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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

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

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) Specific Contract 01
Framework contractor	EU PE&PV research network
Countries of study	Denmark, Greece, Latvia, Netherlands, Portugal, Slovenia
Objectives	The objectives of this project are to: Identify and describe the key stakeholders, processes, roles and responsibilities for updating clinical guidelines on pharmacological treatment in six European countries, relating to the five disease priority areas and active substances 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 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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Role of different organisations participating in the study

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Table of contents

Title of the study

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

List of abbreviations

C	Study coordinator
CP	Contributing partners
CT	Coordinating team
DK	Denmark
DMP	Data Management Plan
DPD	Dihydropyrimidine dehydrogenase
DPIA	Data Protection Impact Assessment
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GR	Greece
LV	Latvia
NCA	National Competent Authority
NL	The Netherlands
NT	National team
PPP	Pregnancy prevention programme
PT	Portugal
QOREC	COnsolidated criteria for REporting Qualitative research
RMMs	Post-marketing risk minimization measures
SC	Steering committee
SI	Slovenia
UCPH	University of Copenhagen
UU	Utrecht University
WP	Work Package

PART I. PROPOSED METHODOLOGY FOR CONDUCTING THE WORK

1.1. Abstract

This project aims to describe and understand the role of healthcare professional associations and public bodies involved in the production of clinical guidelines and the dissemination of emergent safety concerns. The implementation of product specific risk minimization measures (RMMs) in five disease priority areas into clinical guidelines will be assessed in six EU Member States (Denmark, Greece, Latvia, Netherlands, Portugal, Slovenia).

A multiple-case study design will be applied, using document content analysis of clinical guidelines combined with qualitative semi-structured interviews with key informants from organizations that produce guidelines as well as representatives from national competent authorities (NCAs).

The methodology involves three components which will be divided over three work packages (WPs): WP1 “Mapping of relevant organisations”, WP2 “Document collection and analysis of clinical guidelines” and WP3 “Key Informant Interviews”. Findings will be analysed by country, therapeutic area, special population (pregnancy, elderly) and type of health care provider (primary/secondary care).

The knowledge generated by the three WPs will provide evidence needed to produce recommendations for regulators to engage with healthcare professional bodies and other responsible parties to strengthen the role to be played by clinical guidelines in RMMs implementation, outlining feasible concrete steps that EMA and NCAs could consider.

1.2. Background on the research question

Post-marketing risk minimization measures (RMMs) are crucial for providing patients with safe and effective medicines. However, there is significant complexity to implementing RMMs as they seek to modify knowledge and behaviour of a diverse range of individuals (i.e. patients, consumers, caregivers and healthcare professionals) and often require articulation with structures and organizations (i.e. health authorities, academic research centres, healthcare professional associations and patient organizations).

These stakeholders are involved in healthcare in different roles and may be situated at international, European, national, or subnational levels. Some stakeholders provide clinical guidance for healthcare practitioners on medicines' safety and its content may coincide with that of RMMs. For example, recent research on additional RMMs suggests that medical reference books and clinical guidelines are prescribers' preferred channels for keeping up to date with the safety information about medicines, and that prescribers rarely refer to regulatory documents directly (1, 2). This indicates that rather than relying on regulatory sources for medicines' safety updates, some healthcare professionals rely on recommendations from other organizations that may produce guidance according to different biomedical, legal, economic, bioethical, and sociocultural considerations. As suggested in recent conceptual work on the EU regulatory network engagement with patients and healthcare professionals, the clinical management of medicines safety can be assumed to depend on a 'risk governance network' of multiple, informally connected organizations (3).

Due to the diverse network of organizations involved in providing clinical guidance on medicines safety, a key factor for RMM implementation is the alignment of RMMs with the processes of other organizations and entities and the compatibility of the RMM information with other sources of medicine safety information - in addition to other important factors, such as how risk information and risk communication is generated and communicated. Indeed, literature on risk governance networks suggests that the ability of the governance network to provide the intended outcomes depends on the network's capacity and processes for aligning activities and assessments in situations marked by complexity, uncertainty and ambiguity (4).

RMMs go through their own decision-making regulatory pathway at the EMA level, which is then adopted/translated/operationalized at national level by the national competent authorities, eventually implemented by healthcare professionals, and ultimately reaching patients. Thus, to improve RMM implementation and the engagement of the EU regulatory network with relevant stakeholders, it is necessary to understand how clinical guideline development fits that pathway by identifying the key organizations that issue medicine safety guidance and by characterizing their different remits, level of jurisdiction, and perceived roles and responsibilities.

Clinical guidelines that summarise current medical knowledge and provide evidence-based treatment recommendations for specific therapeutic areas are key documents in the networked governance of medicines safety and RMM implementation. They may be issued by public bodies, professional associations, and academic research centres alike, and they play an important role assisting clinicians and patients in their healthcare decisions (Figure 1). However, the connection between RMMs and clinical guidelines has been underexamined. Although 'best practice' procedures for updating clinical guidelines include processes for identifying triggering events, which determine thresholds for initiating updates and evidence monitoring practices (5), the role and extent of RMMs in such processes remain undocumented. Moreover, recent literature on the standardization of clinical guidelines updating processes suggests that there is significant variation in how guideline developers operate, nationally and according to their organizational remits (6). Thus, in addition to identifying and describing key guidance organizations, an important step to improve RMM implementation is to gain better understanding of how RMMs feature and are incorporated in the development of clinical guidelines at organizational level, and more specifically in their processes for guideline revision.

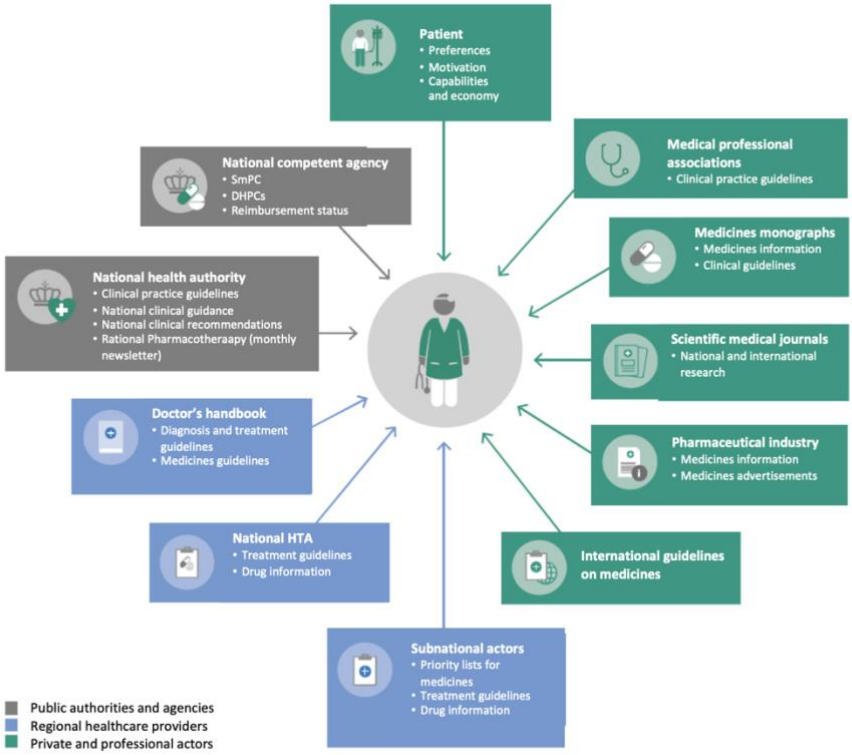

Figure 1. Example of mapping of sources and channels for medicines guidelines for general practitioners in Denmark. Adapted from the National Audit Office (2021).

Whether or not RMMs are adopted into clinical guidelines is also determined by the compatibility and utility of the documents and information provided as part of the RMM (e.g. communication about regulatory actions, product information). The communication channels through which guideline developers receive RMM documents warrant further examination to ascertain whether risk communication measures and materials from regulatory authorities are being consulted and used when updating clinical guidelines.

A number of disease areas and their indicated pharmaceutical products have posed important emergent drug safety risks and therefore required further implementation of RMMs. For this specific project, the focus is on:

- Neurological diseases/Valproate (2018) followed by a pregnancy prevention programme (PPP) (7);
- Infectious diseases/(Fluoro-)Quinolones followed by restrictions in use (2018) (8);
- Inflammatory, autoimmune and cancer diseases/Methotrexate with a measure to prevent dosing errors (2019)(9);
- Diabetes/Metformin (2016) followed by a measure to monitor kidney function of certain patients (10);
- and Cancer diseases/Fluorouracil and related substances guiding to test for lack of dihydropyrimidine dehydrogenase (DPD) before starting fluorouracil, capecitabine, tegafur or flucytosine by injection or infusion (2020) (11).

An overview of the RMMs for these medicinal products can be found in Appendix I. Since these areas have been subject to prominent post-marketing risk communication, and the medicinal products are prescribed by different types of healthcare prescribers, they are appropriate for studying the diffusion of emergent safety information on the national level.

This research, therefore, aims to investigate the role played by national health and regulatory authorities, national clinical guideline developers and (inter)national professional associations in a selected group of European countries when communicating emerging safety information about these five disease areas and active substances to healthcare prescribers. We will focus on identifying the networks and channels through which these organisations receive and disseminate safety information. We will also identify the key factors influencing how individual organisations decide whether safety information is sufficiently serious to act on or disseminate to members and/or the wider public. To explore the variety of diffusion strategies for emergent drug safety information we will focus on a set of disease areas and medicines which have been subject to post-marketing risk communication measures. These medicines are prescribed by different types of health care providers, including general practitioners and specialists. These will be further examined in parallel in six European countries.

The overall aim of the study is to describe and understand the role of healthcare professional associations and public bodies involved in the production of clinical guidelines and the dissemination of emergent safety concerns. From this knowledge we will produce recommendations for regulators to engage with healthcare professional bodies and other responsible parties to strengthen the role to be played by clinical guidelines in RMM implementation, outlining feasible concrete steps that EMA and national competent authorities could consider.

1.3. Objectives

The study aims to describe the processes for updating clinical guidelines with regulatory action and the role of clinical guidelines in the implementation of product specific RMMs using five defined cases of disease priority areas and active substances. The five cases represent medicinal products that are prescribed by a broad selection of health care professionals. These findings will be applied to derive recommendations for strengthening the role of EMA and national competent authorities therein.

In this context, the impact of regulatory actions means investigating the role of clinical guidelines as to the implementation of product specific RMM in five disease priority areas in six EU Member States – Denmark (DK), Greece (GR), Latvia (LV), Netherlands (NL), Portugal (PT) and Slovenia (SI).

Specifically, the objectives of the study are to:

1. ***Identify and describe the key stakeholders, processes, roles and responsibilities for updating clinical guidelines*** on pharmacological treatment in DK, GR, LV, NL, PT and SI, relating to the five disease priority areas and active substances (enumerated in objective 2) with focus on:
    a. Key bodies and organisations responsible for issuing clinical guidelines for the specific therapeutic areas relating to the five disease priority areas and active substances, including national guideline committees and any other responsible bodies at local, national or European level;
    b. Key triggers (e.g. publications, regulatory communications), processes and timelines for updating and publishing clinical guidelines on pharmacological treatment, including communication channels between responsible bodies and organisations and the EU regulatory network institutions relating to the five disease priority areas and active substances;
    c. Key regulatory documents relating to the five disease priority areas and active substances (e.g. public statements on regulatory actions, product information, see Appendix I) and RMM materials used for updating clinical guidelines including their

utility;

d. Key differences in context between countries and therapeutic areas relating to the five disease priority areas and active substances, including enablers and barriers for updating, publication/dissemination and adoption of guidelines in healthcare practice.

2. ***Describe and analyse how product specific RMMs*** for the following disease priority areas and active substances ***have been integrated into relevant clinical guidelines*** in DK, GR, LV, NL, PT and SI, 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:

    a. Neurological diseases/Valproate (2018): Pregnancy prevention programme (PPP);

    b. Infectious diseases/(Fluoro-)Quinolones (2018): Restrictions in use;

    c. Inflammatory, autoimmune and cancer diseases/Methotrexate (2019): Preventing dosing errors;

    d. Diabetes/Metformin (2016): Monitoring kidney function;

    e. Cancer diseases/Fluorouracil and related substances (2020): Test for lack of dihydropyrimidine dehydrogenase (DPD) before starting fluorouracil, capecitabine, tegafur or flucytosine by injection or infusion.

3. ***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, where applicable to the country's context.

1.4. Methodological approach

This qualitative study will employ a multiple-case study design using document analysis of clinical guidelines combined with qualitative interviews with key informants from the organizations/entities that produce guidelines in these specific countries as well as representatives from national competent authorities. The combination of document analysis followed by semi-structured interviews utilizes the capacity of qualitative interviewing to explore subjective, non-observable dimensions of social relations or work processes to supplement and extend understanding of the results from preceding document analysis (12). The use of two sources of data also allows an ongoing validity assessment based on the convergence of information from the two sources (i.e. data triangulation).

Whereas document analysis can capture whether and how regulatory RMMs are incorporated into clinical guidelines, the key informant interviews allow researchers to explore the revision processes that guidelines undergo as well as the perceived roles and responsibilities of the specific organization. The multiple case studies are descriptive in scope and provide means for initial exploration and the identification and characterization of differences between cases (13), such as differences between countries and therapeutic areas, including enablers and barriers for updating and adoption of guidelines in clinical practice.

The study is framed in terms of networked risk governance as this conceptual framework provides a focus on the level of organizations, their guideline developing practices and the network dynamics of organization cooperating across national and regional boundaries and health systems. Alternative theoretical frameworks such as diffusion of innovations model (14) and implementation models were

not selected since they generally emphasize the knowledge and behaviour modifications of the individual clinician while overcoming barriers and enhancing enablers tied to clinical practice (15).

The methodology involves three components which will be divided over three work packages (WP):

WP1. Mapping of organisations

We will undertake a mapping exercise to identify and describe the relevant organizations/entities/national group(s) of experts issuing and updating clinical guidelines for the five priority disease areas in the six included countries. As the case studies represent a selection of medicinal products that are prescribed by different type of health care professionals, it is to be expected that the case studies will provide a representative sample for each country. The national teams will identify relevant organizations/entities/expert groups of clinical specialists in each country. The mapping proceeds 1) identification 2) assessment of eligibility 3) description.

First, organizations will be identified using existing lists and registers, such as the register of officially recognized professional bodies or list of participants for public hearings on clinical guidelines. Multiple lists will be consolidated and supplemented through web-search, through review of publications of clinical guidelines and their authors as well as existing own network of health care professionals. The information will be verified based on results from the EMA request for information to the DRAs in the six Member States[1].

International organizations for these clinical specialties will also be identified. The mapping exercise will involve an iterative approach to searching a range of available online sources and, if necessary, requesting relevant clinical guidelines from the identified organizations. An iterative approach is necessary to ensure that all stakeholders issuing clinical guidance are included, and not only formally established bodies or professional associations. In case material is unavailable or ambiguous, follow-up communication with a stakeholder will be taken.

Secondly, identified organizations will be screened for eligibility. A first draft for inclusion and exclusion criteria has been provided below in Table 1. This list will be verified by each NT, taking into consideration local prescribing practices, and a final overview will be included in the final study protocol.

Table 1. Table of inclusion and exclusion criteria for sample of organizations that develop and disseminate guidelines for the five priority areas.

Inclusion criteria	Exclusion criteria
Public sector organisations that produce clinical guidance for healthcare professionals commonly involved in the treatment and care of the five disease priority areas.	Professional associations, which exclusively serve as trade unions or accreditation regulatory purposes for healthcare professionals.
Professional associations which represent healthcare professionals commonly involved in the treatment and care of the five disease priority areas, namely - general practitioners, gynecologists, psychiatrists, neurologists (Valproate)	Organisations, which disseminate information exclusively at a subnational level (i.e., not for use on national level).

[1] *Request for information for EMA commissioned impact research*, EMA/234019/2022, EMA Pharmacovigilance Office, 19 May 2022

- general practitioners, geriatricians, infectiologists, internists ((Fluoro)quinolones) - dermatologists, gastroenterologists, oncologists, rheumatologists, (Methotrexate) - general practitioners, endocrinologists (Metformin) - oncologists (Fluorouracil and related substances)	
Organisations based in one of the six countries	

Third, eligible organizations will be described according to their features and their role in the development of clinical guidelines (Table 2).

Table 2. Organizational features of guideline developers

Type of organizations	- professional association - interprofessional platform - public authority - non-profit organization
Primary membership/main professional remit	- general practitioners, neurologists, psychiatrists (Valproate) - general practitioners, internists, geriatricians ((Fluoro)quinolones) - oncologists, rheumatologists, gastroenterologists, dermatologists (Methotrexate) - general practitioners, endocrinologists, internists (Metformin) - oncologists (Fluorouracil and related substances)
Guideline development and updating practice	- type guideline developed - updating practice (frequency, scope, governance, literature review practices)

WP2. Document collection and content analysis of clinical guidelines

Guidelines will be retrieved through the organizations' websites and through a domain-specific query using a proprietary search engine (Google Inc.) in which active ingredients and class names of priority medicines will be used as search strings. Secondly, all organisations will be contacted to enquire whether they have produced additional documents in addition to those retrieved. Key informants will also be asked about supplementary guidelines in interviews.

We will review the clinical guidelines (including versions and timelines for updates) that are (publicly) available on/via the websites of the organizations identified in WP1 to determine which guidance, information and/or recommendations relevant to the five case RMMs are available. While these organisations can provide information on medicine safety in various forms (such as position statements, evidence reviews and commentaries, newsletters, bulletins and educational resources), we will restrict document collection to clinical guidelines (and documents that relate strictly to the development and revision thereof, such as manuals) used in clinical practice as they are generally considered the most authoritative documents for clinical guidance.

Quantitative content analysis will be performed on the eligible clinical guidelines. The quantitative analysis provides insights into the proportion of clinical guidelines that have implemented RMMs in our complete sample, on the national level and product level. Guidelines will be analysed using a coding framework designed to extract information relevant to the study. An initial coding manual will be piloted on a subset of eligible clinical guidelines, at least one from each study country, to ensure scope and applicability.

WP3. Key informant interviews

We will undertake in-depth, semi-structured interviews with individuals holding key positions within the relevant guideline issuing organisations and representatives of national competent authorities. Interviewer questions and prompts will attempt to confirm, clarify and address gaps in relation to preliminary findings from the document analysis. In particular, we will investigate how organisations perceive their roles and responsibilities as to the dissemination of safety information, how these are embedded in clinical guidelines and will strive to identify potential factors influencing the decision of individual organisations to act or communicate about a serious safety update via clinical guidelines.

The sequential planning of the WPs uses the capacity of qualitative interviewing to explore subjective, non-observable dimensions of a phenomenon or object to gain a better understanding of the results from preceding content analysis. Whereas content analysis identifies and quantifies salient dimensions of the guidelines, key informant interviews explore the various processes through which the guidelines are produced and updated.

Interview transcripts will be constructed based on audio recording and filed notes taken during interview. The transcripts will be analysed concurrently with conducting interviews in order to make adjustments to the interview guide as new information is acquired. A minimum of 7 participants per country from the interviews is considered sufficient to provide in-depth information and reach saturation for the total number of participants. A purposive sampling method to ensure heterogeneity of participants will be used. The purposeful sampling strategy will be based on organisational mapping (WP1) and document analysis (WP2) with the aim to capture variation in processes, roles and responsibilities for updating clinical guidelines. The researchers will recruit medical specialists across different specialties to diversify the responses obtained and obtain general themes.

Information produced by these three WPs will provide the data needed to accomplish objective 3 of this study, which is to provide recommendations to regulators to engage with healthcare professional bodies and other responsible parties to strengthen the role of clinical guidelines in RMMs implementation.

1.5. Study population

1.5.1. Country

The diffusion of emergent drug safety information will be studied in parallel in six European Member

States. These include Denmark (5.8m inhabitants), Greece (10.4m inhabitants), Latvia (1.9m inhabitants), the Netherlands (17.1m inhabitants), Portugal (10.2m inhabitants) and Slovenia (2.1m inhabitants). Together these countries include an active population of 47.5 million European citizens, which are distributed over the four different geographic regions (North, East, West, South) across the European Union. These countries differ in their social and cultural aspects as well as with regards to the organisation of health systems and provision of care.

1.5.2. Documents and materials

For **WP1 and WP2,** we will study various types of documents and online materials (text) in each of the six countries. These include key regulatory documents, publications, regulatory communications, public statements on regulatory actions, product information, and RMM materials used for updating clinical guidelines and which are produced by stakeholders. This list will be expanded, if needed, based on results from the EMA Request for Information from the six member states. We will assess current versions as well as note the timelines for updates on these materials to assess how these align with the date of RMMs. This will allow us to understand the timeframe from publication of the RMM until implementation into clinical guidelines, next to understanding of the process which will be assessed in **WP3**.

1.5.3. Stakeholders

For **WP3**, we will use qualitative interviews (see 1.10 for approach), including representatives of the following stakeholders in the six countries, to provide a comprehensive overview of processes, facilitators and barriers for integrating information from RMMs in clinical guidelines:

- National competent authorities / Drug regulatory agencies (at least 1 stakeholder per country)
- Public sector organisations and health authorities which produce clinical guidance for healthcare professionals commonly involved in the treatment and care of patients within the five disease priority areas mentioned in objective 2, either nationally or regionally (at least 1 stakeholder per country, when possible)
- Professional associations (or ad-hoc groups) which represent healthcare professionals commonly involved in the treatment and care of patients within the five disease priority areas mentioned in Objective 2, either nationally or regionally (at least 1 stakeholder from each disease priority area per country, see 1.4. WP1)

These stakeholders will be identified and contacted via professional, public and governmental organisations, as well as through the professional network of the researchers involved in this proposal.

1.5.3.1. Stakeholder recruitment (per country)

Stakeholders will be recruited per country as indicated below.

Denmark: Stakeholders from national competent authorities/drug regulatory agencies will be recruited through direct contact with the Danish Medicines Agency (DKMA); stakeholders from public sector organisations and health authorities will be recruited through direct contact from the researchers; health care professionals, including general practitioners and clinical specialists will be recruited through existing networks and professional organizations via direct contact with the respective organisations as well as via newsletters (UCPH has participated in a number of research projects and research networks where medical specialists have been involved, among these general practitioners).

Greece: Stakeholders from national competent authorities/drug regulatory agencies will be recruited

through direct contact with the Greek National Organizations for Medicines (NOM); stakeholders from public sector organizations and health authorities will be recruited through direct contact from the researchers; health care professionals, including general practitioners and clinical specialists will be recruited through existing networks and professional organizations via direct contact with the respective organisations as well as via newsletters (DUTh has longstanding collaborations with the General Hospital of Alexandroupolis, which is one of the most recognized academic hospitals in Greece and plays a significant role in the North-Eastern part of Greece) and primary care units.

Latvia: Stakeholders from national competent authority/drug regulatory agency will be recruited through direct contact with the State Agency of Medicines of Latvia (SAM of Latvia); stakeholders from public sector organisations and health authorities will be recruited through direct contact from the researchers; representatives of professional associations will be recruited through existing networks and professional organizations via direct contact.

Netherlands: Stakeholders from national competent authorities/drug regulatory agencies will be recruited through direct contact with the Dutch Medicines Evaluation board (UU has multiple ongoing collaborations); stakeholders from public sector organisations and health authorities will be recruited through direct contact by researchers based at the National Institute for Public Health and the Environment (RIVM); health care professionals, including general practitioners and clinical specialists will be recruited through existing networks and professional organizations via direct contact with the respective organisations as well as via newsletters (UU has longstanding collaborations with the University Medical Center Utrecht which is one of the largest academic hospitals in the Netherlands and the Netherlands Institute of Health Services Research, which operates a large research network of general practitioners. The Utrecht Pharmacy Practice Network for Education and Research is a part of the UU and operates a large pharmacy practice based research network with links to community and hospital pharmacies ((16)).

Portugal: Stakeholders from national competent authorities/drug regulatory agency will be recruited through direct contact with the National Authority of Medicines and Health Products, I.P. (INFARMED, I.P.), with which the Faculty of Medicine (FMUP) has a direct collaboration. Stakeholders from public sector organisations and health authorities will be recruited through direct contact from the research team. Healthcare professionals, including general practitioners and clinical specialists will be recruited through existing networks and professional organizations/societies via direct contact. FMUP has several collaborations with Hospitals (namely São João University Hospital Center) and primary care units.

Slovenia: Stakeholders from national competent authorities/drug regulatory agencies will be recruited through direct contact with the Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP); stakeholders from public sector organisations and health authorities will be recruited through direct contact by researchers; health care professionals, including general practitioners and clinical specialists will be recruited through existing networks and professional organizations via direct contact with the respective organisations.

1.5.4. Disease priority areas

The disease priority areas and active substances that will be included in this study are:

- Neurological diseases/Valproate (2018): Pregnancy prevention programme (PPP);
- Infectious diseases/(Fluoro-)Quinolones (2018): Restrictions in use;
- Inflammatory, autoimmune and cancer diseases/Methotrexate (2019): Preventing dosing error;
- Diabetes/Metformin (2016): Monitoring kidney function;
- Cancer diseases/Fluorouracil and related substances (2020): Test for lack of dihydropyrimidine

dehydrogenase (DPD) before starting fluorouracil, capecitabine, tegafur or flucytosine by injection or infusion.

1.6. Categories

Information on exposures, outcomes and characteristics such as risk factors is not applicable for this study. This study will include information about the documents identified in WP1 as well as information extracted from documents (document analysis, WP2). In addition, semi-structured interviews will be utilized to explore subjective, non-observable dimensions of social relations or work processes to supplement and extend understanding of the results from preceding document analysis (WP3). This study as such, does not include pre-defined outcomes.

The findings of this study will be discussed and analyzed by geographical region and country (see 1.5.1), by therapeutic area (see 1.5.4), by special population (pregnancy, elderly), by type of health care provider (primary care, secondary care health care provider). National context will be accounted for when analysing and interpreting the results.

Documents identified will be classified as either local, regional, or national and in case of publication by international professional organisations at international level.

1.7. Data sources

Two methods will be used for collecting data in six countries, document analysis of clinical guidelines pertaining to each of the five disease priority areas and active substances and semi-structured interviews with key informants related to the same five cases. Guidance will be prepared to support the mapping of stakeholders and the document analysis.

Semi-structured interviews with key informants will be conducted in the six countries using a topic guide. Interviews will be preferably conducted face-to-face, but if respondents prefer a phone call or online meeting, this will be accommodated. At least 8 key informants will be included per country, including stakeholders from different settings (see 1.5.3., primary care, secondary care, government).

Interview transcripts (text) from semi-structured interviews with stakeholders (representatives of key bodies and organisations) will be produced and will include aspects such as:

- Clarifications and filling gaps in information from documents and online materials
- Utility of RMM materials in guidelines
- Enablers and barriers for updating, adopting, and disseminating guidelines
- Communication channels between responsible bodies and organisations and with EU responsible regulatory network institutions

The topic guide for the stakeholder interviews will cover the following themes: their general role as an organisation; their access to and sources of medicines' safety information; the decisions underpinning the resources they produce (or choose not to develop); and the connections with other organisations. These themes will also be integrated in the content analysis guide. Data saturation will be reached when additional data do not lead to any new emergent themes (17).

The anticipated start date for the mapping (WP1) will be in August 2022 and document analysis (WP2) in September 2022. Semi-structured interviews will be started in October 2022 and are expected to be finished (data saturation reached) in February 2023. The planning accounts for 2 additional months for the project planning in case extended sampling is needed or any delays occur due to local ethical

committee assessments. Anticipated end date of all data collection is February 2023.

1.8. Study size

The sample size will depend on the country (see 1.5.1.) and disease area (see 1.5.4.), but it is estimated that each of the countries will have a range of 7-20 interviewees in total including the various stakeholders (see 1.5.3.).

1.9. Data management

A data management plan (DMP) will be created for the collection, extraction, transformation, loading and analysis of all data. Moreover, we will consider privacy related issues and facilitate a Data Protection Impact Assessment (DPIA). The DMP describes data that will be acquired or produced during research; how the data will be managed, described, and stored, what standards will be used, and how data will be handled and protected during and after the completion of the project. A DPIA is required under the EU General Data Protection Regulation 2016/679 (GDPR) any time a new project is started that is likely to involve "a high risk" to other people's personal information. The DMP and DPIA will be conducted prior to the roll out of the project, once the countries analysis plans are finalized.

Information materials will be obtained through the organizations' website and a domain-specific query using a proprietary search engine (Google Inc.) in which active ingredients and class names are used as search strings. Previous experience showed that relevant documents may be available online but only through search mechanisms. Key informants will also be asked about additional information materials in interviews. All organisations are contacted to ask if they have produced any other relevant documents in addition to those retrieved. Finally, if the websites have a search bar, this will be used to search for each medicinal product and medicinal product class as listed in the safety advisory.

Interview data will either be transcribed manually by the researcher, or by a professional transcriptionist, or with AI modes of transcribing (if available in the native language). The interviews will be transcribed in 'intelligent verbatim', through which all verbal stutters which do not in some way provide useful data are omitted for clarity. Processing of personal data will comply with the EU data protection legislation and in particular the GDPR. Each national team will hold a file containing the personal data (name, contact details and participant code). Only duly anonymized data will be shared with the coordinating team. When anonymization is challenging due to limited number of individuals holding a key stakeholder role, no raw data from the interviews will be shared with the coordinating team. National teams will also be responsible for obtaining, compiling and archiving participants' informed consent forms. The coordinating team will provide a template for an informed consent form in English for interviewees.

1.10. Data analysis

A coding manual will be created by the coordinating team and national teams (see 2.2.) for the document analysis before reading the material to gather the information considered relevant based on the RMM for each of the five disease priority areas and active substances (1.5.4.). This list will then be expanded and amended once a few documents have been reviewed and differences between them identified. Information products will be aggregated according to their source and similarity. The extent to which information products cover the RMM will be graded based on the results of the coding of information products.

The analysis of the semi-structured interviews involves an inductive content analysis based on a close line-by-line reading of the responses and developing a conceptual coding scheme based on the major themes in the interview guide. First five transcripts will be categorized individually by two coders in

each country in native languages. The transcripts will be compared, discussed and if needed a third researchers will be consulted. Coders from all countries will meet prior to the analysis to predefine categories and codes to be used. They meet again to evaluate the categories identified and to write up the results using illustrative quotes.

1.11. Publication and communication of results

The study plan will be delivered in June 2022, the protocol in August 2022, the final report on 1 September 2023 and a study manuscript on 6 November 2023. All these documents will be provided both as Word as well as a PDF file.

The study will be registered in the EU PAS register in June 2022.

The UU (NL) team will take the lead on drafting the preliminary report. The UU (NL) and the UCPH (DK) teams will take the lead on drafting the preliminary manuscript. Both documents will also be reviewed by the consortium partners, and if deemed necessary, by the European Medicines Agency responsible staff. Study results will be published in a peer reviewed journal as well as communicated to key informants participating in the study and their organizations at the end of the project (month 18).

1.12. Reporting of adverse events and suspected adverse reactions

Not applicable

1.13. Limitations of the research methods

It is beyond the methodological scope of the case study approach to produce directly generalizable results. Consequently, the case study of the five disease priority areas and active substances may not be directly generalizable to other therapeutic areas. However, an assessment of transferability of results to other disease areas will be conducted. Although this project includes six countries from different geographical regions in Europe it does not make the study directly generalizable to other European Union Member States in general.

Using organisational websites to collect resources produced by organisations can be limiting and collating the final list of eligible documents for analysis requires an iterative approach. In particular:

a. Websites are not standardised, and it is therefore possible that pages listing appropriate documents are missed. Moreover, some organisations' websites do not have search bar functions, so it is not possible to verify whether every relevant document has been obtained.

b. Some professional associations have a paywall; it is not always possible to know whether relevant documents are accessible to non-paying members.

c. Some organisations may produce documents which are not included on their website (e.g., news items sent out exclusively via email lists).

d. It may be impossible to know whether documents have been removed from the websites.

The document analysis will not qualitatively portray whether and how concerns were included in information; whether they were discussed, mentioned with references, mentioned with conditions etc. As a result, the analysis will not necessarily provide a clear representation of the coverage of medicines safety risks and uptake of RMMs in these documents.

The semi-structured interviews with key stakeholders can have limitations that relate to general

methodological concerns in qualitative data collection and analysis, and additionally the inherent concerns when national teams work independently in their own language when collecting and analysing contextual data. The researchers will incorporate methodological strategies to ensure the trustworthiness of the findings. Such strategies will include addressing credibility, transferability and confirmability by:

- Accounting for personal biases; ongoing critical reflection of methods to ensure sufficient depth and relevance of data collection and analysis;
- Meticulous record keeping, demonstrating a clear decision trail and ensuring interpretations of data are consistent and transparent;
- Seeking out similarities and differences across interviews to ensure that a wide variety of perspectives are represented;
- Including rich and thick verbatim descriptions of participants' accounts to support findings;
- Demonstrating clarity in terms of thought processes during data analysis and subsequent interpretations;
- Engaging and discussing with other researchers in other national teams to reduce research bias;
- Respondent validation: includes inviting participants to comment on the interview transcript and whether the final themes and concepts created adequately reflect the phenomena being investigated;
- Using mixed methods, whereby different methods and perspectives help produce a more comprehensive set of findings (18).

The national teams will reduce bias by validating respondents, making constant comparisons across participant accounts, representing deviant cases and outliers, conducting independent analysis of the data by other team members and comparing that with the remaining national team researchers (19). National team meetings of teams will be held regularly to align data collection, data analysis, and reporting of results (19).

1.14. Protection of human participants

Processing of personal data will comply with the EU data protection legislation and in particular Regulation EU 679/2016 on General Data Protection. Each national team will hold a file (text) containing the personal data (name, contact details and participant code). Only duly anonymized data will be shared with the coordinating team. When anonymization is challenging due to limited number of individuals holding a key stakeholder role, no raw data from the interviews will be shared with the coordinating team. National teams will also be responsible for obtaining, compiling and archiving participants' informed consent forms (word). Audio recordings of interviews will be destroyed after transcribing is done, and the transcripts anonymized to omit details that can lead to identification of the interviewee.

1.15. Ethical aspects

The work performed in WP3 will need approval of local ethical committees in some of the participating countries. Preparation of applications for ethical approval in each country will be initiated as soon as possible in the project but not later than in month 4 and these will be submitted in month 4/5 the latest. To facilitate faster submission, the documents will be submitted in English (to avoid delays due to translations). This allows for 2-6 months processing time at the national level. To account for delays, two extra months have been planned to accommodate extra time needed to conduct interviews.

1.16. Other aspects

Not applicable

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Appendix I: High level information on Risk minimisation measures

The table below provides a high-level overview of the risk minimization measures that were implemented for the five products.:

- Neurological diseases/Valproate (2018) followed by a pregnancy prevention programme (PPP) (7);
- Infectious diseases/(Fluoro-)Quinolones followed by restrictions in use (2018) (8);
- Inflammatory, autoimmune and cancer diseases/Methotrexate with a measure to prevent dosing errors (2019)(9);
- Diabetes/Metformin (2016) followed by a measure to monitor kidney function of certain patients (10);
- and Cancer diseases/Fluorouracil and related substances guiding to test for lack of dihydropyrimidine dehydrogenase (DPD) before starting fluorouracil, capecitabine, tegafur or flucytosine by injection or infusion (2020) (11).

The study protocol (Deliverable 2) will include a complete detailed overview of the content/specific measures taken for each RMM.

Risk minimisation measure	Valproate	(Fluoro-) Quinolones	Methotrexate	Metformin	Fluorouracil & related substances
SmPC updates	X	X	X	X	
Visual reminder on packaging	X		X		
Healthcare professional guide/checklist	X		X		
Patient card	X		X		
Patient guide	X				
Annual risk acknowledgement form	X				
Direct HPC (it is noted the DHPCs are disseminated by the marketing authorisation holders, however NCAs could disseminate them further)	X	X	X		X
Suspension		X (of nalidixic acid, flumequine, pipemidic acid and cinoxacin)			
Aim of RMM	To minimise teratogenic risks through a pregnancy prevention programme	To minimise the risk of long-lasting, disabling and potentially irreversible adverse reactions (including tendon, muscle and joint disorders, neurologic and psychiatric disorders)	To minimise the risk of medication errors and adverse reactions associated with overdose, the following RMM were introduced for methotrexate (for oral and parenteral formulations with at least one indication requiring intake only once a week)	To minimise the risk of lactic acidosis while maintaining the treatment option for patients with only moderately impaired kidney function	To minimise the risk of severe toxicity by pre-treatment testing to identify dihydropyrimidine dehydrogenase (DPD)-deficient patients

PART II. PROPOSED ORGANISATION OF WORK

2.1. Timelines of key deliverables

The study planning presented in this deliverable (D1 Preliminary Study Plan) is based on the timelines agreed upon in the Specific Contract 01 implementing Framework Contract EMA/2020/46/TDA/L4.02 Considering the holiday periods, revised timelines in Table 3 are proposed.

Table 3: Timeline of key deliverables

Timeline	Deliverable
19 April 2022	Start of project
3 June 2022	D1: Preliminary study plan
1 September 2022	D2: Study protocol
1 September 2023	D3: Study Report
6 November 2023	D4: Manuscript

2.2. Teams and people involved

The consortium has installed a steering committee in which all tenderers are represented by 1 person and an alternate person (back-up). The steering committee is chaired by the coordinator of the consortium (Universiteit Utrecht/Utrecht University) who is responsible for organization of meetings (Face-to-Face, tele- and/or web-conferencing), including agenda's and meeting minutes. An alternate coordinator (back-up) has also been installed (University of Copenhagen).

The **Coordinating Team** (CT) is composed by:

- Dr. Helga Gardarsdottir, Associate professor, Utrecht University, Utrecht, The Netherlands (lead)
- Prof. Anna Birna Almarsdóttir, Research leader, Copenhagen, Denmark (back-up)

The **Contributing Partners** (CP) include both the **National Teams** (NTs) and **Other Contributors**.
The NTs are represented in the Steering Committee by:

- Denmark: Prof. Anna Birna Almarsdóttir, Research leader, Social and Clinical Pharmacy, Dr. Mathias Møllebæk, Post-Doctoral Researcher, Copenhagen Centre for Regulatory Science, University of Copenhagen.
- Greece: Dr. Christos Kontogiorgis, Assistant Professor, Laboratory of Hygiene and Environmental Protection, Department of Medicine,Democritus University of Thrace, Alexandroupolis,
- Latvia: Dr. Elita Poplavska,Assistant Professor, The Institute of Public Health of Riga Stradins University.
- Portugal: Dr. Inês Ribeiro Vaz, Coordinator, Unidade de Farmacovigilância do Porto, Faculdade de Medicina da Universidade do Porto.
- The Netherlands: Dr. Helga Gardarsdottir, Associate professor, Dr. Ellen Koster, Associate professor, & Prof.dr. Marieke De Bruin, professor of Regulatory Science, Division Pharmacoepidemiology, Utrecht Institute for Pharmaceutical Science, Utrecht University.
- Slovenia: Prof. Mitja Kos, Head of the Department & Assist. Dr. Ana Kodrič, Department of Social pharmacy, University of Ljubljana, Faculty of pharmacy, Ljubljana.

The Other contributors are represented in the Steering Committee by:

- The Netherlands: Dr. Teresa Alves, Researcher & Dr. Ingrid Hegger, Expert Researcher, the Centre for Health Protection, National Institute for Public Health and the Environment.
- The Netherlands: Prof.Dr. Miriam Sturkenboom, Department Head, Department of Data Science and Biostatistics, Dr. Carlos Durán, Dr. Judit Riera, Dr. Fariba Ahmadizar, UMCU

The Study Coordinator (C) is:

- Dr. Helga Gardarsdottir, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, The Netherlands.

The Steering Committee (SC) is composed by:

- one representative per country and one alternate per country (back-up);
- chair / vice-chair: SC and alternate.

The Coordinator of the consortium is:

- Prof. Olaf Klungel, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, The Netherlands.

The Project Manager of the EU PE&PV research network and the administrative contact for this Specific Contract is:

- Dr. Satu Johanna Siiskonen, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, The Netherlands.

2.3. General approach for the organisation of the study

An online kick-off meeting was organised by the Study Coordinator (C) in **May 2022**, during which all those involved in the project became familiar with their counterparts in other countries and the study coordinator. The CT lead (see 2.2.) is responsible for hosting and preparing the content discussions, which will cover communication aspects, data management, and compliance with timelines and feedback procedures. An email-distribution list will be established to share information among all those involved, and telephone and online meetings are scheduled on a regular basis to oversee project implementation and progress. A data management plan will also be developed.

During May 2022, the development of the study plan was initiated by the CT lead and CP were invited to review and provide input. A similar procedure will be implemented for the study protocol in **June-August 2022**.

In June, a standard format to prepare the overview and timeline will be drafted by the SC and agreed upon by the CT and CPs. In addition, drafting of the study specific key tools will be initiated, including the mapping strategy and content analysis plan (led by UU) as well as the key informant recruitment plan including recruitment materials and interview guide (led by UCPH). All materials will be reviewed by the CT and CPs.

The ***preliminary study plan*** (D1) will be submitted as soon as possible after study start, but not later than due date, July 1 2022. Writing of the ***study protocol*** (D2) will be initiated in June and finalized and submitted with all accompanying materials not later than September 1st 2022. The protocol will also be registered in the EU PAS register. **Between August and September 2022**, following acceptance of the study protocol by the EMA, national teams will initiate local ethical committee approval procedures.

The preparatory work for **WP1**, which involves mapping the relevant organizations issuing and updating clinical guidelines for the five disease areas will start late August, after the summer holidays, and document collection will be initiated by the NTs in each participating country. These overviews will provide the information needed for the content analysis that takes place in **WP2**.

All National Teams will be invited to start recruiting key informants **from October 2022 onwards**, which is the most limiting factor for a successful implementation. The CT will schedule regular online meetings to receive feedback on project progress, including possible challenges related to recruitment. National Teams will conduct the interviews between **October 2022 and February 2023**. To account for delays due to ethics assessments, recruitment or interview scheduling, two extra months have been added to the planning to allow for reaching data saturation. Although adding these two months will impact the time available for analysis the data, each NT has two months to finalize analysis after the extended deadline.

Between January and June 2023, each NT is expected to analyse their local data. The CT will compile those results and compare results across countries. All the analyses are expected to have been delivered to the CT by **1 July 2023**.

The CT lead will take the lead on drafting the preliminary report (**1 April – 1 August 2023**). The preliminary manuscript will be drafted in parallel by CT back-up. Both documents will also be reviewed by the CPs before they are submitted to the European Medicines Agency.

The timeline described below (GANTT chart) provides an overview of the study chronology together with main tasks, including responsible teams, identifying also the main milestones (indicating project progress) and deliverables in accordance with the proposed EMA timeline (see also 1.1.). It is subject to adjustments, as necessary.

2.4. Plan and timelines for deliverables

Timeline	2022								2023									
	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct
Project inception																		
Organization kick-off meeting	C																	
Kick-off meeting	CT																	
Installation Steering Committee	CT																	
Set-up of consortium communication and project meeting schedules	CT																	
Development of preliminary study plan	CT																	
Study plan delivery		D1																
Development of data management plan	CT	CT																
Development of mapping strategy	CT	CT																
Development of content analysis plan	CT	CT	M1															
Development of key informant reqruitment plan & materials		CT	CT															
Development of interview guide		CT	CT	M2														
Writing and reviewing of protocol		CT	CT	CT														
Protocol delivery				D2														
Input and review of project plans and materials	CP	CP	CP	CP														
Registration of study and protocol in EU PAS Register				C														
Monitoring progress	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Data collection and analysis																		
Mapping of organisations				NT	NT	M3												
Document collection					NT	NT												
Content analysis of guidelines					NT	NT	NT											
Seeking Local Ethical Committee Approval					NT	M4												
Recruitment of key informants						NT	NT	M5										
Interviews in 5 countries						NT	NT	NT	NT	M6								
Extended sampling/ethics assessment delays											NT	NT						
Data analysis interview									NT	NT	NT	NT	NT	M7				
Monitoring process	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT
Reporting																		
Drafting preliminary report												CT	CT	CT	CT			
Review of draft report													CP	CP	M8			
Delivery of final report																D3		
Drafting manuscript													CT	CT	CT	CT	CT	
Manuscript review															CP	CP	M9	
Manuscript delivery																		D4

Timing, M1-M18 = 18 months

Milestones:

Month 3: Milestone 1: Content analysis framework ready to be implemented
Month 4:Milestone 2: Interview guide ready
Month 5: Milestone 3: Local ethical committee applications submitted in all participating countries
Month 5: Milestone 4: National overviews of relevant organizations issuing and updating clinical guidelines for the five disease areas
Month 7: Milestone 5: Recruitment of key informant completed
Month 9: Milestone 6: Data collection completed
Month 14: Milestone 7: Coordinating team receives all results from NTs
Month 15: Milestone 8: Draft Report has been written and agreed upon by CPs
Month 17: Milestone 9: Draft Manuscript has been written and agreed upon by CPs

Deliverables:

Month 2: D1: Deliverable 1 Preliminary Study Plan
Month 4: D2: Deliverable 2 Study Protocol
Month 16: D3: Deliverable 3 Study Report
Month 18: D4: Deliverable 4 Manuscript

People involved:

CT: Coordination team
NT: National teams
CP: All Partners

2.5. Communication with EMA and third parties

Liaison with the European Medicines Agency is ensured by the coordinator of the consortium, Prof. Olaf Klungel, since he is the principal contact with regards to the Framework service contract. Meetings between the Agency to discuss the study will be organized at critical moments during the contract (start of contract, final study protocol, results of analysis, study report). These will be attended by the members of the Coordinating team, as deemed necessary. More frequent meetings can be organized at request of the Agency or the consortium.

PART III. QUALITY CONTROL

3.1 General approach to quality management and control

Quality management system for the Coordinator of the consortium (Utrecht University): The Division of Pharmacoepidemiology & Clinical Pharmacology works according to a quality management system based on ISO 9001 principles. The quality management system is system and process oriented and based on continuous improvement. All primary and secondary processes within the division are included in the quality system, from creating research proposals, through managing PhD projects to data management, reporting and archival. The system is based upon standard operating procedures implemented throughout the division with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, as well national and international guidelines and legislation concerning data-handling and privacy issues.

Research Quality Assessment (Utrecht University): In 2017 (evaluation period 2010-2015), the

research quality of the Utrecht Institute for Pharmaceutical Sciences (UIPS) which includes the division of Pharmacoepidemiology & Clinical Pharmacology was assessed by an independent international peer review committee according to the Standard Evaluation Protocol 2015-2021 (SEP) for Research Assessment in the Netherlands. The overall conclusion of the committee was that the division was one of the top ten if not the top five worldwide and that excellent scientific work was being done, grounded in real-world problems and with a notable impact on the regulatory world, particularly in Europe. The scores received were all excellent for the Quality, Relevance to Society and Viability criteria. This report is available upon request.

A number of studies conducted by the Utrecht University research group and the EU PE&PV Research Network are registered in the EU PAS Register (EUPAS32405, EUPAS32408, EUPAS39798, EUPAS42467, EUPAS44970, EUPAS31095, EUPAS39289, EUPAS39361, EUPAS37273, EUPAS39370, EUPAS40489, EUPAS40317, EUPAS39438, EUPAS39798, EUPAS40404, EUPAS42504) and two have been awarded with the ENCePP Study Seal (EUPAS16014, EUPAS31001).

3.2. Specific aspects of quality management and control

Tailored quality control: The CT will rely on a peer review model of consultation to inform and direct the study deliverables using the timeline above to monitor and benchmark progress by which outcomes are assessed. In order to establish a quality control system specific to this study, we have identified key milestones (see 2.4) which will attest to the efficient roll-out and continuity of the service.

These are, respectively:
Aug 2022: Milestone 1: Content analysis framework ready to be implemented
Sep 2022: Milestone 2: Interview guide ready
Oct 2022: Milestone 3: Local ethical committee applications submitted in all participating countries
Oct 2022: Milestone 4: National overviews of relevant organizations issuing and updating clinical guidelines for the five disease areas
Dec 2022: Milestone 5: Recruitment of key informant completed
Feb 2023: Milestone 6: Data collection completed
Jun 2023: Milestone 7: Coordinating team receives all results from NTs
Jul 2023: Milestone 8: Draft Report has been written and agreed upon by CPs
Oct 2023: Milestone 9: Draft Manuscript has been written and agreed upon by CPs

In addition, we have also provided below a list of verifiable indicators along the timeline:

Specific Task	Standard Verifiable Indicators
Kick-off meeting	Agenda Meeting Minutes Action Points Agreed Timeline
Development of content analysis framework	Draft content analysis framework
Pilot testing of interview guide	Pilot interview guide and final version of interview guide
Recruitment of key informants	Number of stakeholders recruited per country
Interviews of key informants	Interview/guides
Drafting preliminary report	Preliminary Report
Review of draft report	Responses received

Drafting manuscript	First draft manuscript
Manuscript review	Responses received

Overarching quality control: Several quality assurance measures are in place that will be maintained in the proposed consortium. We will take into consideration existing guidelines for qualitative research (such as QOREC) and apply them as appropriate. Additionally, we will share approaches to data collection and analysis. Deliverables are peer-reviewed by an advisor (at least one member of the consortium that is not leading nor actively participating in the study). A declaration of competing interests will be required from all those acting as principal investigators or co-investigators. These will be further presented to the Steering Committee who will then assess and act upon any potential conflict of interest. In addition, we aim to comply with ENCePP standards by registering our study on the European Union electronic Register of Post-Authorisation Studies (EU PAS).

3.3. Risks and mitigations strategies

The coordinating team will provide the EMA with regular updates on the project progress and inform the EMA staff in advance if any delays are foreseen so that scheduled EMA response and review times can be adjusted accordingly. For this purpose, monthly communications (either via email or Teams when needed) will be scheduled.

Foreseen external delays, methodological or technical problems and their proposed counter measures:

Risks	Mitigation strategies
Delays in ethical approval	Specific requirements for research and data protection will be addressed at the protocol stage, taking into account national and European setting All documents will be submitted in English, when possible, to avoid delays related to translation times. In Greece, the Bioethics committee requires submitted materials to be translated documents in Greek. Assessment by the Bioethics committee takes one month. A precise time plan will be established to minimize impact on study planning.
Development of interview guide	Given the tight study timeline, pilot testing of interview guide in all countries is not feasible. The interview guide will be translated into six different national languages. An independent review of each translated interview guide will be performed by a native speaker not involved in the study team. In this manner, we aim to identify culture- and language-specific issues to enable adjustment as needed.
Translation of interviews/excerpts	Translations of interviews/excerpts from national languages back to English for data analysis/reporting will be performed by at least two people involved to ensure quality of translations.
Unsuccessful recruitment of key informants	Recruitment of key informants, especially clinical specialists, might prove difficult to recruit in less populated countries, where the number of specialists is reduced. The solution will then include an oversampling of other stakeholders meeting our inclusion criteria

Delays due to illness, absences of a national team members	The national teams are crucial for the study project, as these are responsible for local data collection. To assure continuation of work, each national team has at least two team members and most have more than two team members.
Data leak/loss	To minimize the risk of data leak personal information will not be collected; interview recordings will be deleted immediately after transcripts are made. Transcripts will be stored in a cloud-based joint workspace of Utrecht University to avoid accidental loss.

PART IV. ANY OTHER BUSINESS

Not applicable.

PART V. SUPPLEMENTARY DOCUMENTS

5.1. List of Supplementary documents

- *Request for information for EMA commissioned impact research. Implementation of EU risk minimisation measures for medicinal products in clinical guidelines*, EMA/234019/2022, EMA Pharmacovigilance Office, 19 May 2022.