience in the market. Since the information gathered from clinical trials is often limited to specific populations and time periods, manufacturers should have, based on their understanding of the product, production method, epidemiology of the disease, etc., the ability to define a plan to appropriately monitor the safety profile and effectiveness of the vaccine once it enters a market. Such plans may include among others, phase 4 studies, observational studies, active surveillance for specific adverse events of interest (AESIs) and mechanisms to detect rare (unexpected or unknown) events that may occur at a frequency that is below the detection level in clinical trials.

The World Health Organization does not have any guidance document on how to prepare RMPs and hence applies the European Medicines Agency GVP guidelines for this purpose. This is the required standard for the World Health Organization prequalification team in terms of risk management plans for vaccines.

The RMP project of DCVMN is aimed at assisting manufacturers to get acquainted and in learning how to prepare a robust RMP for a vaccine of their choice, for which they wish to achieve international registration and WHO prequalification.

For more details see also https://www.dcvmn.org/IMG/pdf/rmp_project_proposal.pdf

Five senior subject matter expert consultants[1], experienced in RMP, engaged with manufacturers in five workshops, of approximately 1 hours each, based on Q&A sessions

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[1] AH, PW, BH, KH, ND

Workshop Date Part of the RMP	Question	Answers and Comments
31st.May. 2021 General	What is the best way to present the references? Should it be in each section, or is it best to put it at the end of the document?	It was suggested putting it at the end.
31st.May. 2021 General	What is the difference between a hybrid application and a generic application?	A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the authorised medicine. A company can only market a generic medicine once the 10-year exclusivity period for the original patent licence medicine has expired. A hybrid medicine is similar to an authorised medicine containing the same active substance, but where there are certain differences between the two medicines such as in their strength, indication or pharmaceutical form.
31st.May. 2021 General	It is mentioned that the data lock point (DLP) should not be more than 6 months before the RMP sign off date. Would it still be acceptable if it's more than 6 months? What would be the maximum number of months acceptable for the regulators?	The information should be as recent as possible, and the 6 months are arbitrary. If the DLP is 9 months, the question comes up whether there is any additional information that is not being shared. It was noted that it is possible to have a situation where after 9 months there is no new data, so you can say that the DLP is today. However, that doesn't mean the document goes back 9 months.
31st. May. 2021 General	The EMA template has a section related to the European Economic Area (EEA). We would like to register our product in Brazil and we want to apply for PQ for the product. Regarding the section on EEA, do we need to keep it in the document or put it as not applicable?	It should not be filled in if it is not registered in the EEA. In addition, RMPs don't exist in all countries, and it would be necessary to see the country requirements. It was suggested writing: "currently, there is no submission planned within the EEA". It was also suggested to cross referring it to the vaccines available in Europe for information. Furthermore, the marketing authorization procedure should be kept national if the product is not available in other countries.

31st. May. 2021 General	Should one RMP be available for trivalent and tetravalent flu vaccines?	It would be two different RMPs, as they are two different products. Perhaps using the trivalent RMP as a base could be an option, as many aspects will be the same. It was noted that RMPs are very tied to EU regulations and FDA regulations. If a country does not require an EU RMP, it is acceptable to not prepare an EU RMP. However, some countries may ask for EU RMP. Furthermore, it is important to refer to the country of first submission. It is essential to have open discussions with regulatory authorities (RA) and share all data available with the RA. It was noted that there are sometimes complexities with Ras, as there are some countries with limited experience. RAs could refer to what exists with equivalent products in other countries. In general, if it is not in the law, RAs cannot ask to conduct additional studies.
31st. May. 2021 General	If we have the same technology and process, do we have to submit a different RMP if the vaccine is for a variant COVID-19 strain?	The new variants are raising a lot of questions. It is important to assess the risks (higher/lower), the transmission rates, the target population, the population's sensitivity to the variants, the breakthrough disease in those who have been vaccinated, etc. There are more than 100 publications per day on COVID-19. It is important to do a review of all the studies available and assess the risks from an epidemiological viewpoint. The RMP can only be valid if all questions have been raised and answered. Further, a situation could exist where one product changes, and then an existing RMP may remain unchanged, if there are no other changes in the virus strain. The RMP may be adapted as needed, to a new product and that would be a separate RMP. In addition, if the product has a different name and is a different product for a different variant/strain, i.e. has advantages against the more virulent and transmissible variant/strain, there would probably need to be a new RMP. There would be some similarities in the RMPs, but one would assume that the pre-clinical information would be redone, and the vaccine constituents may need to be different.
14th. June. 2021 General	When we search for safety data of similar products already in the market, we search only for QIV or all	The influenza market is huge. There is a difference between a quadrivalent and trivalent, and technologies (i.e. split or inactivated, or if there is an adjuvant).

	influenza vaccines (split virion, inactivated)?	One need to refer to all influenza vaccines and highlight the differences (if any) with your own vaccine.
14th. June. 2021 General	As our phase III study will be ongoing by the end of this year, could we present the data still blinded for this RMP workshop?	One should present the data available.
14th. June. 2021 General	Can we refer to other products with the same components but different antigenic content (e.g. lower antigenic content)?	If you have other products with the same components but different antigenic content, you can use it as supportive data and justify where the limitations are or why you consider them supportive. Different antigenic content may also be another product. The use may be very different; for instance, if you have lower antigen content, it may also be formulations used for repeat vaccination (booster), whereas you may have higher antigen content for primary vaccinations. As supportive data, that is fine, but there are limitations. It was noted that it is important to decide why it is supportive, because if it has a different antigenic content, what is it doing in the rest of the file? Is it used for safety reasons? If it has not been discussed in clinical development, beware of adding it. It needs to be the same throughout all the RMP modules.

Workshop Date Part of the RMP	Question	Answers and Comments
31st.May. 2021 Part I	We have a question about the hyperlink on the table. This hyperlink refers to the document on the product characteristics that we should submit separately.	For eCTD submission, it would be the publishers who are putting a link between the documents in the different sections. It is only valid for an eCTD, which is a requirement in Europe. If the countries where the original dossier is being submitted do not have eCTD, that hyperlink is not applicable.
31st. May. 2021 Part I	Regarding comorbidities, some risk factors were already inserted into the risk factors section (this vaccine is indicated for healthy children). Here, can we insert possible co-administration with other vaccines or medications considering the risk factors?	If the vaccine is administered to healthy children, there may be no comorbidities if it is generally a healthy population. It would be sufficient to say that healthy children are the target population. Furthermore, it is important to rely on clinical studies performed, noting that risk has to be aligned with the prescribing indications. If the target population are children with underlying diseases, then co-morbidities need to be discussed. It was noted that regarding comorbidities, it depends on the extent of representative subjects in the database. It could well be that some subjects may fall under the missing information section, e.g. with underlying immune issues. This situation would be driven by the data that is available.
31st. May. 2021 Part I	Products have one active substance with a specific pharmaceutical form and strength. When products have the same active substance but in a different pharmaceutical form, a vial and a pre-filled syringe, with different corresponding strengths, should we prepare a separate RMP for those products with different pharmaceutical forms and strengths but with the same active substances?	It would be necessary to explain in one submission what the difference is, qualify them, and conclude in which way you identify a risk. Submitting multiple RMPs would not make sense in this case. If they are different pharmaceutical forms in the same submission, it would only be one RMP. Note that, when talking about strengths, it is possible to have the same concentration in millilitre (ml); however, younger children may receive 0.5 ml and older children 1 ml. It would still be the same strength. If one dossier were to be submitted, then only one RMP would need to be submitted. It is the same product in different forms (vials and syringes), and it would have the same RMP. It was noted that pre-filled syringes differ from multidose vials as multidose vials often contain preservatives. These are two presentations of the same product, even if it's a slightly different mixture in the vial. In addition, multidose vials have a

		risk of overdosing, this risk should be drawn from clinical data. This is not a risk related to the product but due to a lack of understanding and handling of the multidose vial.
	What about a situation where everything would be the same, but the quantity of antigen is different.	All agreed that this would require a different product and different RMP.
07th.June. 2021 Part I	Regarding the item "Is/will the product be subject to additional monitoring in the EU?", we are wondering if it is possible instead of EU, change to Brazil or the intention here is just to add an information regarding EU?	This a requirement inherent to the EU RMP template, although the intent here is to use the template outside the EU. It is therefore not applicable here. To make things clear, there are several options: First, simply not apply that item/question, second, a clear statement "not applicable", or third, a sentence saying that the product is not intended for licensure and use in the EU and that therefore additional monitoring in the EU is not planned/not applicable. Stating that the product will not be submitted in Europe is best and therefore no additional monitoring needed in Europe.

Part II		
31st.May. 2021 Part II	Three possible situations: 1. The originator product has an RMP, in RMP modules SII-SVII, the RMP would not be applicable. 2. The originator product does not have an RMP, but the safety concerns of the substance are published on the CMDh website. 3. The originator product does not have an RMP, and the safety concerns of the substance are not published on the CMDh website. In which scenario would SII-SVII not be applicable?	If they are not applicable, then the product is already licensed for something. If they are not applicable, it would be because there is a variation. However, an RMP still needs to be updated even if a variation is being done and a larger profile is included. If the vaccine uses a new platform and is an innovative product, it seems these sections could be applicable. If other products are within the same therapeutic area but are not exactly the same, it is a precaution to see their RMPs, to see if anything is applicable in this case, e.g. potential risks. If the vaccine is completely new, it is possible to refer it to something else that has been submitted before, using the same active constituents.
31st.May. 2021 Part II, Module S1	What is the recommended word count for the section on the epidemiology of the disease?	In the overview section, there is also a part on epidemiology. It is possible to use the part on epidemiology from the overview and put it in this section. It is best to use the epidemiology data of the country where the company is targeting licensure. It is possible to put the studies in a table, and one might add 10-12 recent epidemiology articles/references.
31st.May. 2021 Part II, Module S2	In the non-clinical part of the safety specification, can we present the information in a table?	It is possible to use tables to present the information, but they should include some comments and conclusions. The comments and conclusions could include the relevance for human data, what was found in animal studies and how relevant the data is for humans.
31st.May. 2021 Part II, Module S2	Regarding the main existing treatment options, do you suggest inserting tables or figures to illustrate this data?	This is usually presented as a text, but it's possible to present it as a table if there are many different treatment options.
31st.May. 2021 Part II, Module S2	Regarding the non-clinical part of the safety specifications, is it necessary to follow the module with the divisions?	There is no right way to present this, and it is good to have an overall table with all tests made and the results.

02nd.June. 2021 Part II, Module S2 and S3	For a trivalent influenza vaccine we don´t have the non-clinical part of the safety specification and the phase 1/2 clinical data for this product: we would like to know if it is acceptable to fill this section with the justification of the technology transfer.	The level of detail for any information provided in the safety specifications in RMP cannot be any higher than that of the specifications provided elsewhere in the CTD. If the level of information suggested below reflects the content of the overall application, then the proposed wording is the obvious choice. A clear reference made in the document to the reference product is probably worth considering, as in case the applicant does not have access to that data from the MAH of the reference product, the authority likely does have. Furthermore, the clinical data showing similarity to the reference product can be included in the clinical section. Bearing in mind that clinical data will always prevail over preclinical ones, that approach can then be expected to be adequate. As an overall rule clinical data prevails to preclinical. Only if the PV shows unexpected AE's, questions can be raised. Bear in mind any differences you are aware of in the strain in this product and the quadrivalent vaccine, which probably will be nihil. Regarding different risks by age group, for vaccines specifically, there may be differences in the schedule by age groups. In that case, it is best to present that as well.
14th.June. 2021 Part II, Module S3	What do you think of a table for vaccines? Should we include age? Just the number of doses and number of participants? The interval between doses? There is only one dose. Do you think it is better understood if we split the ages into a separate table (like table SIII.2: Age group and gender) or compile it into this suggested table?	The table format might look a bit confusing sometimes. There is a concern regarding maximum legibility for the reviewers. It is better to present the age groups in a separate table. Typically for vaccines, the exposure is presented as subjects having received at least one dose and what is also commonly presented is the overall number of doses. One can also provide information on how many subjects have received a complete number of doses. In that case, that is helpful for multidose vaccines, including vaccination schedules, if more than one dose. It can be challenging to retrieve how many subjects have received at least one dose and how many doses have been received per age group. Present how many subjects have received at least one dose by age group and the number of doses. Complete information should be provided, split by age groups, to give an overall view of who received what and the number of doses. Age groups are essential if the risks are different. In this case, the duration of exposure is the number of doses and not the time period. When conducting vaccine studies,

		it may be of interest to show the duration of follow-up, and the follow-up time may be of interest for a certain number of events.
14th.June. 2021 Part II, Module S3	We don't know this concept of exposure and person time for the vaccine. Can we go without this table?	The duration of exposure is how many people had at least one dose and how many people had an entire course (2 or 3 doses). For a 3-dose vaccine, it is possible to have the table divided by how many had 1,2 or 3 doses. At the end, there would be the total number of doses provided. Person time for vaccines is irrelevant.
14th.June. 2021 Part II Module S4	"Exclusion criteria in pivotal clinical studies within the development programme. Discuss the important exclusion criteria in the pivotal clinical studies across the development programme." Can you please provide more explanation?	For the exclusion criteria, the regulators would expect a discussion on the different inclusion and exclusion criteria in that protocol and explanation why they were put in place for the different protocols, that could be a risk mitigation, in some cases this may be for insurance or liability purposes. It is essential to discuss the implications, for example, whether by excluding a certain number of subjects, there would be limitations in the dataset and to what extent such exclusion criteria would apply to the target audience. Are they sufficiently important to have contraindications for the product? If you had restrictions or limitations to the population resulting from exclusion criteria, they might be missing information in some instances. When it comes to identifying missing information, the regulators expect some standard criteria, although they are of limited relevance to vaccines (ex: use under hepatic or renal impairment). See what you had in terms of exclusion criteria, what you had regarding the overall study and what the target population will be. It is possible to have a target population that would be very prone to co-administration with a certain number of drugs, which may not have been addressed. How will my target population look like, and will that be in the dataset? It is necessary to be clear if the vaccine prevents a disease, where other vaccines exist, and compare other vaccines, and see why the exclusion criteria are included. It is a very frequent question raised by health authorities. For example, for the dengue vaccine, and see what their exclusion criteria are. There may be reasons because it is another manufacturing process, and necessary to justify why you don't include or do include. The best example is that you often may not have HIV

		positive or hepatitis B carriers in clinical trials. It's possible to say that these people are missing from the trials, but there is no reason why the vaccine cannot be given to them.
14th.June. 2021 Part II, Module S7	Details of important identified risks, important potential risks, and missing information "This section applies to all stages of the product life cycle. Data should be provided considering all possible sources, e.g. clinical trials from the current application (or from the originator, in case of hybrids or generics); literature, post-marketing data, etc. Do not cross-reference other applications." --- Can you please explain the underlined part?	It is essential to provide data and not say look at another application. A complete answer is required and, it's not possible to not provide details and ask to cross-refer. Each RMP needs to be sound as stand-alone.
14th.June. 2021 Part II, Module S3 and S7	Should we use data only from the phase III clinical trial that our institute performed for this specific vaccine? Or should we describe clinical data for other QIV already in the market?	Other data for existing vaccines would be supportive and enable to illustrate class effects. The data from producer clinical trials will always prevail. However, it may not be able to show everything. For other existing vaccines, there may be a lot more data. Typically, class effects for similar products are considered as potential risks. Identified risks are what one has seen for the own product. In the case, there is a very similar product through a technology transfer. This would depend on the regulatory status for biosimilars, etc. The best way, is to provide full data and refer to similar products. The regulators want to see product specific data. “Copies” of tech transfer are not always 100% “copies”, and the authorities' vision has changed in that regard. It is essential to be very careful and objective with that.
14th.June. 2021 Part II, Module S3 and S7	If this would be the 1st RMP and we don't have any identified risks (not seen in studies). We know from literature and from the marketing that a similar product has some identified and potential risks. Hence,	Use the data you have available. To weigh the risk in terms of what is seen in your own data. One can state that the same potential risk may arise. It is important to be very objective and state this is our data, and we know that similar products identify risks A, B, C, but until now, with the data available, we have not observed any.

	could the potential risks be the same for our product?	
14th.June. 2021 Part II, Module S3 and S7	Considering that the production process for a quadrivalent influenza vaccine (QIV) corresponds to the same as for a trivalent influenza vaccine (TIV), can the same identified and potential risks be used that are available for TIV?	Expose own data and support it with a trivalent vaccine. Adding an antigen makes a difference when it comes to adverse events.
26th.July. 2021 Part II, Module S7	Are skin allergies (such as rash, urticaria, maculopapular, and so on) important risks with vaccines? What about anaphylactic reactions (healthcare professionals are already aware of the risk of anaphylactic reactions for vaccination)?	It is important to ensure any rashes that may appear, are distinguished from serious rashes. An anaphylactic reaction is important. Regulators would consider an anaphylactic reaction as a default risk and even without any cases in your database, you would have to consider that as an important potential risk by default.

Part III		
28th.June. 2021 Part III.1	Ongoing and planned additional pharmacovigilance activities Can you please explain the difference between Category 1, 2 and 3?	This is a very EU-specific categorization. The different categories are based on a Europe-specific legal requirement. This is probably of very limited relevance outside Europe.
28th.June. 2021 Part III.2	In the paragraph “Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification irrespective of whether the studies are to identify and characterise important risks/missing information, or to assess the effectiveness of additional risk minimisation activities using behavioural or safety outcome indicators”. Can you please explain what are safety outcome indicators and examples?	This term does not specifically pertain to safety studies but more to safety concerns like adverse reactions. This could be in the context of the assessment of effectiveness measures. The regulators want to see the measures put in place and assess to what extent the measure serves the purpose. In this context it is about the effectiveness of the risk minimization measures implemented based on the risk identified. It would probably require a post-authorization safety study (PASS) as PASS are commonly used for the measurements of effectiveness. For effectiveness measurement you could develop a questionnaire to show to what extent it was understood what the measures for risk minimization were. It is more difficult if it is to prevent an adverse outcome: it could be e.g. stated here that an AEFI has been identified under some specific circumstances. In such a case you would determine the frequency of the AEFI, think about a potential study design and where to incorporate this issue in the already in the RMP defined preventative measures. One could measure in such a study the observed incidence of your AEFI and evaluate if the observed incidence is no higher than what would be in the uncontrolled circumstances. Regulators specifically ask companies for observed-to-expected analyses, esp. for COVID-19 vaccines. The observed -to-expected analysis is an essential tool in risk assessment.

28th.June. 2021 Part III.2	"Protocols for studies in the pharmacovigilance plan should be provided in Annex 3 of the RMP until completion of the study and submission to the competent authorities of the final study report." Could we consider not providing the study protocol (highlighted) if this is not a regional regulatory requirement? And vice versa, if some requirement is regional regulatory requirement, but it is not in the guideline, could we consider to add in?	This is logical; however, one would have to start again to register in a region or an agency. To present the information later, it would be good to include the information, perhaps not as a full protocol but as a synopsis about the general outline of the planned study. Ideally, this information should be appended. One should be careful as some authorities ask to provide information even if it's not part of the dossier. It is crucial to clarify through open discussions with regulatory authorities (RAs).
28th.June. 2021 Part III	If we provide the synopsis or concept sheet of the protocol, and hand in the first submission of the RMP and the RA wants to discuss the design of the study and we change some parts of the study design, do we need to send a second version of the RMP, with the final protocol attached?	Make sure and emphasize that everything you submit on a planned study design in the first RMP is work in progress.
28th.June. 2021 Part III	What are the legal obligations to conduct long-term safety studies for vaccines?	It is mandatory and not open for discussion. If one proposes upfront to do a PASS, then it has to be done.
28th.June. 2021 Part III	How to capture the missing information?	It all depends on what it is, especially when it comes to exclusion criteria. When advancing in the development stage and widen the exclusion criteria as far as possible to match indications, like the population targeted by the product, there will certainly be restrictions, for example, age restrictions. One can argue that there are no limitations or contraindications for some of the exclusion criteria. The RMP should discuss inclusion and exclusion criteria and their impact on the indication and any additional measures one would have to conduct.

28th.June. 2021 Part III	How is the indication of the meningo C vaccine, for special populations, if they were excluded from the clinical study? Off label? Indication extrapolation considering the comparator package insert used in the clinical study? Would it be a safety concern, considering it to be missing information, as it was not evaluated in the clinical study.	Usually, one cannot do that. All indications are related to own data, must be supported by own data from the clinical studies the company has performed. Off-label is not an indication, hence the need to be careful with the wording. Most authorities don't like off-label data. Regarding missing information, one can't have an indication if there is no data.
28th.June. 2021 Part III	In which situation should we propose a long-term FUP extension in ongoing clinical trials for vaccines?	The authorities will always ask for long-term persistence data if applicable. If one has a vaccine where you can show long-term persistence data with lifelong immunity, one would not need to show data on revaccination. One will have to provide persistence data and advice on revaccination (at which moment, at which dose). In general, 1-2 years of follow-up, that should be fine for the original licensure, but one may be asked what happens after that.
28th.June. 2021 Part III	PASS/PAES activities are only applicable for post-registration regulatory change purposes?	For a PASS or an efficacy study, we have to distinguish between regulators imposing a study or if the company is volunteering to do a study. If one has a change of registration in mind, to submit a variation, in this case such studies would be imposed. They would be post-approval commitments, and once completed, it would potentially become a variation to label. This would also require an update / change to the RMP. One would remove the study as such, which might be still ongoing and mention the results.
28th.June. 2021 Part III	Is PASS only for missing information, specific population or adverse event of special interest? Or any post-marketing safety surveillance study could be a PASS?	A PASS could be for any safety concerns. It can be for missing information, specific population or adverse event of special interest. Later in the product life-cycle, you may have a safety signal, and the regulators may come back to you, telling you to perform a PASS. Regarding effectiveness studies that you are conducting and measures in place for risk minimization, and if you are doing studies on that to evaluate, it will meet the regulatory status of a PASS.

28th.June. 2021 Part III	In which situations should we propose studies to compare the safety of our product with a similar product already on the Market?	Generally, it is in the basic information because one performs clinical studies with own product to compare with a newer product, or with another mode of action. There can be a comparison with former studies of a similar product. Sometimes the authorities want to have a comparison with that product in your basic information. This depends on how you want to market and file your product, depending on the clinical trials you wish to perform as a priority. You can have a theoretical comparison based on literature. Some authorities systematically require such comparisons. However, it is not necessarily a comparison for safety because statistical comparisons cannot be done, especially when it comes to relatively uncommon safety events. Such comparator studies are mostly for immunogenicity, efficacy, and commonplace reactogenicity. It is more than a regulatory call and can be a call for market access; sometimes, they will ask to perform a comparison to the existing product to show how the new product performs.

Part IV		
28th.June. 2021 Part IV	Should we only include in this part the efficacy studies that we will perform to change the license (for example: changes in indication) or should we also include effectiveness studies?	Inform that these changes are ongoing. The labelling will change anyway and one will end up submitting it sooner or later.
28th.June. 2021 Part IV	Plans for post-authorisation efficacy studies - “Protocol(s) should be provided in Annex 5” Could we consider not providing the study protocol if this is not a regional regulatory requirement?	RAs want to see all studies performed with the product as a general approach, and it is best to submit all data you have.

Part V		
12th.July. 2021 Part V	What is the best way to present the data in Risk Minimization Plans for vaccines?	The basic principle is to approach the risk minimization plan according to the product, and there is no specific definition for vaccines or drugs. It depends on what one want to highlight. The first thing to do is to have a real appreciation for the risk, for whom is the risk (patient, prescriber, community) and then present it accordingly. The actual data would be more in the safety specifications. In the risk minimization plan, there is a discussion part on the safety concerns and how they will be addressed. These would be safety concerns and which measures will be proposed. The presentation depends on what one will present in terms of minimization measures. Have a look at RMPs on the EMA website. All the COVID-19 vaccines RMPs are on the EMA website. [2]
12th.July. 2021 Part V	Any differences between generic and innovator molecules concerning minimization plans?	There is a big difference regarding generic and innovator products. For generics, the risk minimization plan is usually minimal. The generic may have one component that raises questions, but that is rare. For an innovative product, RMP needs to be complete and include all the risks well identified, with all the actions taken for the prescriber, the subject, and the community. This might not be as applicable to vaccines as to drugs. It was noted that for an innovator product, the risk management would be specific to the product. If you have an innovative product, you would have to propose your own measures. If you have a generic product, you will follow what is being done for the original substance, and if you require very specific risk minimizations for your product, one might question to what extent it is to be considered a generic. It is important to approach it very carefully. If the clinical studies didn't show a difference in the safety profile, the risk minimization should be minimal.

[2] https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf ; https://www.ema.europa.eu/en/documents/rmp-summary/spikevax-previously-covid-19-vaccine-moderna-epar-risk-management-plan_en.pdf ; https://www.ema.europa.eu/en/documents/rmp-summary/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-risk-management-plan_en.pdf ; https://www.ema.europa.eu/en/documents/rmp-summary/covid-19-vaccine-janssen-epar-risk-management-plan_en.pdf ;

12th.July. 2021 Part V	If any safety concerns are reported from the consumer: Should we consider adding in a risk minimization plan? Irrespective assessment?	Not every adverse event reported by a consumer will result in changes in the risk minimization plan. The report of one consumer should not trigger risk minimization activities. It is strange that a consumer would identify a risk that the company has not identified itself. An example where the safety information was in the SmPC, but was not followed: there was a consumer risk because people were not following the instructions as per SmPC. This was classified as a misdosage in the DSUR. It is important to tackle this from the signal management perspective. The consumer report can constitute to a safety signal like any information from any other source, if you come to conclude that a safety signal that initially came from a consumer report is a safety concern. If that safety concern is then further classified to the rank of an important identified risk, you would have to address that as any important identified risk in the RMP. It would need to be added there (with the risk minimization measures if needed).
12th.July. 2021 Part V	In the case of information from the consumer where they are not following instructions, should we rewrite our instructions?	If the leaflet doesn't explain correctly, then it needs to be corrected. However, just one report is not enough. This can bring lots of work and trigger unneeded efforts. One report is only one out of millions. It was noted that a signal report could qualify as a signal in its own right if there are exceptional circumstances.
12th.July. 2021 Part V	Should the risk minimization plan be done prior to the product reaching the customer? If that is the case, then any remark coming from a customer should not arise, as it is the pharmaceutical responsibility to make sure any potential risks are planned for and the mitigation is applied. If the complaint is by a customer, this should be handled more as an AE rather than a risk minimization procedure.	The risk minimization plan is related to the available data. One report is important to look at and consider, but it does not necessarily mean that the risk minimization needs to be reviewed. It was noted that the risk minimization plan is established before the product comes to the market. However, the RMP is a living document and has to accompany the product through its life cycle. This means the document needs to be updated. AE and risk are not the same. One risk can encompass different types of adverse events. Only in very exceptional circumstances would one report be considered sufficient to conclude on a new risk or signal.

12th.July. 2021 Part V	How to evaluate the effectiveness of a risk minimization activity?	In general, one would expect regulators to ask for effectiveness measures and maybe the additional risk minimization measures. On a simple SmPC wording, such as the inclusion of several AEs in the SmPC as the routine minimization measure, regulators would probably ask for effectiveness measures. If one has additional measures like educational material, restricted access, etc., they would probably ask for it. If you have a very targeted population with a high risk for off-label use, they would probably ask you for research utilization questionnaire (RUQ) from utilization studies or questionnaires on how the educational material was understood. It also depends on the extent to which you have oversight over your measures, ex: access to the information on how many patients have patient profile information, on who received the product. Potentially one can integrate these measures. An example regarding a change of wording which was followed by a questionnaire to see if that was better understood and there would be less chance of misuse.
12th.July. 2021 Part V	Which effectiveness evaluation activity is usually recommended if we propose as a risk minimization measure: a) Including the information related to the safety concern in the package insert warning and precautions/ contraindication sections. b) A Dear Doctor Letter or Health care professional training material c) Restricted prescription	Regarding a), it would probably depend on the type of event or the importance of the warning, and if it is less important, you may get away with routine PV, for example, if you have the typical risk of anaphylaxis like you have with any vaccine. In those cases, you probably will not have to conduct any additional measures. If you have a warning that would restrict to a certain population, in that case, they may ask for a Drug utilization study. For b), the warning is very important, and would foresee using a questionnaire or a Drug utilization study if it would have to change the prescribing patterns. For c), it depends on the oversight mechanisms that you have and on the information that you have received from the distributors or access to health databases. In that case, you could perhaps do database-driven studies, or if not, a prospective RUQ utilization study.

12th.July. 2021 Part V	In which situation is a patient monitoring program recommended as a risk minimization activity?	A patient monitoring program would be an active follow-up of subjects who are under treatment by a given drug. This is something that applies to some therapeutic products where you have to perform such a follow-up. This is highly unlikely to apply to vaccines. If you are contemplating a product that requires a patient monitoring program, then your benefit-risk balance would be unsustainable for a vaccine.
12th.July. 2021 Part V	In section 5.2 (part on target audience and planned distribution path) of the guidance document, can you please elaborate on communication plans?	It is not because you have one report that you need to restart the communications. It cannot only be a country that is reporting a lot, but also the same hospital or MDs reporting.

Part VII		
26th.July. 2021 Part VII	May you explain what is required for parts A, B and C for Annex 3?	Information published on the EMA website is clear and it is what is requested. Overall, the protocols need to be submitted according to the stages of the clinical studies.
26th.July. 2021 Part VII	Regarding Annex 3, should we submit the entire protocol if we don't have the eCTD documents?	The complete protocol should be submitted and regulatory authorities prefer the whole protocol. Sometimes there is only a synopsis submitted because the protocol was still under discussion.
26th.July. 2021 Part VII	In Annex 4 - Specific adverse drug reaction follow-up forms, can you please explain "Provide the specific adverse drug reaction follow-up forms in full"?	At this stage, you may not have any forms and may well never have any. Taking as a fictional example a COVID-19 vaccine, because of specific AEFIs, you could imagine that the regulators would ask the manufacturers to come up with a specific form on the evaluation of the specific events. The request means that if you do have a specific AEFI / AESI, regulators want to see how you are going to collect the information and what information will be collected. The "in full" means the form as it will be sent out to the reporters, i.e. to provide the document as it will be sent out to track each report. If such questionnaires are part of your official PV tools for additional PV, they have to be approved by the regulators and any changes to them need their approval. It also depends on how the information is collected, as it may be GDPR (General Data Protection Regulation) sensitive information.
26th.July. 2021 Part VII	As the forms are related to additional PV activities, should we only include additional forms as per additional PV activities?	This is a specific form related to additional PV activities and very specific ADRs.
26th.July. 2021 Part VII	If we submit the concept sheet as we don't have the whole protocol, in the future when we have the protocol ready, do we need to do a new version of the RMP just to include the annex of the protocol?	Submit the full protocol when you have it, but you do not need to do the RMP again.

26th.July. 2021 Part VII	Can we fill 'not applicable' for any topic of part VII if it is not applicable for our product or the current information of our product?	Non applicable would be fine, however there needs to be a reason to justify this. There may not be ongoing studies for the risk management activities and in that case you might write not applicable because there are no studies that have been defined as needed to be done for PV activities. It is best to provide an explanation. Before submission, you are writing according to what you know at this stage and you therefore plan according to what you know. It may be subject to updates during the process where the application is being reviewed by the authorities and you may have to negotiate or have some measures imposed (ex: studies). It can become applicable at a later stage, even though it may not be applicable now.