Evaluating the Effectiveness of additional Risk Minimisation Measures via Surveys in Europe: Challenges and Recommendations

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This paper was developed by members of ISPE who are part of the Benefit Risk Assessment, Communication, and Evaluation (BRACE) Special Interest Group (SIG), and was also consulted with the full BRACE SIG. The BRACE SIG includes representatives from the pharmaceutical industry, service providers, academia, and government in both North America and Europe. The goal of this paper is to inform future updates of Good Pharmacovigilance Practices Module XVI based on our experience to-date in implementing survey studies to evaluate process indicators for the effectiveness of additional risk minimisation measures. We are pleased to have this opportunity to provide the European Medicines Agency with recommendations to improve the feasibility and scientific rigor of these survey studies. Due to conflict of interest, 2 members of the BRACE SIG (Priya Bahri and Peter Mol) specifically opted out of the development and review of this paper.

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1.0 ABBREVIATIONS

aRMM	additional risk minimisation measure(s)
CHMP	Council for Medicinal Products for Human Use
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
ISPE	International Society for Pharmacoepidemiology
MAH	marketing authorisation holder(s)
PASS	post-authorisation safety study
PIL	patient information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
NIS	non-interventional study(ies)
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
RMM	risk minimisation measure(s)
RMP	risk management plan
SmPC	summary of product characteristics

2.0 INTRODUCTION

Risk management plans (RMPs) have been implemented in the European Union (EU) since 2005. At that time, the concepts of routine vs. additional risk minimisation measures (aRMM) took more structure, and the requirement to describe aRMM in the RMP was introduced.[1,2]

New EU pharmacovigilance legislation, effective in 2012,[3] added an explicit requirement to evaluate the effectiveness of RMM (risk minimisation measures). The 2013 update of Module VIII, Post-authorisation safety studies (PASS), clarified that studies should be classified as PASS based on the main aim for initiating the study, and includes studies with an objective *"to measure the effectiveness of a risk minimisation activity"* as PASS.[4]

In 2014, Module XVI of Good Pharmacovigilance Practices (GVP), risk minimisation measures – selection of tools and effectiveness indicators, was published by the European Medicines Agency (EMA).[5] Module XVI provides a framework to measure the effectiveness of RMM, noting that the evaluation should consider 2 categories of indicators: process indicators, and outcome indicators.[5] Process indicators are further defined as *"measures of the extent of implementation of the original plan, and/or variations in its delivery"*, and may include measures of distribution (e.g. of aRMM educational materials), an assessment of knowledge (e.g. the target population's awareness of messages communicated in aRMM educational materials), and an assessment of clinical actions (e.g. of prescribing behavior). Outcome indicators are defined as safety outcomes, i.e. the frequency and/or severity of the adverse reaction the aRMM intends to prevent or minimise.[5] Annex 1 provides a summary of the applicable EU pharmacovigilance legislation from which recommendations in this paper are built.

Studies to evaluate safety outcomes are not new, and there is abundant experience with such studies whether mandated or initiated voluntarily. In contrast, studies to evaluate the effectiveness of aRMM process indicators in the EU are relatively new. Although surveys are a well-established standard to measure process indicators such as measures of distribution and knowledge, survey studies in general fall lower in the hierarchy of evidence quality due to potential for substantial selection bias. Therefore, it is important that the survey study methodology employed to assess the effectiveness of aRMM adheres to robust scientific principles to promote unbiased and statistically stable results that are interpretable and actionable.

Since the publication of Module XVI, experience among ISPE membership with aRMM effectiveness studies for process indicators has increased substantially, and in our experience, we are uncovering significant operational challenges that negatively impact the feasibility and therefore the scientific validity of these studies. The purpose of this paper is to provide the EMA with feedback based on our experience to-date regarding operational challenges specific to implementing survey studies in the EU to evaluate aRMM process indicators, and to provide recommendations to improve the feasibility and scientific rigor of survey studies to evaluate process indicators for the effectiveness of aRMM. Our goal is to inform future updates of GVP Module XVI and related guidance documents.

3.0 METHODOLOGIC CONSIDERATIONS

3.1.1 Frameworks to Measure Process Indicators

Prieto et al[6] developed a model (Figure 1) for RMM evaluation emphasising a dual-evidence approach, which is reflected in GVP Module XVI.

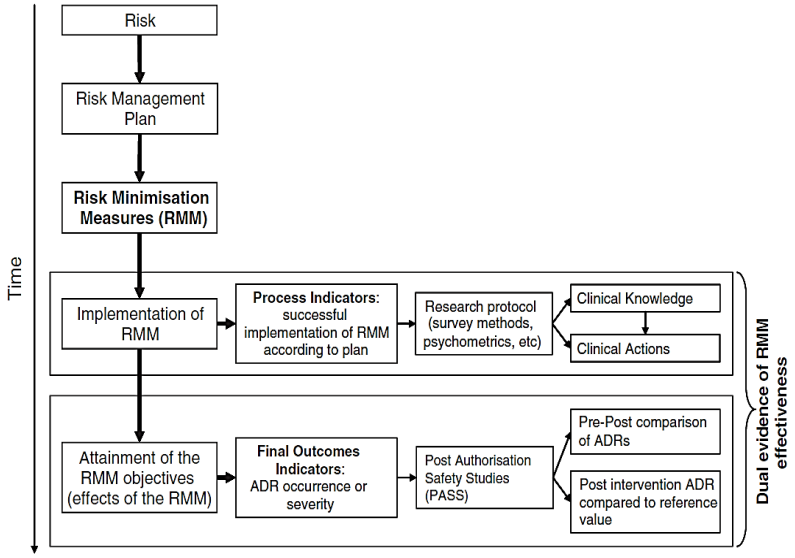

Figure 1. Evaluating the effectiveness of RMM by means of a dual-evidence approach

To improve the design of aRMM and better predict performance, lessons can be learned from social/behavioral science frameworks that measure dissemination and use of interventions under real world conditions. An array of healthcare intervention assessment frameworks are available (e.g. Reach, Effectiveness, Adoption, Implementation, Maintenance [RE-AIM]);[7] ISPE suggests that the marketing authorisation holder (MAH) use a framework to guide their evaluation, selecting from among the many frameworks that are available and providing a rationale for their particular selection (see https://pharmacoepi.org/pub/C62134BB-AD3F-1AFF-FABA-25C83413971E). The value of these frameworks is that they are grounded in the social and behavioural sciences, focus on issues of dissemination and implementation of public health interventions under real-world circumstances, and are intended to guide the development of health care interventions involving behavioural change at both the individual and system levels.

3.1.2 Metrics and Methods

Ideally, aRMM assessments should follow a stepwise approach, encompassing a diverse set of metrics of the entire process including the following:

1. aRMM design metrics – design the programme using proven tools to produce successful outcomes in real world, e.g. by inclusion of stakeholders (e.g. health authorities, healthcare professionals [HCPs], patients) input.

2. aRMM implementation metrics – to verify whether aRMM were developed and delivered as planned, and to assess the extent to which the interventions reached and were adopted by stakeholders. If they were not adopted, consider identifying at what point during the implementation were the measures not adopted, and why.
3. Impact metrics – effectiveness and stakeholder burden:
    a. Effectiveness metrics, e.g. the extent to which the aRMMs achieved goals or target performance thresholds such as awareness, knowledge, behaviors, sustained integration, health outcomes.
    b. Burden metrics, e.g. necessary disruption and unintended consequences.

The focus of this paper is the assessment of aRMM process indicators; specifically, metrics of implementation (e.g. dissemination and use) and knowledge metrics (rates of awareness of key educational messages included in aRMM educational interventions including knowledge of recommended behaviours to minimise risks). We specifically raise the point that surveys are not the optimal method to measure actual behaviour due to potential for response bias, and that there are other mechanisms to more effectively measure behaviour such as drug utilisation studies leveraging automated healthcare databases.

3.1.3 Overview of Survey Studies for the Evaluation of Selected aRMM Process Indicators

Surveys are a well-established standard to measure process indicators such as measures of distribution, utilisation, and knowledge, and may also be used to measure self-reported behaviour. Their strengths are that surveys are the most rigorous method by which to determine what a stakeholder knows or believes because if well designed, they are generalizable, reliable, cost-effective, and versatile instruments to systematically study a large group of individuals[8]. Disadvantages of survey studies include concerns with generalisability and selection bias (e.g. sampling frame is not representative of the full target population, respondent sample may be small, respondents may systematically differ from non-respondents in terms of outcomes measured) and reporting bias (e.g. responses may reflect what the respondent thinks is the desired response, such as recommended behaviours to minimise risks rather than actual behaviours).

As noted in Module XVI, it is important that scientifically rigorous study methodology be employed to assess the effectiveness of aRMM to promote unbiased and statistically stable results that are interpretable and actionable. In this paper, we highlight the numerous operational challenges specific to implementing survey studies in the EU to evaluate selected aRMM process indicators, and implications of these challenges on the validity of the survey results.

3.1.4 Measuring Success

Effective risk management requires measurable objectives, so it is important to determine the critical factors that are more likely to contribute to success or failure; and to define measures of success.

The evaluation of the risk minimisation strategy needs to be designed to address not only its individual elements but also its outcomes. The criteria for overall programme success should be based on scientific data from both outcome (e.g. adverse event rates) and process indicators (e.g. knowledge rates). Measurement metrics could be an absolute number (e.g. a total number of adverse events in the entire data collection system), a relative number (e.g. percentage of treated patients developing the adverse event), or a measure of trend over time. For example, a risk minimisation programme may include the following measures:

- require that at least 80% of prescribers have received and correctly understood educational materials concerning a particular risk and its prevention/ minimisation;
- use a trend analysis to judge if an aRMM is resulting in a desirable change in prescribers' awareness of particular risk, in the way in which a drug is used, or in a decreased trend of the actual incidence/reporting rate of the adverse event over time;
- set a goal, e.g. that no more than 5% of patients treated with drug X also received drug Y concomitantly (as drug Y has a potential to cause adverse effect by interacting with drug X).

Current guidance documents do not stipulate a threshold that would indicate success of the aRMM (e.g. 80% and 5% referenced above), however, evidence of thresholds used for knowledge assessment studies are sometimes available in the public domain (e.g. survey protocols published on the ENCePP website). Thresholds should be considered in the context of what has been observed in similar interventions, i.e. they should be evidence-based as much as possible. These values need to be justified case by case based on the specific risk management context.

One consideration is the degree to which there should be an *a priori* specification of the threshold(s) for determining success of specific risk management measures. The specific metrics to be used and the time frame to measure them should be specified in the evaluation plan. Although important scientifically, the pre-specification of thresholds for determining success of a measure can be problematic. Importantly, most of the time, there is no data available of what the metric was *prior* to implementation of the aRMM. Additionally, if specific target metrics (threshold values) of aRMM at specific time points are specified *a priori* for triggering consideration of risk minimisation programme modification, are there scenarios under which not meeting the pre-specified threshold may not be actionable? For example, what if knowledge rates do not meet the pre-specified threshold, but behaviours and/or actual adverse event outcomes do meet the pre-specified threshold? What if there is country-specific variation in the results of meeting thresholds for success? What is the impact of behaviour change prior to the implementation of aRMM where the issue and its review has been widely publicised? What if the omnibus knowledge rate does not meet the pre-specified threshold, but knowledge

rates for the most important individual risk minimisation messages are well above the pre-specified threshold? Conversely, what if knowledge rates meet the pre-specified threshold, but actual adverse event outcomes are at unacceptable rates? In our experience, determining the success or failure of the full risk minimisation programme needs to be carefully considered, because meeting or not meeting a threshold for success of individual measures within the risk management programme may be acceptable or unacceptable depending on the context (e.g. the safety outcome).

If the threshold for success of a measure is not met, there is the need to analyse reasons for failure such as implementation failure (e.g. insufficient dissemination of aRMM materials) or conceptual failure (e.g. unclear risk messages). After this assessment has been completed, the consideration regarding whether and/or how the measure and/or programme can be modified and re-evaluated should arise. Time points of particular relevance for periodic evaluation include 12-18 months after implementation of a RMM, depending on market penetration, and in time for the evaluation of the renewal of a market authorisation.

4.0 OPERATIONAL CHALLENGES

4.1 EU Regulatory Landscape

4.1.1 Classification of Survey Studies as PASS Studies

In both the 2013 and 2016 updates of Module VIII of GVP studies initiated to measure the effectiveness of a risk minimisation activity are classified as PASS. Module XVI, published in 2014, provides additional explanation in Section XVI.B.4 as follows: *"The legislation defines 'Any study ….measuring the effectiveness of risk management measures' as a post-authorisation safety study [DIR Art 1 (15)]. Therefore, if a study is conducted to assess behavioural or safety outcome indicators the detailed guidance for conducting a post-authorisation safety study, which is provided in Module VIII, should be followed. Such guidance does not apply to the measurement of simple process markers (e.g. distribution of the tools reaching the target population)."* Section XVI.B.4.1 defines process indicators as measures of distribution (reaching the target population), assessing clinical knowledge, and assessing clinical action. Thus,

- Studies to evaluate knowledge are not specifically addressed in the guidance as to whether the PASS guidance should be followed, and based on the current guidance, fall into a "grey zone".
- Survey studies are generally conducted to evaluate the dissemination and use of, and knowledge rates for, aRMM educational interventions. Assuming the survey does not attempt to assess actual behaviour, one *could* interpret Module XVI to imply that the PASS guidance does not need to be followed. However, in practice, several national competent authorities, HCPs, and institutions will automatically classify these survey studies as PASS, especially if stated as such in the protocol and registered on the EU-PAS register.

- To-date, there is limited precedent conducting surveys to evaluate the effectiveness of aRMM process indicators in many EU countries. Additionally, some EU countries do not have clear regulations even for non-interventional studies (NIS); in these countries, surveys may be required to follow clinical trial requirements by default due to the PASS classification, especially if one of the objectives is to assess knowledge of off-label use.

The implication of a PASS classification is substantial, because in many EU countries, PASS studies are automatically required to follow more stringent regulatory notification, submission, and approval procedures than non-PASS NIS. These steps can significantly increase the timeline to launch and execute an effectiveness survey, and therefore jeopardise the ability for timely assessment of educational interventions designed to minimise risk and promote safe use. An example for Spain follows.

- Study design/objective/target population: A cross-sectional survey study conducted in 200 HCPs to evaluate the effectiveness of HCP-directed educational aRMM material (measures of distribution such as awareness and receipt, and assessment of knowledge); no honoraria payment offered.
    - If the survey is classified a post-authorisation study, the “orden SAS/3470/2009” which is the regulation issued by the Spanish health authority, AEMPS, must be followed, which requires 1 of 3 approval paths based on study characteristics as follows:
        - If the survey is classified as observational and the evaluated variable is not a drug, a central ethics committee submission and approval are required (~30 days), plus contract with each HCPs’ institution (even if there are no payments, contract negotiation takes months in Spain);
        - If the survey is classified as observational and the evaluated variable is a drug, the survey would fall under “other designs”. A central ethics committee submission and approval are required (~30 days), plus a notification to the Spanish competent authority (and wait 30 days in case the competent authority determines the study type has been misclassified), plus contract with each HCPs’ institution.
        - If the survey is classified as observational and a condition of authorisation, a central ethics committee submission and approval are required (~30 days), plus submission and approval by the Spain competent authority is required (~60 days), plus contract with the each HCPs’ institution.
    - In contrast, a HCP survey in Spain, if classified as market research, would not require any regulatory notifications/submissions/approvals.

Based on the descriptions above, by treating these survey studies as PASS, the time from survey implementation in Spain can range from a minimum of 60 days (1 month ethics and

minimum 1 month contracting) to 6-12 months (our more usual experience based on length of time to negotiate contracts in Spain).

Module XVI also states *"In designing an evaluation strategy, due consideration needs to be made toward what aspects of process and outcomes can be realistically measured in order to avoid the generation of inaccurate or misleading data or placing an undue burden on the healthcare system or other stakeholders"*.[4] From experience in Spain, because of the PASS designation, surveys to evaluate the effectiveness of aRMM do not qualify as market research, and therefore, even the simplest post-authorisation classification above would require first an ethics submission and approval, followed by an institutional contract to be negotiated with each HCPs' institution before the HCP could complete the survey. Regardless of whether honoraria payments are offered or not, most HCPs are not interested to take the time/burden to negotiate a contract with their institution, potentially introducing severe selection bias in the survey sample. By removing the PASS designation, fielding an aRMM effectiveness survey in Spain could be more similar to how market research studies are fielded, which would greatly increase timeliness, validity, and generalisability of the survey results.

4.1.2 Applicable Country-specific Regulations Vary Widely

In Section 4.1.1, we described the challenges of classifying these studies as PASS, and provided an example for Spain. When conducting a pan-European survey to evaluate aRMM process indicators, country-specific requirements regarding competent authority and ethics committee notification vary substantially.

For HCP-only surveys, some EU countries have minimal requirements. In France, for example, if HCPs are not paid to complete the survey, only a notification to the French competent authority is required. In contrast, if HCPs are paid, the study would also need to be submitted to the board of the French national medical association (CNOM), which adds 60 days before the survey can be performed. Other countries have more stringent requirements. In Belgium, for example, HCP surveys are considered as studies to evaluate the practice of medicine and need to be submitted and approved by each HCPs local ethics committee. Once again, this increases significantly the required time and effort to participate, introducing a potential for severe selection bias.

These considerations are exponentially magnified when performing surveys to evaluate aRMM process indicators in patients. For example, in Germany, each institution participating in a study has the option to either obtain their local ethics approval for the study, or alternatively, can choose to adopt the ethics approval previously provided by an institution affiliated with a designated "lead investigator" for the study. Thus, in Germany, if patients will be recruited by HCPs, one approach to streamline study start-up is to identify a "lead investigator" to submit the study protocol to their applicable ethics committee. Once approved by the lead investigator's ethics committee, other HCPs and their institutions have the ability to either accept the lead investigator's ethics committee approval, or alternatively will require their separate local ethics committee approval. For Germany, the MAH is then faced with the decision to either delay study implementation to allow multiple local ethics submissions and approvals, or, to introduce

selection bias by limiting participation to HCPs who can follow the lead ethics committee opinion. In Italy, if patients are recruited through their treating HCPs, contracts must be executed at the institutional level prior to launching the survey. Additionally, each HCP's institution requires local ethics submission and approval. This process takes several months and also requires funding to support these activities, that is often disproportionate to the subsequent level of effort to collect a few surveys. Therefore, the MAH may limit participation to only a few HCPs and institutions that can complete this process most efficiently or that treat a large number of patients, potentially introducing selection bias. For products indicated for the treatment of rare diseases, the issues are further magnified, where a single HCP may only treat a few patients per year. For countries such as Italy that require site-specific ethics submissions and contract negotiations, numerous submissions would need to take place in order to recruit a statistically robust and generalisable sample of patients.

Due to the wide country-specific variation as well as HCP-specific variation, our experience is that implementing aRMM effectiveness survey studies is not feasible for several EU countries due to excessive timelines to determine and complete these various regulatory requirements.

4.2 Variation due to Country-specific Adaptation of RMMs

The need to adapt aRMMs – both content and assessments – to reflect the 28 member nations and their local healthcare practices is clear. However there are a number of practical implications of country-specific adaptation that may substantially impact the ability to adequately implement and/or evaluate the effectiveness of aRMM, which may in turn compromise the patient safety profile we are indeed trying to improve. This variation currently manifests itself in the following ways:

Requirement for local health authority (HA) review and approval of aRMM materials.

- Upon submission of Pharmacovigilance Risk Assessment Committee (PRAC)-approved aRMM by the MAH, the timelines for local health authority review and approval are highly variable, ranging from 30 days to completely undefined; in practice it may be 6 months or more. Most importantly, this review timeline variability creates delays in the dissemination of important aRMM for the slower countries, and operationally makes the 'start' of the programme more challenging to define for assessments. Furthermore, in situations where safety information is updated, and in turn the aRMM are updated, version control becomes problematic both from a dissemination and evaluation standpoint. For example, a country with relatively faster local health authority review times may have version 3 of a HCP brochure distributed, but a slower review country may still be awaiting approval of version 1. Aside from the potential impact to patient safety, one is then faced with the scientific dilemma of evaluating different versions, making interpretation of results challenging. Depending on the specific assessment timelines outlined in the evaluation protocol, delaying the assessments may not be a viable option as these are generally considered PASS and may require a Type II variation submission procedure and approval by the Council for Medicinal Products for Human Use (CHMP)/PRAC to modify timelines.

- Some local health authorities appear unfamiliar with Module XVI and have sometimes questioned why they have been asked to review the aRMM materials.
- Some local health authorities have requested substantial core content changes to EMA/PRAC-approved educational materials and/or programmes. While these changes may be equally scientifically appropriate or preferred by the health authority due to local practices, the impact of these requested changes make assessing the effectiveness of aRMM difficult in many cases. It becomes impossible to separate local variations in *actual* effectiveness from local variations in the content and/or implementation. Furthermore, the requests for local modification generate one or more additional health authority-MAH review cycles that may impact timelines, as per the first point above.

Local variation in what constitutes an aRMM vs. routine RMM

- In a rapidly technologically advancing world, what is considered routine vs. aRMM appears to differ by local health authority. For example, a paper Summary of Product Characteristics (SmPC) or Patient Information Leaflet (PIL) is undoubtedly considered routine RMM. However, a digital or video version of the SmPC, PIL, or sections thereof, such as the *instructions for use*, even if an exact copy of the information in the SmPC or PIL, can variously be considered routine or additional by different health authorities. If determined to be additional, then Module XVI applies and effectiveness evaluations must be conducted even if not previously approved by PRAC.

In summary, local variation in interpretation of existing guidance has significant impact on the potential operational success and scientific interpretability of the effectiveness of RMM tools. It may in some cases directly impact patient safety because of the delays caused by local health authority review and/or modification. A solution that balances the need for local input and flexibility for the numerous health systems and practices that comprise the European Economic Community, and efficiently implementing tools designed to enhance the benefit-risk profile of medicines, should be found.

4.3 Recruitment Challenges

This section focuses on recruitment considerations and challenges in implementing RMM effectiveness survey studies. Figure 2 provides an overview of these challenges.

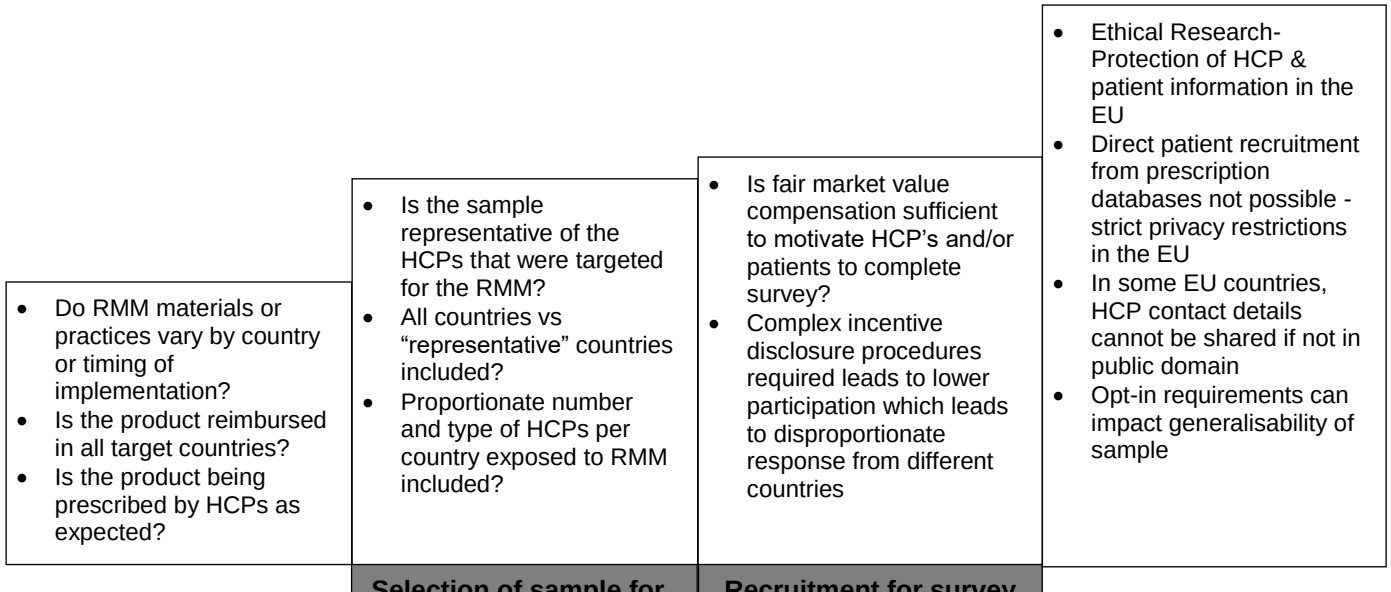

Figure 2. Recruitment Considerations and Implementation Challenges for Evaluation of RMM

4.3.1 Identifying Eligible Participants

When pharmaceutical companies are evaluating the need for and feasibility of aRMMs to manage a risk or improve the benefit-risk profile of a drug, it is often well in advance of the availability of real world drug utilisation data for the drug. GVP Module XVI offers that the MAH should consider a variety of factors when determining the most effective aRMMs, including preventability or clinical actions required to mitigate the risk, the indication, route of administration, the target population, and healthcare setting for the use of the product. The challenge of identifying aRMM assessment participants starts with the selection of the aRMMs; i.e. identifying the optimal target audience for the aRMM. A key element is determining how broad the MAH should “throw the RMM net”, knowing that at least at initial launch, many HCPs may not actually prescribe the product for months but may be selected for a survey querying about an aRMM that was distributed over a year previously.

Once the target population has been defined for implementation of the aRMM, the parameters of that target population must be preserved and considered as the potential universe for recruitment for the subsequent assessment survey. Theoretically, the sampling frame should support recruitment of a representative sample of the HCPs that were targeted for the aRMM. An ideal sampling frame would include all countries where the aRMM were implemented, with survey invitations extended proportionate to the number of HCPs per country that were exposed to the aRMM, and actual survey completion similarly representative. However, feasibility constraints previously discussed may require a more limited sampling frame. Additionally, although the populations targeted for aRMM should be considered, because of privacy or other restricted access to contact information for several EU countries, it may not be possible to use lists developed for implementation of aRMM to subsequently contact the same HCPs to participate in aRMM effectiveness assessment surveys.

Even more difficult than identifying eligible HCP participants is the task of identifying and recruiting patients to participate in aRMM effectiveness assessment surveys. Of particular note is the inability to directly recruit patients through prescription databases because of strict privacy restrictions in the EU to the downstream impact of Health Information Technology for Economic

and Clinical Health law in the US. The MAH must rely on other mechanisms to identify and recruit patients. Frequently, MAHs depend on prescribing physicians to recruit patients for participation in these assessments. In this scenario, bias may be introduced if the survey asks patients to report on the effectiveness of their HCP in the aRMM channel, yet HCPs are not incented to manage additional patient-focused aRMM. Additionally, when HCPs are the primary method used to recruit patients for participation in these assessments, the opportunity for selection bias is further increased, and the patient sample may not be representative of the population of patients receiving the medicinal product.

4.3.2 Incentivising Survey Participation

Recruitment of sufficient numbers and varied demographics of HCPs and patients may be challenging and can be optimised by providing financial incentive to the participant. For physicians, in particular, incentives are often essential to secure HCPs time from their already busy schedules for even the 10-30 minutes needed to participate in a survey. Each country and MAH varies on the amount and format allowed for compensation for survey participation

Rigorous risk minimisation requirements have been introduced by regulators at the same time as public and payer expectations for transparency regarding HCP financial compensation by pharma companies has increased. European Federation of Pharmaceutical Industries and Associations (EFPIA) disclosure requirements are harmonized in the EU, but some countries, like Germany, have overlaid stricter, country-specific disclosure requirements. Specific to German Drug Law 67, where risk minimisation studies are categorized as NIS PASS, a set of disclosure requirements must be met. These include written agreement with the HCP being compensated, listing of all HCPs including their address and country HCP identification number, and provision of these lists to 3 payer organizations. The additional procedures required for conducting surveys in Germany and additional disclosure to payer organisations may result in lower participation and/or selection bias.

Our experience in several EU countries has been that even if we are able to provide fair market value compensation to HCPs who complete the survey, many HCPs or their institutions are not interested in participating because the compensation is very low in comparison to other studies such as clinical trials that compete for their participation. In addition, our experience in some countries (e.g. Italy) is that the compensation requested to cover administrative fees such as ethics submission and review are prohibitively high (e.g. ≥1000€ for ethics submission when only 1 HCP at the institution will subsequently complete a 15-30 minute survey); this is a substantial deterrent to the feasibility of recruiting a generalisable sample from these particular countries. Finally, our experience is that some HCPs perceive limited scientific merit of survey studies, and routinely decline participation solely on principle due to this perception.

4.3.3 Privacy Regulations

Protection of both HCP and patient confidential information is required by national and local laws as well as ethical principles of research.

As mentioned previously, there are regulations in several EU countries (e.g. Germany) that prohibit sharing of HCP contact information/details that are not in the public domain, thus challenging the ability to compile prescriber lists to recruit participants in a HCP survey.

Although survey studies to evaluate process indicators for the effectiveness of aRMM do not endeavour to collect patient health-related information, there is usually a requirement that patients who complete the survey have received the medicinal product, so we likely know what condition/disease they suffer from. Therefore, unless the patient response is completely anonymous (which often is not the case, such as when HCPs recruit patients, or when a patient incentive is offered, or when the survey is administered by telephone), regulations about protected health information apply and informed consent must be provided. The collection of informed consent can be a deterrent to patient recruitment, in that to administering informed consent may take more time than it takes to actually complete the survey, and can be confusing for patients since the study procedures only consist of a single-point-in-time completion of a short survey. Additionally, in some countries, even if a patient self-refers (e.g. learns about the survey from a patient advocacy group), collecting their information directly without the involvement of a HCP is not allowed, which reduces MAHs' ability to implement direct-to-patient recruitment (e.g. via patient advocacy).

5.0 IMPLICATIONS

It is important that scientifically rigorous study methodology be employed to assess the effectiveness of aRMM process indicators. Module XVI notes that, at a minimum, the following elements should be considered in the design and implementation of a survey in order to minimise potential biases and to optimise the generalisability of the results to the intended population:

- Sampling procedures and recruitment strategy;
- Design and administration of the data collection instrument(s);
- Analytical approaches;
- Ethics, privacy, and overall feasibility of a study.

As we have detailed in the Operational Challenges section of this document, our primary concerns based on experience to-date are as follows:

1. Lack of overall feasibility to conduct pan-European survey studies in a timely, efficient, and effective manner, substantially due to the omnibus classification of all studies to evaluate the effectiveness of aRMM as PASS, including survey studies that are focused on measuring process indicators such as dissemination and knowledge (and implications of this PASS classification);
2. Potential for severe selection bias and therefore lack of generalisability of results, given the lack of overall feasibility;
3. Potential for information bias, largely due to:

a. Variation in aRMM including educational interventions between countries based on local competent authority-requested revisions, or different versions of educational interventions in different countries at the time the assessment is conducted;

b. Different country-specific requirements for regulatory and ethics submissions; as a result, in some countries, HCPs are exposed to the protocol and data collection instrument prior to completing a survey, which can lead to response bias.

4. The applicability of pre-set thresholds to measure success, given the above operational challenges.

In summary, given the multiple operational challenges experienced in Europe, feasibility constraints lead to an accumulation of pitfalls that decrease the scientific integrity of the survey. As a result, the quality of cross-sectional survey studies to evaluate aRMM process indicators can be substantially jeopardised. Recommendations to decrease these constraints and therefore improve the quality of these studies are provided in the next section.

6.0 CONCLUSION AND RECOMMENDATIONS

Based on the above issues, the authors' recommendations are summarised in Table 1.

Table 1: Recommendations

Recommendation	Details
Update GVP Modules V, VIII, and XVI (as applicable) to clarify that survey studies to evaluate process indicators of the effectiveness of aRMM are not PASS.	▪ We recommend that cross-sectional survey studies to evaluate process indicators of the effectiveness of aRMM are not categorised as PASS ▪ We recommend aligning GVP Module XVI and CIOMS IX with regard to the classification of behavioural endpoints. Specifically, GVP Module XVI considers behaviour as *process indicators,* while CIOMS IX categorises behaviour as *outcome indicators*. Possibly, this discrepancy is because *knowledge* of expected behaviour is not the same as *actual* behaviour; the former being a process indicator and the latter an outcome indicator. We recommend to clarify the definition and categorisation in a future update of GVP Module XVI. ▪ We recognise that the legislation may be difficult to change; however, GVP guidance could be updated to clarify that, similar to studies that measure distribution of aRMM materials (see Module XVI), studies that measure knowledge via surveys are not PASS ▪ We recognise that studies that measure knowledge of content included in aRMM materials are not market research studies either, and require an increased level of scientific rigor in their design, analysis, and interpretation to provide actionable results to support regulatory decision-making. Module XVI could be updated to clarify a hybrid approach, outlining additional recommendations for robust survey questionnaire design and pre-testing, as well as analytic approaches.
Promote consistent and/or centralised processes to enable survey studies to be fielded in multiple European countries without requiring individual country-specific approvals.	▪ A centralised recognition of competent authority/ethics approvals to conduct aRMM effectiveness survey studies would substantially diminish the operational challenges encountered to-date. For example, in Austria, studies that are notified to the authority, and also posted on ENCePP, do not require separate ethics submissions and approvals. Perhaps EMA could encourage

	similar practices to be adopted by other European countries (e.g. where survey studies that have been vetted by EMA, and/or reviewed/approved by a central European ethics body, could be encouraged to be accepted by multiple countries without requiring additional country-specific competent authority and ethics submissions and approvals).
Update Module XVI to specifically state that survey studies to evaluate process indicators of the effectiveness of aRMM are almost always category 3 (see Module V)	▪ Clarify that aRMM process indicator effectiveness assessment studies do not need to be supervised and assessed by PRAC (unless the survey study has been imposed as a condition to the marketing authorisation) ▪ Consider PRAC-training for aRMM effectiveness survey studies (for example, limit revisions requested to questionnaires that have already been pre-tested with applicable stakeholder groups in multiple languages)
Update Module XVI to further clarify under what conditions routine RMM require effectiveness assessments	▪ Clarify the SmPC and PIL are routine RMM, regardless of mode(s) of delivery (e.g. video, website) ▪ Clarify that in general, routine RMM do not require process indicator effectiveness assessments
Update Module XVI to specify that plans for evaluating the effectiveness of aRMMs should be guided by social science evaluation frameworks.	▪ Clarify that evaluation protocols should be guided by the use of an evaluation framework. MAHs should reference which framework they are using and provide a rationale for selection.

7.0 REFERENCES

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8.0 ANNEX

8.1 Annex 1: Summary of Applicable EU Pharmacovigilance Legislation

The recent publication of GVP by the EMA provided detailed information regarding the requirements for a risk management system (Module V), specific principles underlying the selection of risk minimisation tools alongside effectiveness evaluation of these measures (Module XVI), and strengthening of the requirements for PASS (Module VIII). The introduction of these EU guidelines was considered particularly important, not only because they apply to all medicinal products regardless of the regulatory procedure (centralised, decentralised, mutual recognition, or national), but also because these comprehensive risk management requirements are known to influence many non-EU countries. Table 2 provides a brief summary of these modules and their relevance to risk management strategies and assessment of effectiveness.

Table 2: Summary of Relevant GVP Modules

Module	Description
V: Risk management systems	▪ Addresses both clinical and non-clinical risks as well as any quality issues that may impact patient safety or efficacy ▪ Principles of risk minimisation, and details of routine RMM ▪ Definitions for risk management ▪ Structure of the EU-RMP template and detailed guidance for each section
VIII: Post-authorisation safety studies	▪ Requirements for clinical trials or NIS ▪ Overview of scientific standards and quality standards of non-interventional PASS conducted by the MAH ▪ Impact of the PASS obligation on the risk management system ▪ Procedures that apply to non-interventional PASS for protocol oversight and reporting of study results
XVI: Risk minimisation measures: selection of tools and effectiveness indicators	▪ Development and implementation of additional RMM ▪ Evaluation of the effectiveness of RMM

Module V on risk management systems offers an expanded perspective for assessment of risks in the context of benefit, highlighting the need for a tailored approach due to differences in target populations and healthcare systems across regions. This module replaces prior guidances (i.e. Volume 9A) which were solely focused upon management of risks. As described in Module V, the aim of risk management is to ensure that the benefits should exceed the risks by the greatest achievable margin. One approach to achieve this is through implementation of RMM

which serve to either prevent or decrease the occurrence of the risk or, reduce the severity or impact of the risk on the patient. Thus, GVP Module V presents the new EU-RMP modular format which integrates Part V/RMM with focus upon routine or additional risk minimisation planning as well as methods for evaluation of the effectiveness for each measure. For specific guidance relating to risk minimisation and effectiveness, reference is made to Module XVI.

Per Module XVI, routine RMM include tools such as the SmPC or package leaflets. It is acknowledged that the majority of risks may be adequately addressed by routine minimisation measures; however, for some of them, aRMM are necessary to improve the benefit-risk balance of a medicinal product. Additional RMM may include educational tools or controlled access programmes that aim to positively influence the actions of prescribers and/or patients by limiting access to a medicinal product in order to minimise risk. For aRMM, an evaluation for effectiveness is necessary in order to demonstrate the success, or lack thereof, of an intervention. In special circumstances, effectiveness evaluation may also apply to routine RMM (e.g. risks mentioned in the SmPC that require special monitoring or clinical actions beyond the standard of care).

Module XVI suggests that the evaluation of effectiveness should encompass different aspects of the risk minimisation plan. Process indicators are measures for the various implementation steps to determine the extent that a programme was implemented as per the original plan. Examples of process indicators include metrics for distribution to determine if materials were received by the target audience, assessment of clinical knowledge by applying survey methods to examine the level of awareness of the target audience, and assessment of the resulting clinical actions (i.e. change in prescribing behavior). Outcome indicators such as frequency and/or severity of adverse reactions serve to determine the actual impact upon safety or the overall level of risk outside of an interventional setting. Because a direct measure of the risk may not be feasible sometimes, spontaneous reporting rates, as a method for assessing outcome indicators, can considered under certain circumstances (i.e. strong causal association between a drug and an adverse reaction alongside a negligible background incidence in the population). The feasibility of risk minimisation effectiveness evaluations should be balanced against the undue burden upon a healthcare system.

Module VIII defines PASS as *"any study relating to an authorised medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures"*. Further delineation for the categorisation of effectiveness evaluations as PASS is provided in Module XVI. Module XVI repeats the requirements of Module VIII such that a study that is designed to assess behavioral or safety outcome indicators should be conducted within the guidelines for a PASS. However, the requirement for a PASS "does not apply to the measurement of simple process markers (e.g. distribution of the tools reaching the target population)".

As mentioned above, EU-RMP follows a new modular format and studies dedicated to the effectiveness of RMM should be included in Part III/Pharmacovigilance Plans.

In parallel with publication of the EMA GVP modules, in 2014, the CIOMS IX Working Group issued the “Practical approaches to risk minimisation for medicinal products’ which provides direction and examples in this area of risk management. The CIOMS IX Working Group acknowledges that the field of risk management is rapidly evolving and provides overarching recommendations to maintain a pragmatic, simple, and robust approach to risk minimisation programmes, to the extent feasible. CIOMS IX Working Group recommends that protocols to assess effectiveness be developed prior to implementation of risk minimisation tools with clear objectives for each intervention. Similar to the description provided in GVP module XVI, CIOMS IX also defines 2 types of performance indicators; process indicators or outcome indicators. Process indicators are designed with the aim to assess if the steps carried out as part of the intervention occurred as planned. Process indicators reflecting areas such as exposure (elements of a delivery system), content (risk messages and instructions about desired behavioral action) and utilisation (frequency and duration of the intervention) should be carefully considered and may be measured at 1 point in time or several points over time. Outcome indicators are specific, measurable, safety endpoints that are used to evaluate the overall success of a risk minimisation programme. Outcome indicators may be a well-defined clinical endpoint or an accepted surrogate (i.e. lab measure). Both process and outcome indicators should be relevant and tailored to a specific intervention, well-defined, sensitive, and reliable.