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

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

Deliverable 2: Study protocol

EU PE&PV research network

EUPAS47588

Version 4.2

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 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: Identify and describe the key stakeholders, processes, roles and responsibilities for updating clinical guidelines on pharmacological treatment in six European countries 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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Document version

NAME	DATE	VERSION	DESCRIPTION
Consortium	June 2022	1.0	Study protocol
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UU, UCPH	31 August 2022	4.0	Final version for submission
Consortium	9 October 2022	4.1	Revised implementing EMA comments
Consortium	2 November 2022	4.2	Revised implementing EMA comments

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1. Title of the study

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

2. List of abbreviations

C	Study coordinator
CP	Contributing partners
CT	Coordinating team
DHPC	Direct Healthcare Professional Communication
DK	Denmark
DMP	Data Management Plan
DPD	Dihydropyrimidine dehydrogenase
DUTH	Democritus University of Thrace
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GIN-UGWP	Guidelines International Network's Updating Guidelines Working Group
GR	Greece
LV	Latvia
MS	Member State
NCA	National Competent Authority
NL	The Netherlands
NT	National team
PPP	Pregnancy prevention programme
PT	Portugal
QOREC	COnsolidated criteria for REporting Qualitative research
RFI	Request for information
RMM	Post-marketing risk minimization measure
SC	Steering committee
SI	Slovenia
TA	Therapeutic Area
UCPH	University of Copenhagen
UIPS	Utrecht Institute for Pharmaceutical Sciences
UU	Utrecht University
WP	Work Package

3. Responsible parties

Organisation	Key person	Role(s)	Status
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University of Copenhagen (UCPH) Nørregade 10, 1165 Copenhagen K Denmark	Prof. Dr. Anna Birna Almarsdóttir Dr. Mathias Møllebæk	Co-Investigator	Subcontractor to Utrecht University Coordinating Team (CT) National Team (NT) Denmark
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4. Abstract

Rationale and background
Post-marketing risk minimization measures (RMMs) upon regulatory request 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 and often require articulation with structures and organizations. 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. Although 'best practice' procedures for updating clinical guidelines include processes for identifying triggering events, which determine thresholds for initiating updates and evidence monitoring practices, the role and extent of RMMs in such processes remain undocumented.

Research question and objectives
This project aims to describe and understand processes for updating clinical guidelines and the role of healthcare professional associations and public bodies involved in the production of clinical guidelines and the dissemination of emergent safety concerns.

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 six EU Member States (Denmark, Greece, Latvia, Netherlands, Portugal, Slovenia).

2. *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.

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.

Study design
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, type of population and type of health care provider.

Population
For WP1 and WP2, we will study various types of documents and online materials (text) in each of the six countries. For WP3, we will include representative key informants in the six countries, including stakeholders from national competent authorities, public sector and health authorities, professional associations and expert groups.

Variables
This study will include information about the entities that issue, develop and/or update clinical guidelines identified in WP1 (domains: general information, membership, guideline development), as well as information extracted from clinical guideline documents (document analysis, WP2 – domains: general information, population, target audience, therapeutic area, information on RMM). 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).

Data Sources
Documents and online materials (text) for WP1 and WP2. Transcripts from semi-structured interviews with key informants for WP3.

Study Size
The sample size will depend on the country, but it is estimated that each of the countries will have a range of 7-20 interviewees in total including the various stakeholders.

Data analysis
Content analysis will be conducted using pre-defined coding frameworks (WP1 and WP2). The extent to which information products cover the RMM will be graded based on the results of the coding of information products. Interview transcripts (text) from semi-structured interviews (WP3) will be produced. The analysis of these will involve 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 an interview guide.

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

5. Amendments and updates

Date	Protocol version	Description

6. Milestones

An overview and timeline of project elements, including key milestones and deliverables, in accordance with the accepted Preliminary Study Plan (deliverable D1) is presented in Table 1 and Figure 1. Updates on progress will be communicated during bimonthly meetings between the research team and EMA. In addition, EMA will be informed about the status of milestones in January (recruitment of Key informants & interim results from content analysis), March (data collection completed) and August 2023 (all results received) as these represent critical moments for the project progress.

Table 1: Timeline of key milestones & deliverables

Milestones (M) and Deliverables (D)	Planned date	Actual date
Start of project	NA	19 April 2022
D1: Preliminary study plan	1 July 2022	3 June 2022
M1: Content analysis framework ready to be implemented	1 August 2022	1 August 2022
M2: Interview guide ready	1 September 2022	1 September 2022
D2: Study protocol	1 September 2022	1 September 2022
M3: Local ethical committee applications submitted in all participating countries	1 November 2022	
M4: National overviews of relevant organizations issuing and updating clinical guidelines for the five disease areas	1 November 2022	
M5: Recruitment of key informants completed	1 January 2023	
M6: Data collection completed	1 March 2023	
M7: Coordinating team receives all results from national teams	1 July 2023	
M8: Draft report has been written and agreed upon by consortium	1 August 2023	
D3: Study Report	1 September 2023	
M9: Draft manuscript has been written and agreed upon by consortium	1 October 2023	
D4: Manuscript	6 November 2023	

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

Figure 1: Overall project timeline. CT: coordination team (UU, UCPH), NT: national teams (UU, UCPH, RSU, UP, UL, DUT), CP; all partners

7. Rationale and background

Post-marketing risk minimization measures (RMMs) upon regulatory request 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, educational and 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 implementation processes with the processes of the different organizations and entities and the compatibility of the RMM information with other sources of medicine safety information. In addition, other important factors include how risk information and risk communication are generated and communicated and the time ensued between the announcement of new safety information and the implementation of measures in practice. 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 2). 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 the organizational level, and more specifically in their processes for guideline revision.

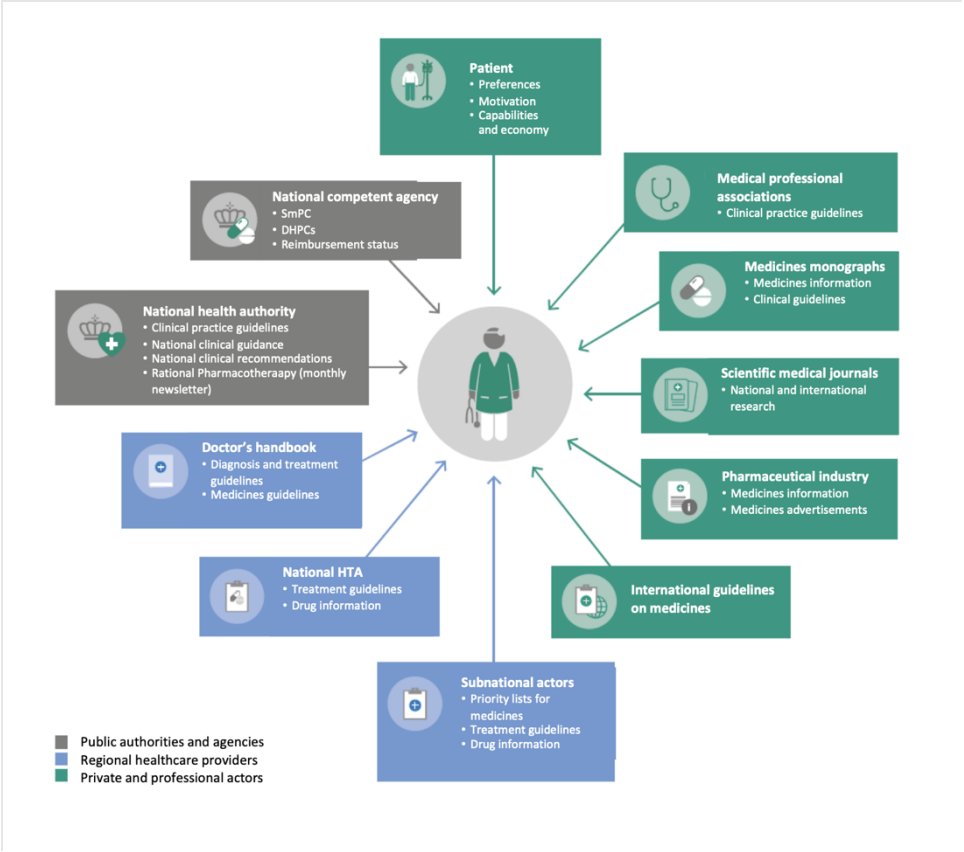

Figure 2. Example of mapping of sources and channels for medicines guidelines for general practitioners in Denmark. Adapted from the National Audit Office (2021).

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.

Several 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 (2019) (8);
- Inflammatory, autoimmune and cancer diseases/Methotrexate with a measure to prevent dosing errors (2019)(9);
- Chronic disease: 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 regard various types of diseases and

therefore diverse healthcare prescribers, they are appropriate to study the diffusion of emergent safety information at 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 or expert groups in a selected group of European countries spread across Europe and with differences in healthcare systems when communicating emerging safety information. We will focus on identifying the networks and channels through which these entities receive and disseminate safety information. We will also identify the key factors (enablers and barriers) influencing how individual entities decide whether safety information is sufficiently serious to act on or disseminate to members and/or the wider public. This includes assessment of the key elements of the risk minimization measure that are included in new or updated clinical guidelines. To explore the variety of diffusion strategies for emergent drug safety information, we will focus on a set of five disease areas and medicines which have been subject to post-marketing risk communication measures. These medicines are prescribed and or dispensed by different types of health care providers, including general practitioners, specialists, nurses and pharmacists. These will be further examined in parallel in six European countries, resulting in 30 case studies (five per country) in total.

The overall aim of the study is to describe and understand processes for updating clinical guidelines and 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.

8. Research question and objectives

The study aims to describe the key elements of risk minimisation measures included in clinical guidelines, processes for updating clinical guidelines with regulatory action and the role of clinical guidelines in the implementation of product specific RMMs. 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 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 issuing clinical guidelines on pharmacological treatment in DK, GR, LV, NL, PT and SI. Focus will be on:

a) Key bodies and organisations responsible for issuing clinical guidelines, 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;

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 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.

Product specific RMMs (objective 2) will be used as a starting point to create a nationally representative overview for objective 1.

2. Describe and analyse how product specific RMMs for the disease priority areas and active substances (see section 7) ***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, time to integration, publication/dissemination, and adoption of guidelines in healthcare practice.

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.

9. Research methods

9.1. Study design

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. Case study is a research design that has been widely used in social science research. In this study, we use a sub-type that is a multi-case design - in contrast to a single case design - which includes multiple cases selected according to a case selection strategy that aligns with the aims and objectives of the research. This study employs a diverse case selection strategy which is characterized by the selection of a set of cases intended to represent the full range of values along at least two dimensions (12). In this study the two dimensions are the five RMMs/TAs and the six countries outlined above. The purpose of selection strategy is to represent a maximum range of geographical diversity across EU members countries as well as maximum range of diversity of stakeholders across therapeutic areas that may be subject to RMMs. By contrasting and comparing the cases in the multi-case design, we learn about commonalities and variations. We also illuminate the potential reasons for these variations. The diverse-case selection strategy enables an in-depth of understanding of RMM implementation including its variation across the EU, which, in turn, allows for the identification of problems to deal with through research or regulatory intervention.

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 (13). The use of two sources of data also allows an ongoing validity assessment based on the convergence of information from the two sources.

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 (14), 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 organizations cooperating across national and regional boundaries and health systems (14-16).

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 organisations/entities/national group(s) of experts issuing and updating clinical guidelines. Identification of organizations/entities/national group(s), hereafter called "entities", will be identified by the national teams and will occur through five case studies. The five case studies (see section 7) represent a selection of medicinal products that are prescribed and dispensed by a broad range of health care professionals, from primary and secondary care as well as nurses and pharmacists. It is therefore to be expected that the case studies will provide a clear overview of RMM uptake in clinical guidelines for each country. An overview of entities that are involved issuing and updating clinical guidelines for each country will be produced. Clinical guidelines are defined as guidelines that summarise current medical knowledge and provide evidence-based treatment recommendations for specific therapeutic areas. This does not include drug monographs or drug information that is copied directly from the regulatory source (product information/label) without any clinical context or where no editing processes are applied (standards, website such as Farmacotherapeutisch Kompas (NL) and pro.medicin.dk – information om medicin (DK)).

In each country, the mapping proceeds by the following steps: 1) identification, 2) assessment of eligibility, and 3) description. The first step is identifying entities, extracting key information that allows for assessment of eligibility (WP1). In case of eligibility, these will proceed to WP2 and WP3 (see figure 3).

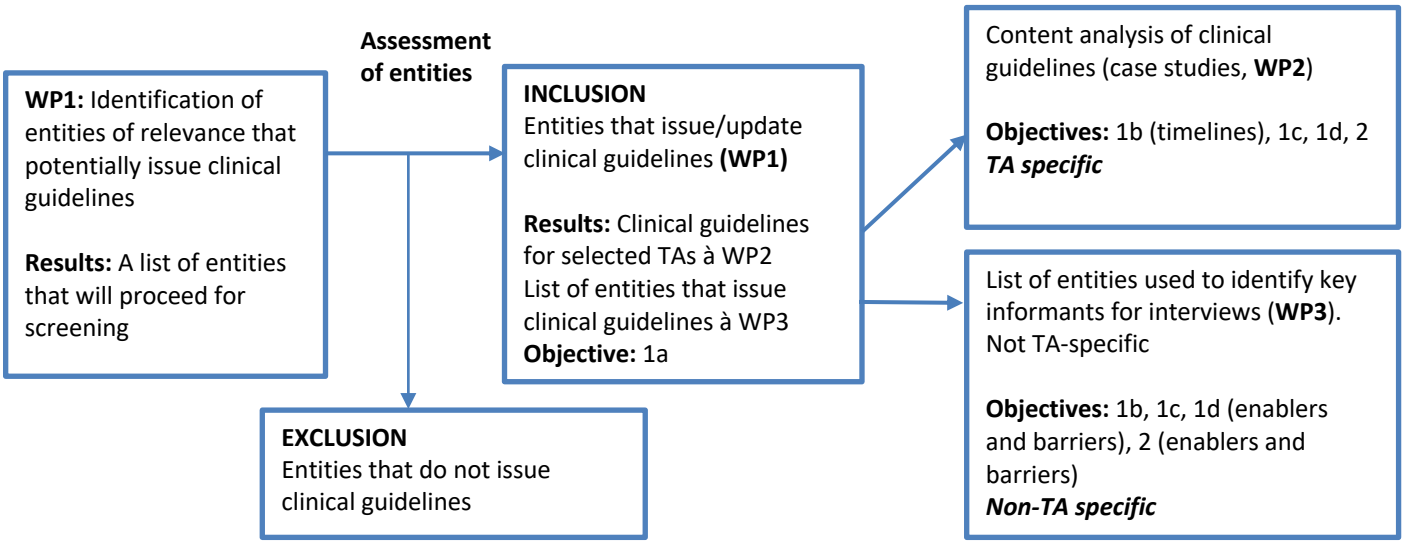

Figure 3. Process overview for mapping of entities that issue/update clinical guidelines and assessment of eligibility of clinical guidelines and key informants for inclusion in WP2 and WP3.

First, entities 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. The information received from the MS will serve as a starting point (see EMA request for information[1] (, Appendix III, page 35). Multiple lists will be consolidated and supplemented through web-search for clinical guidelines, through review of publications of clinical guidelines, including in national clinical journals, and their authors as well as existing own network of health care professionals.

The mapping exercise will involve an iterative approach to searching a range of available online sources for validation purposes, applying both entity-based searchers as well as guidelines-based search (see domain specific query in WP2) as the latter might not always be captured through entity search. When necessary, we will requesting relevant clinical guidelines from the identified entities. An iterative approach is necessary to ensure that all stakeholders issuing clinical guidance are included, and not only formally established bodies or professional associations. This includes a snowballing approach where identified entities will be asked to provide information on other entities that produce clinical guidelines in their country. In case material is unavailable or ambiguous, follow-up communication with a stakeholder will be taken (by email or telephone).

Secondly, identified organizations will be screened for eligibility (see figure 3). An example of potential inclusion and exclusion criteria has been provided below in Table 2 which will align with the tender specification of identifying “Key bodies and organisations responsible for issuing clinical guidelines for specific therapeutic areas, including national guideline committees and any other responsible bodies at local, national or European level”. We define trade unions as organisation of workers intent on "maintaining or improving the conditions of their employment. Their focus is mainly on wages and employee benefits. We defined accreditation bodies as authorative bodies that give formal recognition of the competence of a certification body to provide certification services against a specified standard. For both we do not consider it likely that these issue clinical guidelines, and these are therefore excluded. Local level guidelines, such as single hospital-based guidelines will not be included. Only when no national or regional level guidelines are available, will we proceed with identifying and screening on the supranational level, which could be applicable for countries with lower number of inhabitants. In interviews in WP3, key informants will also be asked about supplementary organizations. Organizations that emerge in interviews in WP3 will be added to the mapping and analysed accordingly.

Table 2. Potential 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 and/or group of experts that produce clinical guidelines 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 for the purpose of accreditation of healthcare professionals.
Professional associations which represent healthcare professionals commonly involved in the treatment and care of the five disease priority areas (including those reported by MS RFI), namely general practitioners, gynaecologists,	Organisations, which disseminate information exclusively at a subnational level (i.e., not for use on national level). This includes for example specific hospital-based prescribing guidelines/formularies. These will only be included when no national level or regional level dissemination is available in the specific country.

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

Inclusion criteria	Exclusion criteria
psychiatrists, neurologists (Valproate) general practitioners, geriatricians, infectiologists, internists, orthopaedist, neurologist, rheumatologist (Fluoroquinolones) dermatologists, gastroenterologists,general practitioners , rheumatologists, (Methotrexate)* general practitioners, endocrinologists (Metformin) oncologists (Fluorouracil and related substances) Nurses Pharmacists	
Organisations based in one of the six countries	

* It is acknowledged that methotrexate is prescribed by oncologists, however this category of prescribers is less relevant with regards to the implementation of the RMM included in this study.

Third, eligible organizations will be described according to their features, including the type of entity, level of operation and information on publication of clinical guidelines (see coding framework WP1).

WP2. Document collection and content analysis of clinical guidelines

Clinical guidelines will be retrieved through the (healthcare) professional organizations' websites and through a domain-specific query using a proprietary search engine (Google Inc., PubMed) in which active ingredients, class names and indications of use for priority medicines will be used as search strings in combination with terms linked to clinical care e.g., guideline, treatment, care. When guidelines are behind a paywall or access is restricted to members, the issuer will be approached by telephone or e-mail to ask for (free) access. Secondly, all organisations that issue guidelines (WP1) will be contacted to enquire whether they have produced other documents in addition to those retrieved (including prior versions). Key informants will also be asked about supplementary guidelines in interviews (in WP3). Guidelines that emerge in interviews in WP3 will be added to the compilation of guidelines and analysed accordingly.

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 (see definition in WP1 page 15). A search timeframe will be applied based on the timelines indicated for approval dates of the RMM in each Member State (see Appendix II, page 33). The duration of time (number of months) from national implementation to implementation of RMM in clinical guidelines will be determined.

Guidelines will be analysed using a coding framework designed to extract information relevant to the study (see coding framework WP2). An initial coding framework was piloted to ensure scope and applicability. This included a pilot test on a subset of eligible clinical guidelines as well as review by consortium members and the EMA.

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 on or communicate about a serious safety update via clinical guidelines.

The sequential planning of the WPs (see figure 2) 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 the interview. The transcripts will be analysed concurrently with conducting interviews in order to adjust the interview guide as new information is acquired. A purposive sampling method to ensure heterogeneity of participants will be used. The researchers will recruit stakeholders and medical specialists across different specialties to diversify the responses obtained and obtain general themes.

In WP3 we will conduct a purposeful sampling of organizations and individuals within the countries and therapeutic areas whom we will engage for interview. 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. Purposeful sampling is a strategy that is widely used in qualitative research to ensure the identification and selection of information-rich cases and the optimal use of limited resources (17). This includes identifying individuals or organizations that are particularly knowledgeable about the object of research. Purposive sampling differs from probabilistic or random sampling strategies that are typically employed to ensure the generalizability of findings through the minimization of potential selection biases. Although both qualitative and quantitative sampling methods are employed to maximize efficiency and validity, qualitative methods are typically employed to achieve depth of understanding whereas quantitative methods are employed to achieve breadth of understanding. (Patton, 2002). That is, qualitative methods emphasize saturation (i.e., reaching a comprehensive understanding by continuing to sample until no new substantive information emerges) whereas quantitative methods emphasize on generalizability (i.e., ensuring that the information gained is representative of the population from which the sample was drawn).

In WP3, we employ sequential sampling strategy that combines inclusive criterion-based sampling and complementary maximum variation-based sampling (18). The sequence is as follows: First, we identify which organizations to include based on the mapping exercise in WP1. Second, we identify which individuals to recruit for participation based on inclusion criteria. Third, we complement the criterion-based sample with relevant organizations to ensure that maximum variation of cases is captured.

The inclusion criteria for the stakeholder engagement are: 1) the entity that authored a guideline of

interest identified in WP2. 2) an entity that includes a stakeholder which represents one of the therapeutic areas (Table 2). The criteria-based sample of organizations will be complemented by a sample of organizations that are not national competent agencies or specific to the therapeutic areas. This complementary sample enables the inclusion of perspectives and knowledge from organizations that have a coordinating function, that operate on a subnational level or that operate more downstream from clinical guideline developers.

The inclusion criteria for individual participants from guidelines developing entities are: 1) individuals who have knowledge and/or experience with updating and publishing the entities' guidelines, including the triggers, processes and timelines. 2) individuals who have experience with updating and/or publishing the specific guideline identified as relevant in WP2. 3) individuals who have experience and/or knowledge with RMMs and their integration into clinical guidelines. In case there are no national guidelines published for one or several case medicines we will engage with professionals that cover "the field of the medicines" and are "key opinion leaders" or that have experience with guideline development not necessarily related to the key case medicines in the study.

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. Previously unidentified guidelines and organizations that emerge in interviews in WP3 will be added to mapping in WP1 and WP2 and analysed accordingly.

As for recruitment strategy, a lack of response from contacted participants will be followed up by reminder email, subsequently reminder telephone call. In case of persistent non-response or rejection, a new contact person will be identified and contacted.

In order to assess transferability of findings to other disease areas, puts the onus on the reader to evaluate the methods, setting and findings, and decide whether they are transferable to their situation (19). To evaluate the transferability of results of this multi-case study, we will provide a thorough and in-depth description of the findings and the context in which these findings are situated. The transferability will be conceptual, i.e. a general picture can be painted of the key triggers for updating clinical guidelines across disease areas will be described explicitly in the findings.

9.2. Setting & study population

9.2.1. Country

The diffusion of emergent drug safety information will be studied in parallel in six European Member States spread across Europe. 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. Therefore, we expect that studying procedures in these countries will provide us with a broad view of processes for including RMMs in clinical guidelines in Europe.

9.2.2. Documents and materials

For **WP1 and WP2,** we will study various types of documents and online materials (text) in each of the

six countries. For WP1, we have selected an initial set of health care professionals groups and organisations based on the products that are included in the five case study RMMs from the selection criteria stated in Table 2. The preliminary list of (national) entities shared by Member States (see Appendix III) will be included in WP1. This list will be augmented by organisations, entities, and expert groups in each country where the health care professionals (Table 2) are involved. This information will be collected via contractors' country networks and web searches. For WP2, we will analyse the identified clinical guidelines and assess if they include information on RMMs which will be noted in the coding WP2 framework (see also variables section 9.3). When RMMs are identified in clinical guidelines we will assess if a reference is made to where these originate from, e.g., from which key regulatory documents, publications, regulatory communications, public statements on regulatory actions, product information, these originate.

We will assess current versions as well as note the time elapsing between and RMM and update of a guideline, whenever possible. 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**.

9.2.3. Key informants

For **WP3**, we will use qualitative interviews (see 9.1, WP3 for approach), including representative key informants in the six countries, to provide a comprehensive overview of processes, facilitators and barriers for integrating information from RMMs in clinical guidelines. Per country, these can include:

National competent authorities (***at least 1*** stakeholder per country)

Public sector organisations and health authorities which produce clinical guidance for healthcare professionals commonly involved in patients' treatment, either nationally or regionally (***at least*** 1 stakeholder per country, when possible). These will be found from a list generated in WP1.

Professional associations (or ad-hoc groups) which represent healthcare professionals commonly involved in the treatment, either nationally or regionally (***at least 1*** stakeholder from each disease priority area per country, see section 7). These will be found from a list generated in 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.

9.2.4. 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). UCPH is an active member of a large pharmacy practice-based research network with links to community and hospital pharmacies.

Greece: The process of recruitment of stakeholders and health care professionals requires a methodological recording of all the available relative organizations, entities, or persons whom the

Greek team can contact. A detailed table with the available organisations and their contact details will be provided from the Greek team to co-partners. Firstly, stakeholders from the national competent authority/drug regulatory agency, which is the Greek National Organization of Medicines (EOF) will be recruited through direct contact via emails sent by the Greek research team. The communication with the members of EOF will be mainly conducted via email and if it becomes necessary for the recruitment strategy will be done by phone. Stakeholders from public sector organizations and health authorities will be recruited through direct contact via emails and phones (when it becomes necessary due to limited time) from the research team; healthcare professionals, including general practitioners and clinical specialists relative to the objectives of the study will be recruited through existing networks and professional associations through direct contact with the respective associations via emails (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. Finally, the Greek team will record the output of every contact to the aforementioned table (reference only to the organisations not to specific persons), whether it was an affirmative response for the interview process or not.

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. RSU, IPH has multiple collaborations with the above-mentioned institutions. These will be used to identify representatives of health authorities, professional associations etc for the initial 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 (20).

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. Contacts will be established first by email and subsequently by telephone, if needed.

Members of the PRAC, assessors and advisors directly involved in the regulatory procedures for the included products will not be included in the stakeholder interviews. Interviewees will be asked prior to interview.

9.2.5. Disease priority areas

The disease priority areas and active substances that will be included in this study for the TA specific objectives are presented in section 7.

9.3. Variables

Information on exposures, outcomes and characteristics such as risk factors is not applicable for this study. This study will include information about the entities that issue, develop and/or update clinical guidelines identified in WP1 as well as information extracted from clinical guideline 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).

WP1. Mapping of relevant organisations

The following information will be registered for identified organisations (see also coding framework for WP1):

- ***General information*** about the entity (name, description, address, telephone number, website, contact person [if applicable], level of operation (international/national/regional/local level).
- Information about ***membership*** including type of entity (professional organisation, interprofessional platform, public authority, public or non-profit organisation, hospital, (group of) experts and other). For each type of entity the primary membership will be noted. For professional organisations, the type of health care provider is based on the case studies: general practitioners (valproate, fluoroquinolones, metformin, methotrexate), neurologists (fluoroquinolones valproate), psychiatrists (valproate), oncologists (Fluorouracil and related substances), orthopaedist (fluoroquinolones), gastroenterologists (methotrexate), internists (fluoroquinolones, metformin), geriatricians (fluoroquinolones), endocrinologists (metformin), rheumatologists (fluoroquinolones, methotrexate), dermatologists (methotrexate), nurses, pharmacists and others. When interprofessional platforms are regarded the type of professionals participating will be noted. For public authority: regulatory authority, ministry of health, other. For public and non-profit organisations, the following will be noted: Health technology assessment bodies, public health organisations, patient organisations, other.
- ***Guidelines development*** including if identified organisations publish guidelines (yes/no), information on developer (developed by organisations, developed by other organisations), the type of document (clinical practice guideline, position paper, educational resource for HCPs, clinical recommendation lists, other).
- Any ***other relevant information*** not covered by coding matrix.

WP2. Content analysis of clinical guidelines

The following information will be registered for identified clinical guidelines:

- ***General information*** on the clinical guideline (name, version number & version date (national level publication), number & version date (only applicable to international guidelines, international level publication) frequency of updating (number/months), website/link, funding reported to be received (yes/no) and country;

- Information about the ***target audience*** of the guideline (coverage [country, regional, other, not specified], setting [primary care, secondary care, both, other, not specified], and medical specialty [general practitioners, neurologists, psychiatrists, oncologists, orthopaedists, internists, geriatricians, endocrinologists, rheumatologists, dermatologists, gastroenterologists, nurses, pharmacists and others), the ***population*** to whom the guideline applies (children [0-9 years], adolescents [10-17 years], adult [18-64 years], seniors [65 and older], pregnant females, other), and treatment (active substance: valproate, fluoroquinolones), methotrexate, metformin, fluorouracil and related substances) and ***therapeutic area*** based on approved indications (neurology, psychiatry, diabetes, infections, immunology, oncology, other);

- **Information about the RMM** included in guideline: information on case study medication safety mentioned (yes/no), content of safety information (original language and English translation), RMM mentioned (yes/no, see Appendix I, page 31-32), RMM tool mentioned (yes/no), type of RMM tool (SmPC, package leaflet, visual reminders on packaging, HCP guide/checklist, patient guide, patient card, annual risk acknowledgement form, DHCP, and suspension), recommendations in relation to RMM included (yes/no), clinical action related to RMM (yes/no, see list in Appendix I), explicit mention of reference for RMM information (yes/no), reference (in case explicit mention of reference is yes).

WP3. Interviews of key informants

The following information will be collected in the interviews:

- Updating approach: Continuous updating/Regular updating
- Decision to update
- Updating scope: Full updating/ Partial updating
- Impact of the new evidence
- Signal for an update
- Surveillance process
- Time of validity
- Timeframe for updating
- Tools and resources
- Up to date status
- Update cycle
- Update unit

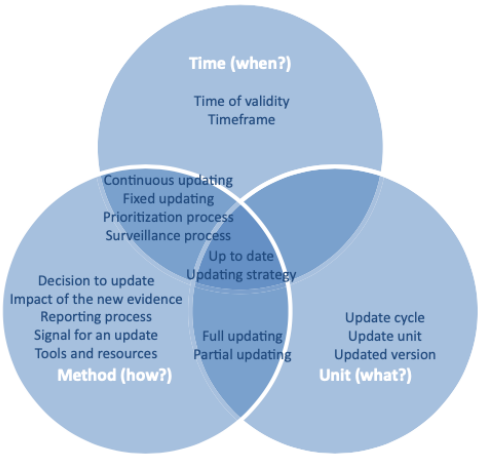

Figure 4. Clinical guidelines updating conceptual domains. (19)

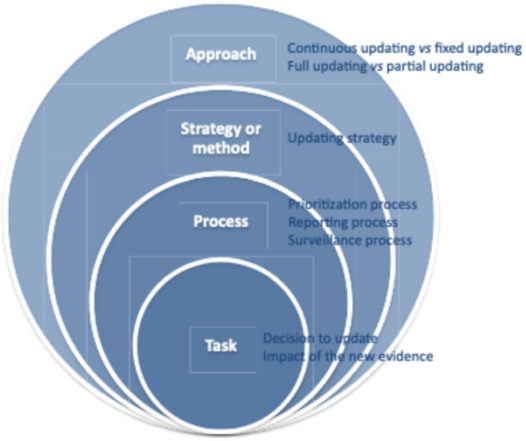

Figure 5. Clinical guidelines updating strategic domains. (19)

These items describe central aspects of the clinical guideline updating processes and were identified and defined in recent research from The Guidelines International Network's Updating Guidelines Working Group (GIN-UGWP) in their framework for the conceptual domains related to updating of clinical guidelines (21). The terms were organized in conceptual domains (time, methods, and unit; see figure 4) and on a continuum from strategic level to concrete task level (i.e., strategic domains; approach, strategy, process, and task; see figure 5).

The findings of this study will be discussed and analysed by geographical region and country (see 9.2.1.), by therapeutic area (see section 7), by special population (pregnancy, elderly), by type of health care provider (primary care, secondary care health care provider, nurse, pharmacist, as appropriate). National context will be accounted for when analysing and interpreting the results. Moreover, collecting the information allows us in the analysis to describe what inhibits, delays, or complicates the process (barriers) and what facilitates and ensures important aspects of the process (enablers).

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

9.4. 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.

Semi-structured interviews with key informants will be conducted in the six countries using an interview guide. Interviews will be preferably conducted face-to-face, but if respondents prefer a phone call or online meeting, this will be accommodated. A minimum of 7 and a maximum of 20 key informants will be included per country, including stakeholders from different settings (primary care, secondary care, government).

The initial draft of the interview guide is composed of six sections with the aim of collecting information on the items outlined the GIN-UGWP framework in a coherent, easy-to-follow sequence. Each section fulfils different objectives with regard to collecting new information and confirming information collected in WP1 and WP2 (see Table 3). Interview sections are preceded by meta-commentary to

introduce subsequent sections and their rationale and, thus, to ensure interview coherence and focus. Interview questions are formulated to produce optimal information-rich interviews and consistency across case-countries. The formulation of questions follows qualitative interviewing methodology to produce questions that are participant-oriented, clearly worded, single-facetted.

Data saturation will be reached when additional data do not lead to any new emergent themes (23).

Table 3. Outline of interview guide sections and corresponding objectives.

Interview section	Objectives
I. Introduction to interview	Establish consent to participate and record interview Clarify objective and rationale with study Clarify rationale for informant's participation
II. About professional association	Confirm existing background information on informant and organization Collect additional background information on informant and organization
III. Clinical guidelines	Confirm that search, retrieval and analysis of the guidelines relevant to the interview have been exhaustive Collect information on other, potentially relevant guidelines
IV. Development and timeframe for guidelines updates	Collect open-ended description of guideline updating process (open question) Collect information on key approach and typical strategies, processes, and tasks in guideline updating (see figure 4 for details)
V. Communication channels with other organizations	Collect information on the organization's collaboration with other organizations Collect information on established information channels with other organizations relevant to the study
VI. Closure	Invite informant to provide relevant, unsolicited information Thank informant for participation Inform generally about prospects of the study (e.g., tentative timeline and intention to publish results in in scientific journal)

Pilot testing of the interview guide will be undertaken through external assessment by experts and field testing. To ensure the appropriateness and comprehensiveness of the topic guide in relation to the objectives of the study three experts in clinical guidelines based in different case-countries will be engaged to provide an assessment. Experts will be identified through consortium networks. Also, field testing in which the interview situation will be simulated with potential participants will be conducted in two different case-countries. The aims of field testing are to ensure intelligibility; improve relevance of questions and their sequence; to assess whether the questions are understood correctly by interview participants; to estimate the time needed for each session; and to identify potential limitations of the interview guide (19-22).

9.5. Study size

The sample size will depend on the country (see 9.2.1.) and disease area (see section 7), but it is estimated that each of the countries will have a range of 7-20 interviewees in total including the various stakeholders (see 9.2.3.).

9.6. 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 it 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 transcripts 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.

9.7. Data analysis

A coding framework will be created by the coordinating team and national teams 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. The coding framework can 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.

Interview transcripts (text) from semi-structured interviews with stakeholders (representatives of key bodies and organisations) will be produced. 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 researcher 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.

The process for updating clinical guidelines, based on results from WP2 and WP3 will be presented in a visualized manner, e.g.., using process maps

9.8. Quality control

9.8.1. 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 research 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.

Handling of all data and IT management in this project will be conducted in line with EU requirements and ISO standards for data security and personal data protection.

9.8.2. 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 section 6) which will attest to the efficient roll-out and continuity of the service.

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).

9.9. Limitations of the research methods

Although this project includes six countries from different geographical regions in Europe it might not make the study directly generalizable to other European Union Member States, albeit that its findings and recommendations might provide valuable insights.

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 in WP2 will describe which information about product specific RMMs are integrated into clinical guidelines. However, as this data collection proceeds from pre-determined values operationalized in the coding manual, the analysis will not include a qualitative description of how RMMs are represented in clinical guidelines (e.g., in what context they or the safety concerns they describe are integrated, whether they are discussed at length, mentioned with reference to explicit RMMs, or mentioned in footnotes etc).

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. It is also not feasible to pilot test the interview guide in all countries due to time constrains. 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 (24).

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 (25). National team meetings of teams will be held regularly to align data collection, data analysis, and reporting of results (25).

10. 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.

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.

11. Management and reporting of adverse events/ adverse reactions

Not applicable

12. Plans for disseminating and communicating study results

The final report will be delivered 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 has been registered in the EU PAS register (EUPAS47588).

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. 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).

13. References

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Supplementary documents

Appendix I: High level information on Risk minimisation measures

Risk minimisation measure	Valproate	Fluoroquinolones	Methotrexate	Metformin	Fluorouracil & related substances
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
RMM Tool*					
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)			
Measures**					
	Valproate medicines are contraindicated, i.e., must not be used, in girls and women able to have children unless the terms of a special **pregnancy prevention programme** are followed. These include: -an *assessment* of	Restrictions on the use of fluoroquinolone antibiotics will mean that they should not be used: -to treat infections that might get better without treatment or are not severe (such as throat infections); - to treat non-bacterial infections, e.g. non-	-Only doctors with expertise in using methotrexate-containing medicines to prescribe them. -Healthcare professionals to ensure that patients or carers are able to follow the once-weekly dosing schedule.	EMA concluded that the large patient population with moderately reduced kidney function can benefit from use of metformin. Clear dosing recommendations and monitoring before and during treatment aim to minimise any	EMA has recommended that patients should be tested for the lack of the enzyme dihydropyrimidine dehydrogenase (DPD) before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the

	each patient's potential for becoming pregnant, - *pregnancy tests* before starting and during treatment as needed, - counselling about the risks of valproate treatment and the need for *effective* contraception throughout treatment, - a *review of ongoing treatment* by a specialist at least annually, - introduction of a new *risk acknowledge-ment form* that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.	bacterial (chronic) prostatitis; - for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder); - to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used. Importantly, fluoroquinolones should generally be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided.	-To avoid confusion, recommendations to split the dose should be deleted from the product information for the tablet formulation. -Packaging for all methotrexate-containing medicines for once-weekly use to include a prominent reminder of how the medicine should be used. -Patient card emphasising the weekly dosing for inflammatory diseases to be provided with oral medicines. -Healthcare professionals to be provided with educational materials for oral medicines and to counsel patients accordingly. -Tablets to be available in blister packs instead of bottles (or tubes) in order to help patients follow the once-weekly dosing.	possible increased risk in these patients. The contraindication for patients with severely reduced kidney function will remain (GFR less than 30 ml/min). Reduced doses should be considered for patients with moderate reduction of kidney function according to dosage recommendations provided in the updated product information. The product information also details risk factors for lactic acidosis which should be reviewed prior to and during treatment.	related medicines, capecitabine and tegafur
Clinical Action					
	Contraindicated in girls and women able to have children, unless terms of a special pregnancy prevention programme are fulfilled	Avoid therapy in patients who are older	Should only be prescribed by physicians with expertise in using methotrexate medicines	Reduced dose for patients with moderate kidney function	Phenotype and/or genotype testing for DPD deficiency before starting treatment with fluoropyrimidines
	Assess potential of patient for becoming pregnant	Avoid therapy in patients who have renal impairment	Give clear instructions to patients about one-weekly dosing	Assess patient risk factors for lactic acidosis prior to and during treatment	Treatment is contraindicated in patients with complete DPD deficiency (fluoropyrimidines)
	Pregnancy test before starting and during treatment	Avoid therapy in patients who have had solid organ transplantation	Check that patients (or carer) understand that the medicines must be used once a	Use in patients with GFR<30 ml/min is contraindicated	A reduced starting dose should be considered in patients with partial DPD

			week, repeat this check every time the medicine is issued or dispensed		deficiency (fluoropyrimidines
	Counselling about the risks of treatment and the need for effective contraception throughout treatment	Avoid therapy in patients treated with corticosteroid	Council patient (or carer) on signs of methotrexate overdoes and give instructions to promptly seek medical advice in case of suspected overdose	Consider using individual tables in patients with reduced kidney function that use fixed-dose combination products	Therapeutic drug monitoring of fluorouracil in patients receiving continuous fluorouracil infusions
	Review ongoing treatment at least annually	Discontinue fluoroquinolone treatment at the first sign of tendon pain or inflammation or in case of symptoms of neuropathy		Fixed-dose combination dapagliflozin/metformin (Ebymect, Zigduo) are not recommended when GFR<60 ml/min	Pre-treatment testing for DPD deficiency is not required for treatment with flucytosine
	Go through risk acknowledgement form at each annual review	Do not use in patients who have had a serious adverse reactions associated with quinolone or fluoroquinolone medicines		Fixed-dose combination canagliflozin/metformin (Vokanamet) are not recommended when GFR<45 ml/min	Treatment is contraindicated in patients with complete DPD deficiency (flucytosine)
	Do not start therapy unless alternative treatments are not suitable (including girls below age of puberty)			Fixed-dose combination empagliflozin/metformin (Synjardy) are not recommended when GFR<45 ml/min	Treatment should be stopped in case of drug toxicity (flucytosine)
	Women and girls who have been prescribed valproate should not stop taking their medicine without consultation			Fixed-dose combination canagliflozin/metformin (Vokanamet) should not be started when GFR<60 ml/min	
	If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative option			Fixed-dose combination empagliflozin/metformin (Synjardy) should not be started when GFR<60 ml/min	
	A patient guide and a patient card should be provided to all women of childbearing potential			In patients with GFR of 60-89 mL/min, maximum daily dose (MDD) of 3000 mg divided in 2-3 doses per day; dose reduction may be considered in relation to declining renal function	
				In patients with GFR of 45-59 mL/min, MDD	

				of 2000 mg divided in 2-3 doses per day	
				In patients with GFR of 30-44 mL/min, MDD of 1000 mg divided in 2-3 doses per day	
				Starting dose at most half of the maximum dose in patients with GFR of 30-59 mL/min"	

*This table includes the tools for risk minimisation which EMA has considered most relevant to integration in clinical guidelines in their request for information to Member States but does not include a complete list of all RMM tools required by PRAC for the case examples.

** For complete information on overview of the measures taken for each active substance see links below:

https://www.ema.europa.eu/en/news/new-measures-avoid-valproate-exposure-pregnancy-endorsed

https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products

https://www.ema.europa.eu/en/news/prac-recommends-new-measures-avoid-dosing-errors-methotrexate

https://www.ema.europa.eu/en/news/use-metformin-treat-diabetes-now-expanded-patients-moderately-reduced-kidney-function

https://www.ema.europa.eu/en/news/ema-recommendations-dpd-testing-prior-treatment-fluorouracil-capecitabine-tegafur-flucytosine

Appendix II: Information on approval dates for RMMs received from MS RFI

Risk minimisation measure	Valproate	(Fluoro-) Quinolones	Methotrexate	Metformin	Fluorouracil & related substances
SmPC updates	DK: Jul 18 GR: Mar 22 LV: Aug-Nov 18 NL: Jul 18 PT: Jun 19 SI: Dec 18	DK: May 19 to Sept 20 GR: Jan 19-Sep 21 LV: Q2 19 NL: Apr 19 to Feb 20 PT: Jun 19 to Jul 20 SI: Apr 19 to Jun 20	DK: Sep 18 to Jul 19/Mar 21 GR: May 19/Apr 20/Jun 21 LV: Jan 20 NL: 20 PT: Jan-Aug 20 SI: Oct 20	DK: May-Dec 17/Nov 19 GR: Oct 20 LV: Q1 17 NL: Dec 16/Jan 17 PT: May 18 SI: Mar 17	
Visual reminder on packaging	DK: Oct 18 GR: May 19 LV: Nov 18-Jan 19 NL: Oct 18 PT: Jun 2019 SI: Dec 18		DK: Sep-Dec 18/Mar 21 GR: Jul 20 LV: Jan 20 NL: Jan 20-Nov 21 PT: Jan-Aug 20 SI: Oct 20		
Healthcare professional guide/checklist	DK: Sep 18 GR: May 19 LV: Nov 18 NL: Nov 18 PT: Nov 18 SI: Nov 18		DK: Mar 20 GR: Jul 20 LV: Sep 19 NL: Oct/Nov 20 PT: Jan20 SI: Mar 21		
Patient card	DK: Sep 18 GR: May 19 LV: Aug-Nov 18 NL: Nov 18 PT: Nov 18 SI: Nov 18		DK: Mar 20 GR: Jul 20 LV: Nov 19 NL: Apr 20 PT: Jan-Aug 20 SI: Oct 20		
Patient guide	DK: Sep 2018 GR: May 19 LV: Nov 18 NL: Nov 18 PT: Nov 18 SI: Nov 18				
Annual risk acknowledgement form	DK: Aug 18 GR: May 19 LV: Nov 18 NL: Nov 18 PT: Nov 18 SI: Nov 18				
Direct HPC (it is noted the DHPCs are disseminated by the marketing authorisation holders, however NCAs	DK: Sep 18 GR: Dec 18 LV: Nov 18 NL: Nov 18 PT: Nov 18 SI: Nov 18	DK: Apr 19 GR: Apr 19 LV: Apr 19 NL: Mar 19 PT: Oct 18 SI: Mar 19	DK: Sep 19 GR: Sep 19 LV: Nov 19 NL: Oct 19 PT: Dec 19 SI: Sep 19		DK: May 20 GR: May 20 LV: Jun 20 NL: May 20 PT: May 20 SI: May 20

could disseminate them further)					
Suspension		DK: - GR: - (susp. 12, NR) LV: - (susp. 19, NR) NL: - (susp. 17, NR) PT: - SI: - (susp. Apr 19, NR)			

*This table includes the tools for risk minimisation which EMA has considered most relevant to integration in clinical guidelines in their request for information to Member States but does not include a complete list of all RMM tools required by PRAC for the case examples. NR: not registered

Appendix III: List of organisations that received information on RMM as indicated by MS.

Country	Organisation
Denmark	Dansk selskab for klinisk onkologi [Danish Society of Clinical Oncology] Dansk dermatologisk selskab [Danish Dermatology Society] Dansk reumatologisk selskab [Danish Society for Rheumatology] Dansk selskab for Almen medicin [Danish Society for General Medicine] Dansk selskab for gastroenterologi og hepatologi [Danish Society for Gastroenterology and Hepatology] Dansk selskab for geriatric [Danish Geriatric Society] Dansk hæmatologisk selskab [Danish Society for Hematology] Dansk pædiatrisk selskab [Danish Society for Pediatrics] DCCG.dk [Danish Colorectal Cancer Group] Dansk selskab for Klinisk Biokemi [Danish Society of Clinical Biochemistry]
Greece	Information not shared by NCA
Latvia	Professional Association of Neurologists, Professional Association of Children's Neurologists, Professional Association of Psychiatrists, Professional Association of Children's Psychiatrists, Professional Association of Pediatrists, Professional Association of General Practitioners (2 associations), Professional Association of Gynecologists and Obstetrics, Professional Association of Internists Professional Association of Urologists Professional Association of Traumatologists Professional Association of Infectiologists Professional Association of Pulmonologists Professional Association of Anaesthesiologists Professional Association of Intensive Therapy Specialists Professional Association of Dermatovenerologists Professional Association of Oculists Professional Association of Dentists Professional Association of Surgeons Professional Association of Midwifes, Professional Association of Pharmacists
Netherlands	Geneesmiddeleninformatiebank.nl Nederlandse vereniging voor Neurologie [Dutch Society for Neurology] Nederlandse vereniging voor Psychiatrie [Dutch Society for Psychiatry] Vereniging voor Manisch Depressieven en Betrokkenen [Association for Manic Depressive and Those involved] Epilepsie vereniging Nederland [Epilepsy Association Netherlands] Nederlandse vereniging voor Reumatologie [Dutch Society for Rheumatology] Nederlandse vereniging voor Dermatologie en Venereologie [Dutch Society for Dermatology and Venereology] Nederlandse vereniging voor Gastro-enterologie [Dutch Society for Gastroenterology] Nederlandse vereniging voor Maag-Darm-Leverartsen Nederlandse vereniging voor Medisch Oncologie [Dutch Society for Medical Oncology] Nederlandse vereniging voor Chirurgisch Oncologie [Dutch Society for Surgival Oncology] Nederlandse vereniging voor Radiotherapie en Oncologie [Dutch Society for Radiotherapy and Oncology] Nederlandse Huisartsen Genootschap [Dutch General Practitioners Association] Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie [The Royal Dutch Society for the Promotion of Pharmacy] De Nederlandse Vereniging voor Ziekenhuisapothekers [Dutch Society for Hospital Pharmacists]
Portugal	Information not shared by NCA
Slovenia	Medical Chamber Association of Gynecologists and Obstetricians Association for Outpatient Gynecology Section of Gynecology and Obstetrics Trainee Specialists

	Pediatric Association Section of Pediatric Neurology Neurologist Association Psychiatrists Association Association for Child and Adolescent Psychiatry Section of Psychiatry Trainee Specialists Association of General Practitioners Chamber of Pharmacists

Appendix IV: Request for information for EMA commissioned impact research – responses from the six Member States

See separate PDF-file.