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Tracking Of Additional Risk Minimization Measures (Armm)-An Ardent Patient-Centric Activity For A Successful Risk Management Program

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Abstract

Tracking of additional Risk Minimization Measures (aRMM) is a critical aspect for the success of the Risk Management Program. This was also substantiated by the present editorial with 5 years analysis of Medicines and Healthcare products Regulatory Agencies (MHRA)'s inspection metrics. It also showed a paradigm shift from a compliance-driven thinking to patient safety-driven thinking of regulatory agencies. The success of the risk management program in general and the risk management plan in particular depends on the proper tracking of aRMMs

Keywords: Additional Risk Minimization Measures; Risk Management Plan; Risk communication; Inspection observations; Tracking, Patient safety

Abbreviations

aRMM	additional Risk Minimization Measures
MHRA	Medicines and Healthcare products Regulatory Agencies
RMP	Risk Management Plan
PV	Pharmacovigilance
MAH	Marketing Authorization Holder
PIL	Product Information Leaflet
SmPC	Summary of Product characteristics
NCA	National Competent Authorities
RIMES	Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies

Introduction

Risk Minimization is a crucial activity directed to foster public health by implementing mitigation strategies. This has been even more relevant in today's world, wherein Risk Management Plan (RMP) has become a globally accepted document, due to the evolving pharmacovigilance (PV) landscape in the rest of the world. As RMP requirement has become standard across the regulated/semi-regulated regions, the need to maintain and track additional Risk Minimization Measures (aRMM) globally for overall program effectiveness evaluation is imperative.

Regulatory guidance was not explicit about the operational aspect of aRMM tracking until EMA released draft guidance of GVP Module XVI (EMA/204715/2012 Rev 3* - Draft for public consultation). Even then, it does state that you are supposed to track aRMM. However, every aRMM is different, hence strategic decision-making while planning is important.

There is a multifaceted rationale, proving that aRMM tracking is beneficial for overall program success.

Importance of aRMM

The foremost reason is legal requirements. More specifically the European Regulations Directive, 2010/84/EU, Regulation EU No 1234/2010, IR Art 34(3), GVP Module V, VII, and XVI, mentions that the Marketing Authorization Holder (MAH) must prepare an effective assessment report for aRMM.

The second rationale and predominantly moral one is patient safety, the risk minimization measures are designed and implemented to control the risk that medicine is posing to the patients who are consuming it. Patient safety is at the center when medicines are in the developmental stage and even after

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their market launch. Failing to effectively implement aRMM can directly affect patient safety. Due to patient-centric activity, aRMM is also an area of higher critical findings during inspections being faced by MAHs.

Method and Result

Risk minimization activities are the aim of the authorities when inspections are planned. This fact was evident from the last five year's MHRA inspection metrics. In the critical observation (Fig 3) over the past five years, it was observed that most of the findings focused on the implementation and effectiveness of risk mitigation actions. The trend shows the critical observations in the area of aRMMs are increasing significantly year by year. In the last 5 years, more than 8 critical findings from MHRA in the area of aRMM were observed. Risk management remains the topic for which the largest number of critical findings have been reported overall. More specifically, failure to implement additional Risk Minimization Measures (aRMMs) of marketed products as agreed in the RMP and effectiveness plan & failure to distribute educational material and update Product Information Leaflet (PIL) and Summary of Product characteristics (SmPC) on time were the top most observations. Non-compliance to previous inspection findings on aRMM implementation is an additional factor to consider as critical by MHRA.

A graph that demonstrates critical findings (Fig 1, Fig 2, Fig 3) from MHRA.

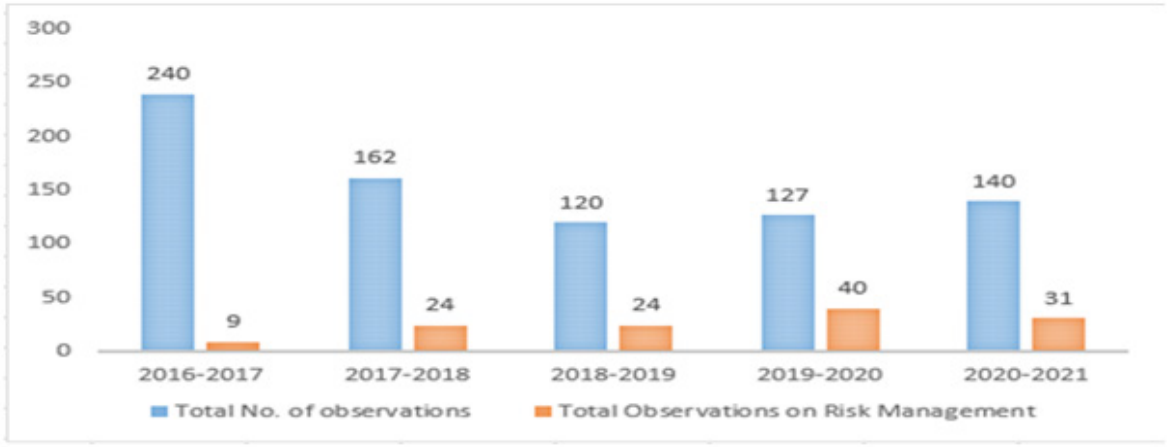

Figure 1: Breakdown of total no. of observations against no. of risk management observations over five years

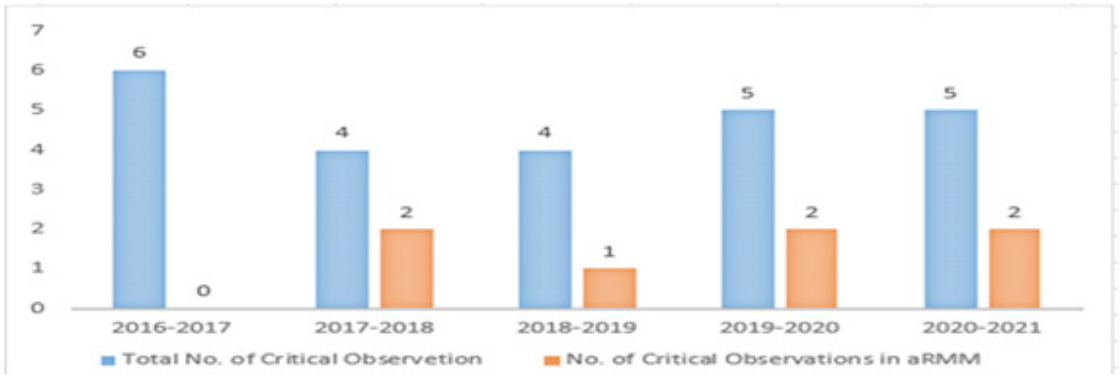

Figure 2: Breakdown of the total no. of observations against the proportion of risk management observations over five years

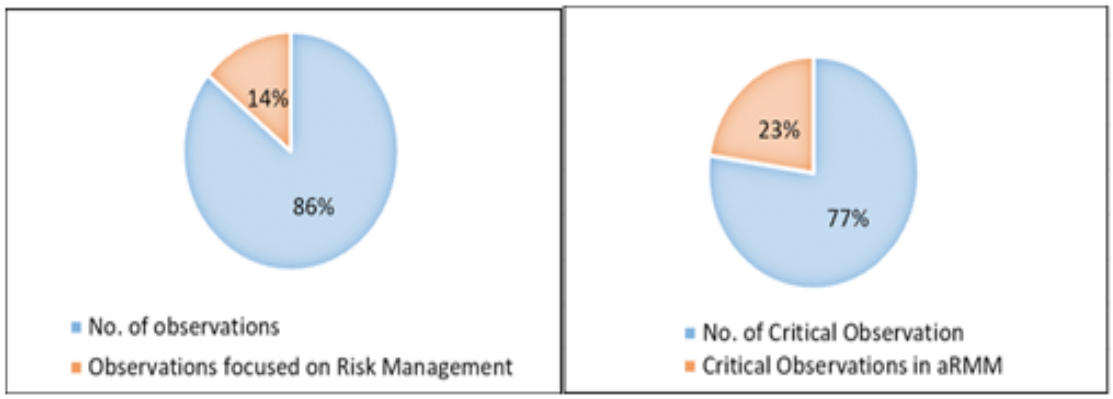

Figure 3: Proportion of the total no. of observations and critical observation with respect to aRMM

Discussion

aRMM tracking:

It is evident from observations that risk management and aRMM are major domains in pharmacovigilance, and they requires system improvements.

To understand more deeply the aRMM tracking and effectiveness management, it is important to understand basic terminologies.

Ø Process Indicator: Process indicators are parameters of implementation for the original risk minimization plan, and/or variations in its delivery.

Ø Outcome Indicator: Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimization measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective. The outcome indicator for success or failure should be determined as a priority and on a case-by-case basis.

Ø Effectiveness assessment: This is an assessment of the degree of the outcome of a program in achieving its goals. The process requires the determination of evaluation objectives, methods, and criteria of evaluation and the presentation of findings, impact analysis, and program outcome.

Process of aRMM tracking:

Post substantiation of aRMM tracking, procedural aspects, and organizational level are to be considered for pragmatic tracking.

As per our experience, aRMM tracking can be managed by applying a pragmatic approach. It can be managed by tracking.

Administrative details: In routine PV practices, an element such as molecule, the MA approval date, the country, and other variable depend on the client's practice.

Scientific details: Scientific details regarding aRMM materials such as risk, population, etc.

Status: Status of each aRMMs, submitted to authority, pending or approved.

Conclusion: In this part of tracking, one would be able to conclude an aRMM program based on process indicator tracking of administrative details, scientific details, and status along with outcome indicator details from safety analysis.

Interdependency of aRMM implementation and tracking:

Risk minimization plans and additional risk minimization activities are very much cross-related to other PV activities such as Aggregate Reports, Signal, and Safety Contact centers to receive feedback.

On the other hand, it is not possible to receive tracking data without external stakeholders as there is a high amount of interdependency for aRMM implementation and tracking. Interdependency network such as the following provides robust hand-shaking of data for tracking (Fig 4).

Rationale and benefits of aRMM Tracking

If MAH tracks the process indicators with the help of the status of distribution and implementation of aRMM, it does help in checking program success and resultant actions for patient safety.

Tracking will also help to align the National Competent Authorities (NCA) specific regulatory requirements if updated.

A study conducted to identify significant barriers to risk management implementation and methodological challenges encountered by local safety managers in the European Union and the UK owing to differences in country-specific regulations and regional national competent authority's guidance also signifies the crucial role of aRMM tracking as it directly affects the success of the programme. (5)

The integration of risk minimization with clinical drug development and commercialization work streams throughout the product lifecycle. The Author articulates a vision and a propose

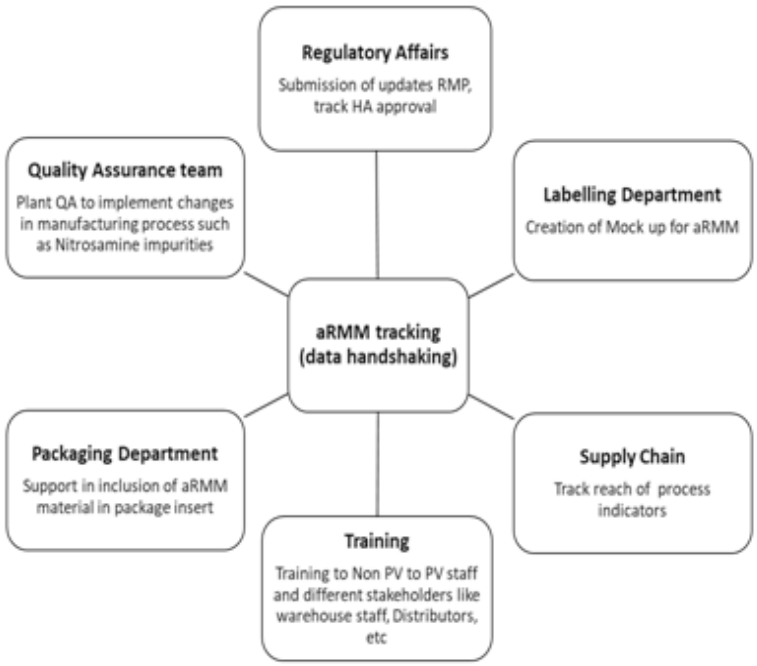

Figure 4: Hand-shaking of data for aRMM tracking

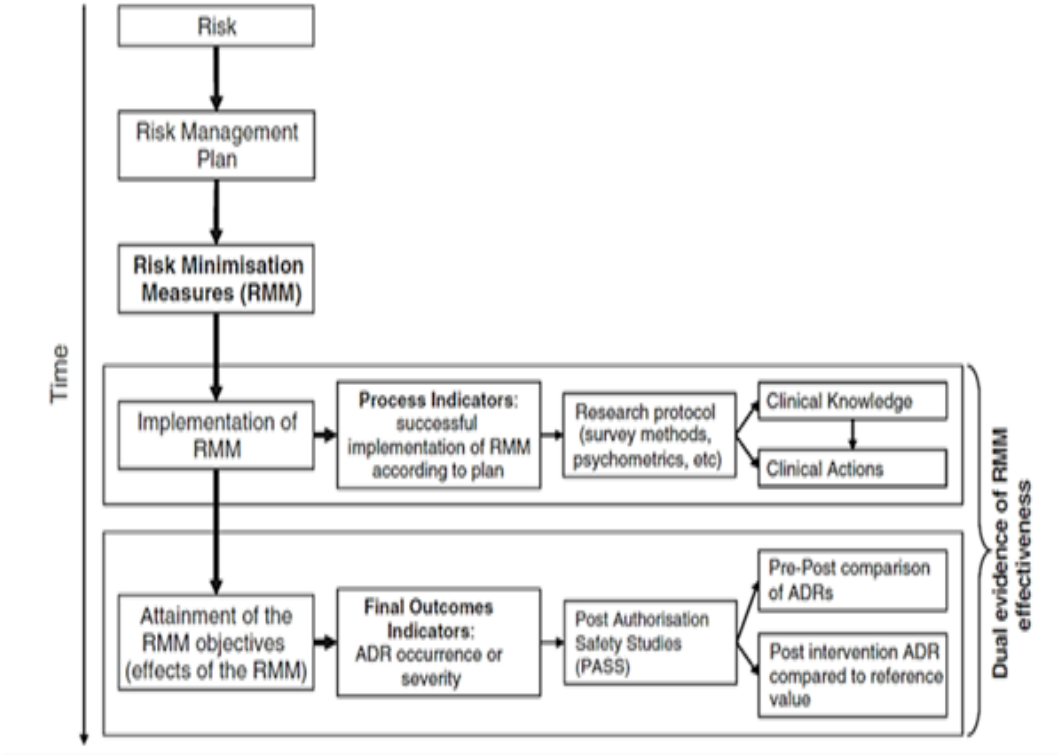

Figure 5: Evaluating the effectiveness of RMM by employing a dual-evidence approach

broad adoption of organizational models for incorporating risk minimization expertise into the drug development process. (3)

The connecting dots of effectiveness evaluation, which primarily center on how tracking of process indicators plays a role in the programme performance, are included in figure 5, which was discussed byISPE members in 2016. In past, an Reporting recommendations Intended for pharmaceutical risk Minimization Evaluation Studies (RIMES) checklist was designed to assess the Quality of Studies Evaluating Risk Minimization Programs for Medicinal Products. One of the components of this checklist is process indicators focusing on reach, adoption, and implementation indicators as parameters supporting effectiveness assessment programs. (4)

There have been important discoveries in aRMM activity over the past five years of monitoring, and most of them missed implementing materials. With the following analysis, it was determined that monitoring aRMM is crucial to implementing additional Risk Minimization Measures (aRMM). A better tracking system for aRMM fosters more compliant and effective Risk Management, ensuring better patient safety

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