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

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

## Deliverable 3: Study report

**EU PE&PV research network**
**EUPAS47588**

**Version 2.0**

This document includes the first 7 pages of the Study Report. The full report will be available as soon as the manuscript describing the results of the project has been published.

The research leading to these results was conducted as part of the activities of the EU PE&PV (Pharmacoepidemiology and Pharmacovigilance) Research Network which is a public academic partnership coordinated by the Utrecht University, The Netherlands. The project has received support from the European Medicines Agency under the Framework service contract EMA/2020/46/TDA/L4.02. The content of this report expresses the opinion of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

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

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| **Title** | Implementation of EU risk minimisation measures for medicinal products in clinical guidelines |
| **Study ID** | EMA/2020/46/TDA/L4.02 (Lot 4: Qualitative research)<br>Specific Contract 01<br>EUPAS47588 |
| **Framework contractor** | EU PE&PV research network |
| **Countries of study** | Denmark, Greece, Latvia, Netherlands, Portugal, Slovenia |
| **Objectives** | The objectives of this project are to:<br>• Identify and describe the key stakeholders, processes, roles and responsibilities for updating clinical guidelines on pharmacological treatment in six European countries.<br>• Describe and analyse how medicinal product specific RMM for the five disease priority areas and active substances have been integrated in relevant clinical guidelines in six European countries, identifying the key elements of risk minimisation included in new or updated clinical guidelines, key milestones and enablers and barriers for updating, publication/dissemination and adoption of guidelines in healthcare practice.<br>• Provide recommendations for regulators to engage with healthcare professional bodies and other responsible parties to strengthen the role of clinical guidelines for RMM implementation, outlining feasible concrete steps EMA and national competent authorities could consider. |
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**Document version**

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|---|---|---|---|
| Consortium | 11 July 2023 | 1.0 | Study report |
| Consortium | 25 September 2023 | 2.0 | Revised Study report implementing comments received from EMA and PRAC |

# Contents

# 1. Abstract

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

*Keywords*
Multiple-case study, document analysis, Risk minimisation measures (RMMs), qualitative interviews, clinical guidelines

*Rationale and background*
While regulatory implementation of marketing authorisations and risk management plans is a well-established process, implementation of RMMs in healthcare practice can be challenging as they seek to modify knowledge and behaviour of a diverse range of individuals. In this context, clinical guidelines that summarise current medical knowledge and provide evidence-based treatment recommendations for specific therapeutic areas are considered important documents in the networked governance of medicines safety and RMM implementation.

*Research question and objectives*
To describe and understand processes for updating clinical guidelines and the role of healthcare professional associations and public bodies involved in this process. Objectives include to:

> *Identify and describe the key stakeholders, processes, roles, and responsibilities for updating clinical guidelines* in six EU Member States (Denmark, Greece, Latvia, Netherlands, Portugal, Slovenia).
>
> *Describe and analyse how product specific RMMs* for five disease priority areas and active substances *have been integrated into relevant clinical guidelines* in DK, GR, LV, NL, PT and SI.
>
> *Provide recommendations for regulators* to engage with healthcare professional bodies and other responsible parties to strengthen the role of clinical guidelines for RMM implementation.

*Study design*
A multiple-case study design, using document content analysis of clinical guidelines (work package WP1 “Mapping of relevant organisations”, WP2 “Document collection and analysis of clinical guidelines”) combined with qualitative semi-structured interviews with key informants from organisations that produce guidelines as well as representatives from national competent authorities (NCAs) (WP3 “Key Informant Interviews”).

*Population*
Documents and online materials (text) related to clinical guidelines (for WP1, WP2). Stakeholders from national competent authorities, public sector and health authorities, professional associations, and expert groups (WP3).

*Variables*
WP1: Information about entities that issue, develop and/or update clinical guidelines (domains: general information, membership, guideline development). WP2: Information extracted from clinical guideline documents (domains: general information, population, target audience, therapeutic area, information on RMM). WP3: subjective, non-observable dimensions of social relations or work processes (from semi-structured interviews).

*Data Sources*
Documents/online materials (text, WP1/WP2). Transcripts from interviews with stakeholders (WP3).

*Study Size*
Each country included at least 7 (range 7-20) interviewees, including various stakeholders.

*Data analysis*
Content analysis, using pre-defined coding frameworks (WP1 and WP2). Inductive content analysis (WP3). A conceptual coding scheme was developed based on the major themes in a predefined interview guide.

*Results*
232 entities were identified (WP1), of which 81 (34.9%) were involved in development of 252 guidelines relevant to the five disease priority areas. 136 (54.0%) guidelines were included in the WP2 analysis. These covered five countries (no guidelines updated post RMM implementation were found in PT) and all active substances, with most being related to Valproate treatment (24.8%) and fewest to Metformin treatment (15%). Most clinical guidelines were at the national level (76.5%), covered both primary and secondary care (83.2%) and multiple medical specialties (40.9%). RMMs required for the medicinal products included in the case studies were found in 25.0% (34/136). Overall, metformin RMM information was most frequently incorporated (12/24) and Fluorouracil RMM information the least (1/34). In 9 out of these 34 guidelines the specific RMM tool from which RMM information was derived was mentioned.

71 stakeholders were interviewed across the six countries. Five themes were derived:

1) *Actors involved in guideline development and updating* - most often a group of experts appointed by a professional association, university hospital or a governmental entity.

2) *Interviewees' view of clinical guidelines* –should be short and concise, present high-quality evidence and be tailored to the country's healthcare system.

3) *Developing and updating clinical guidelines* - All were based on a mix of national and foreign/international guidelines, except for PT, which used mostly foreign guidelines. Well-defined and reliable timeframe for updating the guidelines was not present in any country.

4) Channels for disseminating guidelines - Except for GR, all countries made guidelines available on central web databases. Large extent of guideline dissemination takes place beyond databases through professional networks (emails, websites or newsletters of professional medical associations, internal clinical and conference discussions).

5) *RMMs in clinical guidelines* - Interviewees involved in guideline development and updating indicated that RMMs were seldom directly considered in their work. They often knew about safety issues dealt with in the RMMs through other channels (such as collegial networks). Reasons given for not embedding RMMs in clinical guidelines could be divided into a) the RMM not fitting the guideline format, b) unrealistic timeline, or c) lack of knowledge.

*Discussion*
This study showed great variability in the number of actors issuing guidelines and number of issued guidelines for the selected disease areas per country. RMM implementation rate in guidelines was rather low. Despite varying ideas of what role a guideline should constitute, it was evident that most interviewees did not see RMMs as necessary or central components in clinical guidelines.

Based on the results, it is recommended in the future to:

- target RMMs only to the relevant HCPs and to tailor a more targeted main message to each HCP group;
- Clinical guidelines should contain direct hyperlinks to their corresponding RMMs;
- The RMMs should preferably be available in easily searchable central databases, either at the NCA or the EMA;
- Clinicians should be educated about the background of and the need for RMMs as well as their role in implementing them.

*Milestones*

Major milestones: “Recruitment of Key informants” (1 January 2023); “Data collection completed” (1 March 2023) and “All results received” (May 2023).