Technical specifications – invitation to tender: re-opening of competition
EMA/2020/46/TDA/30

Annex V
Response template – Award criteria, Lot 4: Qualitative research

Tender information

Tender title	***Dissemination of additional risk minimisation measures for patients and healthcare professionals in EU/EEA countries***
Tender ID	**EMA/2020/46/TDA/30 (Lot 4: Qualitative research)**
Date of tender submission	17 January 2025
Framework contractor	Nivel
Country(-ies) of study	The Netherlands, Finland, Italy, Hungary, Lithuania, Romania
Objectives	The overall objective is to gain in-depth understanding of the current practice of dissemination of aRMM materials for patients and healthcare professionals in clinical practice, including the challenges encountered by stakeholders involved in the dissemination process and their preferences for aRMM tools and how they want to receive them. A secondary objective is to provide recommendations to regulators for regulatory decision-making on aRMM based on patients' and healthcare professionals' preferences and needs.
Scientific contact person	Prof. dr. Liset van Dijk, Nivel / Dr. Anne Brabers, Nivel
Administrative contact person(s)	Sergueï Markovic, Nivel

Role of different organisations participating in the study

Table 1 Organisations participating in the project and their roles

Organisation	Key person	Role(s)	Status	Estimated budget allocation
Nivel Otterstraat 118-124 3513 CR Utrecht The Netherlands	Prof. dr. Liset van Dijk Prof. dr. Judith de Jong Dr. Anne Brabers Dr. Marcia Vervloet Researcher	Lead Co-lead Day-to-day project coordinator/ senior researcher Senior researcher Researcher	Consortium leader	*35%*
Syreon Research Institute Budapest, Mexikói út 65, 1145, Hungary	Dr. Balázs Babarczy Dr. Tamás Ágh	Country lead/ senior researcher Senior researcher	Subcontractor	*10.5%*
University of Eastern Finland Yliopistonranta 8, 70210 Kuopio, Finland	Prof. dr. Katri Hämeen-Anttila Dr. Emma Aarnio Researcher	Country lead Senior researcher Researcher (post-doc)	Subcontractor	*13%*
University of Naples, C.so Umberto I, 40, 80138 Napoli NA, Italy	Prof. Enrica Menditto Prof. Valentina Orlando Dr. Sara Mucherino	Country lead Co-Country lead Researcher	Subcontractor	*11%*
Universitatea Babes-Bolyai Mihal Koălniceanu 1 400084, Cluj-Napoca, Romania	Dr. Alexandra Onisor Associate professor Marius Ungureanu Assistant professor dr. Oana Blaga Dr. Stefania Szeibert-Kerekes	Country lead/day-to-day project coordinator for UBB Senior researcher Researcher Researcher	Subcontractor	*10.5%*
Vilnius University Universiteto g. 3, Vilnius, 01513 Vilniaus m. sav., Lithuania	Assoc. prof. dr. Indrė Trečiokienė Assoc. prof. dr. Jurate Gudonytė	Country lead Senior researcher	Subcontractor	*10.5%*
DESAN Research Solutions	Han van Dongen	Director	Subcontractor	*9.5%*

Content

Title of the study

Dissemination of additional risk minimisation measures for patients and healthcare professionals in EU/EEA countries

List of abbreviations

Table 1: List of abbreviations

Abbreviation	
ADR	Adverse Drug Reaction
aRMM	Additional Risk Minimisation Measure
CFIR	Consolidated Framework for Implementation Research
COREQ	Consolidated criteria for reporting qualitative research
COST-ENABLE	Cooperation in Science and Technology - European Network to Advance Best practices & technoLogy on medication adherencE
CROSS	Consensus -Based Checklist for Reporting of Survey Studies
DURDAM	Drug utilization Research Databases Appraisal of Maturity
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU-TOPIA	EU-topia: TOwards imProved screening for breast, cervical and ...
FAIR	Findability, Accessibility, Interoperability and Reusability
GDPR	General Data Protection Regulation
GRAMMS	Good Reporting of A Mixed Methods Study
HCP	Health Care Professional
ICT	Information and Communication Technology
ISO	International Standards Organisation
LOWI	National Body of Scientific Integrity in the Netherlands
MA	Market Authorisation
MAH	Marketing authorisation holder
MS	Multiple Scleroris
Nivel	Netherlands institute for health services research
OECD	Organisation for Economic Co-operation and Development
PaRIS	Patient-Reported Indicator Surveys
QR-code	Quick Response code
RDA	Rethinking Scientific Data
REMEDi4All	Repurposing Medicines for all
RMM	Risk Minimisation Measures
SELFIE	Sustainable Integrated Care Model for multi-morbidity delivery financing and performance
SIMPATHY	Stimulating Innovation in the Management of Polypharmacy and Adherence Through the Years
VSNU	Vereniging Samenwerkende Nederlandse Universiteiten
WP	Work Package

PART I PROPOSED METHODOLOGY FOR CONDUCTING THE WORK

1.1. Abstract

This project will study the dissemination of additional risk minimisation measures (RMM) for patients and HCPs in EU/EEA Member States. Hereby, we include six countries with different healthcare systems: the Netherlands, Finland, Italy, Hungary, Romania and Lithuania. The study will include the following steps: 1) desk research, 2) online interviews with marketing authorization holders (MAH), 3) a focus group with representatives of national competent authorities, 4) online surveys and focus groups among healthcare professionals (HCPs), patient organisations and patients, and 5) a webinar with representatives from all EU/EEA member states to discuss the results of the study. The results of the project will help inform regulatory decision-making on the selection of aRMM (aRMM) tools and on

evaluating their overall effectiveness. The study will be performed by a multidisciplinary team of researchers with extensive experience in international health services research and the methods conducted within the study.

1.2. Background on the research question

Risk Minimisation Measures (RMM)
Risk Minimisation Measures (RMM) have been introduced to prevent or reduce the occurrence of adverse reaction from exposure to a medicinal product, or, in case an adverse reaction occurs, to reduce its negative impact.[1] RMM are introduced by the European Union (EU) pharmacovigilance legislation via risk management systems. RMM consist of the RMM message and the RMM tool. The RMM message is the key information about the risk and the actions to be taken by the healthcare provider and/or the patient for minimising the risk. The RMM tool serves to disseminate the RMM message and to support/control adherence to the intended actions for risk minimisation. There are two types of RMM tools that EMA can impose, namely routine RMM tools (e.g. the package leaflet and the summary of product characteristics), and aRMM tools (aRMM tools). These additional tools are imposed in case routine RMM are insufficient to control risks (Hapani 2022) and have to be put into place.

The project described in this proposal focuses on **additional RMM tools**. There are two types of these tools:

1) educational/safety advice tools: these advice tools target healthcare professionals (HCPs) or patients, and may consist of, for example, a patient or HCPs guide or patient card. Some of these tools for professionals are intended to support the dialogue with the patient about the risks and required actions to minimise the risk.
2) risk minimisation control tools such as the need for a healthcare facility accreditation of the available equipment and qualified HCPs as a requirement for using the medicinal product.

The implementation pathway
The implementation of RMM, including aRMM, follows the path as depicted in Figure 1. First, at market authorization (MA) EMA imposes RMM, which then will be disseminated to the target population: HCPs and/or patients. The RMM, including the aRMM, need to increase knowledge and affect attitudes towards the medication and its risks which then must feed into behavioural changes within the target population and in the end in better health outcomes for patients. Below we shortly describe some background related to this pathway.

Figure 1: The implementation pathway of aRMM (adapted from EMA)[2]

Regulatory implementation of aRMM
Not all medicinal products have aRMM. Of the 231 medicines that were approved via the centralized EMA procedure from 2010 to 2015, 30% had aRMM at the time of licensing. The proportion was higher between 2010-2012 (38%) compared to 2013-2015 (28%) (Francisca 2018). A review of the EPAR

[1] https://www.ema.europa.eu/en/documents/ scientific-guideline/ guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection- tools_en-3.Pdf
[2] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

database found that of 717 included medicines (2006-2015), 26% had an aRMM (Rubino & Artime 2017).

Dissemination of aRMM to target population

Studies have shown variation in the dissemination of aRMM, i.e. in the reach of aRMM among patients and HCPs (Landberg 2018; Mayall 2021). The dissemination and implementation of aRMM requires contribution from a range of stakeholders including EMA, national competent authorities, MAHs, HCPs and patients.[3] As such stakeholder input is crucial for optimizing dissemination and implementation strategies. A major effort in this area was done by Bahri et al (2021 who studied how to best include stakeholder input in the development and implementation of RMM and aRMM after there were concerns about insufficient implementation of the 2014 RMM for valproate as emerged from the 2017-2018 European Union Procedure on the Teratogenic Risk of Valproate (Bahri 2021). They identified some major gaps in the way stakeholder input was used in RMM implementation and identified that "achieving stakeholder agreement on RMM and catalysing healthcare leadership for RMM implementation may be the most challenging for regulators because this concerns connecting more with patients and HCPs, their real-world experiences and potential for behavioural change within healthcare systems" (literal quote from Bahri 2021, p. 207).

For developing dissemination and implementation strategies collecting information from multiple stakeholders is key. Examples of such strategies include engagement or training of stakeholders, support clinicians or develop stakeholder interrelationships (Waltz 2015). The Consolidated Framework for Implementation Research (CFIR)[4] is a well-known and useful framework for identifying implementation determinants and implementation strategies in the major implementation domains 'Innovation', 'Outer setting', 'Inner setting', 'Individuals' and 'Implementation process' (Damschröder 2022). We will use the CFIR as framework in this project (see section 1.4). The CFIR is also a strong framework to use for an analysis of the context in which aRMM is implemented, which is important as EMA and the national competent authorities allow and encourage MAHs to implement and disseminate aRMM tailored to the needs of their local healthcare settings (Hapani 2022). As such, it is local stakeholders who can then provide the input needed to align the aRMM as much as possible in order to lower the burden of complying with both EMA and national competent authority requirement. Digital aRMM provide new opportunities because they, for example, give flexibility in design, enhance easier updating processes, and create opportunities to increase engagement with important information (Da Silva-Tillmann 2002).

Effectiveness: from knowledge/attitudes to behaviour and outcomes

aRMM can focus on different key elements which provide guidance for implementation of aRMM for Member States. The major key element is behavioural change, targeted both at the major target groups of aRMM: patients and HCPs. Other key elements include knowledge change. In a study of 68 medicines, Zomerdijk et al. (2013) found that of the 801 key elements of the aRMM, 57% fell in the category "behavioural change" (Zomerdijk et al. 2013). aRMM in this category recommend patients and HCPs to take actions. For patients such action can be to contact a HCP in case of an adverse drug reaction (ADR). For HCPs these for example include providing guidance to patients on contraindications, use of comedications etc. Another example is to perform a pre-assessment before prescribing or to examine the patient regularly to proactively check for early ADRs (Zomerdijk et al. 2013). This needs to lead to better health outcomes. In order to study this pathway, effectiveness studies are needed.

Evaluating the effectiveness of RMM refers to monitoring outcomes of the RMM and is mandatory for MAH in case of aRMM.[5] aRMM put pressure on the health care system and MAHs, reason why their use

[3] https://www.ema.europa.eu/en/documents/ scientific-guideline/ guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection- tools_en-3.Pdf
[4] https://cfirguide.org/choosing-strategies/
[5] https://www.ema.europa.eu/en/documents/ scientific-guideline/ guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection- tools_en-3.Pdf

should be rational and effective (Zomerdijk et al. 2013; Mueller 2023). Effectiveness is important in terms of "reaching the target populations, knowledge adoption and attitude formation in the target populations and their taking of the intended actions for risk minimisation and health outcomes in terms of reduced occurrence or severity of adverse reactions or the reduced adverse impact of such reactions on patient or public health"[6]. In effectiveness studies these outcomes are operationalized in different ways such as process indicators, receipt of the aRMM, better clinical knowledge and clinical action that was undertaken (Rubino & Artime 2017; Vora 2018; Essink 2023). Effectiveness of aRMM was found in several cross-national studies targeting a variety of medicines (Mayall 2021; Lem 2022; Rutskova 2023), although sometimes this was only true for one stakeholder but not the other (Jacquot 2019, Colas 2024) or for one of the studied outcome indicators but not the other (Vora 2018). Other studies failed to find an effect or found only limited effects, also due to low response rates in the surveys used (Agyemang 2017; Landsberg 2018; Toussi 2020; Wu 2024). Effectiveness of aRMM is not always studied. Essink et al (2023) found that of the 134 included medicinal products (authorised between July 2012-December 2021) less than half were studied in an effectiveness evaluation (47%) and for only one out of five of these 134 products the effectiveness studies were completed within five years after the market authorization. Also many studies proved to be delayed (Essink 2023). Reasons for delay might be slow recruitment of participants, low prescribing rates for the medications or logistic challenges (Mazzaglia 2018; Essink 2023). The lack of effectiveness studies may be a reason why only very few aRMM are discontinued (Francisca 2021).

1.3. Objectives

Overall objective

The overall objective is to gain in-depth understanding of the current practice of dissemination of aRMM materials for patients and HCPs in clinical practice, including the challenges encountered by stakeholders involved in the dissemination process and their preferences for aRMM tools and how they want to receive them. A secondary objective is to provide recommendations to regulators for regulatory decision-making on aRMM based on patients' and HCPs' preferences and needs.

1.4. Methodological approach

Medications and aRMM under study

For this study EMA has selected seven medications as a case study. For each medication, a number of aRMM have to be studied, which vary across the medications (Table 2).

[6] Literally adapted from https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

Table 2: Medicinal products and their aRMM material that will be included in the study

Medicinal Product Name	aRMM material
Xeljanz (tofacitinib)	Patient alert card Guide for HCPs Prescriber checklist
Aubagio (teriflunomide)	Patient educational card Educational material for HCPs
Valproate containing medicinal products	Patient guide Patient card Healthcare professional guide Risk acknowledgement form
Lemtrada (alemtuzumab)	Patient guide Patient alert card Healthcare professional guide Prescriber checklist
Eylea (aflibercept)	Patient information guide Physician information pack
Retinoids containing medicinal products	Prescriber checklist/acknowledgement form Pharmacist checklist Patient reminder card
Lixiana (edoxaban)	Patient alert card Prescriber guide

Mixed-method approach

Before we provide our methodological approach in detail, we want to lay out our **vision** on the methods used in the project.

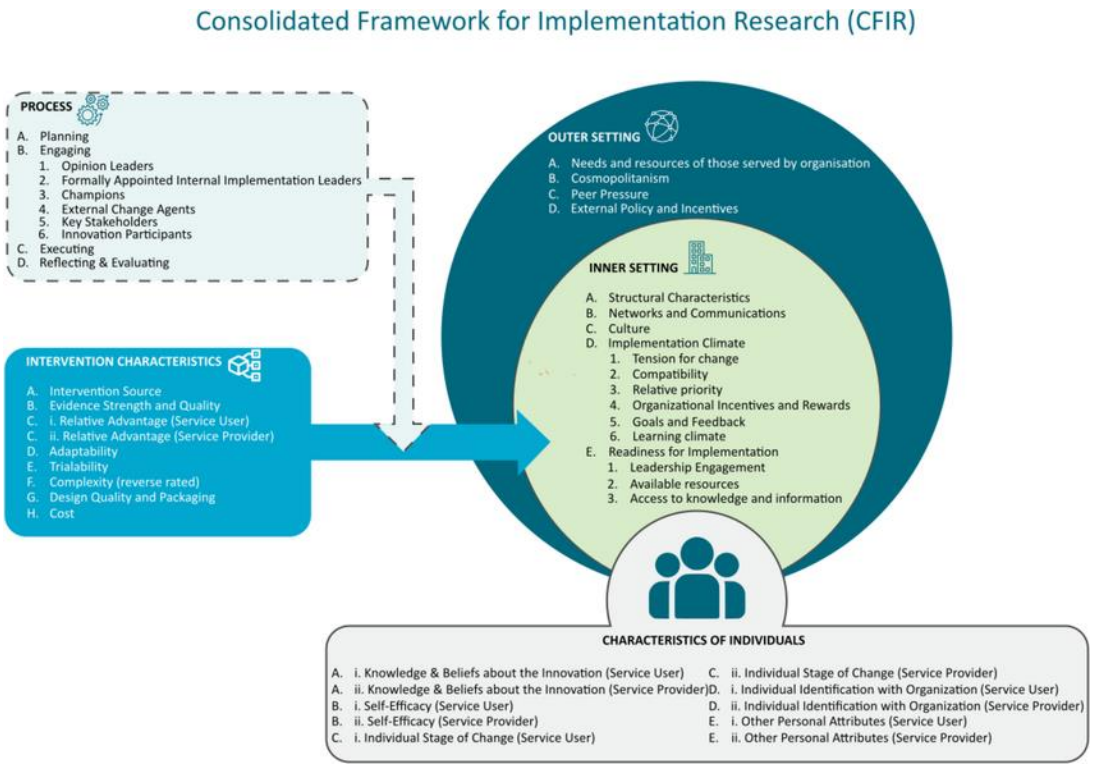
- Based on the objectives of the study, it is our vision that a mixed-method approach is needed to capture the dissemination of aRMM to its fullest extent. In such an approach, combining qualitative and quantitative data will provide a more complete and nuanced understanding of the dissemination of aRMM in EU/EEA Member States. Using these multiple research methods we will be able to cross-verify findings and thus increase the overall validity of the study. Also it allows us to combine the more in-depth analyses of qualitative research with the broader possibilities to generalise findings provided by using quantitative methods. For our study, we also find support for this approach by previous research (Landsberg 2018; Wu 2024).
- Although the seven medicinal products in table 2 are available in the six countries included in this study, for some of the medicinal products the number of patients that use the product is (very) low. For example, in the Netherlands in 2022 only 50 persons used Lemtrada (alemtuzumab)[7] (on a population of 18 million people), and 1.668 persons used Aubagio[8]. Similarly, in Italy consumption of Lemtrada (alemtuzumab) is also very low with a decreasing trend during years, with less than 0.005 DDD per 1000 inhabitants per day recorded in 2023 (on a population of around 58 million people)[9]. In Finland there were 123 users of Lemtrada (alemtuzumab) between 2013-2019 (on a population of around 5,5 million people) (Rauma 2022). For Aubagio, there were 787 patients that have had reimbursements during the second quarter of 2024 in Finland[10].
- With such a low number of users, and no national registration of who the users are, it is a challenge to sample a representative group of patients to fill out an online questionnaire. Therefore, and for feasibility reasons, we decided to do a survey study among patient organisations to get insight in the patient perspective. To reach the patient organisations we use purposive sampling. We will make an overview of the relevant patient organisations in the six countries (like the MS Association Netherlands for Lemtrada in the Netherlands, and the Finnish Rheumatism Association for Xeljanz in Finland). In addition, we will make a short questionnaire for patients and ask patient organisations to spread the link to this questionnaire

[7] https://www.gipdatabank.nl/databank?infotype=d&label=00-totaal&tabel=B_01-basis&geg=gebr&item=L04AA34
[8] https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel=B_01-basis&geg=gebr&item=L04AA31
[9] https://www.aifa.gov.it/documents/20142/2594020/AIFA_Rapporto%20OsMed_2023.pdf
[10] https://tietotarjotin.fi/en/statistical-data/2051231/statistical-database-kelasto

through for example their newsletter. We think this is the only way to get a representative view of the patient perspective. We envision that spreading our survey through professionals or via social media only is not sufficient.

- Also, with low numbers of patients using a certain medicine, (most) professionals will have limited experience. Therefore, we will use the same approach for professionals: we start with professional organisations, and then ask them for support to spread the questionnaire, next to spreading it via social media and mailing.
- We jointly develop a data collection plan that includes instructions of how to conduct the data collection for each of the included methods.
- For the development of the questionnaires and the topic lists for the focus groups to evaluate dissemination and implementation, we will use the updated version of Consolidated Framework for Implementation Research (CFIR; Damschröder 2022, see figure 2 below). For the five domains of the CFIR, being 'Innovation', 'Outer setting', 'Inner setting', 'Individuals' and 'Implementation process', we extract and analyse both generic context factors (across all countries) as well as country-specific context factors. In addition, we extract and analyse factors that apply to all stakeholders, as well as stakeholder-specific factors in order to capture experiences that are relevant for other countries (and/or stakeholders) as well.

Figure 2: Consolidated framework for Implementation Research*



* *Figure taken from Damschröder et al (2022).*

Our choice of countries for the study

- The EU consists of Member States that widely vary regarding health care systems, regulatory context, culture, and opinions on medication. The basis of international health services research is to study those differences and their impact on outcomes. Looking at the study in the current proposal, we expect that the implementation of aRMM differs between Member States. This is, among others, based on the study of Yasuoka et al. (2019) showing that risk minimisation activities were largely influenced by differences in regulatory thinking, medical systems, and

cultural differences.

- Therefore, we conduct the study in six different countries to capture differences with regards to the subject of the study. This selection of countries provides – as requested – regional differentiation across the EU as well as variation in the health care system, see table 3.
- The following countries will be included: the Netherlands (western Europe), Finland (northern Europe), Italy (southern Europe), Lithuania (north-eastern Europe), Romania (eastern Europe) and Hungary (central Europe).
- All seven included medicinal products are available in all six included countries.
- Within the research team, we have included a research organisation from all included countries. Those organisations function as focal point within each country.
- All these research teams have extensive experience of earlier projects with the methods used in this research, as shortly explained hereafter:
  - **Nivel** is running multiple implementation studies, using the CFIR framework. Also, Nivel has ample experience in survey research in both patients and professionals both at the national and international level as well as in qualitative research. Moreover, Nivel performed a study that was the basis for the setup of a nationwide network for patient information on medication coordinated by the Dutch Medicines Evaluation Board. Also Nivel has ample experience in coordinating and executing studies at the EU-level on a wide range of topics.
  - The researchers from the **University of Eastern Finland**, Pharmaceutical Policy research group have strong expertise in pharmaceutical systems and their regulated environment, as well as utilizing social science research methods, including various survey and interview methods, for example in COST-ENABLE-consortium. The research group has ongoing research collaboration with several patient organisations, and it utilizes principles of co-research in its research. There is a patient expert as a member of the research group.
  - **Syreon** (Hungary) performed qualitative barrier analyses in the Horizon project EU-TOPIA, EU-TOPIA-East and REMEDi4All, and used thick description to analyse the implementation of integrated care models in SELFIE.
  - The **University of Naples Federico II** (Italy), through the Center of Pharmacoeconomics and Drug Utilization Research (CIRFF), performed both quantitative and qualitative studies at both the nationale level (e.g PRIN 2022_20227C2YLA funded by the Italian Ministry of Research, European Commission – Next Generation EU) and international level (e.g., ENABLE COST Action CA19132 funded by the European Commission; SIMPATHY 663082 funded by the European Union's Health Programme 2014–2020).
  - **Vilnius University** (Lithuania) has extended experience in national projects collecting national data (National Wise list project, National e-pharmacy utilization research project, etc.) as well as international experience in survey and focus group research (COST Enable project, DURDAM project, etc.)
  - The **Department of Public Health (Universitatea Babeș-Bolyai)** (Romania) has been involved in over 50 research in projects collaborating with partners from over 30 countries. Besides implementation studies addressing patients with chronic conditions (i.e., cancer, psoriasis, diabetes, depression), the department has been implementing projects addressing health promotion (e.g., health literacy, health communication and health education) of non-communicable diseases and health system research (e.g., health workforce, healthcare management and leadership). The studies ran in the department involved mixed-methods research methodology.

Table 3: Overview of the countries included in the study and their region and health care system

Country	Region in Europe	Health care system*
The Netherlands	West	Social insurance system, with multiple health insurers
Finland	North	National Health Insurance system
Italy	South	National Health Service
Lithuania	North-East	National Health Insurance Fund
Romania	East	Social health insurance system
Hungary	Central	Social health insurance system with a single health insurance fund

** Taken from: https://health.ec.europa.eu/state-health-eu/country-health-profiles_nl*

Work packages

Figure 3 shows the WPs we use, the aims per WP and the main methods used. We will use the same surveys, focus groups, and interviews to collect data for WP1-4. Each work packages answers its own objective (Figure 3). The full description of the goal can be found in the detailed WP descriptions, given after figure 3 and table 4. Table 4 gives an overview of which method is used in which WP, and refers for each task in a specific WP to the section where a more detailed description is given for that task. An overview of which task will be done by which country is given in table 11.

Figure 3: Overview of the study

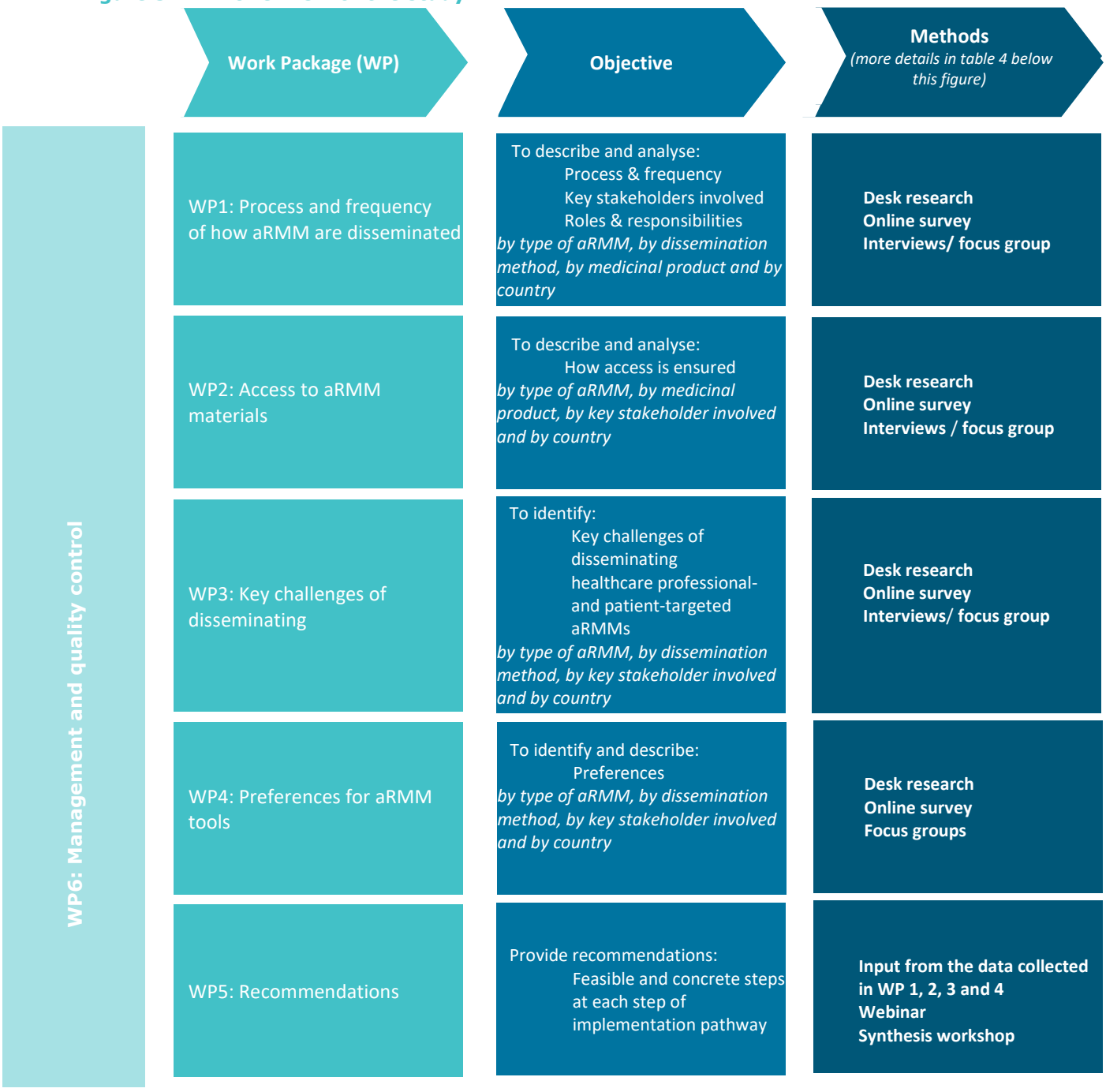


Table 4: Overview of the methods used in each work package

	WP1	WP2	WP3	WP4	WP5	WP6
Desk research	1.1	2.1	3.1	4.1		
Interviews marketing authorisation holders	1.2	2.2	3.2			
Focus group national competent authorities	1.3	2.3	3.3			
Survey professionals	1.4	2.4	3.4	4.2		
Survey patient organisations	1.4	2.4	3.4	4.2		Management & Quality control
Short survey patients		2.6		4.3		
Focus groups professionals (back up interviews)	1.5	2.5	3.5	4.4		
Focus groups patients (back up interviews)		2.7		4.5		
Webinar					5.1	
Synthesis workshop researchers					5.2	

WP1: Describe and analyse the process and frequency of how aRMM are disseminated

In this WP we will describe and analyse the process and frequency (where appropriate) how RMM are disseminated in the six selected countries, and how patients and HCPs receive product-specific aRMM materials for the medicinal products listed in table 1. We will start with desk research and then perform online surveys, focus groups and interviews.

Objective

Describe and analyse the process and frequency (where appropriate) how aRMM are disseminated in at least five (in our proposal six) EU/EEA countries with geographical spread, and how patients and HCPs receive product-specific aRMM materials for the medicinal products listed in table 2, identifying the key stakeholders involved in each step of the dissemination pathway (i.e., prescriber, pharmacist, marketing authorisation holder, national competent authority) and their roles and responsibilities, by type of aRMM, by dissemination method (e.g., email, website, paper based, QR code on primary packaging or product information leaflet, other), by medicinal product and by country.

Task 1.1 Desk research (M1-3)

- This task is to do preparatory work for the online surveys, focus groups and interviews in the following tasks. We will perform a scan of the literature to gain insight into whether information is available about the process and frequency of how aRMM are disseminated. For example, the Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures (Rev 3)[11] gives information about the dissemination of aRMM.
- For scientific literature, we will use Pubmed and Embase as search engines. We have already developed a first search string that has been used while preparing this proposal (Additional[tiab] Risk Minimisation Measurements). In case we get this study granted, we will further develop the string with help of an experienced librarian.
- In addition to the electronic databases and to cover relevant grey literature on the subject, a search of grey literature will be conducted. We will search in several databases that specifically focus on this type of literature such as https://easy.dans.knaw.nl/ui/datasets/id/easy-dataset:200362, http://sumsearch.org/ and Google scholar.
- The information found in the literature scan will be used to construct the questionnaires for the survey, the focus groups and the interviews and will be used as input for the analyses of the qualitative data.

Task 1.2 Interviews with MAHs (M2-4)

- The next step is performing semi-structured interviews with a pre-developed interview guide with representatives of the MAHs of the medicinal products included in table 2.
- The aim of the interviews is to discuss the pathway of disseminating aRMM, and what their roles and responsibilities are in the process of disseminating aRMM.
- Before the interviews, we will send the MAHs that participate in the interviews some short

[11] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-rev-3_en.pdf

questions by e-mail to get insight in some factual information, e.g. what the dissemination methods are for the aRMM material of their medicinal product. During the interviews we are then able to dive into the considerations for the choices that are made within the dissemination process, and why they see certain roles and responsibilities for themselves.

- Information from the desk research will also be used to construct the questions for the interviews and the short questions that will be send by e-mail before the interviews.
- For five out of the seven included medicinal products (Xeljanz, Aubagio, Lemtrada, Eylea and Lixiana) the relevant MAH will be interviewed. For both the Valproate and Retinoids containing products more MAHs are available of which a maximum of three MAHs will be interviewed for both products. We will ask EMA for contact persons of the MAHs in the participating countries and/or use our network. For each product the contact person of the MAH in the first responding country (and for Valproate and Retinoids containing products the first three) will be interviewed.
- A proposal for these MAHs will be made by the research team and discussed with EMA in a regular meeting. This implies that a maximum of 11 MAH's will be interviewed (5 MAHs for the specific products + 3*2 MAH's for the groups of products). With this number of interviews, we expect to reach data saturation for the views of MAH on their role and responsibilities in aRMM as well on the ways to distribute aRMM. Normally with around 12 interviews data saturation is reached (Guest et al. 2006).
- We ask for informed consent of the respondent at the start of the interview (before the first substantive question) and will follow and Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- The online interviews will take place using Microsoft Teams, and will last 30-60 minutes. Interviews will be audiotaped and transcribed.
- Reporting for the interviews will be done based on the criteria for reporting on qualitative research of the Consolidated criteria for reporting qualitative research COREQ. Domains in COREQ include (i) research team and reflexivity, (ii) study design and (iii) data analysis and reporting (Tong et al., 2007).

Task 1.3 Focus group with national competent authorities (M2-4)

- Alongside task 1.2 we will also perform a focus group with the national competent authorities from all six participating countries.
- The aim of the focus group is to discuss the process of disseminating aRMM, and the roles and responsibilities in the process of disseminating aRMM from the perspective of the national competent authorities.
- Before the focus groups, we will send the representatives of the national competent authorities that participate in the focus groups some short questions by e-mail to get insight in some factual information, e.g., what are the dissemination methods for the aRMM material in their country. Within the focus group we are then able to get information about the considerations for the choices that are made within the dissemination process, and why they see certain roles and responsibilities for themselves.
- Information from the desk research will also be used to construct the questions for the focus group and the short questions that will be send by e-mail before the interviews.
- The national competent authorities from the six participating countries will be invited for one focus group in which they participate together.
- We ask for informed consent of the respondent at the start of the focus group (before the first substantive question) and will follow and Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- The focus group will be in English and will take place using Microsoft Teams, and last for 90-120 minutes. The focus group will be audiotaped and transcribed.
- Reporting for the focus group will be done based on the criteria for reporting on qualitative research of the Consolidated criteria for reporting qualitative research COREQ. Domains in COREQ include (i) research team and reflexivity, (ii) study design and (iii) data analysis and reporting (Tong 2007).

Task 1.4 Online surveys among HCPs and patient organisations (M4-8)

- An online survey will be set up with the purpose to collect information from HCPs and patient organisations.
- Within this online questionnaire, we ask HCPs and patient organisations how professionals and patients receive aRMM material. In addition, HCPs are asked about their roles and responsibilities. Patient organisations are also asked whether they see a role and responsibilities for themselves.
- The questionnaires for the survey will be developed based on the results of the desk research and expert opinion of the research team that has ample experience in questionnaire development. The CFIR will be the basis for developing the questionnaires. As CFIR is an extensive framework, a selection of constructs will be used. This selection will independently be made in several rounds by the Nivel researchers including two CFIR experts (Vervloet, Van Dijk). After that the chosen constructs will be compared between the researchers. Any disagreement will be solved through consensus.
- In addition, results of the interviews with MAH and the focus group with national competent authorities will be taken into account in the development process. The development will be an iterative process, in sessions where the researchers will discuss consecutive versions of the questionnaire.
- We ask for informed consent of the respondent at the start of the questionnaire (before the first substantive question) and will follow and Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- We will make one questionnaire for HCPs and one for patient organisations. At the beginning of the questionnaire respondents can indicate which medicinal product they use, prescribe and/or provide and then go to the section of the questionnaire that contains the relevant questions for that product and the belonging aRMM material.
- The questionnaire contains questions with predefined answer options. Besides the structured questions, if necessary, an explanation will be requested regarding the answer using an open question. In addition, if the answers to the questionnaire give reason to do so, we will include our questions with regard to that in the interview guide of the focus groups with patients or HCPs.
- The questionnaire will be piloted by asking one or two representatives from patient organisations and HCPs in each country from our network for a cognitive interview.
- The online survey will be developed in English and subsequently translated to the national languages of the six participating countries. If necessary, specific answer options, or an additional question, that is only relevant for one specific country, can be added.
- The questionnaires will be programmed for all countries by DESAN in the national languages of the six participating countries. DESAN is a Dutch mail house that has a lot of experience with doing questionnaire research, both nationally and internationally. Nivel has worked for over many years together with DESAN and has a Service Level Agreement with DESAN. DESAN is ISO 27001 and ISO 20252 certified. By collecting the data from all countries through one organisation, we ensure that all data is coded in the same way. Furthermore, adaptations made to the 'main' questionnaire can easily be adapted in the questionnaires for the participating countries by DESAN. Also, DESAN handles the data collection for all countries.
- Both the questionnaire for professionals and patient organisations will be programmed as an open link. This implies that we can distribute the questionnaire through different channels.
- For each product the relevant patient organisation(s) in the six countries will be searched. For example, Xeljanz is a medicinal product for rheumatism, so we can contact ReumaNederland (the Netherlands) or Coalitia Organizatiilor Pacientilor cu Afectiuni Cronice din Romania (Romania). Table 5 gives a examples of relevant patient organisations that can be contacted in the six countries.
- For professionals we will contact professional organisations, like the Royal Dutch Pharmacists Association (the Netherlands) or the Romanian Association of Pharmacies and Pharmacists (Romania). See table 5 for a examples of relevant professional organisations. We will ask them

to include a link to the questionnaire in their newsletter. The exact strategy to distribute the questionnaires will be determined during the project and may vary per country to reach a representative population.
- After data cleaning, data will be analysed according to the description in section 1.10.
- Reporting for the questionnaire will be done based on the criteria for reporting on survey research of the Consensus-Based Checklist for Reporting of Survey Studies (CROSS).

Table 5: Examples of relevant professional and patient organisations in the countries

Professional organisation (country)	Patient organisation (country)
• Finnish Society for Rheumatology (Finland) • Cardiac Society (Finland) • Hungarian Research Organization of Family Physicians (Hungary) • Hungarian Medical Chamber (Hungary) • Italian Society of Clinical Pharmacy (Italy) • Lithuanian Rheumatology Association (Lithuania) • Lithuanian Pharmaceutical Chamber (Lithuania) • Royal Dutch Pharmacists Association (The Netherlands) • Nederlandse Vereniging voor Cardiologie (The Netherlands) • Romanian Association of Pharmacies and Pharmacists (Romania) • Romanian Society for Rheumatology (Romania)	• Finnish Psoriasis Association (Finland) • Finnish Epilepsy Association (Finland) • Hungarian Rheumatology Patients' Association (Hungary) • Foundation for Hungarian Multiple Sclerosis Patients (Hungary) • Expert Patient Academy and the European Project EUPATI (Italy) • APMARR National Association of People with Rheumatological and Rare Diseases (Italy) • Lithuanian Council of Patient Organization Representatives (Lithuania) • MS Vereniging Nederland (The Netherlands) • ReumaNederland (The Netherlands) • Asociația Învingătorilor Sclerozei Multiple (Romania) • Asociația pacienților cu afecțiuni neurodegenerative din România (Romania)

Task 1.5 Focus groups among HCPs (M10-11)
- The aim of the focus groups is to gain a deeper insight/better understanding of the first results of the online surveys of task 1.4.
- Information from the desk research and the online surveys will be used to construct the topic list for the focus group. The CFIR-constructs will thus be the major basis for the focus groups.
- There will be two focus groups with professionals in each participating country, one for medical doctors and one for pharmacists. Thus in total, 12 focus groups with HCPs will be held. Each focus group consist of 8-10 participants, being a usual and optimal number of participants for focus groups[12]. The major reason to have separate focus groups for medical doctors and pharmacists is that we think their views on implementation and dissemination of aRMM might differ.
- If not enough professionals can be recruited for one focus group, for example because they are not all available at the same moment, we will conduct individual interviews as a back-up option.
- We ask for informed consent of the respondent at the start of the focus groups (before the first substantive question) and will follow and Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- The focus groups will be in the national language of each country and will take place using Microsoft Teams (or another programme that is familiar in a specific country, like Zoom or Skype), and last for 90-120 minutes. The focus groups will be audiotaped and transcribed.
- Reporting for the focus groups will be done based on the criteria for reporting on qualitative research of the Consolidated criteria for reporting qualitative research COREQ. Domains in COREQ include (i) research team and reflexivity, (ii) study design and (iii) data analysis and reporting (Tong 2007).

WP2: Access to aRMM materials

[12] https://participatiekompas.nl/media/pdf/handleiding_focusgroepen_2019_april_-tg.pdf

In this WP we will describe how access to paper based and digital aRMM materials for patients and HCPs is ensured at each step of the dissemination pathway in the six selected countries. We will start with desk research and then perform online surveys, focus groups and interviews.

Objective:
Describe and analyse how access to paper based and digital aRMM materials for patients and HCPs is ensured at each step of the dissemination pathway, by type of aRMM, by medicinal product, by key stakeholder involved (i.e., prescriber, pharmacist, marketing authorisation holder, national competent authority) and by country.

Tasks 2.1 to 2.5
Tasks 2.1 to 2.5 are similar to tasks 1.1 to 1.5. The difference between the tasks lies in the aim. Tasks 2.1 to 2.5 seek for information access to paper based and digital aRMM materials for patients and HCPs. In Table 6, we specify where more detailed information can be found.

Table 6: Overview of description of methods used for WP2 tasks 2.1 to 2.5

	Description of work can be found here
Task 2.1: Desk research	Task 1.1
Task 2.2: Interviews MAH	Task 1.2
Task 2.3: Focus group national competent authorities	Task 1.3
Task 2.4: Survey professionals and patient organisations	Task 1.4
Task 2.5: Focus groups professionals (back up interviews)	Task 1.5

Task 2.6 Short survey among patients (M4-8)
- Besides the survey among patient organisations as described in WP1, we also aim to distribute very short questionnaire among patients. We see this questionnaire as an extra way of collecting data from the patient perspective, next to the questionnaire among patient organisations which is the main way to get insight in the patient perspective.
- This short questionnaire focuses on whether patients have received the relevant aRMM material (i.e. whether they have access to the material). To reach patients, we ask the participating patient organisations to spread a link and/or QR-code to the questionnaire through, for example, their newsletter. Furthermore, we will ask a selection of pharmacies to give patients who come to collect one of the included medicinal products a flyer with the link and/or a QR code to the questionnaire. Also we will spread the link through the social media network of the researchers.
- We ask for informed consent of the respondent at the start of the questionnaire (before the first substantive question) and will follow and Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- DESAN will programme the questionnaire and handle the data collection for all the countries (see task 1.4), following the same procedures and quality checks.
- After data cleaning, data will be analysed according to the description in section 1.10.
- Reporting for the questionnaire will be done based on the criteria for reporting on survey research of the Consensus -Based Checklist for Reporting of Survey Studies (CROSS).

Task 2.7 Focus groups among patients (M10-11)
- The aim of the focus groups is to gain a deeper insight/better understanding of the first results of the short online survey of task 2.6.
- Information from the desk research and the online surveys will be used to construct the topic list for the focus group and CFIR will be a major basis. There will be one focus group discussion with patients in each participating country, making a total of 6 focus groups. Each focus group consist of 8-10 participants, being a usual and optimal number for focus groups[13]. If not enough patients can be recruited for one focus group, for example because they are not all available at the same

[13] https://participatiekompas.nl/media/pdf/handleiding_focusgroepen_2019_april_-tg.pdf

moment, we will conduct individual interviews as a back-up method. We strive to include patients for different medicinal products and thus also for different modes of aRMM.
- Recruitment of patients will be done via the short questionnaire for patients where we add a question whether patients will participate in a focus group or an interview. In case this does not result in enough response, we will recruit participants for the focus groups through our large network and with the help of patient organizations.
- We ask for informed consent of the respondent at the start of the focus group (before the first substantive question) and will follow and Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- The focus groups will be in the national language of each country and will in principle take place using Microsoft Teams (or another programme that is familiar in a country, like Zoom or Skype), and last 90-120 minutes. The focus group will be audiotaped and transcribed. For analyses see section 1.8.
- Reporting for focus groups will be done based on the criteria for reporting on qualitative research of the Consolidated criteria for reporting qualitative research COREQ. Domains in COREQ include (i) research team and reflexivity, (ii) study design and (iii) data analysis and reporting (Tong 2007).

WP3: Identify and describe the key challenges of disseminating additional RMM materials

In this WP we will identify and describe the key challenges in the dissemination process of aRMM materials. We will start with desk research and then perform online surveys, focus groups and interviews.

Objective:

Identify and describe the key challenges of disseminating a. healthcare professional-targeted aRMM materials to all eligible HCPs who prescribe or use the medicinal products listed in table 2 in healthcare and b. patient-targeted aRMM materials to all eligible patients who are prescribed the medicinal products listed in table 2, by type of aRMM, by dissemination method (e.g., email, website, paper-based, QR code on primary packaging or product information leaflet, other), by stakeholder involved in each step of the dissemination pathway (i.e., prescriber, pharmacist, marketing authorisation holder, national competent authority) and by country.

Tasks 3.1 to 3.5

The methods used for tasks 3.1 to 3.5 are similar to tasks 1.1 to 1.5 and the data will be collected within the same surveys, focus groups and interviews. The difference between the tasks lies in the aim. Tasks 3.1 to 3.5 seek for key challenges in the dissemination process of aRMM materials. In Table 7, we specify where more detailed information can be found.

Table 7: Overview of description of methods used for WP3 tasks

	Description of work can be found here
Task 3.1 Desk research	Task 1.1
Task 3.2 Interviews MAH	Task 1.2
Task 3.3 Focus group national competent authorities	Task 1.3
Task 3.4 Survey professionals and patient organisations	Task 1.4
Task 3.5 Focus groups professionals (back up interviews)	Task 1.5

WP4: Identify and describe patients' and HCPs' preferences for additional RMM tools

In this WP we will identify and describe preferences of patients and HCPs for aRMM tools. We will start with desk research and then perform online surveys and focus groups among both groups.

Objective:

Identify and describe patients' and HCPs' preferences for aRMM tools for patients and HCPs, and how they prefer to receive them, by type of aRMM, by dissemination method (e.g., email, website, paper-based, QR code on primary packaging or product information leaflet, other), by stakeholder involved in each step of the dissemination pathway (i.e., prescriber, pharmacist, marketing authorisation holder, national competent authority) and by country.

The methods used in this WP for tasks 4.1 to 4.5 are similar to tasks in earlier WPs and the data will conducted within the same surveys and focus groups. The difference between the tasks lies in the aim. Tasks in WP4 focus on the objective described right above. In table 8, we specify where more detailed information can be found.

Table 8: Overview of description of methods used for WP4 tasks

	Description of work can be found here
Task 4.1 Desk research	Task 1.1
Task 4.2 Survey professionals and patient organisations	Task 1.4
Task 4.3 Short survey patients	Task 2.6
Task 4.4 Focus groups professionals (back up interviews)	Task 1.5
Task 4.5 Focus groups patients (back up interviews)	Task 2.7

WP5: Provide recommendations how the challenges may be leveraged and the dissemination of additional RMM may be facilitated

In this WP we will provide recommendations to facilitate the dissemination of aRMM. We will use the data collected in WP1, 2, 3 and 4 as input for this WP. In addition, we will organise a webinar for stakeholders and a synthesis workshop for researchers.

Objective:

Provide recommendations on how the challenges identified under objective 3 may be leveraged and the dissemination of aRMM for patients and HCPs facilitated, outlining feasible concrete steps EMA and national competent authorities could consider at each step of the dissemination pathway.

Task 5.1 Webinar (M13)

We will organise a webinar for all relevant stakeholders (e.g. national competent authorities, MAHs, patient organisations, professionals) across the EU/EEA, to jointly reflect on and discuss the results of the study.

- Nivel will prepare and organise the webinar based on the results of the desk research, online survey, focus groups and interviews. Nivel will host the meeting. The other partners will support.
- Participants will be invited by Nivel and the focal points in the other countries and include stakeholders from all six countries, as well as the other EU Member States as these countries might have information to add.
- The webinar will take 90 minutes and will consist of a presentation by Nivel with main results and recommendations and a table discussion with stakeholders.
- All participants are asked to actively contribute via chat, rapid questions rounds and using polls, in order to stimulate the dialogue between participants.
- The webinar will be held in English.
- The webinar will be chaired by the head of Nivel's international department (De Jong).
- The meetings will be recorded to be able to use the results in the study report. The results will be described to broaden the information collected in the rest of the study and describe their applicability also for other countries.

Task 5.2 Synthesis workshop researchers (M13)

- With this task we aim to come to set of recommendations for EMA including concrete steps for each step of the dissemination pathway.
- We are organizing an online synthesis workshop to discuss the recommendations with all members of the consortium. This is for efficiency reasons. We expect that we will reach decisions more quickly if we jointly discuss the results of the research in a structured manner and under the guidance of an experienced moderator (compared to communicating mainly via mail and written documents).
- We organize a workshop consisting of two half-days with representatives of the focal points. We use day 1 to translate the results to a set of general recommendations. On day 2 we will

discuss the implementation of the recommendations into the dissemination pathway in more detail. What needs to be done, how can we achieve this and which stakeholders need to do what. An experienced moderator (De Jong) will chair the workshops to ensure they run as efficiently and effectively as possible.

- The workshops will be recorded for reasons of supporting the drafting of the recommendations on paper by the Nivel team. The final set of recommendations will be sent out to the focal points for feedback and accordance.

WP 6: Management and quality control (M1-M16)
This work package is described in part II of this document.

1.5. Study population

The study population consists of:

- **Marketing authorisation holders** (MAHs). For five out of the seven included medicinal products (Xeljanz, Aubagio, Lemtrada, Eylea and Lixiana) the relevant MAH will be interviewed. For both the Valproate and Retinoids containing products more MAHs are available. For both groups of products a maximum of three MAHs will be interviewed. A proposal for these MAHs will be made by the research team and discussed with EMA in a regular meeting. This implies that a maximum of 11 MAHs will be interviewed (5 MAHs for the specific products + 3*2 MAHs for the groups of products). With this number of interviews, we expect to reach data saturation with regards to views on roles and, as normally around 12 interviews data saturation is reached (Guest et al., 2006).
- **National competent authorities**. All relevant national competent authorities in the six participating countries will be included in the study. As such, data saturation is not an issue here: we want a complete picture of all participating countries.
- **Professionals (prescribers, pharmacists).** As many as possible professionals in the six countries that prescribe the included medicinal products (both general practitioners and specialists) and as many pharmacists as possible. We will reach the professionals through professional organisations, and the network of the researchers. Furthermore, we will conduct two focus groups with professionals in each country (one with medical doctors and one with pharmacists). By combining these methods, we strive to reach data saturation.
- **Patient organisations.** We will approach the relevant patient organisations in the six countries. As such, data saturation is relevant here: we invite all relevant patient organisations.
- **Patients**. As many as possible patients in the six countries that use one of the included medicinal products. As argued above, some of the products have a low number of users, and no national registration of who the users are is available. Therefore, we include patient organisations in our study to get insight in the patient perspective. In addition, we ask patient organisations to spread the survey to reach patients. We envision that spreading our survey through professionals or via social media only is not sufficient. Furthermore, we will conduct a focus group with patients in each country. By combining these methods, we strive for a maximum of validity and reliability.
- **Stakeholders of all EU/EEA Member States** involved in the dissemination of aRMM. For the webinar, we will also invite stakeholders of other EU/EEA Member States than the ones participating in the study. Through participation of stakeholders from other countries, eventually missing challenges of the dissemination of aRMM can be identified. This ensures data saturation.

1.6. Categories

Given the nature of the study, this section is not applicable.

1.7. Data sources

We will use several data sources: scientific and grey literature, online questionnaires, interviews, focus groups and a webinar. The literature search, online questionnaires, interviews, and focus groups are performed in all six participating countries. For the webinar we will invite stakeholders from the six participating EU Member States as well as the other EU Member States. Table 9 shows the details.

Table 9: Data collection per country

Country	Data collected & type of data	(Nr of) participants	Period of data collection (start – end)
The six included EU Member States *(The Netherlands, Finland, Italy, Hungary, Lithuania, Romania)*	• Scientific and grey literature	-	M1-3
	• Quantitative data from an online survey	• As many relevant patient organisations as possible from the six countries (around 5-10 per country, total around 30-60) • As many professionals as possible (we strive for 50-100 professionals per country)* • As many patients as possible (we strive for 50-100 patients per country)*	M7-8**
	• Qualitative data from interviews	11 interviews with MAHs	M3-4**
	• Qualitative data from focus groups	• 1 with all national competent authorities from the six countries (total around 6)	M3-4**
		• 6 (one in each country) with approximately 8-10 patients per FG (total around 48-60)	M10-11
		• 12 (two in each country) with approximately 8-10 professionals per FG (total around 96-120)	M10-11
	• Qualitative data from the webinar	40-50 in total	M13
All other EU Member States	• Qualitative data from the webinar	40-50 in total	M13

** We will spread the questionnaires for professionals and patients through different channels to reach as many respondents as possible. However, for some of the medicinal products there is a low number of users. We therefore cannot guarantee that these numbers will be reached. When the number of response is higher than expected, these responses will of course be included in the analysis.*

*** Within the WPs above a longer period is mentioned, because there also the preparation of the focus groups, interviews and questionnaires is included. These are only the months of the data collection.*

1.8. Study size

- A maximum of 11 **interviews** will be conducted with the MAH. This number is calculated as follows: for five out of the seven included medicinal products (Xeljanz, Aubagio, Lemtrada, Eylea and Lixiana) the relevant MAH for one country will be interviewed. For both the Valproate and Retinoids containing products more MAHs are available. For both groups of products a maximum of three MAH will be interviewed. This implies that a maximum of 11 MAH will be interviewed (5 MAHs for the specific products + 3*2 MAHs for the groups of products). With this number of interviews, we expect to reach data saturation with regards to the views of MAH on their role and responsibilities in aRMM as well on the ways to distribute aRMM, as normally around 12 interviews data saturation is reached (Guest et al., 2006I).
- In total 19 **focus groups** will be conducted. First, 1 focus group will be organised with representatives from the national competent authorities of all six participating countries. Assuming that there is one national competent authority per country, we expect 6 participants. Furthermore, we organise in each country 2 focus groups with HCPs and 1 with patients,

respectively. We expect approximately 8-10 participants per focus group, being a usual and optimal number of participants for focus groups[14], making a total of 96-120 participants for HCPs (12 * 8-10 HCPs) and 48-60 patients (6 * 8-10 patients). In case focus groups are too difficult to arrange, for example of conflicting schedules of respondents, we will perform interviews instead. Our previous experience shows that including this flexibility ensures the best level of response and most representativity.

- The **online surveys** will be spread via patient and professional organisations as well as through our large network and through as many other different channels as possible. By using as many different channels as possible, we aim to reach enough HCPs, patient organisations and patients. We expect around 5-10 patient organisations for the 7 medicinal products per country, making a range of 30 to 60 patient organisations (5-10 organisations * 6 countries). As the number of users of medicines included in the survey vary across products and across countries, and is in some cases low, we strive to receive 50-100 questionnaires per country for patients and 50-100 per country for professionals. Although we will make every effort to ensure the highest possible response among patients and professionals, we cannot guarantee these numbers.
- For the **webinar** we invite all the relevant bodies, organisations and stakeholders that participated in the online questionnaires, focus groups and interviews in each of the six included countries, as well as relevant bodies, organisations and stakeholders from other EU Member States. We expect to have around 40-50 participants for the webinar.

1.9. Data management

A data management plan will be developed following the FAIR principles[15] (Findability, Accessibility, Interoperability and Reusability). At a minimum, the plan will include a detailed description of:

- the data that we expect to produce (e.g., data from the online questionnaires, interviews, focus groups and webinar);
- how, when, and where data will be acquired; data processing systems (e.g., software (Stata, MaxQda, AtlasTi or Excel), algorithms, workflows);
- file formats with justification; quality assurance and control measures used during collection, analysis, and processing;
- data management systems (version control, backup procedures and timing, security and protection, and responsibilities).

To assess the implementation level of the FAIR data principles in the data we collect, we will use the core criteria of the FAIR data maturity model developed by the RDA FAIR Data Maturity Model Working Group[16]. We will submit this plan as an appendix to the study protocol (deliverable 2; appendix deliverable 2.1; see Table 10) to EMA. One of the researchers will be appointed to be responsible for day-to-day management of the data which will be stored at a secured area of the Nivel server. After the project data will be stored on a different server, where only the project leads (van Dijk; de Jong) have rights to access; data will be stored for a maximum of 10 years. Other partners will follow the same procedures as Nivel for storing and archiving data, including protections needed according to privacy regulations.

1.10. Data analysis

We perform a mixed methods study, using desk research, online surveys, interviews, focus groups and a webinar. Here we describe, for the online surveys, the interviews, the focus groups and the webinar, how we analyse the data collected. The information collected during the desk research will be

[14] https://participatiekompas.nl/media/pdf/handleiding_focusgroepen_2019_april_-tg.pdf
[15] https://www.force11.org/group/fairgroup/fairprinciples
[16] https://www.rd-alliance.org/groups/fair-data-maturity-model-wg

summarized and subsequently used as input for the development of the online surveys and the interview/focus group guides.

Desk research
Selected documents will be summarised in an extraction table. Data that are extracted include: authors' names, year of publication, country/countries of publication and project, main topic/angle of the publication, methods used, main results (relevant for the study) and author's conclusion. Narrative synthesis will be conducted to summarize the information from the publications. A narrative synthesis uses a textual approach to analyse the relationships within and between studies.

Online surveys
- Descriptive analyses will be used to analyse the data from the online surveys from HCPs, patient organisations and patients and organized according to the chosen CFIR constructs.
- The results will be presented in figures (e.g. bar charts, pie charts) and tables. Each figure and table will be accompanied with a short description of what is presented within the figure/table.
- If relevant and possible, differences between countries, RMM and medicinal product will be analysed and described (e.g. differences in preferences for aRMM tools). NB: Because of the low number of users for some medicinal products, we do expect that not all subgroup analyses are possible.
- An experienced researcher of the team records all analysis steps in a syntax. This syntax is checked by a second experienced researcher from the project team.
- We will use Stata version 16.0 for the analyses.
- Reporting for the surveys will be done based on the criteria for reporting on survey research of the Consensus-Based Checklist for Reporting of Survey Studies (CROSS).

Interviews and focus groups
- Interviews and focus groups will be audiotaped and transcribed. The interviews with the MAH and the focus group with the national competent authorities will be in English. The focus groups with professionals and patients in the six countries will be in the national language of each of the six participating countries.
- The transcripts of these focus groups will be analysed by the focal points of each country in their own language. They will report the results in English.
- We will use thematic analysis with a mainly deductive approach to analyse the data. Thematic analysis is appropriate to obtain insight in views, opinions, knowledge, experiences, or norms and values. A deductive approach means analysing the data based on a number of predetermined themes, which we, based on the desk research and the use of the CFIR framework, expect to be reflected in the data. In order to be sure we do not miss information, we will inductively add codes in case they are not included in our framework for the analysis.
- For the first 3 interviews for MAH, two Nivel researchers will independently analyse the transcripts using software for qualitative data (MaxQda or Excel). The researchers will compare their codes and discuss discrepancies; the remaining interviews will be analysed by one researcher and will be checked by a second researcher.
- The 19 focus groups (1 with national competent authorities, 12 with professionals and 6 with patients), will be independently analysed by one researcher in each country and codes will be discussed in an online meeting (prepared by Nivel) among the six coding researchers . The researchers will compare their codes and discuss discrepancies. After the meeting they will check their own coding. Finally, the coding results will be discussed in the full research team. This way we diminish coding bias as much as possible.
- We will use deductive coding, meaning that we use the same predefined set of codes for each interview/focus group based upon the interview/focus group guide used in the interviews and focus groups. During the coding process, codes will be added if deemed necessary.
- We will draft tables where we present the results of the interviews and focus groups by, if relevant and possible, type of aRMM, by medicinal product, by dissemination method, by key

stakeholder involved and by country. These tables will be drafted by one researcher and will be independently checked by two other researchers.
- In the presentation of the results, quotes from the interviews and focus groups will be used to illustrate the results presented in the tables.
- Reporting of the interviews and focus groups will be done based on the criteria for reporting on qualitative research of the COREQ.

Webinar
- The webinar will be audiotaped and transcribed.
- Comparable to the interviews and focus groups, two researchers of Nivel will independently analyse the transcript using software for qualitative data (MaxQda). Aim of this analysis is to examine whether the preliminary results and conclusions of the study are complete, or whether additions or adjustments have to be made. The researchers will compare their findings and discuss discrepancies. Finally, the results will be discussed in the full research team.

Overall
To integrate the data from the different and mixed methods, we will follow the GRAMMS framework for overall mixed methods integration and reporting (O'Cathain 2008) which contains six steps: (1) describing the justification for using a mixed methods approach to the research question; (2) describing the design in terms of the purpose, priority and sequence of methods; (3) describing each method in terms of sampling, data collection and analysis; (4) describing where integration has occurred, how it has occurred and who has participated in it; (5) describing any limitation of one method associated with the present of the other method and (6) describing any insights gained from mixing or integrating methods (adapted from O'Cathain 2008).

1.11. Publication and communication of results

Major deliverables
Four major deliverables and three appendices (all to D2) will be delivered (see table 10). The first two deliverables will lay down the base for the study, the last two deliverables will contain the results.

Table 10: List of Deliverables

Deliverable number	Deliverable name	Related to WP	Lead	Type	Delivery month
D1	Preliminary study plan	All	Nivel	Proposal	2
D2	Study protocol	All	Nivel	Proposal	4
D3	Study report	All	Nivel	Report	14
D4	Manuscript scientific article	All	Nivel	Manuscript	16
Appendix to deliverables					
D2.1	Data management plan	All	Nivel	Appendix to D2	4
D2.2	Communication plan	All	Nivel	Appendix to D2	4
D2.3	Publication plan	All	Nivel	Appendix to D2	4

Data management plan
See section 1.9.

Communication plan
At the start of the study, we will develop and implement a communication- and dissemination plan to make our work broadly known and to interact with a range of target groups (e.g. health care professionals, patients, educators/scientists, employers) about our lessons learned/strategies/products. This communication- and dissemination plan will be drawn and shaped at the start of the project and will be adapted over the course of the project. The basis of this plan is an impact creation strategy (see: Hansen 2013). It distinguishes between the steps needed for impact

creation before, during, and beyond the project and the different users of the results.

Publication plan
There will be two public publications: the study report and a scientific manuscript. Table 12 (see page 27) shows the timelines for both these publications. The scientific manuscript will be published open access. Authors need: 1) to have a substantial contribution to the conception or design of the work or the analysis or interpretation of data and 2) to be involved I drafting the work or reviewing it critically for important intellectual content and 3) give final approval of the version to be published and 4) to agree to be accountable for all aspects of the work.[17]

1.12. Reporting of adverse events and suspected adverse reactions
Given the nature of the study, this section is not applicable.

1.13. Limitations of the research methods
- Representativeness:
  1) We include 6 countries spread across the EU. We choose countries from different regions, size and healthcare systems. Still, other countries might have information to add. Therefore, we will organise a webinar, in which representatives from all EU/EEA member states can participate and reflect on the preliminary outcomes of the study.
  2) The online surveys for HCPs, patient organisations and patients will be spread via our large network and through as many different channels as possible. With this, we strive to reach enough HCPs, patient organisations and patients. Still, we might miss information from certain groups, for example from patients that are not able to fill out surveys online. Therefore, we will organise in each country one focus group with HCPs and one with patients. In these focus groups, the participants can reflect on the preliminary outcomes of the questionnaires. If possible, we will recruit participants for the focus groups among the groups that are that are least represented in the survey. To also recruit patients that are not able to fill out online questionnaires for the focus groups, we will ask patient organisations whether they can recruit patients for the focus groups.

- Content: Participants of the interviews or focus groups might not want to share information about for example criteria for successful dissemination of aRMM, or barriers. Particularly for MAHs, this may involve competitively sensitive information. In order to minimise this risk we will not share the results using names and names of organisations for specific statements except for if the participant gives informed consent.

- Bias in coding: In order to avoid bias in coding, part of the data will be double coded by two researchers (until there is sufficient agreement between the researchers). Finally, the coding results will be discussed in the full research team.

- Bias in analysing survey data: In order to avoid mistakes in analysing the survey data, the steps to analyse the data will be recorded in a syntax by an experienced researcher. This syntax is checked by a second experienced researcher from the project team. In case of doubt about the analyses, we will consult a statistician at Nivel.

1.14. Protection of human participants
All countries adhere to their national Code of Conduct for Research Integrity as well as will adhere to EU Union Requirements. Informed consent for the interviews and focus groups will be asked orally and recorded; if required in a country, written consent will be arranged. Informed consent for the online

[17] Adapted from: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

surveys will be asked at the start of the questionnaire. Respondents of the online surveys, interviewees and participants in the focus groups are informed that they can refrain from the study at any time. Names of participants in the online surveys, interviews, focus groups and webinar will not be released. No individual patient-level data will be used (see also section 2; Quality control).

1.15. Ethical aspects

The study is coordinated by the Netherlands. According to the Dutch legislation, approval by a medical ethics committee is not obligatory for carrying out this study. The reasons for this are that this study does not concern medical scientific research, and that participants are not subject to procedure or are required to follow rules of behaviour. Participation in the online surveys, interviews, focus groups and webinar is voluntary and representatives are not forced to participate, or to answer questions within the survey, interview, focus group, or webinar. They can stop with the questionnaire, interview, focus group, or webinar at any time without having to give a reason. However, as international publishers increasingly ask for prove of ethical approval and in some of the countries ethical approval is an obligation, we will apply for ethical approval in all countries in line with the regulations in each country. For example, for the Netherlands and Finland this means getting a waiver and in Romania and Hungary this means a full ethical approval from the ethics committee.

1.16. Other aspects

No other aspects to be reported.

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PART II. PROPOSED ORGANISATION OF WORK

2.1. General approach for the organisation of the study

Figure 3 showed the structure of the project. The study is divided into six work packages that will be performed (partly) at the same time. In section 1.4 we have explained this in more detail.

Planning in short

The preliminary study plan (D1; delivery date: month 2) and the study protocol (D2, D2.1, D2.2, D.3; delivery date: month 4) will include the plans for WP 1-6. The study report, which will reflect the results of WP 1 to WP5 will be delivered in month 14 and the manuscript for a scientific article in month 16 (see also table 12; GANTT chart).

Organisation of work and quality assurance

- The way we organise the study is that we work simultaneously on WP1 to 4.
- In M1-4 of the study we develop the preliminary study plan, and the study protocol. We also perform the desk research, to get input for the questionnaire and the guides for the focus groups and interviews. We will perform this part of the study from month 1-4 as a solid basis for the other parts of the project.
- In M4-8 the online questionnaires for HCPs, patient organisations and patients will be developed and conducted. We know from our experience that 4 weeks are needed to develop a solid questionnaire using an iterative process in which multiple researchers are involved. Then the questionnaire needs to be programmed in the different languages, and checked by the countries (in total around 2 months) and the questionnaire needs to be online for around 2 months, so that there will be enough time to distribute the questionnaire through different channels. Analyses will be performed in month 9 and further.

- Questions following from analysing the results of the questionnaire will be included in the focus group guides for HCPs and patients, that thus will be developed in M10. M10-11 are used to conduct the focus groups.
- In M13 the webinar and the synthesis workshop for researchers will be organised, with preparations starting in M12.
- The last months will be used for further analysing and reporting (see also the GANTT-chart in section 2.2).

We will follow the following principles

- The project leads (van Dijk, de Jong) install the teams (including supporting staff)
- The project leads and the day-to-day coordinator (Brabers) determine all procedures (reporting; quality assurance; development of deliverables).
- The project leads develop an internal management plan concerning: 1) Activities and interrelations; 2) Work breakdown structure + Time schedules; 3) Costs per phase, per commitment; 4) Quality management /Human resources (Nivel + subcontractors); 5) Management of communication; 6) Risk and mitigation management; 7) Management of project related procurements; 8) Managing stakeholder involvement; 9) Monitoring progress by using state-of-the-art tools to monitor the progress of the projects (PERT, GANTT).
- The project leads and day-to-day coordinator will be committed to optimal risk management by continuously identifying, evaluating, and prioritising risks through coordination resources to minimise, monitor, and control the probability or impact of unfortunate events or to maximise the realisation of opportunities.
- Serious risks and problems that might affect the major outcomes of the project will always be communicated to EMA by Nivel via the project coordinator and or the co-lead, also a member of the Management Team of Nivel.
- All deliverables will be linked to a lead researcher and all deliverables will be reviewed by the entire project team. If necessary, the team will consult experienced international researchers at Nivel (e.g. Hansen, van der Heide) for additional advice on the desired and agreed quality of deliverables.
- The study report and the manuscript will be reviewed – per standard – via Nivel's internal scientific review procedure, and by all researchers involved in the project.

The **meetings within the project** will be organised as follows

- Meetings at Nivel-level: project lead and back-up project lead are responsible for organising the meetings, the day-to-day coordinator prepares the meetings. Project lead, back-up project lead and day-to-day coordinator have weekly meetings to discuss the progress and content of the project. Also, supporting staff will be invited to the meetings for those parts of the study where their input is needed.
- Meetings of the complete project team: over the course of the project the complete project team will meet every month to discuss progress, results, and the draft-reports. Nivel's project leader is responsible for the coordination.
- Meetings of representatives of the project team with EMA to discuss the study plan (M2), the study protocol (M4), the report (M14) and manuscript (M16) as well as other milestones (see table 12).

2.2. Roles and responsibilities

Nivel (Netherlands) is the responsible coordinator for as a lead for all six WPs, the other countries are responsible for the tasks described in Table 11 in their own country. Table 11 shows the project team members, their function in the study and a further description of this function.

Table 11: Team: tasks, roles and function in the study with description

Person name	Organisation	Function in the study	Description of the function
Prof. dr. Liset van Dijk	Nivel	Project lead	Will safeguard the excellence of the project. Project management including planning of the budget. International contacts. Involved in development of all questionnaires, analysing and reporting (including editing), writing first draft of the executive summary
Prof. dr. Judith de Jong	Nivel	Vice project lead	Project Management. International contacts. Analysing and reporting, involved in development of all questionnaires, moderator in WP5 tasks
Dr. Anne Brabers	Nivel	Day-to-day coordinator, senior researcher	Monitoring progress of the project, coordination of desk research, survey, focus groups, interviews, and webinar including development of questionnaires. Analysing and reporting.
Dr. Marcia Vervloet	Nivel	CFIR-expert / Senior researcher	Will lead the discussions on the CFIR-based content in the questionnaires and topic lists, advise on the analysis and review the CFIR-based parts of the report.
Researcher	Nivel	Researcher	Performing research tasks, like developing online survey and interview guide, coordinating the cognitive interviews, organising the webinar, analysing and reporting.
Sergueï Markovic	Nivel	Project controller	Project controller for the project
Dr. Balázs Babarczy	Syreon Research Institute	Country lead / senior researcher	Hungary, Finland, Italy, Romania, and Lithuania will perform and be responsible for the following tasks in their own country: *Desk research* Searching for country specific information on medication use and literature *Survey* Recruiting patient and professional organisations and via them patients and professionals Reviewing questionnaires, and translating in own language, Performing 1-2 cognitive interviews Monitoring response in own country Check and supporting in interpreting results from own country *Focus groups patients and professionals* Reviewing interview guide Selecting/recruiting patients/ professionals Organizing one focus group for patients and one for professionals Analyzing the transcript Make a summary *Focus group national competent authorities* Getting Nivel in touch with national competent authority Reviewing topic list if wanted
Dr. Tamás Ágh	Syreon Research Institute	Senior researcher	
Prof. dr. Katri Hämeen-Anttila	University of Eastern Finland	Country lead	
Dr. Emma Aarnio	University of Eastern Finland	Senior researcher	
Researcher	University of Eastern Finland	Researcher (post-doc)	
Prof. Enrica Menditto	University of Naples	Country lead	
Prof. Valentina Orlando	University of Naples	Co-country lead	
Dr. Sara Mucherino	University of Naples	Researcher	
Dr. Alexandra Onisor	Universitatea Babes-Bolyai	Country lead/day-to-day project coordinator for UBB	
Marius Ungureanu	Universitatea Babes-Bolyai	Senior researcher	
Dr. Oana Blaga	Universitatea Babes-Bolyai	Researcher	
Dr. Stefania Szeibert-Kerekes	Universitatea Babes-Bolyai	Researcher	
Assoc. prof. dr. Indrė Trečiokienė	Vilnius University	Country-lead	

Assoc. prof. dr. Jurate Gudonytė	Vilnius University	Senior researcher	*Interviews MAH* Getting Nivel in touch with MAH (if possible) Reviewing interview guide if wanted *Synthesis and reporting* Participating in workshop Reviewing report if wanted Participating in webinar if wanted
Han van Dongen	DESAN	Director	Mail house that is responsible for programming the questionnaires for all countries and the data collection of the questionnaires for all countries.

2.3. Plan and timelines for deliverables

The plan and timeline for deliverables will follow the schedule provided by EMA. The Gantt chart below (Table 12) provides an overview of the six WPs, the subsequent activities and a proposed timeline for the activities and deliverables. WPs 1 to 4 consist of desk research, surveys, and focus groups and/or interviews. In WP5, a webinar and a synthesis workshop for the researchers will be organised. The first months of the WPs consist of desk research (M1-3). From month 2 onwards, we start with preparing and organising the focus group with national competent authorities and the interviews with marketing authorisation holders. The first four months will also be used to yield the first two deliverables: the preliminary study plan (M2) and the study protocol (M4). As part of the study protocol we also suggest to develop data management, communication and publication plans. Subsequently, during the months 4-8 we will develop the three questionnaires and prepare the data collection for the questionnaires. The data collection of the three questionnaires will take place in months 7-8 (with some back-up time in month 9). In months 10-11 the focus groups with professionals and patients will be conducted. We start with the recruitment of respondents for all the methods from the start of the project. Finally, as part of WP5 a webinar will be organized and a syntheses workshop for researchers, both in month 13. The last months will be used to yield the third and fourth deliverable, respectively: the study report (M14), and the manuscript (M16). However, we will start with writing the study report from the beginning of the project. For the manuscript the study report is an important building block. To ensure the project team gets to high-quality deliverables, we have set up a sixth WP on management. Within this WP, the project members will meet on a regular basis to align and discuss the project's progress. A mid-term and end-term evaluation meeting is also foreseen and will be an opportunity to reflect on the project's achievements and lessons learned.

Table 12: GANTT chart for the study

		M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 14	M 15	M 16
	WP 1:																
T1.1	Desk research	■	■	■													
T1.2	Interviews MAHs		■	■	■												
T1.3	Focus group authorities		■	■	■												
T1.4	Survey professionals + patient organisations[1]				■	■	■	■	■								
T1.5	Focus group professionals										■	■					
	Recruitment of respondents[2]	■	■	■	■	■	■	■	■	■	■	■					
	WP 2:																
T2.1	Desk research	■	■	■													
T2.2	Interviews MAHs		■	■	■												
T2.3	Focus group authorities		■	■	■												
T2.4	Survey professionals + patient organisations				■	■	■	■	■								
T2.5	Focus group professionals										■	■					
T2.6	Short survey patients				■	■	■	■	■								
T2.7	Focus group patients										■	■					
	Recruitment of respondents[2]	■	■	■	■	■	■	■	■	■	■	■					
	WP 3:																
T3.1	Desk research	■	■	■													
T3.2	Interviews MAHs		■	■	■												
T3.3	Focus group authorities		■	■	■												
T3.4	Survey professionals + patient organisations				■	■	■	■	■								
T3.5	Focus group professionals										■	■					
	Recruitment of respondents[2]	■	■	■	■	■	■	■	■	■	■	■					
	WP 4:																
T4.1	Desk research	■	■	■													
T4.2	Survey professionals + patient organisations				■	■	■	■	■								
T4.3	Short survey patients				■	■	■	■	■								
T4.4	Focus group professionals										■	■					
T4.5	Focus groups patients										■	■					
	Recruitment of respondents[2]	■	■	■	■	■	■	■	■	■	■	■					
	WP 5:																
T5.1	Webinar													■			
T5.2	Syntheses workshop													■			
	WP 6: Management																
T6.1	Kick-off meeting	■															
T6.2	Progress meetings		■	■	■	■				■	■			■	■		■
T6.3	Evaluation meetings								■								■
	Deliverables																
D1	Preliminary study plan		x														
D2	Study protocol				x												
D2.1	*Data management plan*				x												
D2.2	*Communication plan*				x												
D2.3	*Publication plan*				x												
D4	Study report														x		

		M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	M 13	M 14	M 15	M 16
D5	Manuscript																x

[1]*Period for developing survey, programming survey and data collection.*
[2]*We start with the recruitment of patient organisations, professionals, patients, marketing authorisations holders and national competent organisations from the start of the project. Depending on the phase of the project, we will focus on one or more groups for recruitment.*

2.4. Allocation of resources

Nivel will coordinate the project, and also has some additional work, next to the country specific work that all six countries have. Table 13 provides an overview about how we plan resources in the study for Nivel and the other countries. We describe this planning for the different methods we use (and mention the tasks in which this method will be used).

Next to this, DESAN will participate in the study:

- DESAN will programme the questionnaires for all countries and handle the data collection of the questionnaires for all countries.

Table 13: Allocation of resources to functions per main task in days

	Project leads Nivel	Coordi-nator Nivel	Resear-chers Nivel including research support	Country leads other countries (for 5 countries in total)	Resear-chers other countries (for 5 countries in total)	DESAN Field work	Total
Desk research Includes tasks: 1.1, 2.1, 3.1 and 4.1	1	1	5	2.5	15		*24.5*
Interviews MAHs Includes tasks: 1.2, 2.2, 3.2	0.5	2	15	1	5		*23.5*
Focus group Competent authorities Includes tasks: 1.3, 2.3, 3.3	0.5	2	15	1	5		*23.5*
Survey HCPs and patient organisations Includes tasks: 1.4, 2.4, 3.4, 4.2	1	4	28	7.5	40	40	*120.5*
Focus groups HCPs Includes tasks: 1.5, 2.5, 3.5, 4.4	0.5	4	18	7.5	80		*110*
Short survey patients Includes tasks 2.6, 4.3	0.5	3	16	2.5	15	12	*49*
Focus groups patients Includes tasks 2.7, 4.5	1	4	18	5	80		*108*
Webinar Includes task 5.1	1	2	4	5	2.5		*14.5*
Synthesis workshop Includes task 5.2	1	2	3	5	7.5		*18.5*
Management overall Includes WP6	5	12		10			*27*
Total	***12***	***36***	***122***	***47***	***250***	***52***	***519***

Other resources include costs for:

- Webinar hosting (WP5)
- Open access (WP1-5)
- Travel costs (WP1-4)
- Accountant costs (WP6)
- Transcribing interviews and focus groups (WP1-4)

Overall, the division of the budget across the WPs is as follows: Nivel: 35%, Hungary: 10.5%, Italy:11%, Romania: 10.5%, Finland: 13%, Lithuania: 10.5%, and DESAN: 9.5%.

2.5. Communication with EMA and third parties

- It is our vision that communicating with EMA during the project is of utmost importance.
- Several meetings will be organised by Nivel:
  - The project will start with a kick-off meeting between Nivel and EMA (M1).
  - A meeting to discuss the preliminary study plan (M2)
  - A meeting to discuss the study protocol and to show the first results from the desk research (M4)
  - A meeting to discuss the concepts of the interview guides for the focus group with national competent authorities and interviews with marketing authorisation holders (M3)
  - A meeting to discuss the concepts of the online questionnaires for professionals, patient organisations and patients (M4)
  - A meeting to discuss the concepts of the interview guide for the focus groups with professionals and patients (M10)
  - A meeting to show first impressions of the results of the focus group with national competent authorities and interviews with MAHs (M5)
  - A meeting to show first impressions from the online questionnaires with professionals, patient organisations and patients (M9)
  - A meeting to show first impressions from the focus groups with professionals and patients (M13)
  - A meeting to discuss the programme of the webinar (M13)
  - A meeting to discuss the draft report (M14)
  - A meeting to discuss the manuscript (M16)
- From each meeting minutes will be written by Nivel and shared with EMA.
- Regular updates on the progress of the project will be sent to EMA once a month by the project leader.
- Serious risks and problems that might affect the major outcomes of the project will always be communicated to EMA by Nivel via the project coordinator and or the co-lead, also a member of the Management Team of Nivel. Furthermore, Nivel is available for ad hoc teleconferences as needed.
- Communication with third parties will take by communicating about the project results through the website of Nivel, social media and by sending a press release (news item).

Development of communication products

The development of communication products will be the responsibility of Nivel, the project lead with support from a communication officer at Nivel. To create the communication products, the project lead will work laterally with the whole team to develop materials which a factually accurate, but also easy to read and which are developed in line with appropriate public relations messaging. Content will be shared with EMA, before it is made public. Table 14 summarizes the products.

Table 14: Communication products

Communication product	Content Creation Approach
Press release (news item)	The Press Release will be written in the style of a news story (Who, where, what, when, why & how) and will seek to flag the newsworthy elements of the story in a way which is both readable and engaging for a non-technical audience. We would propose that an engaging quotation from a spokesperson be added, although this is not always necessary. The Press Release will be one page in length, and will detail a contact person for more information, plus other relevant links.
Social Media	The press release will be shared on platforms like Linked-in. Furthermore, we will provide a message for tweeting after the final report is publicly available. This message will be written in simple yet engaging language, and will reference any appropriate hashtags. This item will also be shared by all six countries through the Linked-In account of their organisation.
News item on the Nivel website and on the websites of the participating organisations of the other countries	A news item for publication on the Nivel website will be created. Regarding structure, it would follow the classic 5Ws+1H (who, where, what, when, why & how) and we would also suggest to incorporate some quotations into the news item to give it authority and engagement. Reference will be made to the publicly available report. This news item will also be made available through the websites of the participating organisations in Finland, Italy, Lithuania, Hungary, and Romania.

Data availability

- The summary with the results from the desk research will be made available for EMA, after the literature search has been finished in M3 (M4).
- An anonymous report from the online surveys will be made available for EMA (M14).
- An anonymous report from the interviews and focus groups will be made available for EMA after all focus groups and interviews are performed (M14).

PART III. QUALITY CONTROL

3.1. General approach to quality management and control

The team has excellent awareness of the importance of quality control systems for the execution of services foreseen.

- Nivel follows the Code of Conduct of the Association of Universities in the Netherlands (VSNU) and is a member of the National Body of Scientific Integrity (LOWI) and in the consortium agreement we will lay down that partners will follow the same principles.
- Quality management: The quality management systems (QMS) of Nivel is independently certified as compliant with ISO9001:2015, which is an international consensus on good quality management practices and the most appropriate for knowledge intensive organisations. The achievement and confirmation of this certification indicates Nivel's dedication to quality, not only in its research and project activities, but also interactions with clients and other external actors. By earning an ISO ISO9001:2015 certification, Nivel has been internationally recognised as conducting robust and effective internal business processes that support continuous organisational improvements and learning. We are able to maintain this through three core principles: diverse and effective feedback mechanisms; open and transparent communications; and standardised operating procedures. To verify Nivel's business process quality assurance is up to ISO standards, Nivel is audited annually by Certified independent external auditors
- For its research outputs, Nivel has developed quality guidelines and instructions and has installed a quality working group that monitors and advises on the use of the guidelines. Nivel, being the consortium lead, will oversee that these quality control guidelines and instructions are adhered to in all phases of the project. In addition, and as stipulated by EMA in the technical specifications of the tender, we will ensure that the study is registered in the HMA-EMA Catalogue of real-world data studies and will as such follow the code of conduct of the European

Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Research deliverables will adhere to the standards provided by EMA in the technical specifications.

- Risk management: Nivel and its partners will maintain a direct focus on all relevant risks in the entire project and in the various work packages and components. The project leaders will be committed to optimal risk management by continuously identifying, evaluating, and prioritising risks through coordination of resources to minimise, monitor, and control the probability or impact of unfortunate events or to maximise the realisation of opportunities. Nivel is committed (and uses ICT-tools) to detect risks early and provide solutions quickly and will ensure that partners are aware of risk mitigation processes. Serious risks and problems that might affect the major outcomes of the project will always be communicated to EMA by Nivel via the project coordinator and or the co-lead, also a member of the Management Team of Nivel. Table 15 describes the management of some specific risks in more detail.
- Data protection: All personal data will be processed according to EU data protection legislation such that it will meet the requirements of Regulation (EU) 2018/1725. We will process all personal and sensitive personal data accessed or collected during this project in accordance with Article 4 EUDPR which requires that data are:
  - processed lawfully, fairly, transparently;
  - collected for a specific, explicit and legitimate purposes;
  - adequate, relevant and limited to what is necessary for the stated purpose;
  - accurate and where necessary kept up to date;
  - kept in a form which permits identification for no longer than is necessary for the purpose
  - processed in a secure manner
- Data privacy: Data will only be collected from persons aged 18 years or older, unless agreed differently with the Contracting Authority. Collection of sensitive personal data via surveys, workshops or interviews may require that a Data Privacy Impact Assessment (DPIA) is undertaken in accordance with Article 39 EUDPR. We shall assess the potential need for a DPIA and if deemed we will draft a DPIA.
- Data security: Data will be stored in Nivel's and partners' secure data processing environments. Nivel has an Information Security Management System (ISMS) which falls under Nivel's Quality Management System which complies with the provisions of Coreon's Code of Conduct for Medical Research of the Foundation Federation of Dutch Medical Scientific Societies, the Netherlands Code of Conduct for Research Integrity 2018, IS0-27001 and GDPR. Nivel has a security officer and data protection officer who monitor compliance with security provisions and Nivel's information security policy that is periodically audited. All information security incidents are reviewed by the security officer and the data protection officer to assess the course of action in case of a potential data breach. Nivel also has an ICT Crisis Management Plan and carries out periodic exercises in that area.
- Project management: Project leaders and supporting staff working on behalf of Nivel are well-trained, experienced and have strong ICT-based tools to monitor projects. In addition, we will install a day-to-day coordinator who will monitor the progress of the project against the tasks, deliverables, and milestones, and will, in alliance with the partners, set up a contingency plan in case of any deviations in tasks, deliverables and milestones.
- Nivel is in favour of an open culture in which all team members feel safe to discuss any matters freely. An internal and external confidential counsellor is available to all Nivel staff members. As of December 2018, the Dutch code of conduct for Scientific Integrity is applied to all scientific staff that work for Nivel. In addition, Nivel also adheres to the code of conduct on health research.

Table 15: Management of critical risks

Description of risk	WP(s)	Severity level	Likelihood	Proposed risk-mitigation measures
Recruitment for the interviews and focus group is not completed within due time	WP1-4	High	Moderate	• We will start approaching MAHs and national competent authorities as soon as possible. We will ask EMA for contacts of MAH. We will interview the MAH in the first country that agrees to participate. • We make appealing and clear information. • We will remind by e-mail and in case this does not work, we will contact respondents personally by phone. • In case due to language and/or technical barriers representatives of the national competent authorities cannot participate in the focus group, an interview in the national language will be done by the focal point of that country.
Response on the online surveys and focus groups for HCPs, patient organisations and patients is (too) low within due time	WP1-4	High	Moderate	• We will distribute the questionnaire through as many channels as possible. Hereby we make use of the large network of the consortium. We also ask patient organisations to spread the questionnaire. • Within the questionnaire we include a question to recruit patients and professionals for the focus groups. In case this does not result in enough response, we will recruit participants for the focus groups through our patient organisations and/or our large network. • If participants are not able to participate in focus groups, countries may decide to conduct individual interviews either online or by phone. • For patients that are not able to fill out the questionnaire online because of low digital skills, countries have the flexibility to decide to establish a procedure for contacting them by phone and filling in the online survey within the open link programmed by DESAN while speaking with them by phone. • We make appealing and clear information. • We make the questionnaires as short as possible.
Quality of deliverables not according to expectations	WP1-5	High	Low	For each deliverable, a thorough review will be performed by all members of the team. The overall quality of deliverables is to be monitored by the day-to-day coordinator. The expertise and capacity available in the team make the likelihood of this risk low.
Data protection & GDPR failures	WP1-5	High	Low	Nivel has two designated lawyers who combine their experience in data protection regulation and the GDPR and one of whom holds an EU data protection certificate. Nivel holds an ISO 9001 certificate for its research process since 2000 and has strong regulations on data protection. DESAN is ISO 27001 and ISO 20252 certified.
Difficulties on carrying out the work plan in a potential new pandemic or due to issues related to the situation in Ukraine and the Middle East	WP1-4	Low	Low-medium	The project has been designed so that all activities can be performed online. Research work can also be performed from a distance.
Poor performance or management issues with a partner	WP1-5	High	Low	All partners are experienced in performing complex international projects and are fully committed to the project. Project management monitoring will incorporate measures to anticipate and resolve potential problems.
Withdrawal of one of the partners	WP1-5	High	Low	All partners are experienced in performing complex projects. Regular communication and telecons will be held to keep everyone involved. If a partner actually withdraws, the work will be performed by one of the other partners.

3.2. Specific aspects of quality management and control

None

PART IV. ANY OTHER BUSINESS

No other businesses to be reported.

PART V. SUPPLEMENTARY DOCUMENTS

5.1. List of Supplementary documents

- Letter enclosing the tender on the official letter headed paper of the tenderer and signed by an authorised representative of the tenderer
- A completed tenderer's declaration (Annex I)
- A financial tender using the costing sheet (Annex II)
- A completed minimum technical requirements declaration (Annex III)
- Subcontractors declarations (Annex IV)
- A completed checklist (Annex VI)
- Letters of intent

5.2. Supplementary documents (Optional)

Not applicable.