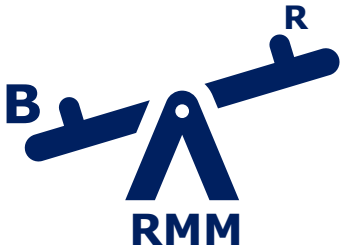
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Risk minimisation in healthcare - Updates on policy, practice, research and engagement

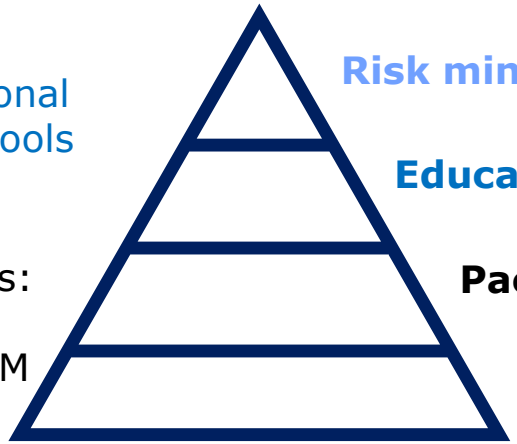
PCWP & HCPWP April 2025

Priya Bahri, European Medicines Agency, H-QS-PhV

Risk minimisation measures (RMM)



- ***RMM messages:*** the key information about the risk and the actions intended to be taken by the healthcare professional or the patient for minimising the risk
- ***RMM tool:*** the tool by which the RMM messages are disseminated and adherence to the intended actions for risk minimisation is supported and/or controlled



1 Priya Bahri: Risk minimisation in healthcare

Additional RMM toolbox

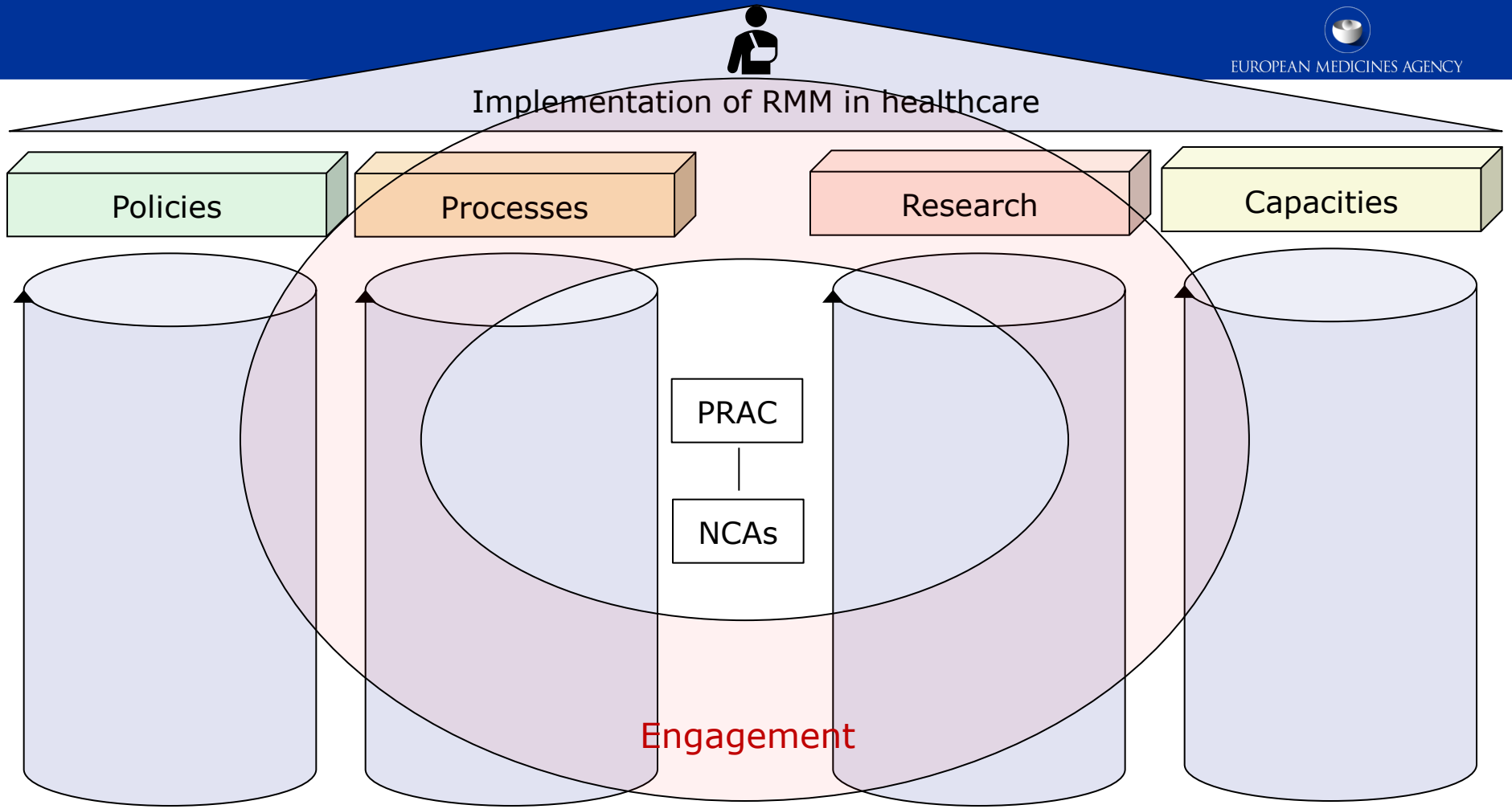
Table XVI.2.: Educational/Safety advice tools

Educational/Safety advice tools
Guides for patients or healthcare professionals for risk minimisation
Healthcare professional checklist for risk minimisation
Risk awareness dialogue form/aid
Patient card
Patient diary for risk minimisation

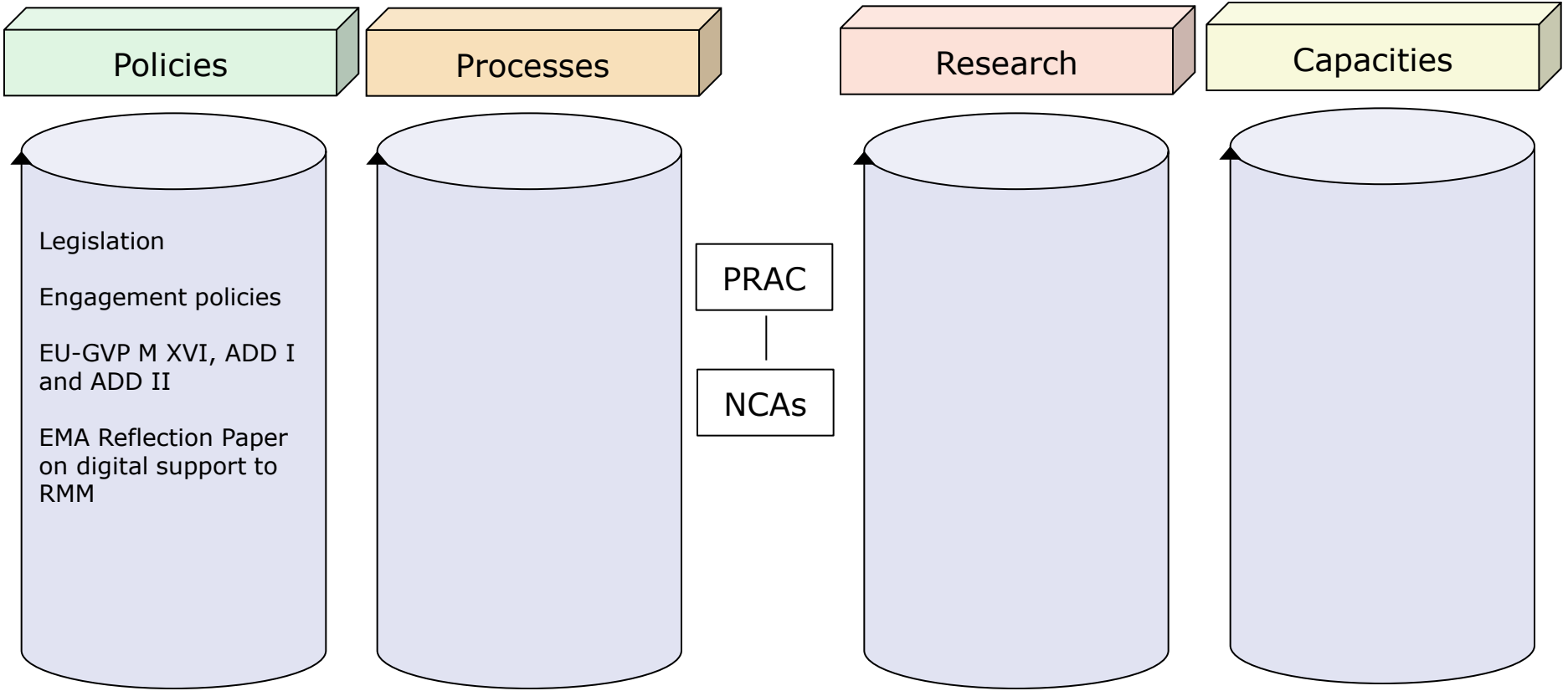
Table XVI.3.: Risk minimisation control tools

Risk minimisation control tools
Healthcare professional qualification required for the prescribing, dispensing and/or administration of the medicinal product, and/or the supervision of the administration by the patient
Healthcare facility accreditation of the available equipment and qualified healthcare professionals required for using the medicinal product at this facility
Traceability system to be completed at dispatch of the medicinal product from the manufacturing site, all distribution points and the healthcare facility where the medicinal product is dispensed or administered
System for documented exchange of patient information (e.g. results of medical tests) one healthcare professional is required to receive from another healthcare professional
Check of patient certificates of medical interventions required for the prescribing or dispensing of the medicinal product

[EU-GVP Module XVI revision 3]



Implementation of RMM in healthcare



HMA
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SCIENCE MEDICINES HEALTH

26 July 2024
EMA/204715/2012 Rev 3

Guideline on good pharmacovigilance practices (GVP)

Module XVI – Risk minimisation measures (Rev 3)

Date for coming into effect of first version	1 March 2014
Date for coming into effect of Revision 1	28 April 2014
Date for coming into effect of Revision 2	31 March 2017
Draft Revision 3 finalised by the Agency in collaboration with Member States	18 November 2020
Draft Revision 3 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	7 January 2021
Draft Revision 3 adopted by the EMA Executive Director*	1 February 2021
Release for public consultation	3 February 2021
End of consultation (deadline for comments)	28 April 2021
Revised draft Revision 3 finalised by the Agency in collaboration with Member States	4 July 2024
Revised draft Revision 3 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	22 July 2024
Revised draft Revision 3 adopted by the Executive Director as final**	26 July 2024
Date for coming into effect of Revision 3*	6 August 2024

* The revised final guidance is applicable to new applications for marketing authorisation, new risk minimisation measures and new studies evaluating risk minimisation measures for authorised medicinal products but not immediately applicable to existing risk minimisation measures and ongoing activities regarding risk minimisation measures; however, where existing risk minimisation measures are amended, the revised guidance should be taken into account and applied if this is considered likely to increase the effectiveness of the risk minimisation measure without jeopardising its familiarity for patients and healthcare professionals using the concerned medicinal product.

*Note: Draft Revision 3 released for public consultation versus Revision 2 included the following:

- Changes to XVI.A. to clarify the role of risk minimisation for risk management planning and for the impact on the risk-benefit balance of medicinal products, and the role of effectiveness evaluation of risk minimisation measures, and to delete/merge concepts already included in other sections of the Module;
- Addition of XVI.B.2. to give more guidance about the criteria for applying/requesting additional risk minimisation measures;
- Changes to XVI.B.3.1. with a new classification for educational materials;
- Changes to XVI.B.3.4. regarding the concept of controlled access systems and examples illustrating the requirements;
- Addition of XVI.B.4. to clarify the role of risk communication, dissemination and implementation as a relevant part of any additional risk minimisation activity;

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

Table of contents

XVI.B.2. Categories and tools of risk minimisation measures

XVI.B.2.1. Categories of risk minimisation measures and their relationship

In terms of the tool, RMM can be categorised into routine (see XVI.B.2.2.) and additional (see XVI.B.2.3.) RMM.

The SmPC is the fundamental routine RMM tool, where the risk of the medicinal product and the intended actions for risk minimisation are described. As such the SmPC forms the basis for the descriptions of the risk and the intended actions in the package leaflet and for other routine RMM and, where required, additional RMM.

Where applicable, the SmPC should mention that additional RMM materials exist for a specific risk and may include information where they can be accessed. If an additional RMM material is targeted at patients, the package leaflet should contain information on the availability of this material and may include accessibility information too.

Additional RMM tools are meant to emphasise the information on the risk and the intended actions for risk minimisation contained in the SmPC and to support and/or control the adherence to the intended actions.

XVI.B.2.2. Tools of routine risk minimisation measures

Routine RMM tools are those which apply to every medicinal product; an exception are visual enhancements and special warnings/information on precautions on the packaging which are routine RMM tools that are not needed for every medicinal product and have to be specifically included in the marketing authorisation if required (see XVI.C.1.1.).

Routine RMM tools include those listed in Table XVI.1. and are detailed in XVI.Appendix 1.

Further, the pharmaceutical form or formulation of a medicinal product may play an important role in minimising the risk, e.g. in minimising the risk of incorrect dosing or administration, misuse or abuse.

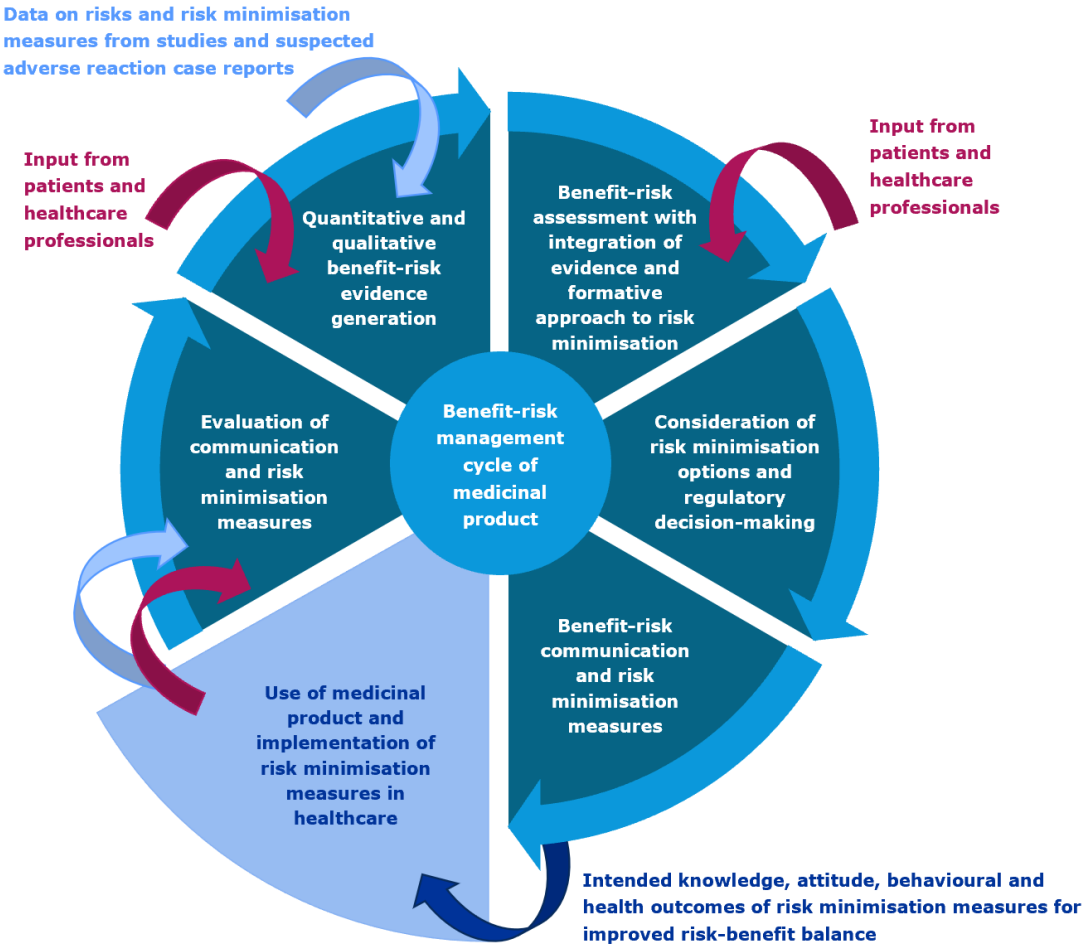
Table XVI.1.: Routine risk minimisation measure tools

Routine RMM tools
Summary of product characteristics (SmPC)[9]
Package leaflet (PL)[10]
Labelling of immediate and outer packaging[11]
Pack size
Classification of the medicinal product (legal status)

[9] In rare situations, the SmPC may include a boxed warning in bold font type (see XVI.App1.1.1.).
[10] In rare situations, the PL may include symbols, pictograms and/or warnings on dark background (see XVI.App1.2.1.).
[11] In rare situations, the labelling may include special warnings, information on precautions and/or pictograms (see XVI.App1.3.1.).

Implementation pathway of risk minimisation measures (RMM)

[EU-GVP Module XVI revision 3]



EU-GVP Module XVI rev 3

- Acknowledges medicine use as part of life-cycle
- Takes an implementation science approach
- Considers context and impacting factors of RMM
- Emphasises stakeholder engagement
- Distinguishes between implementation to be evaluated and implementability as subject to proactive formative approach for RMM decisions and design

Formative approach on risk minimisation

Relates to:

- **Implementability**

  = expected opportunities of a risk minimisation measure to be implemented effectively in terms of achieving the intended outcomes and avoiding the potential for unintended outcomes, based on evidence and input from patients and healthcare professionals

- **Underlying healthcare system factors**

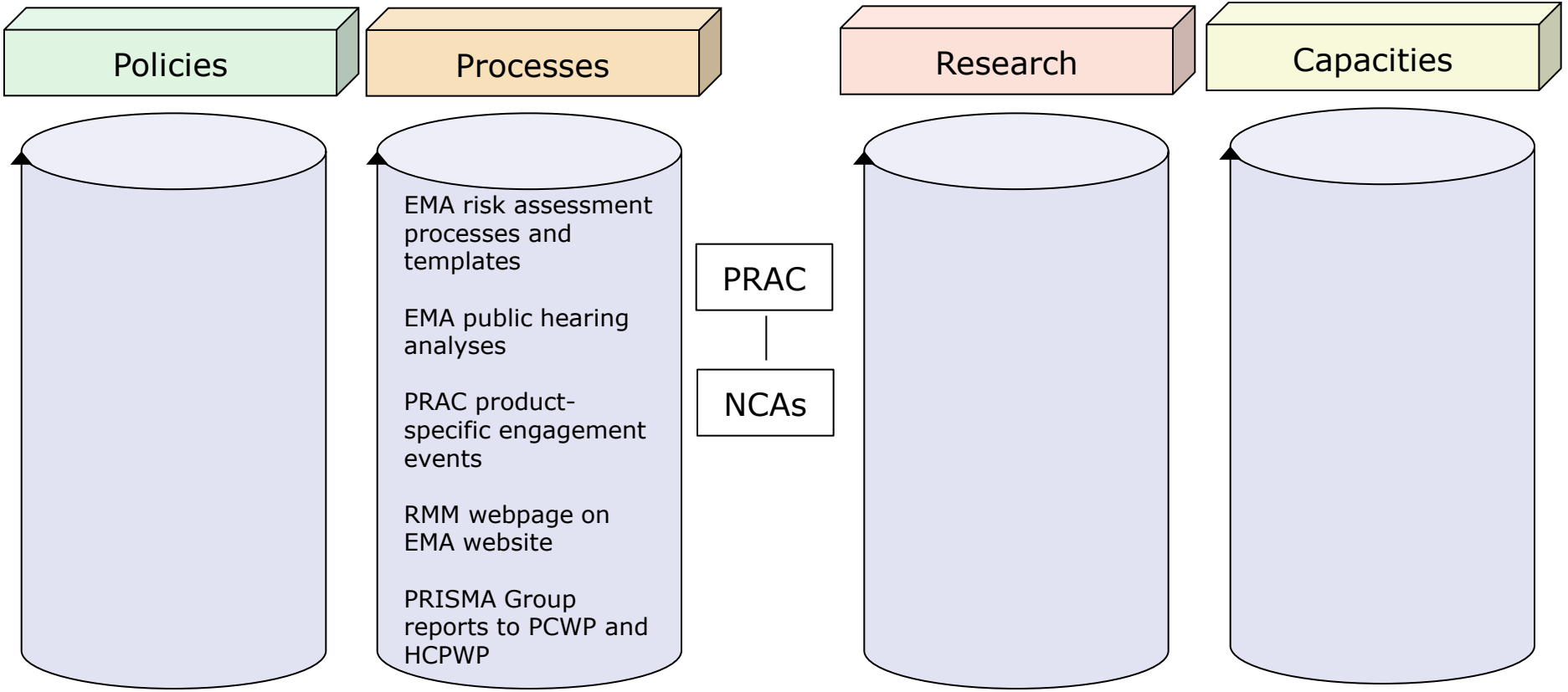
❖ Context of medicine use, disease management and overall clinical context

❖ Healthcare settings and processes, typical patient environments, circumstances and care processes and how RMM could be integrated into the processes

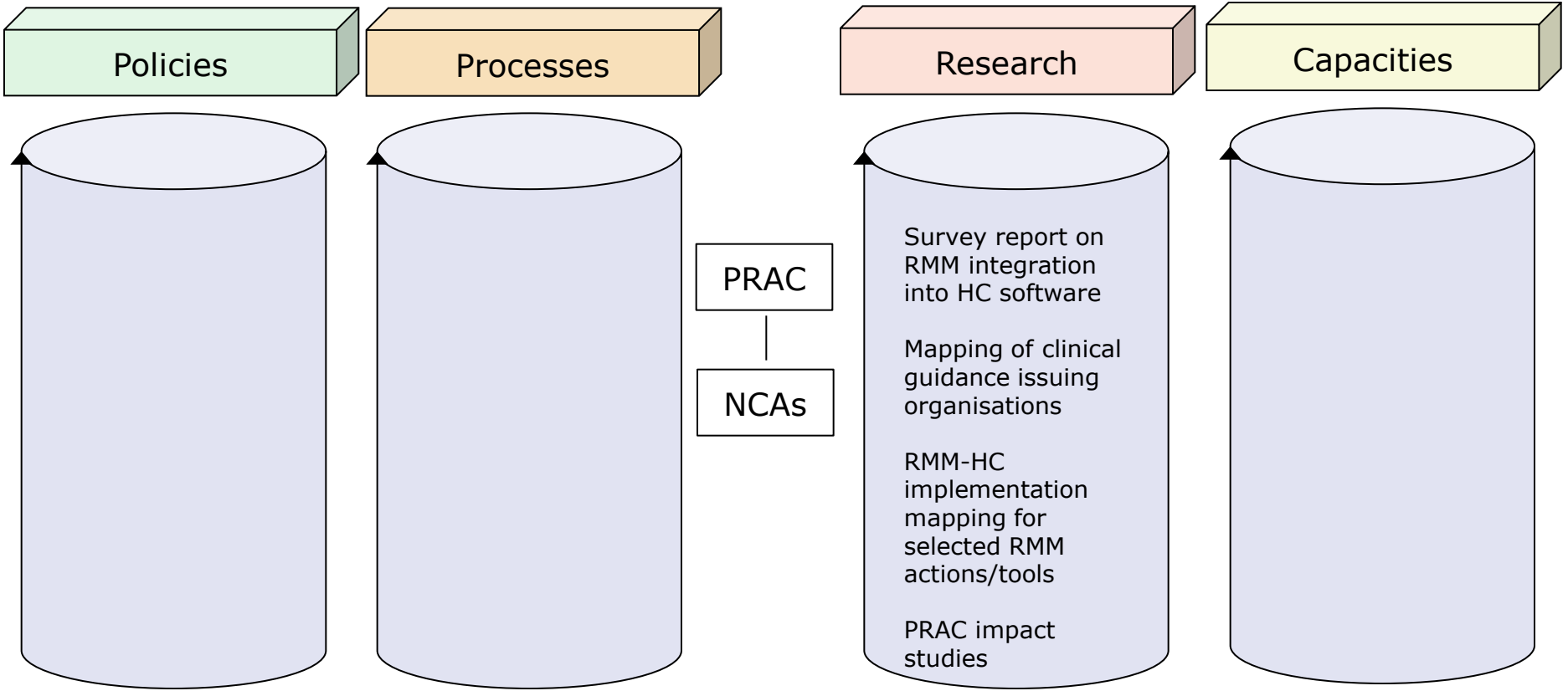
❖ Health information diffusion, existing knowledge, attitudes and behaviours in target populations, and individual and system factors to adopt changes

[EU-GVP Module XVI Revision 3]

Implementation of RMM in healthcare



Implementation of RMM in healthcare



EMA/2020/46/TDA/L4.02
Specific Contract 01

Implementation of EU risk minimisation measures for medicinal products in clinical guidelines

Deliverable 1: Preliminary Study Plan

EU PE&PV research network

Drug Safety
https://doi.org/10.1007/s40264-024-01487-5

ORIGINAL RESEARCH ARTICLE

Challenges in the Implementation of EU Risk Minimisation Measures for Medicinal Products in Clinical Practice Guidelines: Mixed Methods Multi-Case Study

Mathias Møllebæk[1] · Helga Gardarsdottir[2,3] · Alexia-Georgia Bikou[4] · Ana Kodrič[5] · Ana Marta Silva[6] · Armin Andersen[7] · Christos Kontogiorgis[8] · Elita Poplavska[9] · Fariba Ahmadizar[10] · Foteini Dermiki-Gkana[8] · Ieva Rutkovska[9] · Inês Ribeiro Vaz[6] · Mitja Kos[5] · Paula Barão[11] · Renske Grupstra[2] · Teresa Leonardo Alves[12] · Anna Birna Almarsdóttir[1]

Accepted: 7 October 2024

Abstract

Introduction Risk minimisation measures (RMMs) aim to ensure safe use of medicines, but their implementation in clinical practice is complicated by the diversity of stakeholders whose clinical decision making they seek to inform. Clinical practice guidelines (CPGs) are considered integral in clinical decision making.

Objectives To determine the extent to which RMMs are included in the relevant CPGs and to describe factors that determine RMM inclusion.

Methods A multi-case study design using quantitative document analysis of CPGs combined with qualitative interviews with informants from organisations that issue CPGs. Cases from five therapeutic areas (TAs) with a regulatory requirement for further RMMs were studied individually in six EU member states (Denmark, Greece, Latvia, Netherlands, Portugal and Slovenia). Clinical practice guidelines were analysed using pre-defined coding frameworks. Interviewees were sampled purposively for experience and knowledge about CPG development and RMM inclusion. Verbatim interview transcripts were analysed inductively.

Results In total, 136 CPGs were analysed, and RMM information about TAs was included in 25% of CPGs. Based on 71 interviews we found that factors that determine RMM inclusion in CPGs include clinicians' low awareness of RMMs despite awareness of RMMs' safety concern, low expectation of RMMs' clinical utility, and unfamiliarity with pharmacovigilance data supporting RMMs and perceived incompatibility of CPGs' scope and purpose and RMM information.

Conclusions The inclusion of RMM information in relevant CPGs is remarkably limited. It may be explained by characteristics of CPGs and of RMMs as well as lack of connection between national regulators and organisations and authors developing CPGs. More collaboration between stakeholders, national regulators and the EMA may advance implementation.

Key Points

By analysing guidelines for five different medicines in six EU member states we found that only 25% of guidelines include relevant risk minimisation information from regulators.

In interviews, guideline authors said that guidelines focus on clinical actions, and regulators' risk information is not always clinically relevant nor fully transparent to clinicians. This calls for more collaboration between guideline authors and national and European regulators to ensure the effective implementation of risk minimisation efforts.

Extended author information available on the last page of the article

1 Introduction

In the European Union (EU), medicine regulators may require marketing authorisation holders (MAHs) to develop and disseminate risk minimisation measures (RMMs) to ensure patients' safe and effective use of medicines, such as pregnancy prevention programmes or measures to monitor patients for certain risk factors [1]. Requiring RMMs is usually decided upon at the level of the European Medicines Agency (EMA) (for centrally authorised products) or by the national competent authorities (NCAs) (for nationally authorised products) [2]. Then, requirements for RMMs are operationalised by NCAs, subsequently implemented in clinical practice by healthcare professionals (HCPs), and ultimately reaching patients [2]. Given this implementation pathway (which may vary moderately with specific

Published online: 21 November 2024

Study on RMM in clinical guidelines – Study objectives

Overall aim:

- To determine the extent to which risk minimisation measures (RMM) are included in the relevant clinical practice guidelines (CPGs) and
- To describe factors that determine this RMM inclusion.

Specific objectives:

- Identify entities issuing CPGs
- Retrieve relevant CPGs and analyse CPGs in terms of RMM inclusion
- Describe CPG update process and factors for RMM inclusion

Recommendations

[Moellebaek et al 2024]

Study on RMM in clinical guidelines - Study cases

Table 1 Medical products and related RMMs that were implemented

Therapeutic area	Indicated pharmaceutical products	Year of EMA approval of the RMM	Aim of implemented RMM	Implemented RMM tools[a]
Neurological diseases	Valproate	2018	To minimise teratogenic risks through a pregnancy prevention programme	SmPC updates; visual reminder on packaging; healthcare professional guide/checklist; patient card; patient guide; annual risk acknowledgement form; direct to healthcare professional communication
Infectious diseases	(Fluoro-)quinolones	2019	To minimise the risk of long-lasting, disabling and potentially irreversible adverse reactions (including tendon, muscle and joint disorders, neurologic and psychiatric disorders)	SmPC updates; direct to healthcare professional communication; suspension
Inflammatory, autoimmune and cancer diseases	Methotrexate	2019	To minimise the risk of medication errors and adverse reactions associated with overdose, the following RMMs were introduced for methotrexate (for oral and parenteral formulations with at least one indication requiring intake only once a week)	SmPC updates; visual reminder on packaging; healthcare professional guide/checklist; patient card; direct to healthcare professional communication
Diabetes type II	Metformin	2016	To minimise the risk of lactic acidosis while maintaining the treatment option for patients with only moderately impaired kidney function	SmPC updates
Cancer diseases	Fluorouracil and related substances	2020	To minimise the risk of severe toxicity by pre-treatment testing to identify dihydropyrimidine dehydrogenase (DPD)-deficient patients	Direct to healthcare professional communication

[Moellebaek et al 2024]

Study on RMM in clinical guidelines - Study results

Relevant CPGs: 136

RMM inclusion: 25% of CPGs; usually one sentence only

Factors that determine RMM inclusion in CPGs:

- Clinicians' low awareness of RMM despite awareness of the safety concern
- Low expectation regarding clinical utility of RMM, RMM information not always perceived as clinically relevant
- Unfamiliarity with pharmacovigilance data supporting RMM, not fully transparent what underpins ins RMM
- Perceived incompatibility of CPGs' scope (clinical actions) and purpose versus RMM information

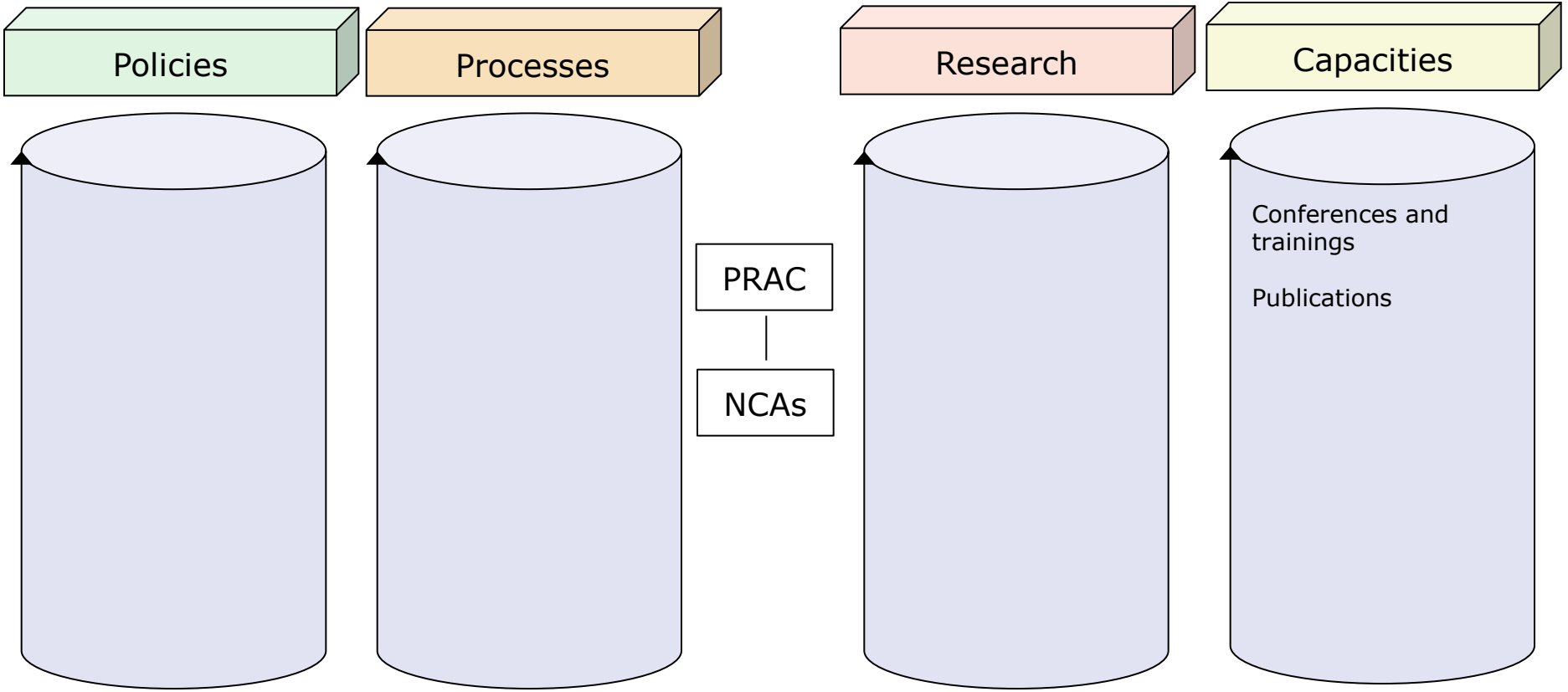
[Moellebaek et al 2024]

Study on RMM in clinical guidelines - Conclusions

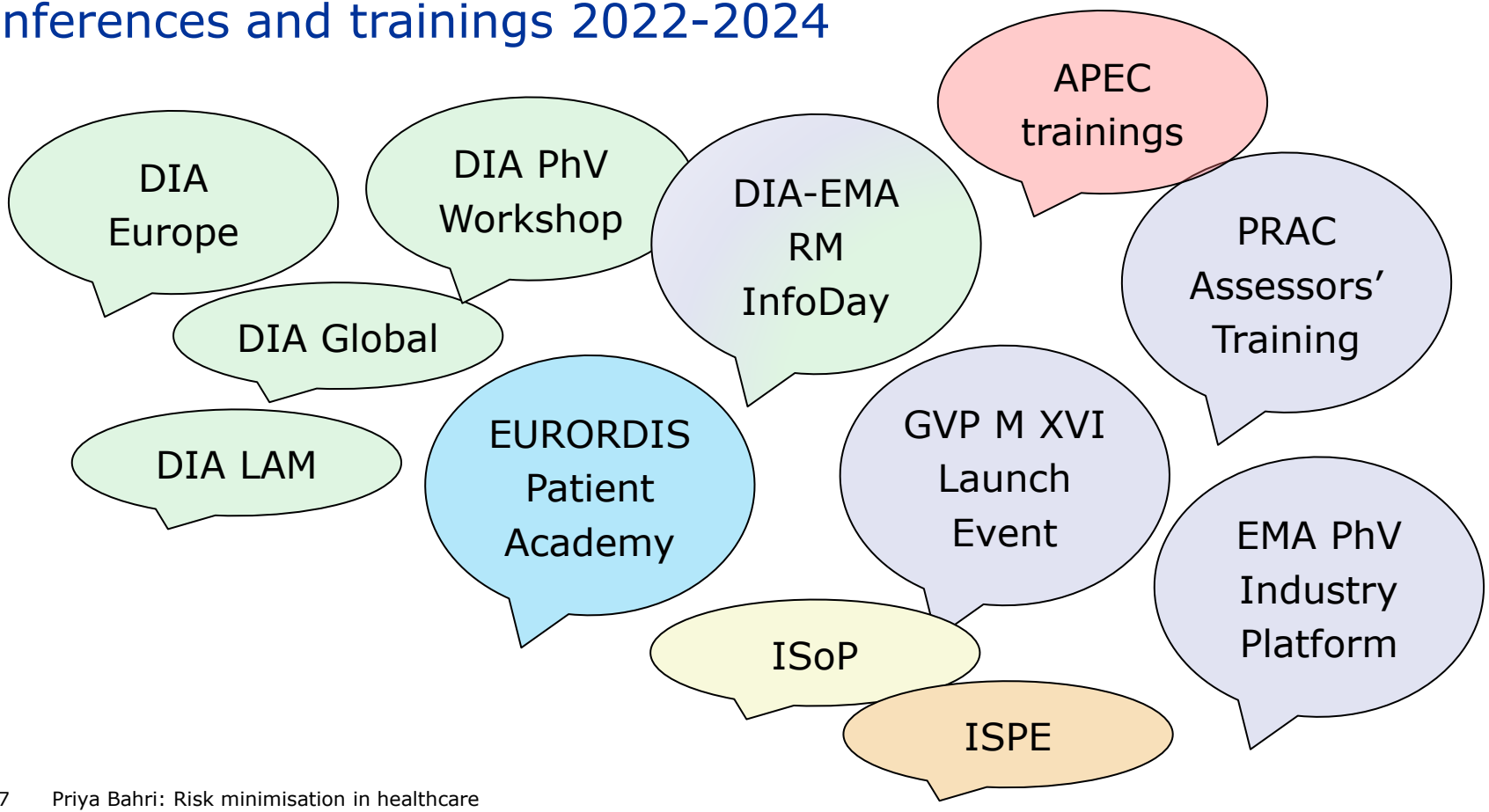
- Remarkably limited inclusion of RMM in CPGs, may be explained by characteristics of CPGs and of RMMs as well as lack of connection between national regulators and CPG issuing organisations/authors
- Issues raised by CPG authors pertain to need for more fundamental alignment of perspectives between clinical and regulatory domains, such as reciprocal institutional confidence, evidentiary norms, and clinical relevance criteria
- Previous studies have argued for the important role that CPGs may have for the implementation of RMMs
- Study authors recommend to improve HPs' RMM awareness, more collaboration to advance RMM integration in CPGs (via weblinks), monitoring of national implementation of RMMs, RMM website, and further research and educational programmes about pharmacovigilance for HPs

[Moellebaek et al 2024]

Implementation of RMM in healthcare



Conferences and trainings 2022-2024



Drug Safety (2024) 47:941–956
https://doi.org/10.1007/s40264-024-01451-3

REVIEW ARTICLE

The STAR Compass to Guide Future Pharmacovigilance Based on a 10-Year Review of the Strengthened EU System

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Accepted: 29 May 2024 / Published online: 10 July 2024

Abstract
This article reflects on the 2010 pharmacovigilance legislation of the European Union (EU). Its legislative aim of better patient and public health protection through new responsibilities for pharmaceutical companies and regulatory bodies is considered to have been achieved and is well supported by the good pharmacovigilance practices 'EU-GVP'. For future progress, we set out a vision for high-quality pharmacovigilance in a world of ongoing medical, technological and social changes. To deliver this vision, four principles are proposed to guide actions for further progressing the EU pharmacovigilance system: synergistic interactions with healthcare systems; trustworthy evidence for regulatory decisions; adaptive process efficiency; and readiness for emergency situations (the 'STAR principles'). Like a compass, these principles should guide actions for building capacity, technology and methods; improving regulatory processes; and expanding policies, frameworks and research agendas. Fit for the future, the EU system should achieve further improved outputs in terms of safe, effective and trusted use of medicines and positive health outcomes within patient-centred healthcare.

1 Introduction and Objective

The year 2022 marked the 10th anniversary of the coming into application of legislation that profoundly changed and strengthened pharmacovigilance in the European Union (EU) [1, 2]. Since then, we have observed multiple drivers for change of a global and interdependent nature, which have been accelerated during the SARS-CoV-2 coronavirus disease (COVID-19) pandemic and now require adapted medicines regulatory strategies. In particular, these drivers concern the following.

- Health and healthcare, including:
  changing patterns in burden of disease and health challenges, new diagnostic methods, innovative platforms for medicines, personalised medicines, increasing patient-centred, home-based and virtual delivery of healthcare.
- Data and media technology, including:
  ongoing digitalisation of daily life and healthcare with real-world data collection, new methods for data

Key Points

Four principles are suggested to further progress pharmacovigilance in the European Union (EU) and achieve better outputs in terms of safe, effective and trusted use of medicines and positive health outcomes within patient-centred healthcare

These principles should guide actions for system improvements through addressing challenges and using opportunities that arise from the ongoing medical, technological and social changes our world is facing

The suggestions are a result of an in-depth review of data and of insights into the regulatory pharmacovigilance system of the EU, 10 years after its current legal basis became applicable in 2012

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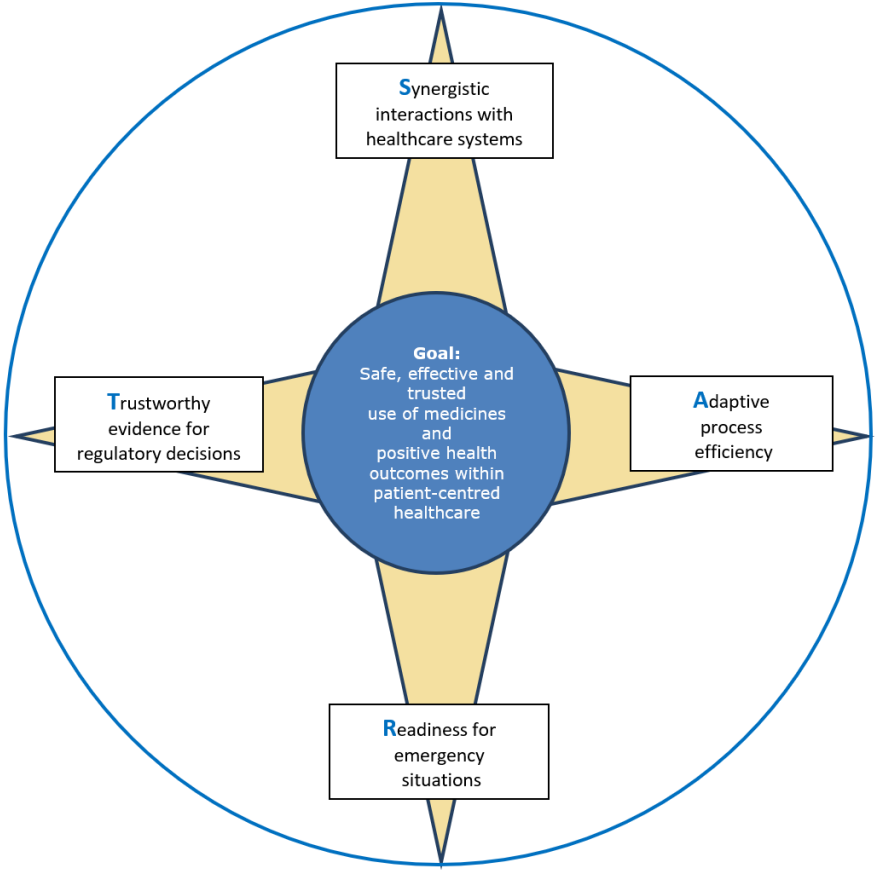

Engagement of patient and HP representatives in RMM

Opportunities:

- Provide insights on RMM options and implementability, to support regulatory decisions on RMM in a formative approach
- Contribute to the development of tailored RMM materials and RMM dissemination plans, e.g. through user-testing of RMM materials by marketing authorisation holders
- Support the dissemination via multiple channels
- Advise and participate in the evaluation of RMM effectiveness

Principles:

- Non-promotional nature
- Independence of the patient and healthcare representatives

Ways and forums for engagement at EMA:

- PRAC membership from the communities
- Written consultations
- Scientific advisory groups
- Ad hoc expert groups
- Public hearings

For medicinal products

- Working parties/groups

For general topics

[EU-GVP Module XVI revision 3]

PRAC Risk Minimisation Alliance (PRISMA) Group

Looking at RMM options in different lights

= perspectives of all stakeholders with a focus on barriers and enablers of RMM implementation in healthcare

Collating a knowledge base for RMM development and implementability based on RMM evaluations and a formative appraoch

Formative approach for RMM decisions and design is the gap to fill with healthcare systems insights and the PRISMA group which includes patient, GP prescriber, hospital and community pharmacist perspectives can be of added value to facilitate this approach

Pilot phase: PRISMA Group achievements in July 2022-23

- High interest from PRAC rapporteurs and members and important dialogue fostering:
  - ❖ Clinical mindset
  - ❖ Patient and healthcare professional perspectives
  - ❖ Healthcare systems insights
- Proposals on PRAC lists of questions to stakeholders regarding RMM and for competent authorities in support of RMM implementation
- Conduct of two surveys and analyses presented to PRAC:
  - ❖ Integration of RMM in dispensing and prescribing software
  - ❖ Internet access to RMM materials
- Development of a new patient journey-based PRISMA discussion framework and testing for specific RMM-tool in general terms; this provided useful input for PRAC, with positive reception at PRAC Dec 2023

Transitional phase: PRISMA Group achievements in 2024

- Input to GVP Module XVI revision 3 and ADD I (terminology for RMM toots; stakeholder engagement) in 2024
- Report on integration of RMM in dispensing and prescribing software with proposals for collaboration under drafting in 2024/5 based the PRISMA survey I in 2023; as a contribution to Reflection Paper on digital support to RMM in 2025
- Specifications for EMA webpage on RMM with links to the webpages of national competent authorities for access to RMM materials agreed in 2024, based on PRISMA survey II in 2023; webpage set up ongoing in 2025
- Reviewed Impact study report article on RMM integration in clinical guidelines in 2024; follow-up mapping of guideline issuing organisations in 2025
- Inspired new qualitative Impact studies with focus on healthcare systems topics started in 2024/5
- Contributions from PRISMA group members to EMA and DIA events in 2024
- Development of a discussion framework and processes for PRISMA started in 2023/4 for the operationalisation in 2025/6
- Presentation of PRISMA work to PCWP and HCPWP in 2024, to be continued in 2025…

2025

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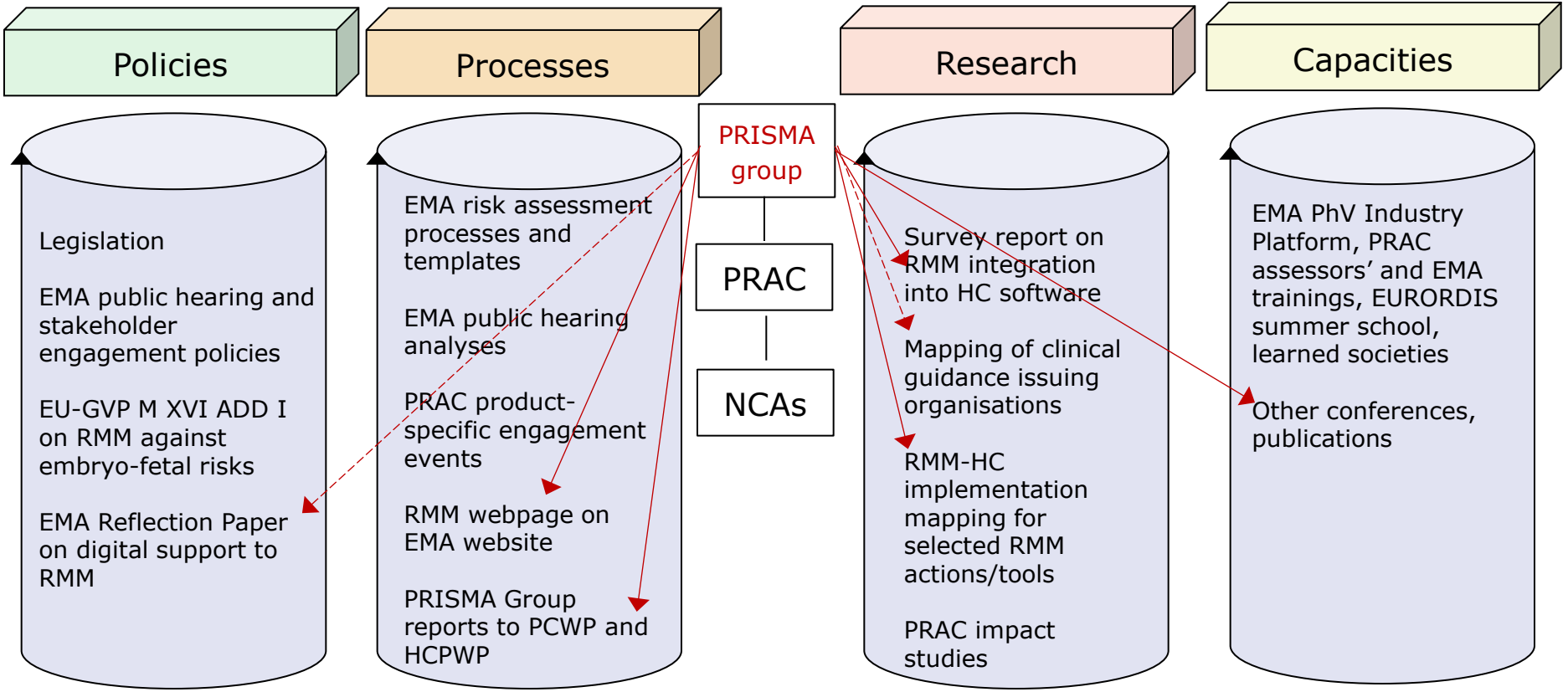
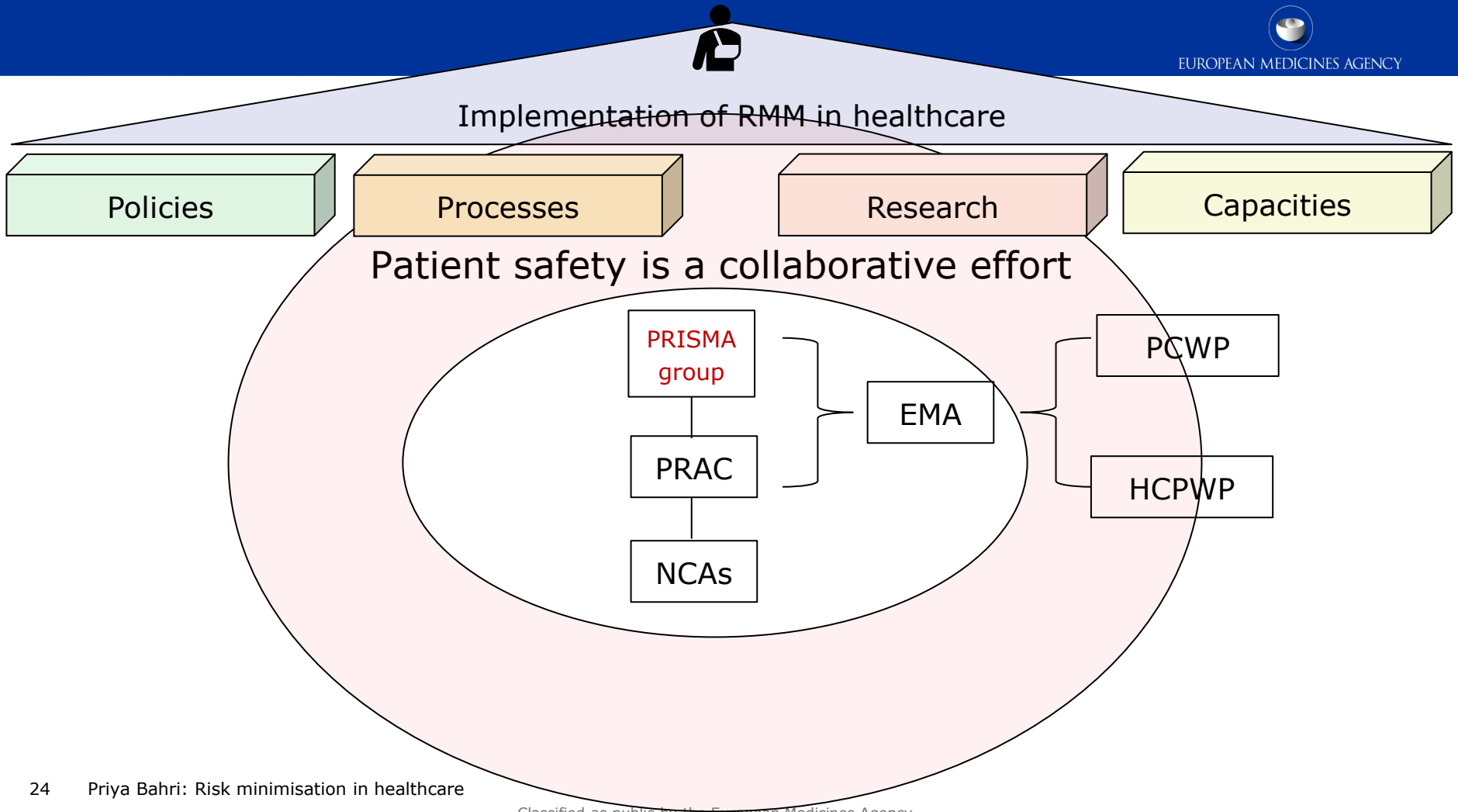
Implementation of RMM in healthcare





Thank you

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