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Risk Management Plans

01.
Risk Management Plans

"The purpose of a risk management plan (RMP) is to ***document the risk management system*** *deemed* ***necessary to identify, characterize and minimize essential*** *drug risks."*

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¿What is Risk Management?

It is the proactive identification and implementation of **strategies** to manage **significant** risks to individuals and populations.

In the context of medicines and public health, risk management refers to the **optimization** of the benefit-risk balance of medicines, mainly through activities of: **RISK ASSESSMENT** and **RISK MINIMIZATION.**

Pre-marketing safety assessment
Targeted safety studies
Post-marketing surveillance
- Spontaneous reporting & Signal Detection
- Data mining / Registries / Case series
- Stimulated reporting
- Active surveillance

Observational/Epidemiology studies
Targeted clinical investigations
Descriptive studies (natural history of disease, drug utilization)

Prescribing information
Patient information leaflets
Dear Doctor letters
Educational programmes
Mandatory registration
Restricted access
Controlled distribution
Withdrawal or suspension

Global Clinical Trials Playbook. DOI: 10.1016/B978-0-12-415787-3.00013-8

"Make sure that the benefits outweigh the risks as much as possible."

(Professor H Leufkens University of Utrecht/MEB the Hague)

2017 - TO DATE

2012
New Legislation. EMA Module V,Post-authorization data, minimization measures.

2007
Management plans, more focus on the context of drug use, molecular/genetic correlation

2005**
Exposure correlates (channeling, compliance, duration of use, confusion due to indication)

1987
Spontaneous Adverse Event Count - Raw Data

Introduction to RMP New legislation

Key considerations in risk management plans. Maarten Lagendijk Risk Management Section.
https://www.ema.europa.eu/en/documents/presentation/presentation-key-considerations-risk-management-plans-maarten-lagendijk_en.pdf
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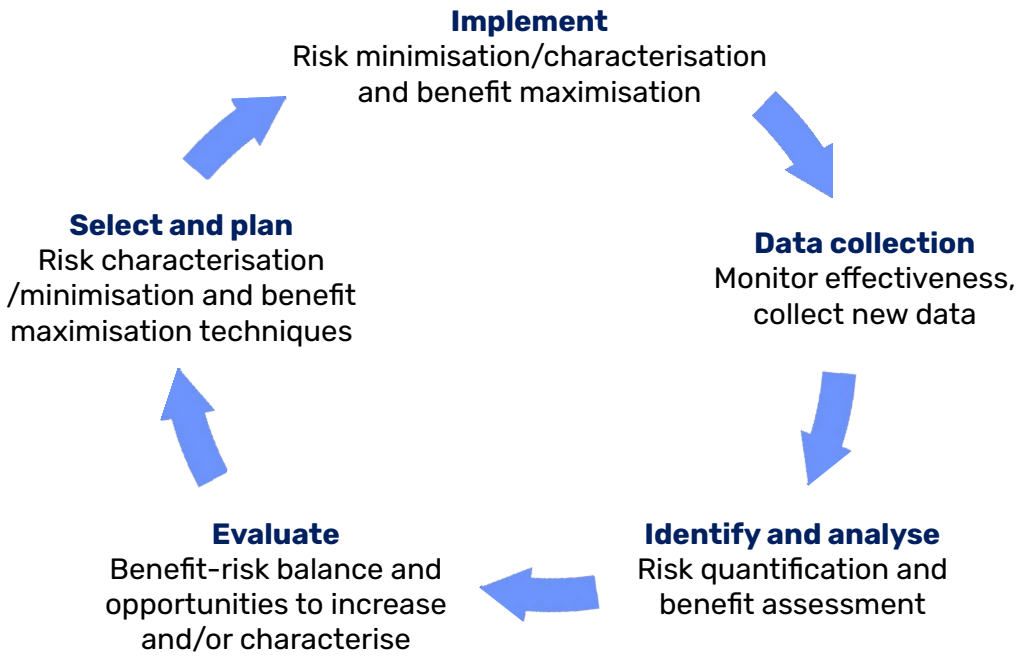
Life cycle and other considerations

The risk management cycle



1. **Identify and analyze:** risk quantification and benefit assessment
2. **Evaluate:** benefit-risk balance and opportunities to increase and/or characterize
3. **Select and plan:** risk characterization/characterization and benefit maximization techniques
4. **Implement:** risk minimization/characterization and benefit maximization
5. **Collect data:** monitor efficiency and collect new data

REA "Del ant. riesco 'risco', because of the danger they pose."

"specific risk:1. m. Econ. risk that can be reduced by diversification."

https://toolbox.eupati.eu/resources/risk-communication-in-medicines/
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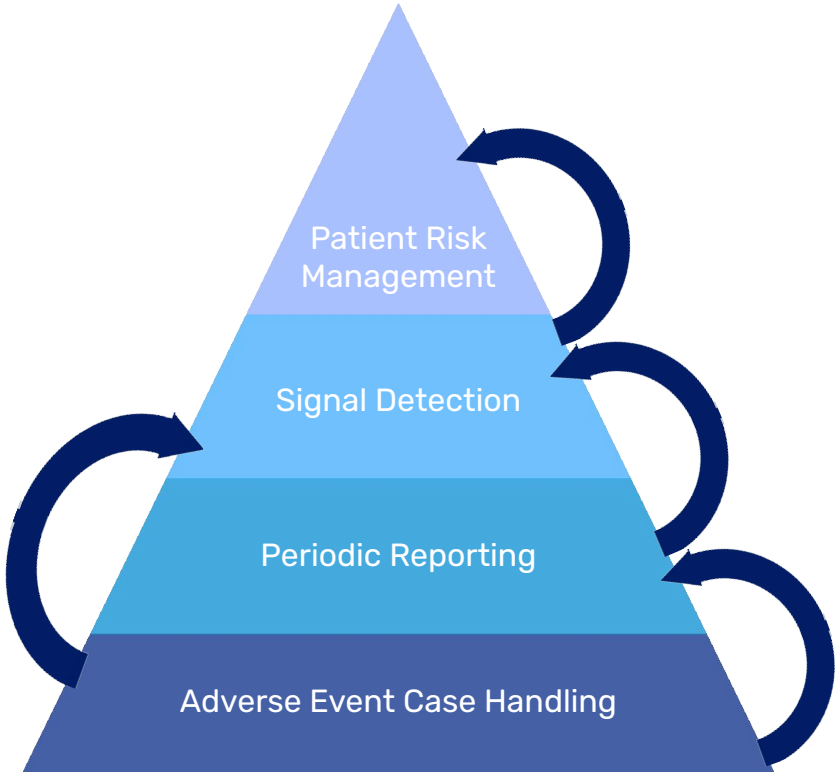
What comprises it?

Analysis of the safety information of a product, which allows us to characterize the risks of drugs and thus minimize their probability of occurrence in patients.

Objectives

- Identification or characterization of the drug safety profile - Risks.
- Pharmacovigilance Plan
- Risk Minimization Plan



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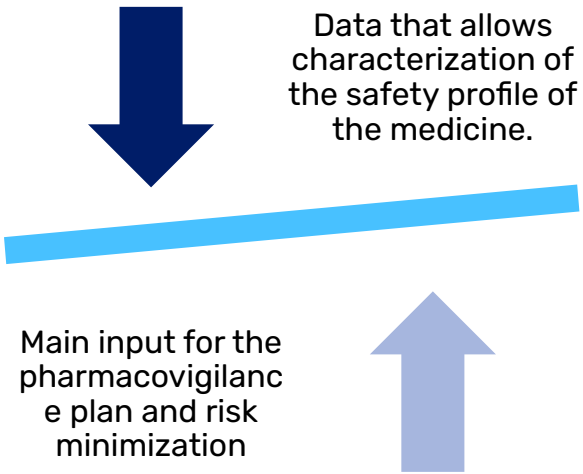
01. Safety Specifications (Risks)



Safety issues that have clinical significance to **affect the benefit-risk** ratio of the drug or pose a **potential threat** to public health are considered risks.

IDENTIFIED

Clinical manifestation with clear association with the product (Rmina)- Additional Med.

POTENTIAL

Clinical manifestation with possible association with the product. (CT-Sp)

MISSING INFORMATION

Population/setting not tested in clinical trial (CT) and no confiable data available (CT-Solicited).

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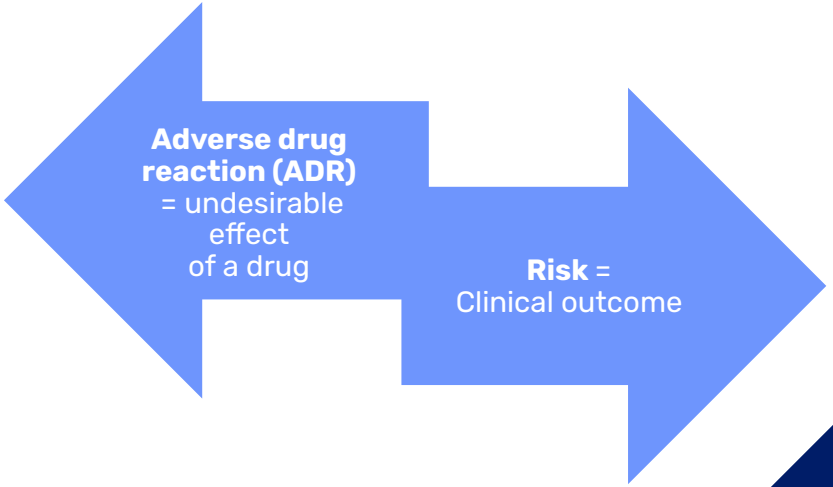
Difference ADR vs. Risk

ADR*	Associated risk.[1]	Associated Risk Significant [2]
Prolongation of QTs	Torsade de Pointes (TdeP)	Torsade de Pointes (TdeP)
Vasospasmo Art. Coronary	Cardiac Arrhythmia	Serious Cardiac Arrhythmia
CPK increase	Myopathy	Rhabdomyolysis
Neutropenia	Infection	Serious infection/sepsis
Nausea and vomiting	Dehydration	Renal insuficiency



1. The clinical outcome of AMR.
2. The clinical outcome of the AMR, which affects the benefit-risk balance of the product 3.

* In some cases ADR could be a risk (they have the same PT).

02. Pharmacovigilance Plan

TO

Identify and/or characterize the RISKS.

Identified in the Security Specifications.

Activities performed by the MAH (Marketing Authorization Holder)

Registrant

ROUTINE

- Set of primary/minimal activities necessary to comply with the requirements Legal/Regulatory pharmacovigilance.
- For well-characterized safety issues, routine pharmacovigilance may be sufficient.

ADDITIONALS

- Other activities considered non-routine.
- Divided by activity type: 1, 2 or 3: "imposed", "specific obligations", "required",. (Ex. Non-clinical studies, remarks).

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For the purpose of RMP, only routine pharmacovigilance activities beyond adverse reaction notification and signal detection are included.

Routine

Specific adverse reaction follow-up questionnaires for safety concerns

- Guided questionnaire for PML (Product A);
- Guided questionnaire for Hepatitis B reactivation (Product B);
- Guided questionnaire Malignancy (Product C)

Other forms of routine pharmacovigilance activities for safety concerns

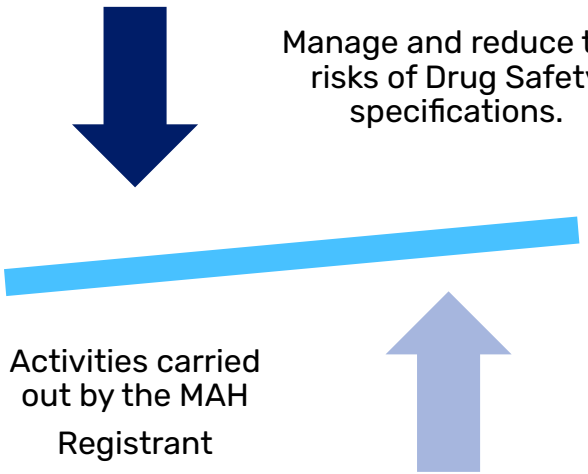
- Enhanced passive surveillance;
- Observed versus expected analyses;
- Cumulative reviews of adverse events of interest;
- Monitoring and special reporting in the PSURs (events under close monitoring)
- One-off cumulative reviews of adverse events of interest (other legally binding post-authorisation measures)

Additionals

Non routine PV activities

- Non-clinical studies;
- Clinical trials;
- Epidemiological (non-interventional or interventional);
- Non-interventional studies

03. Minimization Measures



RUTINA

- Standard set of activities performed for all products.
- They are established for all drugs and most safety issues can be addressed through these procedures.
- It is considered suficient to maintain a satisfactory balance between benefit and risk.

ADDITIONALS

- These are all other sets of activities, which go beyond routine activities.
- Exceptionally, for selected major risks.
- They should focus on significant safety risks where prevention/mitigation can be achieved.
- Consideration should also be given to not imposing an undue burden on patients and the healthcare system.

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Minimization Goals

- Optimize the safe and efficient use of a drug throughout its life cycle, so that the benefits of a drug outweigh the risks by the greatest possible margin for the individual patient and for the target population as a whole.

- **Plans to evaluate the efficiency of additional RMinA should be included in the RMP, while the results should be reported in the PBRERs.**

Categories:

1. Risk communication to stakeholders
2. Restrict access to the product
3. Product presentation restrictions

Ejemplo:

1. Educational activities
2. Enabling activities
3. Control-based activities

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Routine

The labelling (e.g., on inner and outer carton

Pack size

SmPC/CDS

The legal status of the product

The package leaflet

Formulation

Additionals

Educational outstretches

PPP

Prescriber checklist

HCP training materials

Patient alert card

HCP and Patient/Carer Guide

Patient diary

Mitigation measures must always be evaluated
The objective of the assessment is to facilitate early corrective action if necessary.

Support from health authorities

Evidence of applicability

Introduction or Discontinuation of Additional Risk Minimisation Measures During the Life Cycle of Medicines in Europe

Reynold D. C. Francisca[1,2] · Emna Baba[2] · Christina E. Hoeve[1,2] · Inge M. Zomerdijk[1,2] · Miriam C. J. M. Sturkenboom[3] · Sabine M. J. M. Straus[1,2]

Conclusions We found low probabilities of introduction and discontinuation of aRMMs (excluding DHPCs) during the product life cycle for medicines authorised between 2006 and 2017. The low rate of discontinuation may potentially be due to a lack of robust data on effectiveness of aRMMs. Further research is needed to get more insight into the dynamics of aRMMs during the medicine life cycle.

Evaluation of the Implementation of Additional Risk Minimization Activities in Europe, the USA, and Japan

Yuka Yasuoka[1,2] · Masayuki Kaneko[1] · Mamoru Narukawa[1]

Conclusions Risk minimization activities were considered to be largely influenced by differences in regulatory thinking, medical systems, such as the number of healthcare providers per patient and the insurance system, and cultural differences. For drugs with a risk for teratogenicity and those with side effects that differ from conventional therapies, there was a tendency to commonly implement additional activities.

International meeting of the French society of neurology 2020

Drug safety in multiple sclerosis: From reporting to signal detection and benefit-risk management

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[d] *Réseau Normand pour la prise en charge de la SEP, Caen, France*

Conclusion. – Improvement of the PV system procedures has led to significant progress in the detection of signals, allowing better assessment of the benefit-risk balance and the implementation of risk management plans for MS treatments. The involvement of neurologists is essential to improve knowledge on the benefit-risk balance of these drugs. In addition, adverse drug reactions reporting by persons with MS should be encouraged.

Implementation Challenges/Experience

Legal framework
There is no legal term that regulates in favor of its implementation/monitoring/use/application

Concept **Risk minimization**

Data, feedback, public health pillar

Effectiveness
Synergy with the authority is necessary

Response times
Live documents - evaluated versions

Impact network
Uses, distribution, administration and nature of the measure

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