Dissemination of additional risk minimisation measures for patients and healthcare professionals in EU/EEA countries (DIS-aRMM study)

Protocol, version 3.0 29-08-2025

HMA-EMA Catalogue of RWD Studies registration number: EUPAS1000000524

FWC/EMA/2020/46/TDA/L4.01 – SC01

Nivel (Netherlands Institute for Health Services Research)

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August 2025

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1. Title

Dissemination of additional risk minimisation measures for patients and healthcare professionals in EU/EEA countries (DIS-aRMM study)

2 & 3. Tenderer and Responsible parties

This study will be performed in six countries, namely the Netherlands, Finland, Hungary, Lithuania, Italy and Romania. Hereafter, information about the partners in each country is given.

Tenderer: Nivel (Netherlands Institute for Health Services Research)
Scientific contact person and main authors protocol: Prof. dr. Liset van Dijk, Nivel (principal investigator)
Dr. Anne Brabers, Nivel (day-to-day coordinator)
Dr. Madelon Kroneman, Nivel (senior researcher)
Administrative contact person: Sergueï Markovic, Nivel

Table 1 Organisations participating in the project and their roles

Organisation and address	Key person	Role(s)
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 Dr. Iris van der Heide Dr. Madelon Kroneman	Lead Co-lead Day-to-day coordinator/ senior researcher Senior researcher Senior researcher Senior researcher
Syreon Research Institute Mexikói út 65 1145 Budapest Hungary	Dr. Balázs Babarczy Dr. Tamás Ágh	Country lead/ senior researcher Senior researcher
University of Eastern Finland Yliopistonranta 8 70210 Kuopio Finland	Prof. dr. Katri Hämeen-Anttila Dr. Emma Aarnio Mella Louhisalmi	Country lead Senior researcher
University of Naples C.so Umberto I, 40 80138 Napoli NA Italy	Prof. Enrica Menditto Prof. Valentina Orlando Dr. Sara Mucherino	Country lead Country co-lead Researcher
Universitatea Babes-Bolyai Mihal Koălniceanu 1 400084, Cluj-Napoca Romania	Dr. Alexandra Onisor Assoc. prof. dr. Marius Ungureanu Assis. prof. dr. Oana Blaga Dr. Stefania Szeibert-Kerekes	Country lead Senior researcher Researcher Researcher
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4. Abstract

Title with subtitles
Dissemination of additional risk minimisation measures for patients and healthcare professionals in EU/EEA countries (DIS-aRMM study)

Version and date
Version 3, 29-08-2025

Name and affiliation of main author
dr. Anne Brabers (Nivel)

Rationale and background
Additional risk minimisation measures (aRMM) tools for medicinal products are imposed in case routine RMM tools are insufficient to control risks. These tools have to be put into place. For aRMM to be effective, the materials should reach the users, who then should use these as expected. Current literature barely focuses on the distribution process of aRMM materials. From a regulatory perspective, little is known about the practical aspects and roles and responsibilities of the stakeholders involved in the dissemination processes at the national level. Therefore, this study focuses is on the physical dissemination of aRMM materials for seven selected medicinal products.

Research question and objectives
The overall objective is to gain in-depth understanding of the current practice of dissemination of aRMM materials for patients and healthcare professionals (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 for regulatory decision-making to regulators on aRMM based on patients' and HCPs' preferences and needs.

Study design
This study includes six countries with different healthcare systems: the Netherlands, Finland, Italy, Hungary, Romania and Lithuania. The study has a mixed-method approach, combining qualitative and quantitative methods and includes the following steps: 1) desk research, 2) online interviews with marketing authorisation holders (MAHs), 3) a focus group with representatives of national competent authorities (NCAs), 4) online surveys and focus groups with HCPs, patient organisations and patients, and 5) a webinar with stakeholders from all EU/EEA member states to discuss the results of the study. The webinar includes stakeholders from countries not participating in the study.

Study population
Marketing authorisation holders (MAHs), national competent authorities (NCAs), healthcare professionals (HCPs) (prescribers, pharmacists), patient organisations, and patients.

Variables
Relevant outcomes in this study are: process and frequency of how aRMM are disseminated; roles and responsibilities of key stakeholders (prescriber, pharmacist, MAH, NCA) in the dissemination process; access to aRMM materials for patients and HCPs; key challenges of disseminating aRMM; preferences for aRMM tools for patients and HCPs. The results of the project will help to inform

regulatory decision-making on the selection of aRMM tools and to evaluate their overall effectiveness.

Data sources

Scientific and grey literature, interviews with MAHs, focus groups NCAs, patients and HCPs, online questionnaires for patient organisations, patients and HCPs and a webinar for all stakeholders.

Study size

A maximum of 11 interviews with MAHs, 1 focus group with NCAs, 12 focus groups with HCPs (2 per country), 6 focus groups with patients (1 per country), around 30-60 patient organisations for the online questionnaire (5-10 per country), around 50-100 patients for the online questionnaire (per country), around 50-100 professionals for the online questionnaire (per country) and 40-50 participants for the webinar.

Data analysis

Results from the desk research will be summarized. For the online questionnaires, descriptive statistics will be performed. For the interviews and focus groups, thematic analyses with a mainly deductive approach will be used to analyse the data. The results of the webinar will be used to broaden the information collected in the rest of the study.

Milestones

Preliminary study plan (D1; due 28-04-2025), Study protocol (D2; due 27-06-2025), Study report (D3; due 28-04-2026) and Manuscript (D4; due 29-06-2026).

4.1 List of abbreviations

Table 2 List of abbreviations

Abbreviation	
aRMM	Additional Risk Minimisation Measure
CFIR	Consolidated Framework for Implementation Research
COREQ	Consolidated criteria for reporting qualitative research
CROSS	Consensus -Based Checklist for Reporting of Survey Studies
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAIR	Findability, Accessibility, Interoperability and Reusability
GDPR	General Data Protection Regulation
GVP	Guideline on good pharmacovigilance practices
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
NCA	National competent authority
Nivel	Netherlands institute for health services research
QR-code	Quick Response code
RDA	Rethinking Scientific Data
RMM	Risk Minimisation Measures
VSNU	Vereniging Samenwerkende Nederlandse Universiteiten
WP	Work Package

5. Amendments and updates

Not applicable yet.

6. Milestones

Table 3 Milestones

Milestone	Description	Planned date
D1	Preliminary study plan	28-04-2025
D2	Study protocol	27-06-2025
D3	Study report	28-04-2026
D4	Manuscript	29-06-2026
Start data collection		March 2025
End data collection		March 2026

7. Rationale and background

7.1 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][2] 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 additional RMM tools (aRMM tools). These additional tools are imposed in case routine RMM tools are insufficient to control risks (Hapani 2022).

The project described in this protocol focuses on dissemination of **aRMM material**. There are two types of aRMM 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 the 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.

7.2 The implementation pathway

The implementation of RMM, including aRMM, follows the path as depicted in Figure 1. First, at market authorisation (MA) EMA requires RMM, which then will be disseminated to the target population: HCPs and/or patients. RMM, including 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 some background related to this pathway[2] is described.

[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

Figure 1 The implementation pathway of RMM (including aRMM) (adapted from EMA)[3]

7.3 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 et al. 2018). A review of the EPAR database[4] found that of 717 included medicines (2006-2015), 26% had an aRMM (Rubino & Artime 2017).

7.4 Dissemination of aRMM to target population

Previous studies showed variation in the dissemination of aRMM and in the reach of aRMM among patients and HCPs (Landberg 2018; Mayall 2021). Collecting information from multiple stakeholders is key to develop dissemination and implementation strategies. Examples of such strategies include engagement or training of stakeholders, supporting clinicians and developing stakeholder interrelationships (Waltz 2015). The Consolidated Framework for Implementation Research (CFIR)[5] 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). The CFIR is a strong framework to use for an analysis of the context in which aRMM are implemented, which is important as EMA and the national competent authorities (NCAs) allow and encourage marketing authorisation holders (MAHs) to implement and disseminate aRMM tailored to the needs of their local healthcare settings (Hapani 2022). This study will look at both paper and digital aRMM. 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).

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

[4] Reference number 13 from Rubino and Artime (2017): European Medicines Agency. European Public Assessment Reports. n.d. [cited 2016 Feb 3]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124

[5] https://cfirguide.org/choosing-strategies/

7.5 Focus of this study: physical dissemination of paper and digital aRMM

As defined by EMA in the Guideline on good pharmacovigilance practices (GVP, 2024, p19/20)[6], a RMM effectiveness evaluation includes: "the extent to which the RMM has been disseminated to the target population(s) as planned, the extent to which the RMM has led to the intended knowledge and behaviours in the target population(s), or whether other behavioural outcomes have occurred; and the extent, as measurable, to which the intended health outcomes have been achieved within relevant timeframes, or whether other health outcomes have occurred". Within the literature, some information about the effectiveness of aRMM is available, mainly focused on knowledge and behavioural changes and outcomes (e.g. Mayall 2021; Lem 2022; Rutskova 2023; Jacquot 2019; Colas 2024; Vora 2018; Agyemang 2017; Landsberg 2018; Toussi 2020; Wu 2024).

Insight into the dissemination process itself is also crucial to be able to assess the effectiveness. There is little focus in the literature on the dissemination process of aRMM. A review by Artime et al. (2020) shows that most studies on the effectiveness of aRMM addressed outcome indicators (e.g. prescribing behaviour) and only a minority (19%, 19 out of 102 studies) addressed process indicators such as physical dissemination. According to Artime et al. (2020, p388), "process indicators measure the extent to which aRMMs were implemented (e.g. receipt of the materials by the target audience) and whether they are used as expected (e.g. if the target audience reads the materials or whether they distribute them to patients), and the impact of the educational materials on the level of knowledge and/or behaviour of the recipient around key safety messages". Nine percent (n=9) of the 102 studies addressed the receipt of aRMM by healthcare professionals and 6% (n=7) of the 102 studies addressed the receipt by patients. The studies in the review found that 57% (median) of the healthcare professionals received the aRMM, and 56% (median) of the patients (Artime et al. 2020).

For aRMM to be effective, the materials should reach the users who should use it as expected. Therefore, this study focuses on the physical methods of dissemination of aRMM materials for selected products. Users of these materials are patients in the case of patient alert cards, and physicians in the case of checklists and training. Pharmacists contribute to the system by passing safety related information and/or RMM materials on to the patient. Materials may be made available by NCAs and should be made available by MAHs. As digital information is becoming increasingly available, the dissemination of aRMM is shifting in several countries from paper based to digital based. This may bring different challenges, for instance for those who do not have sufficient digital skills.

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

8. Research questions and objectives

8.1 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.

8.2 Specific objectives

1. Describe and analyse the process and frequency (where appropriate) how aRMM are disseminated in at least five EU/EEA countries with geographical spread, and how patients and healthcare professionals receive product-specific aRMM materials for the medicinal products listed in Table 4, 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.
2. Describe and analyse how access to paper based and digital aRMM materials for patients and healthcare professionals 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;
3. Identify and describe the key challenges of disseminating
    a. healthcare professional-targeted aRMM materials to all eligible healthcare professionals who prescribe or use the medicinal products listed in Table 4 and
    b. patient-targeted aRMM materials to all eligible patients who are prescribed the medicinal products listed in Table 4, by type of additional RMM, 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;
4. Identify and describe patients' and healthcare professionals' preferences for aRMM tools for patients and healthcare professionals, 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;
5. Provide recommendations how the challenges identified under objective 3 may be leveraged and the dissemination of aRMM for patients and healthcare professionals facilitated, outlining feasible concrete steps EMA and national competent authorities could consider at each step of the dissemination pathway.

8.3 Medications and aRMM under study

For this study EMA has selected seven medications as a case study. For each medication, a number of aRMM materials has to be studied. These materials vary across the medications (Table 4).

Table 4 Medicinal products and their aRMM materials 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

9. Research methods

9.1 Overall study design and setting

9.1.1 Overall study design

Based on the objectives of the study, 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 provides a more complete and nuanced understanding of the dissemination of aRMM in EU/EEA Member States. Using multiple research methods, it is possible to cross-verify findings and increase the overall validity of the study. Also, it allows to combine the more in-depth analyses of qualitative research with the broader possibilities to generalise findings provided by using quantitative methods. Support for this approach is also found in previous research (Landsberg 2018; Wu 2024).

9.1.2 Countries

- The EU consists of Member States that widely vary in health care systems, 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 study protocol, the expectation is 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, the study is conducted in six different countries to capture differences with regard to the subject of the study. The selection of countries provides regional differentiation across the EU as well as variation in the health care system, see Table 5.
- 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.
- In each country, a national research organisation serves as focal point.

Table 5 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

9.1.3 Number of users per product per country

Although the seven medicinal products in Table 4 are available in all six countries included in this study, the number of patients that use the medicinal products differs per product and per country. Table 6 gives an overview of the number of patients per medicinal product per product.

309 **Table 6 Number of patients per medicinal product per country**

Country	Population	Xeljanz	Aubagio	Lemtrada	Eylea	Lixiana	Valproate containing products	Retinoids containing products
NL[1]	~18 million	1.756 patients in 2022	1.668 patients in 2022	50 patients in 2022	32.916 patients in 2023	63.866 patients in 2023	45.258 patients in 2022	59.073 patients in 2023
FI[2]	~5.5 million	789 patients that were reimbursed during 2024	895 patients that were reimbursed during 2024	123 patients between 2013-2019 (Rauma, 2022)	Eylea: 20.833 number of injections during 2017 (Karesvuo et al. 2020) (estimate of the number of patients would be around 3.500 with an injection interval of 2 months);	18.045 patients that were reimbursed during 2024	29.393 patients that were reimbursed during 2024	Number of patients that were reimbursed in 2024: ATC code D05BB: 3.262 ATC code D10BA: 21.451
IT[3]	~58 million	0.05 DDD per 1000 inhabitants per day in 2023. Packages not traceable via sources.	0.02 DDD per 1000 inhabitants per day in 2023. 15,502 packages*	less than 0.005 DDD per 1000 inhabitants per day in 2023. Packages not traceable via sources.	less than 0.005 DDD per 1000 inhabitants per day in 2023. Packages not traceable via sources.	3,67 (class A) DDD and 1,2 (class H) DDD per 1000 inhabitants per day in 2023	2,4 DDD per 1000 inhabitants per day in 2023. 5,077,410 packages*	0,2 DDD per 1000 inhabitants per day in 2023. 316,711 packages*
HUN[4]	~9.5 million	14 boxes / 0 patients from 202403 to 202502**	6968 boxes / 644 patients from 202403 to 202502 Teruflunomide Sandoz: 326 boxes / 51 patients from 202403 to 202502	103 boxes / 0 patients from 202403 to 202502**	Eylea: 0 boxes / 0 patients from 202403 to 202502**	231513 boxes / 25087 patients from 202403 to 202502	Convulex: 8026 boxes / 13357 patients from 202403 to 202502 Depakine: 14733 Boxes / 15867 patients from 202403 to 202502	5528,3 boxes / 6880 patients from 202403 to 202502
LIT[5]	~3 million	68 reimbursed medicine users in 2024	278 reimbursed medicine users in 2024	5 reimbursed medicine users in 2024 (purchased	Not applicable (Purchased through central procedure. To	22.385 reimbursed medicine users in 2024	8.034 reimbursed medicine users in 2024	141 reimbursed medicine users in 2024 (Neotigason is

				through central procedure)	estimate possible number of users - in 2024 4.481 patients where prescribed ranibizumab)			the only reimbursed medicine in the group of retinoids)
ROM[6]	~19 million	560 patients in 2024	1.154 patients in 2024	4 patients in 2024	19.879 patients in 2024	-	145.700 patients in 2024	21.199 patients in 2024

* Packages distributed via pharmacies and hospitals outpatient distribution

** For data protection reasons, annual patient numbers are only included in the Tables for data above 50. In cases where the resulting value is less than 50, zero is included in the statements. This also means that the zero values in the Tables can be between 0 and 49. source: https://www.neak.gov.hu/felso_menu/szakmai_oldalak/publikus_forgalmi_adatok/gyogyszer_forgalmi_adatok/gyogyszer_forgalmi_adatok

1 Source: GIP database www.gipdatabank.nl

2 Source: Statistical Database Kelasto (available from https://tietotarjotin.fi/en/statistical-data/2051231/statistical-database-kelasto), Rauma et al. Safety of alemtuzumab in a nationwide cohort of Finnish multiple sclerosis patients. J Neurol. 2022; 269(2):824-835. Karesvuo et al. Correlation between the rate of intravitreal injections, use of aflibercept as a second-line treatment and visual impairment for wet AMD in Finland. Acta Ophthalmol. 2020; 98(5):472-476. Finnish Medicines Agency 2020: https://www.julkari.fi/handle/10024/147205

3 Source: IQVIA Rha Datasource and AIFA. Rapporto Osmed 2023

4 Source: National Health Insurance Fund of Hungary (Hungarian acronym: NEAK)

5 Source: Information on reimbursed medicine users, data obtained from the National Health Insurance Fund of Lithuania. This includes only patients that were reimbursed. There still might be few patients that paid for medicines out of pocket or through private insurance funds.

6 Source: This is national-level data (of the year 2024), based on information submitted by healthcare providers to the insurance house. It reflects the total number of patients who received the medication nationwide, based on prescriptions issued by healthcare professionals.

- Based on Table 6, it appears that the number of users is (very) low in all countries, particularly for the medicinal products Lemtrada, Xeljanz, and Aubagio. For Eylea, the number of users differs per country. For the other products, there are higher numbers of users in all countries (except for the retinoid containing products in Lithuania).
- With a low number of users for several medicinal products, 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, a survey study among patient organisations will be organised to get insight in the patient perspective. To reach patient organisations purposive sampling will be used. An overview will be made 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, a short questionnaire will be developed for patients and patient organisations will be asked to spread the link to this questionnaire through, for example, their newsletter. This is probably the only way to realise a representative view of the patient perspective. Spreading the survey through professionals or via social media only is expected to be insufficient, at least for those medicinal products with low number of users.
- Also, because of the low numbers of users for certain medicinal products, most professionals will have limited experience. Therefore, the same approach is used for professionals: professional organisations will be approached, and then asked for support to spread the questionnaire, next to spreading it via social media and mailing.
- The HCP questionnaire targets professionals who prescribed or dispended at least one of the included medicinal products in the past 12 months. The patient questionnaire targets patients who used at least one of the included medicinal products in the past 12 months.

9.1.4 Implementation framework: CFIR

To analyse the results of the questionnaire and focus groups the updated version of Consolidated Framework for Implementation Research (CFIR; Damschröder 2022, see Figure 2 below) will be used. For the five domains of the CFIR, i.e. 'Innovation', 'Outer setting', 'Inner setting', 'Individuals' and 'Implementation process', both generic context factors (across all countries) as well as country-specific context factors will be extracted and analysed. In addition, both factors that apply to all stakeholders and stakeholder-specific factors in order to capture experiences that are relevant for other countries (and/or stakeholders) will be extracted and analysed.

Figure 2 Consolidated framework for Implementation Research*

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

9.2 Design per work packages

This study collects primary data. This section provides a description of all work packages (WPs). Figure 3 shows the WPs, the aims per WP and the main methods used. The same surveys, focus groups, and interviews will be used to collect data for WP1-4. Each work package has its own objective which is summarised in Figure 3. The full description of the objectives can be found in the detailed WP descriptions, given after Figure 3 and Table 7. Table 7 provides an overview of the methods per WP, and refers for each task in a specific WP to the section where a more detailed description is given for that particular task. For each of the included methods, a data collection plan will be developed that includes instructions for the countries of how to conduct the data collection. Annex 3A gives the planning of the study in a GANTT chart.

Figure 3 Overview of the study

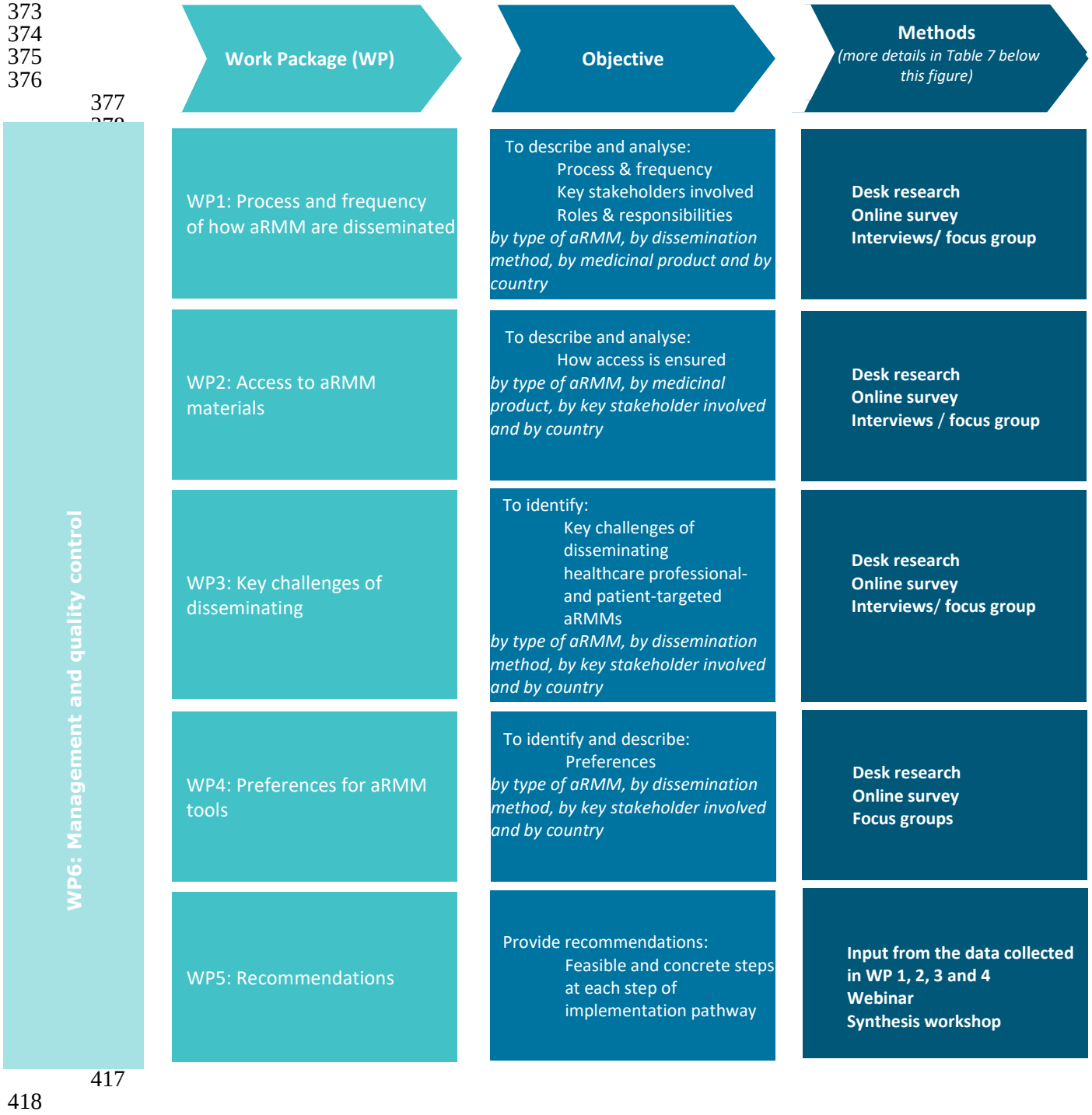

Table 7 Overview of the methods used in each work package

	WP1	WP2	WP3	WP4	WP5	WP6
Desk research	1.1	2.1	3.1	4.1		
Interviews with marketing authorisation holders	1.2	2.2	3.2			
Focus group with 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 with professionals (back up interviews)	1.5	2.5	3.5	4.4		
Focus groups with patients (back up interviews)		2.7		4.5		
Webinar					5.1	
Synthesis workshop researchers					5.2	

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

This WP describes and analyses 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 4. This WP starts with desk research followed by online surveys, focus groups and interviews.

Objective

Describe and analyse the process and frequency (where appropriate) how RMM are disseminated in six EU/EEA countries with geographical spread, and how patients and HCPs receive product-specific aRMM materials for the medicinal products listed in Table 4, 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 aims to do preparatory work for the online surveys, focus groups and interviews in the following tasks. A scan of the literature will be performed to gain insight into the information that 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)[7] gives information about the dissemination of aRMM.
- For scientific literature, PubMed and Embase will be used as search engines. The search strings are included in Annex 3B of this protocol.
- In addition to the electronic databases and to cover relevant grey literature on the subject, a search of grey literature will be conducted by the respective sub-contractor in each of the participating countries (the guiding document including instructions for the grey literature search for sub-contractors can be found in Annex 3C). Several databases will be searched 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.

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

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 selected medicinal products.
- The aim of the interviews is to discuss the dissemination pathway of aRMM materials, and what the roles and responsibilities of MAHs are in the process of disseminating aRMM materials. Also questions to cover the frequency of the dissemination of aRMM materials will be included (e.g. how continuous availability of the patient-targeted aRMM materials to be handed over to patient by a healthcare professional is ensured for healthcare settings).
- For the exact questions, see the interview guide included in Annex 3D.
- Information from the desk research will be used to construct the questions for the interviews and the short questions that will be sent by e-mail before the interviews.
- Before the interviews, a limited number of short questions will be send by email to the MAHs that participate in the interviews to get insight in factual information, e.g. what the dissemination methods are for the aRMM material of their medicinal product (see Annex 3D for the short questionnaire). During the interviews it is then possible 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.
- 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 and a maximum of three MAHs will be interviewed for both products.
- The research team will make a proposal for these MAHs which will be discussed with EMA in a regular meeting. 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, it is expected that data saturation for the views of MAH on their role and responsibilities in aRMM as well on the ways to distribute aRMM is reached. Usually, 12 interviews are sufficient to reach data saturation (Guest et al. 2006).
- We will use public data from the article 57 database[8] of EMA to contact each MAH. The MAH contact details in this database refer to pharmacovigilance enquiries. The contacted person will be asked for a MAH representative with knowledge and oversight of risk minimisation activities for the concerned products in the countries included in the study. The idea is to conduct one interview with preferably 1-2 persons (each from a different country) per MAH per product, ensuring that, collectively, all countries are covered.
- We ask for informed consent of the respondent at the start of the interview (before the first substantive question) and will follow 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 NCAs (M2-4)

- Alongside task 1.2 a focus group with the national competent authorities from all six participating countries will be performed.
- The aim of the focus group is to discuss the dissemination process of aRMM, and the roles

[8] Public data from Article 57 database | European Medicines Agency (EMA)

and responsibilities in the process of disseminating aRMM from the perspective of the NCAs.

- For the exact questions, see the interview guide included in Annex 3E.
- Before the focus group, a limited number of questions will be send by e-mail to the representatives of the NCAs that participate in the focus group to get insight in factual information, e.g., whether the aRMM materials are available on their website (see Annex 3E for the short questionnaire). Within the focus group it is then possible 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 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 jointly participate. In this invitation the seven medicinal products included in this study are already mentioned.
- Informed consent of the respondent will be asked at the start of the focus group (before the first substantive question) and will follow 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 a maximum of 120 minutes. The focus group will be audiotaped and transcribed.
- Although the focus group will be conducted by experienced researchers, who know how to keep an interview on track, two hours might be challenging to discuss all relevant aspects for all seven products in all six countries. Therefore, as a mitigation measure, factual information will be collected prior to the focus group (e.g. what are the dissemination methods for the aRMM materials in their country). Another proposed mitigation measure is that in case not all relevant aspects are discussed, the respective national competent authorities will be approached by phone or mail to discuss the remaining issues, or a short (max 30-45 min) second meeting will be set up with the respective national competent authorities to discuss these issues.
- 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, HCPs and patient organisations are asked how professionals and patients receive aRMM material. Patient organisations are asked whether they see a role and responsibilities for themselves in the dissemination of aRMM.
- 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.
- In addition, results of the interviews with MAHs and the focus group with NCAs 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. The CFIR will be taken into account as the analyses will be based on this framework.
- The questionnaires are included in Annex 3F.
- We ask for informed consent of the respondent at the start of the questionnaire (before the first substantive question) and will follow Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- We will make one questionnaire for HCPs and one for patient organisations. This ensures that the results can be stratified by stakeholder. At the beginning of the questionnaire

respondents can indicate which medicinal product they use, prescribe and/or dispense and then go to the section of the questionnaire that contains the relevant questions for that product and the associated aRMM material. This ensures that the results can be stratified by medicinal product and aRMM material.

- The questionnaire contains questions with predefined answer options. If explanation is needed, this will be requested regarding using an open question.
- If the answers to the questionnaire give reason to do so, questions will be included accordingly in the interview guides of the focus groups with patients or HCPs. The exact content of these questions will depend on the results of the questionnaire. For example, in case the results of the questionnaires show that aRMM materials are not handed over to patients, questions to get insight in the underlying reasons will be asked in the focus groups and interviews. Another example is that if some result is prominent in one country compared to the other countries, questions to try to understand why that is the case will be asked.
- 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 a specific country, can be added.
- DESAN will program the questionnaires for all countries in their national languages. DESAN is a Dutch mail house that has ample experience in questionnaire research, both nationally and internationally. Nivel has a longstanding working relationship 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, it is ensured 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. In handling the data collection, DESAN will add a variable that indicates in which country the survey is filled out. This ensures that the results can be stratified by country.
- Both the questionnaire for professionals and patient organisations will be programmed and made available using an open link so that the questionnaire can easily be distributed through different channels. Furthermore, both questionnaires will be programmed mobile friendly, enabling respondents to easily fill out the questionnaire on their mobile phone.
- For each product, the relevant patient organisation(s) in the six countries will be identified and contacted. For example, Xeljanz is a medicinal product for rheumatism, so ReumaNederland (the Netherlands) or Coalitia Organizatiilor Pacientilor cu Afectiuni Cronice din Romania (Romania) will be contacted. Table 8a gives an overview of relevant patient organisations per product that were already identified and will be contacted in the six countries.
- For professionals, professional organisations will be identified and contacted, like the Royal Dutch Pharmacists Association (the Netherlands) or the Romanian Association of Pharmacies and Pharmacists (Romania). See Table 8b for an overview of relevant professional organisations per product per country that were already identified. Professional organisations are asked 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 and per organization to reach an adequate population.
- After data cleaning, data will be analysed as described in 9.8 Data analysis.
- 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).

599 **Table 8a Overview of relevant patient organisations per country, per product**

Country	General	Xeljanz (rheumatism and gastroenterology)	Aubagio (multiple sclerose)	Lemtrada (multiple sclerose)	Eylea (macular degeneration)	Lixiana (anticoagulants)	Valproate containing products (epilepsy)	Retinoids containing products (acne and psoriarss)
NL	Patiëntenfederatie Nederland	1) Reuma Nederland 2) Crohn en Colitis NL	MS Vereniging Nederland	MS Vereniging Nederland	1) Macula vereniging 2) Oogvereniging	Nederlandse Hartstichting	EpilepsieNL	Psoriasispatiënten Nederland
FI	SOSTE Finnish Federation for Social Affairs and Health EUPATI Finland	1) Finnish Rheumatism Association 2) IBD and Other Intestinal Diseases Association	Finnish Neuro Society	Finnish Neuro Society	Finnish Federation of the Visually Impaired	Heart Association	Finnish Epilepsy Association	Finnish Psoriasis Association
IT	Cittadinanzattiva APS	1) National Association of People with Rheumatological and Rare Diseases (APMARR) 2) National Association for Chronic Inflammatory Bowel Diseases (AMICI Italia)	Italian Multiple Sclerosis Association (AISM)	Italian Multiple Sclerosis Association (AISM)	1) Association of Patients with Ocular Diseases (APMO) 2) Association of Patients with Maculopathy or Age-Related Macular Degeneration (A.P.A.M. Onlus) 3) Association Macula Committee	1) Italian Heart Failure Association (AISC) 2) Association for the Fight against Cerebral Stroke (ALICe Italia)	1) Italian Epilepsy Federation (FIE) 2) The Italian Association for Drug-Resistant Epilepsy (A.I.E.F. APS) 3) Italian Epilepsy Association	1) Italian Association of Patients with Psoriasis and Psoriatic Arthritis (AIPA Italia) 2) Association for the Defence of Psoriatic Patients (ADIPSO) 3) Italian Psoriatic Association Friends of the Corazza Foundation (APIAFCO)
HUN	Hungarian Alliance of Patient Organizations (BEMOSZ-HAPO) https://www.bemosz.hu/	1) Hungarian Rheumatology Patients' Association https://izuletibetegsegek.hu/ 2) Hungarian League of Patients with Rheumatic Diseases https://www.facebook.c	National Association of People with Multiple Sclerosis https://www.msmba.hu/	National Association of People with Multiple Sclerosis https://www.msmba.hu/	1) Retina Hungary Association of Patients with Retinal Dystrophies and Age-related Macular Degeneration https://www.facebook.com/RetinaMagyarorszagEgyesulet/?locale=hu_HU	1) SZÍVSN National Patients' Association https://szivsn.hu/en/contact/ 2) Hungarian Society of Cardiovascular Rehabilitation https://mkrt.hu/	Hungarian Epilepsy League https://epilepszia.hu/	Association of Hungarian Psoriasis Clubs https://mpke.hu/

		om/ReumabetegekaCelzottTerapiaertKozhasznuEgyesulet/?locale=hu_HU MCCBE - Hungarian Crohn's & Colitis Association https://www.mccbe.hu/			2) The Hungarian Federation of the Blind and Partially Sighted (MVGYOSZ) https://mvgyosz.hu/en/mvgyosz-mainpage/	3) Association for Stroke Prevention https://europaiszabadauszo.wordpress.com/		
LIT	Lithuanian Council of Patient Organization Representatives https://www.eu-patient.eu/Members/The-EPF-Members/Full-Membership/Council-of-Representatives-of-Patients-Organizations-of-Lithuania/	1) Lithuanian arthritis association (Lietuvos artrito asociacija) http://www.arthritis.lt/kontaktai/ 2) Crohn's and Ulcerative Colitis Society of the Republic of Lithuania https://draugija.info/	Lithuanian Multiple Sclerosis Union https://www.liss.lt/liss-struktura/	Lithuanian Multiple Sclerosis Union https://www.liss.lt/liss-struktura/	Association of Patients with Retinal Diseases https://tinklaine.lt/kontaktai/	Association of Patients with Cardiovascular Diseases "healthy Heart" https://www.sveikasirdis.com/	Lithuanian Association for People with Epilepsy https://epile.lt/kontaktai/	Lithuanian Psoriasis Patients' Association https://www.zvyneline.eu/contacts
ROM	1) CASPA - Patient associations community (ro., Comunitatea asociațiilor de pacienți) https://www.caspa.ro/ - has 235 Patient Associations in Romania (Oncology, Diabetes, Tuberculosis, HIV, Hemophilia, Hematology, Transplant, Genetics - Rare Diseases, Neuro-	1) Romanian Society of Rheumatology (Ro., Societatea Română de Reumatologie) - https://srreumatologie.ro/ 2) Transylvanian Association of Patients with Inflammatory Rheumatic Diseases (Ro., Asociația pacienților cu boli reumatismale inflamatorii din	1) Multiple Sclerosis Association Bucharest (Ro., Asociația de Scleroză Multiplă București) - https://www.asmb.ro/ 2) Multiple Sclerosis Association Romania (Ro. , Asociația de Scleroză Multiplă din România) - https://www.sclerozamultipla.ro	Rare Diseases Association Ocular - Aniridia Romania (Ro., Asociația Bolilor Rare Oculare - Aniridia România)	1) Heart Association (Ro., Asociația Inimii) - https://inimalor.ro/ PRO-CARDIO 2) Association of Patients with Cardiovascular Diseases (Ro., Asociația Pacienților cu Afecțiuni Cardiovasculare) - https://asociatiaprocardio.ro/ 3) Association of patients with genetic	Romanian Epilepsy Patients Association (Ro.,Asociatia Pacientilor cu Epilepsie din Romania) - https://www.aspe.ro/	Association of Patients with Autoimmune Diseases (Ro., Asociația Pacienților cu Afecțiuni Autoimune - APAA) - https://www.apaa.ro	

	Psychiatric, Hepatic, ENT. 2) Coalition of Organizations of Patients with Chronic Diseases in Romania (Ro., Coaliția Organizațiilor Pacienților cu Afecțiuni Cronice din România) - https://www.copac.ro/ 3) National Alliance for Rare Diseases (Ro., : Alianta Nationala pentru Boli Rare) www.bolirareromania.ro Romanian Scleroderma Patients Association (Ro., Asociatia Pacientilor cu Sclerodermie din Romania) - https://www.sclerodermie.ro/	Transilvania) - https://art-cluj.ro/ 3) Association of Rheumatism Patients from Banat AREBA (Ro., Asociatia pacientilor cu reumatism din Banat) 4) Association of Patients with Autoimmune Diseases APAA (Ro., Asociaţia Pacienţilor cu Afecţiuni Autoimune) - https://www.apaa.ro/ 5) Romanian League Against Rheumatism Association (Ro., Asociatia Liga Romana Contra Reumatismului) 6) ASPIIR The Romanian Association of People with Inflammatory Bowel Diseases (Ro., ASPIIR Asociaţia Persoanelor cu Boli Inflamatorii Intestinale din Români) - https://aspiir.ro/ 7) APAH-RO Association of patients with liver diseases in Romania (Ro. Asociația pacienților cu afecțiuni hepatice din	3) Multiple Sclerosis Survivors Association (Ro., Asociația Învingătorilor Sclerozei Multiple - https://www.invingatorisclerozeimultiple.ro/ 4) Romanian Association of Patients with Neurodegenerative Diseases (Ro., Asociatia Pacientilor cu Afectiuni Neurodegenerative din Romania) - https://afectiuni-neurodegenerative.ro/ 5) SM SPEROMAX ALBĂ Association - www.smalba.ro 6) Bihor Multiple Sclerosis Foundation (Ro., Fundaţia de Scleroză Multiplă Bihor) - www.scleroza-multipla.ro 7) Romanian Multiple Sclerosis Society (Ro., Societatea de Scleroză Multiplă din România) www.smromania.ro 8) Bistrita Multiple Sclerosis Association		heart diseases in Romania (Ro., Asociația pacienților cu boli cardiace genetice din România) https://asociatia-cardiogen.ro/ 4) Association My Child My Heart (Ro., Asociatia Parintilor Copiilor cu Defecte Cardiace Congenitale) - https://www.acmim.ro/ 5) Association Children's Heart (Ro., Asociația Inima copiilor) - www.inimacopiilor.ro 6) Pulmonary Hypertensive Patients Association (Ro., Asociația Pacienților Hipertensivi Pulmonari) - https://hipertensiunepulmonara.ro/ 7) ALIA | Asociația pentru lupta împotriva AVC (Ro., ALIA | Association for the fight against stroke) - https://alia.org.ro/			

		românia) - https://hepato.ro/ 8) Association Sano-Hep Buchares (Ro., Asociatia Sano-Hep filiala Bucuresti) - https://www.sanohep.ro	(Ro. Asociaţia de Scleroză Multiplă Bistriţa) : asociatiasmbistrita@yahoo.com 9) Multiple Sclerosis Association Botoșani (Ro. Asociaţia de Scleroză Multiplă Botoșani) smbotosani@yahoo.com 10) Regional Association SM (Ro., Asociația Regională SM) - http://www.sclerozamultiplaconstanta.ro/ 11) Multiple Sclerosis Association Dâmbovița (Ro., Asociaţia de Scleroză Multiplă Dâmboviţa) smdambovita@yahoo.com 12) SM Hope Prahova Association (Ro., Asociația SM Speranţa Prahova) asoc_speranta_ph@yahoo.com 13) Multiple Sclerosis Association Sibiu (Ro.,					

			Asociatia de Scleroza Multipla din Sibiu) - as_sm_sibiu@yahoo.com 14) Association Asmelydon Câmpulung (Ro., Asociația Asmelydon Câmpulung) asmelydon@yahoo.com 15) Regional Association of Multiple Sclerosis Patients Timișoara (Ro., Asociatia Regională a Bolnavilor de Scleroză Multiplă Timișoara) arbsmtm@yahoo.com 16) Association of Multiple Sclerosis Vâlcea (Ro., Asociatia de Scleroză Multiplă Vâlcea) smvalcea@yahoo.com ANAP - Association of patients with neurodegenerative diseases in Romania (Ro., Asociația pacienților cu afecțiuni neurodegenerative din România)					

			https://afectiuni-neurodegenerative.ro/ Here is the link with a pdf document where all the above associations are presented in detail: https://drive.google.com/file/d/15mJeVC4rvSRMLsy4Hrq4y2g9rFqJa-_s/view?usp=drive_link					

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601 **Table 8b Overview of relevant professional organisations per country, per product**

Country	General	Xeljanz (rheumatism and gastroenterology)	Aubagio (multiple sclerose)	Lemtrada (multiple sclerose)	Eylea (macular degeneration)	Lixiana (anticoagulants)	Valproate containing products (epilepsy)	Retinoids containing products (acne and psoriarss)
NL	1) Federatie Medisch Specialisten 2) KNMP (Royal Dutch Pharmacists Association) 3) Nationaal Huisartsen Genootschap 4) Landelijke Huisartsen Vereniging 5) Nederlandse Vereniging van Ziekenhuisapothekers (NVZA)	1) Nederlandse Vereniging voor Reumatologie 2) Nederlandse Vereniging voor Maag, Darm, Lever artsen	Nederlandse Vereniging voor Neurologie	Nederlandse Vereniging voor Neurologie	Het Nederlands Oogheelkundig Gezelschap	Nederlandse Vereniging voor Cardiologie	Nederlandse Vereniging voor Neurologie	De Nederlandse Vereniging voor Dermatologie en Venereologie
FI	1) The Finnish Medical Association 2) The Finnish Medical Society Duodecim 3) Association of Finnish Pharmacies 4) Finnish Pharmacists' Association 5) The Finnish Pharmacists' Society	1) Finnish Society for Rheumatology 2) Finnish Society of Gastroenterology	Finnish Neurological Society	Finnish Neurological Society	Finnish Ophthalmological Society	Finnish Cardiac Society	Finnish Neurological Society	Finnish Dermatological Society
IT	1) Italian Society of Pharmacology (SIF) 2) Italian Society of Hospital Pharmacy and Pharmaceutical Services	1) Italian Society of Rheumatology (SIR) 2) Italian Society of Gastroenterology and Digestive Endoscopy (SIGE)	Italian Society of Neurology (SIN)	Italian Society of Neurology (SIN)	Italian Society of Ophthalmology (SOI)	Italian Society of Cardiology (SIC)	1) Italian Society of Neurology (SIN) Italian Society of Gynaecology and Obstetrics (SIGO)	1) Italian Society of Medical, Surgical, Aesthetic Dermatology and Sexually Transmitted Disease (SIDeMaST)

	of Health Authorities (SIFO) 4) National Federation of the Orders of Surgeons and Dentists (FNOMCeO) 5) Italian Society of Clinical Pharmacy and Therapy (SIFACT) 6) Italian Society of Preparatory Pharmacists (SIFAP)	3) Italian Association of Hospital Gastroenterologists and Digestive Endoscopists (AIGO)					2) Association of Italian Hospital Obstetricians Gynaecologists (AOGOI) 3) Italian Association Against Epilepsy (AICE)	
HUN	1) Hungarian Research Organization of Family Physicians http://www.csakosz.hu/info.aspx?sp=1 / 2) Hungarian Medical Chamber https://mok.hu/	1) Hungarian Association of Rheumatologists https://www.mre.hu/ 2) Hungarian Society of Gastroenterology https://mgtiroda.hu	Hungarian Neuroimmunology Society https://neuroimmun.hu	Hungarian Neuroimmunology Society https://neuroimmun.hu	Hungarian Ophthalmological Society https://szemeszet.ophthalmol.hungarica.eu/	Hungarian Society of Cardiology https://mkardio.hu/info.aspx?sp=200&web_id=	Hungarian Neurogical Society https://mitt.hu/en	Hungarian Dermatological Society https://derma.hu/info.aspx?sp=200
LIT	Lithuanian Pharmaceutical Chamber https://www.vaistininkai.lt/index.php/kontaktai Lithuanian Pharmaceutical Union https://www.lfsajunga.lt/en/apie-lfs	1) Lithuanian Rheumatology Association http://www.reumatologuasociacija.lt/en/contacts/ 2) Lithuanian Gastroenterology Association https://gastroenterologija.lt/	Lithuanian Neurology Association https://www.neuronas.lt/kontaktai/	Lithuanian Neurology Association https://www.neuronas.lt/kontaktai/	Lithuanian Society of Ophthalmologists https://akiudraugija.lt/kontaktai/	Lithuanian Society of Cardiology https://lcs.lt/kontaktai/	1) Lithuanian Neurology Association https://www.neuronas.lt/kontaktai/ 2) Lithuanian Epileptology Society https://rekvizitai.vz.lt/imone/lietuvos_epileptologijos_draugija/	Lithuanian Society of Dermatovenereologists https://ldvd.lt/kontaktai

ROM	1) Romanian Association of Pharmacies and Pharmacists Romanian College of Physicians (Ro., Colegiul Medicilor din România) - https://www.cmr.ro/ 2) National Society of Family Medicine/General Medicine (SNMF) Association (Ro., Asociația Societatea Națională de Medicina Familiei/Medicină Generală - SNMF) - https://snmf.ro/ 3) National Institute for Public Health (Ro., Institutul Național de Sănătate Publică) 4) Romanian Association for Health Promotion (Ro. Asociatia Romana de Promovare a Sanatatii) - www.arps.ro 5) National Organization for Patients' Protection (Ro., Asociatia Nationala pentru Protectia Pacientilor) - www.protectiapacientilor.ro	1) Romanian Society for Rheumatology (Ro., Societatea Română de Reumatologie) - https://srreumatologie.ro/ 2) SRED - Romanian Society of Digestive Endoscopy (Ro., Societatea Română de Endoscopie Digestivă - https://sred.ro/ 3) Romanian Society of Gastroenterology and Hepatology (Ro., Societatea Română de Gastroenterologie și Hepatologie) - https://srgh.ro/ 4) Group GastRo - National Society for Family Medicine (Ro., Grupul GastRo - Societatea Națională de Medicina Familiei) https://www.gastromf.ro/ 5) RCCC - Romanian Crohn's Disease and Ulcerative Colitis Club (Ro., RCCC - Clubul Român de boală Crohn şi colită ulcerativă)	1) Romanian Society of Neurology (Ro., Societatea de Neurologie din România) - https://www.neurology.ro/ 2) NeuroCare Association - https://neurocare.ro/	1) Romanian Society of Neurology (Ro., Societatea de Neurologie din România) - https://www.neurology.ro/ 2) NeuroCare Association - https://neurocare.ro/	1) Romanian Society of Ophthalmology (Ro. Societatea Română de Oftalmologie https://oftalmologiaromana.ro/ 2) Romanian Society of Strabology and Pediatric Ophthalmology (Ro., Societatea Romana de Strabologie si Oftalmopediatrie) - https://www.srsop.ro/	1) Romanian Society of Cardiology (SRC) (Ro., Societatea Romana de Cardiologie (SRC) - https://www.cardioportal.ro/ 2) CardioGen Association - https://asociatia-cardiogen.ro/ 3) "Pop de Popa" Foundation for the Protection of Patients with Cardiovascular Diseases (Ro., Fundația "Pop de Popa" pentru Ocrotirea Bolnavilor cu Afecțiuni Cardiovasculare) - https://fobac.ro 4) Romanian Society of Hematology (Ro., Societatea Română de Hematologie) - https://www.srh.org.ro/ 5) Romanian Society of Arterial Hypertension (Ro., Societatea Română de Hipertensiune Arterială) - https://www.societate-hipertensiune.ro/ 6) Stroke Romanian Association (Ro., Asociaţia Naţională	1) Romanian Society Against Epilepsy (SRIE) (Ro., Societatea 2) Romana Impotriva Epilepsiei (SRIE) - https://ilae-romania.ro/home-en/about-us/	1) Romanian Society of Dermatology (Ro., Societatea Română de Dermatologie) - https://srd.ro/ 2) Romanian Association of Dermatology and Venereology (Ro., Asociația Română de Dermatologie și Venerologie) - https://ardv.ro/

						Româna de Stroke) - https://anrs-neurologie.ro/ 7) Association Romanian Society for the Prevention and Medical Recovery of People with Cerebrovascular Accident (Ro., Asociația Societatea Română pentru Prevenirea si Recuperarea Medicală a Persoanelor cu Accident Vascular Cerebral - http://accidentulvascular.ro		

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Task 1.5 Focus groups among HCPs (M10-11)

- The aim of the focus groups is to gain a deeper insight and 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 groups. The CFIR-constructs will be the major basis for the focus groups.
- The topic list has not yet been developed, as its content depends on the questionnaire results.. During the study, a draft version of the topic list will be shared with EMA for review.
- 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 consists of 8-10 participants, being a usual and optimal number of participants for focus groups[9]. The main reason for having separate focus groups for medical doctors and pharmacists is that believe their views on the implementation and dissemination of aRMM may differ. Recruitment of focus group participants will be done through the questionnaire. At the end of the questionnaire it is asked whether the respondent wants to participate in a focus group. If so, the respondent is asked to fill out contact details: email address or phone number. In the questionnaire it is also ask which of the seven medicinal products prescribers/specialists prescribe and for pharmacists, which product(s) they dispense. This enables to select a variety of prescribers/specialists/ pharmacists for the focus groups and to ensure that all medicines are covered.
- If not enough professionals can be recruited for one focus group, for example due to limited simultaneous availability, individual interviews will be conducted as a mitigation measure. Another mitigation measure is that if recruitment via the questionnaire is not sufficient to cover all the seven medicinal products, healthcare professional organisations from Table 8b will be approached to recruit participants for the missing products.
- We ask for informed consent of the respondents at the start of the focus groups (prior to the first substantive question) and will follow Regulation (EU) 679/2016 (the General Data Protection Regulation) in this respect.
- The focus groups will be in the national languages of the respective participating countries and will take place using Microsoft Teams (or another programme that is familiar in a specific country, like Zoom), and last for 90-120 minutes. The focus groups will be audiotaped and transcribed. In case Zoom is used, settings that allow for recordings will be deleted.
- Although the focus group will be conducted by experienced researchers, who know how to keep an interview on track, 90-120 minutes might possibly be challenging to discuss all the relevant aspects with HCPs. As mitigation measure it is proposed that if not all relevant aspects are discussed, the respective HCPs will be approached by phone or mail to discuss the remaining issues, or a short (max 15-30 min) second meeting will be set up with the respective HCPs to discuss these issues provided that they have given consent to contact them again.
- 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).

9.2.2 WP2: Access to aRMM materials

This WP describes how access to paper based and digital aRMM materials for patients and HCPs is ensured for each step of the dissemination pathway in the six selected countries. This WP starts with desk research, followed by online surveys, focus groups and interviews.

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

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.

To assess whether aRMM materials are paper based or digital, the dissemination method from the perspective of the user will be used. So, if the user (i.e. patient or healthcare professional) receives the aRMM materials on paper, is the aRMM material is considered to be paper based and when the user receives it via e-mail or through a link on a website, it is digital. A patient alert card, for instance, can be a paper based (or plastic) card that is provided by the HCP or via the packaging. From the perspective of the patient receiving this card it is considered to be paper based. For HCPs that receive the same card digitally and print them to disseminate them to patients, this patient alert card is considered to be digital.

Task 2.1 Desk research (M1-3)

- For this WP, the focus of the desk research (see for more detailed information about the desk research task 1.1) is on access to aRMM materials for patients and HCPs.
- Within the desk research, the international and grey literature is searched for studies regarding the physical dissemination of aRMM. It is possible that within the studies found, there is also information about access to aRMM materials for patients and HCPs. For example, Artime et al. (2020) found in their review that in the studies that addressed the receipt of aRMM by HCPs and patients, that 57% (median) of the HCPs received the aRMM, and 56% (median) of the patients. Such information will be included in the relevant section(s) of the report.

Task 2.2 Interviews with MAHs (M2-4)

- The interviews with MAHs that were described in task 1.2 (see task 1.2 for more detailed information) will also be used to get insight in the access to aRMM materials for HCPs and patients from the perspective of the MAHs.
- For example, MAHs are asked to describe how they ensure access to aRMM materials for HCPs and patients.
- For the exact questions, see the interview guide included in Annex 3D.
- The data analysis of the interview data is described in section 9.8.

Task 2.3 Focus group with NCAs (M2-4)

- The focus group with NCAs that was described in task 1.3 (see task 1.3 for more detailed information) will also be used to get insight in the access to aRMM materials for HCPs and patients from the perspective of the NCAs.
- For example, NCAs are asked how, from a regulatory point of view, ensure access to aRMM materials.
- For the exact questions, see the interview guide included in Annex 3E.
- The data analysis of the focus group is described in section 9.8.

Task 2.4 Online surveys among HCPs and patient organisations (M4-8)

- The online surveys to collect information from HCPs and patient organisations that were described in task 1.4 (see task 1.4 for more detailed information) will also be used to get insight in the access to aRMM materials from the perspective of HCPs and patient organisations.
- In the HCP questionnaire, question(s) will be included to get insight in whether they receive the aRMM materials for the products included in this study.

- In the questionnaire for patient organisations, question(s) will be included to get insight in whether into whether they draw their members' attention to aRMM materials.
- The data analysis of the survey is described in section 9.8.
- The questionnaires are included in Annex 3F.

Task 2.5 Focus groups among HCPs (M10-11)

- The aim of the focus groups (see task 1.5 for more detailed information) is to gain a deeper insight/better understanding of the first results of the online survey of the previous task.
- The exact content of the follow-up questions included in the topic list will depend on the results of the questionnaire. An example of a follow-up question for this WP is to get insight into whether and how they received the aRMM materials and what challenges they encountered in disseminating them in their healthcare facility.
- The data analysis of the focus groups is described in section 9.8.
- The topic list has not yet been developed, as its content depends on the questionnaire results.. During the study, a draft version of the topic list will be shared with EMA for review.

Task 2.6 Short survey among patients (M4-8)

- In addition to the survey among patient organisations as described in WP1, a short questionnaire among patients will also be distributed. This questionnaire is a way of collecting data from the patient perspective, in addition to the questionnaire among patient organisations which is the main source to gain 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). Patients will be asked which medicinal product they use and for each of the relevant aRMM materials for a specific product whether or not they received these aRMM materials, and if they received the aRMM materials, how they received it. As such, it is ensured that the results can be stratified by medicinal product, by type of aRMM and by dissemination method.
- The questionnaire is included in Annex 3F.
- The questionnaire for patients will be made available using an open link, enabling that the questionnaire can be distributed through different channels. Furthermore, the questionnaire will be programmed mobile friendly for respondents to easily fill out the questionnaire on their mobile phone.
- To reach patients, different strategies will be used:
    - 1) The participating patient organisations are asked to spread a link and/or QR-code to the questionnaire, for example via their newsletter and social media accounts.
    - 2) Furthermore, to also reach patients who are not a member of a patent organisation, a selection of pharmacies, representing a mix of community and hospital pharmacies within our network, will be asked to hand out flyers to patients who collect one of the included medicinal products. The flyer provides brief information about the research and the aim of the research and includes also a link and/or a QR code to the questionnaire for patients. Furthermore, a contact address is included in case the patient has questions or encounters difficulties with filling out the questionnaire. This approach can only be applied to products that are supplied through pharmacies and have a sufficient number of users so that there will be a realistic chance that the pharmacy has patients that come collect the product during the data collection period.
    - 3) The link will be distributed through the social media network of the researchers.
- Although almost all people in the participating countries have access to internet and use internet on a daily base (e.g. in the Netherlands 95% of the people uses internet on a daily

base and in Romania 95% of the surveyed population considered having digital skills to navigate the Internet to find health information), filling out an online questionnaire might be a challenge for some groups of patients (e.g. the elderly). Therefore, some mitigation measures are proposed:

  - 1) Countries have the flexibility to establish a procedure to contact patients who are not able to fill out the online survey contact by phone. The interviewing researcher can then fill out the online survey for the patient using the open link programmed by DESAN.
  - 2) There is the possibility for patients to use a 'read-aloud function' in the questionnaire. This means that the questions are read out aloud at a pace chosen by the respondent. DESAN and Nivel have experience with this for the Netherlands, and this method will also be used for the patient questionnaires in the other languages in this study.
  - 3) For patients that have visual impairments it is possible to enlarge the font size in the questionnaire, so it is easier to read the questions. This group is also offered the opportunity to view the questionnaire in a light or dark modus. DESAN and Nivel already have experience with this for Dutch questionnaires.

- Informed consent of the respondent is asked at the start of the questionnaire (before the first substantive question) and will follow 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. In handling the data collection, DESAN will add a variable that indicates in which country the survey is filled out. This ensures that the results can be stratified by country.
- After data cleaning, data will be analysed according to the description in section 9.8.
- 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.
- The topic list has not yet been developed, as its content depends on the questionnaire results.. During the study, a draft version of the topic list will be shared with EMA for comment.
- Information from the desk research and the online survey 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 with patients in each participating country, making a total of 6 focus groups. Each focus group consists of 8-10 participants, being a usual and optimal number for focus groups[10].
- Recruitment will be carried out via the short questionnaire for patients which will include asking whether they would be willing to participate in a focus group or an interview. In the questionnaire it will also be asked which of the seven medicinal products patients use, making it possible to select a variety of patients for the focus groups and to ensure that all medicines are covered.
- If not enough patients can be recruited for one focus group, for example due to limited simultaneous availability, individual interviews will be conducted as a mitigation measure.
- Another mitigation measure is that if recruitment via the questionnaire does not sufficiently cover all seven medicinal products – which is likely for the products with a low number of users, then patient organisations from Table 8a and our own large network will be

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

approached to recruit participants for the remaining products.

- Informed consent of the respondent will be asked at the start of the focus group (prior to the first substantive question) and will follow 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 9.8.
- Although the focus group will be conducted by experienced researchers, who know how to keep an interview on track, 90-120 minutes might possibly be challenging to discuss all the relevant aspects with patients. As mitigation measure in case not all relevant aspects are discussed, is to approach the respective patients by phone or mail to discuss the last points, or to set up a short (max 15-30 minutes) second meeting with the respective patients to discuss these points. This will only be done in case patients have given consent to contact them again.
- 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).

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

This WP will identify and describe the key challenges in the dissemination process of aRMM materials. The WP starts with desk research, followed by 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 4 in healthcare and b). patient-targeted aRMM materials to all eligible patients who are prescribed the medicinal products listed in Table 4, 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.

Task 3.1 Desk research (M1-3)

- For this WP the focus of the desk research is on the key challenges in the dissemination process of aRMM materials (see for more detailed information about the desk research task 1.1).
- Within the desk research, the international and grey literature is searched for studies regarding the physical dissemination of aRMM. It is possible that these studies describe challenges regarding the dissemination process of aRMM materials. For example, Hapani et al. (2022) found in a survey among local safety managers that frequent version updates of digital aRMMs were challenging. Such challenges can be used as input for the development of the interview guides and surveys, and additionally can be included in the section in the report where the challenges per stakeholder are described.

Task 3.2 Interviews with MAHs (M2-4)

- The interviews with MAHs described in task 1.2 will also be used to get insight in the key challenges of the dissemination process of aRMM materials from the perspective of MAHs (see task 1.2 for more detailed information).
- For example, MAHs will be asked to describe the challenges in the dissemination of the

aRMM materials for the included medicinal products, and whether these challenges differ between the countries included in the study.

- For the exact questions, see the interview guide included in Annex 3D.
- The challenges mentioned in the interviews will be categorised based on theme by one researcher and checked by another. Within the report the mentioned themes will be presented per stakeholder, alongside with some examples.

Task 3.3 Focus group with NCAs (M2-4)

- The focus group with NCAs described in task 1.3 will also be used to get insight in the key challenges of the dissemination process of aRMM materials from the perspective of NCAs (see task 1.3 for more detailed information).
- For example, NCAs will be asked what challenges and concerns they identify in the dissemination of aRMM materials.
- For the exact questions, see the interview guide included in Annex 3E.
- The challenges mentioned in the interviews will be categorised based on theme by one researcher and checked by another. Within the report the mentioned themes will be presented per stakeholder, alongside with some examples.

Task 3.4 Online surveys among HCPs and patient organisations (M4-8)

- The online surveys to collect information from HCPs and patient organisations described in task 1.4 will also be used to get insight in key challenges of the dissemination process of aRMM materials from the perspective of HCPs and patient organisations (see task 1.4 for more detailed information).
- In the HCP questionnaire, question(s) will be included to get insight in the challenges experienced by HCPs, e.g. in the distribution of aRMM materials to patients.
- In the questionnaire for patients organisations, question(s) will be included to get insight in whether they are aware of challenges or receive signals from their members regarding challenges in the dissemination of aRMM materials.
- Where possible, answer categories will be based on the information collected in the desk research, focus group with NCAs and the interviews with MAHs. Besides predefined answer options, an open answer category to add additional challenges will be included.
- The data analysis of the survey data is described in section 9.8.
- The questionnaire is included in Annex 3F.

Task 3.5 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 survey of the previous task (see task 1.5 for more detailed information).
- The exact content of the follow-up questions included in the topic list will depend on the results of the questionnaire. An example of follow-up question is to gain insight in the underlying reasons for the key challenges indicated in the questionnaire.
- The topic list has not yet been developed, as its content depends on the questionnaire results.. During the study, a draft version of the topic list will be shared with EMA for comment.

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

This WP will identify and describe preferences of patients and HCPs for aRMM tools. The WP starts with desk research, followed by 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.

Task 4.1 Desk research (M1-3)

- For this WP the focus of the desk research is on the preferences of patients and HCPs for aRMM tools, and how they prefer to receive them (see for more detailed information about the desk research task 1.1).
- Within the desk research, the international and grey literature is searched for studies regarding the physical dissemination of aRMM. It is possible that these studies, patients' and HCPs' preferences for aRMM tools are included. If available, this information will be used as input for the development of the interview guides and surveys, and additionally be included in the section of the report where the preferences of patients and HCPs are described.

Task 4.2 Online surveys among HCPs and patient organisations (M4-8)

- The online surveys to collect information from HCPs and patient organisations described in task 1.4 will also be used to get insight in preferences for aRMM tools from the perspective of HCPs and patient organisations (see task 1.4 for more detailed information).
- In the HCP questionnaire, question(s) will be included to get insight in how they prefer to receive aRMM tools. This will be asked for the relevant tools in Table XVI.2. of the Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures[11]. The following aRMM tools are included in the questionnaire (see also Annex 3F): educational material for HCPs (guide, information pack), healthcare provider checklist, patient guide, patient card (alert/educational/reminder), risk acknowledgement form (only for prescribers).
- In the questionnaire for patients organisations, question(s) will be included to get insight in what according to them is the preferred way to receive aRMM tools. This will be asked for the relevant patient tools included in Table XVI.2. of the Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures[11]. The following aRMM tools are included in the questionnaire (see also Annex 3F): patient guide and patient card (alert/educational/material).
- The data analysis of the survey data is described in section 9.8.
- The questionnaire is included in Annex 3F.

Task 4.3 Short survey among patients (M4-8)

- The online surveys among patients described in task 2.6 will also be used to get insight in preferences for aRMM tools from the perspective of patients (see task 2.6 for more detailed information).
- In the patient questionnaire, question(s) will be included to get insight in how patients prefer to receive aRMM tools. This will be asked for the relevant tools for patients included in Table XVI.2. of the Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures[11]. The following aRMM tools are included in the questionnaire (see also Annex 3F): patient guide and patient card (alert/educational/reminder).
- The data analysis of the survey data is described in section 9.8.
- The questionnaire has not yet been developed. An overview of the proposed topics included

[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

in the questionnaire is included in Annex 3F. During the study, a draft version of the questionnaire will be shared with EMA for comment.

Task 4.4 Focus groups among HCPs (M10-11)

- The aim of the focus groups is to gain a deeper insight and better understanding of the first results of the online survey of the previous task (see task 1.5 for more detailed information).
- The exact content of the follow-up questions included in the topic list will depend on the results of the questionnaire. An example of a follow-up question for this WP is one to get insight in the underlying reasons of the preferences indicated in the questionnaire.
- The topic list has not yet been developed, as its content depends on the questionnaire results.. During the study, a draft version of the topic list will be shared with EMA for review.

Task 4.5 Focus groups patients (M10-11)

- The aim of the focus groups (see task 2.7 for more detailed information) is to gain a deeper insight/better understanding of the first results of the online survey of the previous task.
- The exact content of the follow-up questions included in the topic list will depend on the results of the questionnaire. An example of (a) follow-up question(s) for this WP is to get insight in the underlying reasons of the preferences indicated in the questionnaire.
- The topic list has not yet been developed, as its content depends on the questionnaire results.. During the study, a draft version of the topic list will be shared with EMA for review.

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

This WP will provide recommendations to facilitate the dissemination of aRMM. The data collected in WP1, 2, 3 and 4 will be used as input for this WP. In addition, a webinar for stakeholders and a synthesis workshop for researchers will be organised.

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)

- A webinar for all relevant stakeholders (such as national competent authorities, MAHs, patient organisations, professionals) across the EU/EEA will be organised to jointly reflect on and discuss the results of the study. The webinar serves several purposes, namely to create broader awareness of the results in the EU and to explore whether the results of the study are also recognisable for other countries. Not all participants will be familiar with the study; therefore, some main results of the study will be presented as input for the discussion during the webinar.
- 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 additional information. Participants will be recruited through the contacts of the researchers in the participating countries, but also via organisations like the European Forum for Primary Care, the Health Policy Platform of the EU, ESPACOMP and via the healthcare professional and patient organisations reflected in Tables 8a and 8b.

- 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 question 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 meeting 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 for other countries as well.

Task 5.2 Synthesis workshop researchers (M13)

- This task aims to come to set of recommendations for EMA including concrete steps for each step of the dissemination pathway for aRMM.
- We are organizing an online synthesis workshop to discuss the recommendations with all members of the consortium. This is for efficiency reasons. It is expected that decisions will be reached more quickly if the results of the research are discussed jointly in a structured manner and under the guidance of an experienced moderator (compared to communicating mainly via mail and written documents).
- A workshop consisting of two half-days with representatives of the focal points will be organised. Day 1 will be used to translate the results to a set of general recommendations. Day 2 will be used to discuss the implementation of the recommendations into the dissemination pathway in more detail; what needs to be done, how can this be achieved 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 to support the drafting of the recommendations by the Nivel team. The final set of recommendations will be sent out to the focal points for feedback and accordance.

9.3 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). For each MAH more than one person can participate in the interview (with a maximum of 2-3 persons). With this number of interviews, it is expected that data saturation with regards to views on roles will be reached. Usually, data saturation is reached after 12 interviews (Guest et al., 2006).
- **National competent authorities** (NCAs). All relevant national competent authorities in the six participating countries will be included in the study. For each country a maximum of two persons of the NCA can participate in the focus group. As such, data saturation is not an issue here: as there is 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. Professionals will be reached through

professional organisations reflected in Table 8b*, social media (e.g. the LinkedIn page of Nivel and partners), and the network of the researchers (e.g. contacts with academic research centres for GPs and pharmacists). Furthermore, two focus groups with professionals will be conducted in each country (one with medical doctors and one with pharmacists). By combining these methods, data saturation is strived for.

- **Patient organisations.** Relevant patient organisations* in the six countries will be approached. As such, data saturation is not an issue here: all relevant patient organisations will be invited.
- **Patients**. As many patients as possible in the six countries that use one of the included medicinal products will be approached for participation. As argued above, some of the products have a low number of users, and no national registrations of users are available. Therefore, patient organisations are included in the study to get insight in the patient perspective. In addition, patient organisations are asked to distribute the survey to reach patients. It is expected that distributing our survey through professionals or via social media only is not sufficient. Furthermore, focus groups with patients will be conducted in each country. By combining these methods, a maximum of validity and reliability is strived for.
- **Stakeholders of all EU/EEA Member States.** For the webinar, also stakeholders of other EU/EEA Member States than the ones participating in the study will be invited. Through their participation, any remaining challenges in the dissemination of aRMM can ultimately be identified. This ensures data saturation.

* To identify relevant HCP and patient organisations in each country, the relevant medical conditions for each of the seven medicinal products are identified. Subsequently, a search is conducted – for example, using by Google – for patient organisations related to that medical condition. For HCP organisations, the professionals involved in treating the condition were first identified after which a search was conducted for organisations representing those professionals.

9.4 Variables

The relevant outcomes in this study are:

- The process, frequency and how aRMM materials are disseminated;
- Roles and responsibilities of key stakeholders (prescriber, pharmacist, MAH, NCA) in the dissemination process;
- Access to aRMM materials for patients and HCPs;
- Storage of aRMM materials;
- Key challenges of disseminating aRMM materials;
- Preferences for aRMM tools for patients and HCPs.

9.5 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 stakeholders from the six participating EU Member States as well as the other EU Member States will be invited. Table 9 shows the details.

1074 **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 1 or 2 participants per national competent authority from the six countries (minimum 6, maximum 12) • 6 (one in each country) with approximately 8-10 patients per FG (total around 48-60) • 12 (two in each country) with approximately 8-10 professionals per FG (total around 96-120)	M3-4** M10-11 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

1075 * The questionnaires for professionals and patients will be spread through different channels to reach as many respondents
1076 as possible. However, for some of the medicinal products there is a low number of users. Therefore, it cannot be
1077 guaranteed that these numbers will be reached. When the number of responses is higher than expected, these responses
1078 will of course be included in the analysis.
1079 ** Within the WPs above a longer period is mentioned, because there is also the preparation of the focus groups,
1080 interviews and questionnaires is included. These are only the months of the data collection.

1081 9.6 Study size

1082 • A maximum of 11 **interviews** will be conducted with MAHs. This number is calculated as
1083 follows: for five out of the seven included medicinal products (Xeljanz, Aubagio, Lemtrada,
1084 Eylea and Lixiana) the relevant MAH for one country will be interviewed. For both the
1085 Valproate and Retinoids containing products there are more MAHs and for each of them a
1086 maximum of three MAH will be interviewed. This implies that a maximum of 11 MAH will be
1087 interviewed (5 MAHs for the specific products + 3*2 MAHs for the groups of products). With
1088 this number of interviews, data saturation is presumably achieved with regards to the views
1089 of MAHs on their role and responsibilities in aRMM as well on the ways to distribute aRMM,
1090 as normally around 12 interviews data saturation is reached (Guest et al., 2006l).
1091 • In total 19 **focus groups** will be organised. First, 1 focus group will be organised with

representatives from the national competent authorities of all six participating countries. Each participating country has a NCA. Each NCA will be invited to participate, with a maximum of two persons per NCA. So a minimum of 6 participants is expected (if all NCAs are able and willing to participate) and a maximum of 12 participants. Furthermore, in each country 2 focus groups with HCPs will be organised and 1 with patients. is the expectation is that approximately 8-10 HCPs / patients per focus group will participate. This is a usual and optimal number of participants for focus groups[12], making a total of 96-120 participants for HCPs (12 * 8-10 HCPs) and 48-60 patients (6 * 8-10 patients). In case focus the groups are too difficult to arrange, for example or example due to limited simultaneous availability, interviews will be performed instead. Previous experiences show that including this flexibility ensures the best response and the best representativity.

- The **online surveys** will be distributed via patient and professional organisations, our extensive network and as many other different channels as possible, with the aim of reaching a sufficient number of HCPs, patient organisations and patients.
- It is estimated that each country will have approximately 5-10 patient organisations for the 7 medicinal products per country, making a total of 30-60 patient organisations (5-10 organisations * 6 countries). Because the number of users of medicines included in the survey varies across products and countries, and is sometimes low, the aim is to obtain 50-100 patient questionnaires per country and 50-100 professional questionnaires per country for professionals. Because the number of users of medicines included in the survey varies across products and countries, and is sometimes low, the aim is to obtain 50–100 patient questionnaires per country and 50–100 professional questionnaires per country.
- Although every effort will be made to ensure the highest possible response rate among patients and professionals, there is no guarantee these targets will be met.
- For the **webinar** all the relevant bodies, organisations and stakeholders that participated in the online questionnaires, focus groups and interviews in each of the six included countries will be invited, as well as relevant bodies, organisations and stakeholders from other EU Member States. The expectation is that 40-50 stakeholders will participate in the webinar.

9.7 Data management

A data management plan is developed following the FAIR principles[13] (Findability, Accessibility, Interoperability and Reusability). The plan (see Annex 3G) includes, among others, a 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).

[12] https://participatiekompas.nl/media/pdf/handleiding_focusgroepen_2019_april_-tg.pdf
[13] https://www.force11.org/group/fairgroup/fairprinciples

9.8 Data analysis

This study is a mixed methods study, using desk research, online surveys, interviews, focus groups and a webinar. This section describes for each method how the data will be analysed. Furthermore, for each objective the methods used to collect data elements/variables for stratification are described.

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 this study) and author's conclusion. Narrative synthesis will be conducted to summarize the information from the included publications. A narrative synthesis is a method used to summarize and explain findings from multiple studies that relies primarily on the use of words and text to summarize and explain the findings of the synthesis (e.g. Popay et al., 2006). Key elements are that it is textual and not statistical, it describes similarities and differences, it organizes the findings thematically, and the findings are placed in a broader context. The summarized information will be used as input for the development of the online surveys and the interview/focus group guides.

Online surveys

- Before analysing the data some checks will be done, e.g. empty questionnaires will be removed from the data set and multiple choice questions inconsistencies are checked.
- 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, aRMM, dissemination method, by stakeholder (patient, patient organisation or healthcare professional) 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, it is likely that not all subgroup analyses can be done. For privacy reasons, numbers below 10 will not be reported, as this could allow identification of respondents. In that case, data will be combined. Examples include combining information from more countries, from the same aRMM or from the same dissemination method.
- The open answers will be categorised based on theme by one researcher and checked by another. The report will present the most mentioned themes, alongside with some examples.
- 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.
- Stata version 16.0 will be used 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 MAHs and the focus group with the NCAs will be in English. The focus groups with HCPs and patients in the six countries will be in the national language of each of the six participating countries.

- The transcripts of the focus groups with HCPs and patients will be analysed by the focal points of each country in their own language. They will report the results in English. By analysing the results of those focus groups per country, it is possible to stratify the results by country.
- 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 based on the desk research and the use of the CFIR framework are possibly reflected in the data. To ensure that no information is missed, additional codes will be inductively added if they are not included in the analytical framework for the analysis.
- For the first 3 interviews for MAHs, two Nivel researchers will independently analyse the transcripts using software for qualitative data (MaxQda or Excel). These 3 interviews will thus be double coded. The researchers will compare their codes and discuss discrepancies; the remaining interviews will be analysed by one researcher and 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 (10% of the text of the focus groups will also be coded by another researcher of that country) and codes will be discussed in an online meeting (prepared by Nivel) among the six coding researchers (except for the focus group among national competent authorities, which will be conducted and analysed by Nivel). 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 coding bias is avoided as much as possible.
- Deductive coding will be used, meaning that the same predefined set of codes will be used 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.
- Tables will be drafted where the results of the interviews and focus groups will be presented 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 must be made. The researchers will compare their findings and discuss discrepancies. Finally, the results will be discussed in the full research team.

Stratification in the data analysis

To be able to stratify the results within the data analysis, several data elements/variables will be collected within the different research methods. Hereafter, an overview of these data elements/variables is given that allow for stratification by **type of aRMM**, by **dissemination method**, by **medicinal product**, by **country**, and by **key stakeholder**.

Table 10 Data elements/variables to enable stratification

Stratification by:	Data element/variable to enable stratification
Type of aRMM	The surveys include questions for each aRMM in the study. Respondents will be asked which products are relevant to them and guided to the relevant questions only. Per product a question will be included whether the aRMM was received/provided for each relevant aRMM.
Dissemination method	For each aRMM the dissemination method will be asked in the surveys (e.g by paper, electronically, orally, other).
Medicinal product	The questionnaires will include a question that ask what kind of medicinal product is relevant for the patient organisation / used by the patient / prescribed or dispensed by the HCP. Based on this question, results can be stratified by medicinal product. Example question into use of the included products for patient: Do you use [product name]? yes/no Questions into involvement with included products by HCPs: Have you prescribed/dispensed [product]? Yes/No
Country	Questionnaire data from patients organisations, patients and HCPs and the focus groups among patients and HCPs will be collected by country. For each of the three questionnaires an own open link will be programmed for each country. The open link through which the respondent completed the questionnaire shows the country where the respondent comes from. DESAN will combine the country files and add a variable in the total datasets (one dataset for patient organisations, one for patients and one for HCPs) that indicates in which country the survey is filled out. As such, the results can be stratified by country. For the focus groups, there will be transcripts per country and each country will make a summary of the results in English. As such, the results can be stratified by country.
Key stakeholder	There are different data collection methods for the different stakeholders: NCA's: focus group MAH: interviews HCPs: questionnaire and focus groups Patient organisations: questionnaire Patients: questionnaire and focus groups For each method the data will be collected and analysed separately, so the results can be stratified by key stakeholder.

In cases of a low number of respondents, respondent groups may be clustered logically, for instance by combining countries with similar dissemination methods.

Overall

To summarize, within this study both qualitative and quantitative data will be collected. This data will be collected in sequential order, e.g. the questionnaires among HCPs and patients (quantitative) will be followed by focus groups (qualitative). Furthermore, triangulation is applied in this study. Triangulation implies that more than one approach is used to study a phenomenon. The dissemination of aRMM materials will be examined from the perspective of different stakeholders, using different methods (e.g. interviews, focus groups, questionnaires and desk research). Together the findings of all the different data collection methods will result in conclusions and recommendations.

To integrate the data from the different study elements, the Good Reporting of A Mixed

Methods Study (GRAMMS) framework for overall mixed methods integration and reporting (O'Cathain 2008) will be followed. This framework 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).

9.9 Quality control

General approach to quality management and control

The team has excellent awareness of the importance of quality control systems for the execution of this study.

- 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 it will be laid 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. Nivel is 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. Furthermore, 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 study is registered in the HMA-EMA Catalogues of RWD studies (registration number EUPAS1000000524) and will as such follow the code of conduct of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Annex 2 includes the ENCePP checklist for study protocols for this study. 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.

- 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. All personal and sensitive personal data accessed or collected during this project will be processed 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. The potential need for a DPIA will be assessed and if deemed necessary a DPIA will be drafted.
- 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, there is 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.

9.10 Limitations of the research methods

There are several limitations associated with our approach. Below these limitations and the measures taken to limit these are discussed.

- **Limitations related to representativeness**
  Although all efforts will be done to include a representative sample of all stakeholders, we might not succeed. Thus, there are some risks that may influence the results. For instance, there may be an overall low number of included patients and other key stakeholders orpatients with low health literacy or reading problems may not participate . Also, selection bias may occur due to

purposive sampling. Also, a limitation is that due to purposive sampling it is not possible to calculate response rates for the surveys. Finally, a limitation of using open link questionnaires is that respondents might fill out the questionnaire more than once. However, in the current study respondents have no interest in completing the questionnaire more often to make a statement to influence policy.

To mitigate these problems, the following measures will be taken:

Six countries spread across the EU are included. These are countries from different regions, with different sizes and healthcare systems. Still, other countries might have information to add. Therefore, a webinar will be organised in which stakeholders from all EU/EEA member states can participate and reflect on the preliminary outcomes of the study.

For three of the seven included medicinal products the number of users is low. This might have impact on the stakeholder recruitment, especially on the recruitment of patients and HCPs for the questionnaires and focus groups. **Broad dissemination** of the online surveys for HCPs, patient organisations and patients is therefore foreseen, namely through relevant patient and professional organisations reflected in Table 8a and 8b, through the social media network of the researchers (e.g. the LinkedIn page of Nivel and partners) and through a selection of pharmacies within our network. This aims to ensure participation from a sufficient number of HCPs, patient organisations and patients Patient and professional organisations are reached using purposive sampling. Also reaching professionals and patients through a variety channels limits the risk of selection bias as patients and professionals that are not member of a patient or professional organisation can participate as well.

Still, information from certain groups might be missed, for example from patients (e.g. elderly) that are not able to fill out surveys online. To mitigate reading difficulties, patients will have access to a text-to-speech function and countries may conduct surveys by phone. In each country two focus group with HCPs and one with patients will be organised. In these focus groups, the participants can reflect on the preliminary outcomes of the questionnaires. If possible, participants for the focus groups will be recruited among the groups with the lowest representation in the surveys. To also recruit patients that are not able to fill out online questionnaires for the focus groups, patient organisations are asked whether they can recruit patients for the focus groups. Focus groups with patients and healthcare providers will be held in the national language. Questionnaires will also be translated into the national languages.

- **Limitations related to content**

1) Hesitance to share information

Participants of the interviews or focus groups may 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, the results will not include names and names of organisations for specific statements except for if the participant gives informed consent.

2) Social desirability bias

Besides that participants do not want to share information, they also might answer in a manner they expect others want to hear (i.e. socially desirable answers). For this study, participants can for example indicate that they distribute aRMM materials to patients while not doing that. To avoid socially desirable answers as much as possible, several measures will be taken. First, the questions in the interviews, focus groups and questionnaires will be formulated as neutrally as

possible. Furthermore, the questionnaires are anonymous. As an open link is used for all the questionnaires, it is not possible to link responses to specific participants. Also, the results will be reported without referring to names and names of organisations (except if the participant give informed consent for this). Finally, patients will be informed that answers on the questionnaire and/or focus groups are not shared with their HCPs and that participation in the study will not influence their treatment.

3) Recall bias

Finally, recall bias is possible, especially if experiences are a while ago. For example, it is possible that participants cannot remember exactly if and from whom they received the aRMM materials. Structured questionnaires can help to clarify participants' recollections.

- **Limitations related to the data analysis**

1) Bias in coding

In order to avoid bias in coding, part of the data of the focus groups and interviews 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.

2) Bias in analysing survey data

In order to avoid mistakes in analysing the survey data, all steps in the data analysis 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, a statistician at Nivel will be consulted.

10. 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 surveys will be asked at the beginning 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 identifiable patient-level data will be used.

10.1 Ethical aspects

The study is coordinated by the Netherlands. According to the Dutch legislation, approval by a medical ethics committee is not obligatory to carry out this study[14]. The reasons for this are that this study does not concern medical scientific research, and that participants are not subject to any 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, each country will apply, or already applied, for ethical approval in line with the regulations in each country. Finland and the Netherlands already received a waiver for this study. Lithuania will ask for a waiver in August 2025. Romania and Hungary need a full ethical approval from the ethics committee and will submit their request in August 2025. Italy does not need to apply for ethical approval, as this is not required according to the guidelines of their Competent Authority.

[14] https://www.ccmo.nl/onderzoekers/wet-en-regelgeving-voor-medisch-wetenschappelijk-onderzoek/uw-onderzoek-wmo-plichtig-of-niet

11. Management and reporting of adverse events/ adverse reactions

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

12. Plans for disseminating and communicating study results

12.1 Major deliverables

Four major deliverables and three appendices (all to D2) will be delivered (see Table 11). The first two deliverables will lay down the base for the study, the last two deliverables will contain the results.

Table 11 List of Deliverables

Deliverable number	Deliverable name	Related to WP	Lead	Type	Delivery month
D1	Preliminary study plan	All	Nivel	Study outline	2
D2	Study protocol	All	Nivel	Protocol	4
D3	Study report	All	Nivel	Report	14
D4	Manuscript scientific article (open access)	All	Nivel	Manuscript	16
Annex to deliverables					
D2.1	Data management plan	All	Nivel	Annex 3G of the protocol	4
D2.2	Communication plan	All	Nivel	Annex 3H of the protocol	4
D2.3	Publication plan	All	Nivel	Annex 3H of the protocol	4

12.2 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. Annex 3H includes the communication and publication plan in more detail.

12.3 Communication with EMA and third parties

- To discuss regular updates on the progress of the project EMA and Nivel will have a meeting once a month (in principle the first Tuesday of the month at 10 o'clock).
- Data collection materials, such as survey drafts and topic lists for focus groups will be shared with EMA for input before they are disseminated.
- From each meeting with EMA, minutes will be written by Nivel and shared with EMA.

- 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 place by communicating about the project results through the website of Nivel, social media and by sending a press release (news item). No results shall be made available to third parties prior to review of the full study report by PRAC. The mentioned communication products in Table 3H.4 in Annex 3 are related to D3 (the final report) and D4 (manuscript). One news item for D3 and one news item for D4 will be made. Drafts of these news items will be shared with EMA to be able to review the news items prior to publication. The exact date of publication of the news items will be made in agreement with EMA.

12.4 Data availability

All study results from all WPs will be included in one single study report (i.e. deliverable 3). The following interim results will be shared and discussed with EMA at the monthly stock-take meetings:

- 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).

A synopsis of the study protocol and the abstract of the final report will be published in the HMA-EMA Catalogues of real-world data sources and studies.

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Annex 1 Stand-alone documents

None

Annex 2 ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Dissemination of additional risk minimisation measures for patients and healthcare professionals in EU/EEA countries (DIS-aRMM study)

EU PAS Register® number: EUPAS1000000524
Study reference number (if applicable): SC01/EMA/2020/46/TDA/L4.01

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[15]	x	☐	☐	6 and Annex 3A
1.1.2 End of data collection[16]	x	☐	☐	6 and Annex 3A
1.1.3 Progress report(s)	x	☐	☐	6 and 12
1.1.4 Interim report(s)	x	☐	☐	6 and 12
1.1.5 Registration in the EU PAS Register®	x	☐	☐	Title page and 9.9
1.1.6 Final report of study results.	x	☐	☐	6 and Annex 3A

[15] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[16] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	x	☐	☐	7
2.1.2 The objective(s) of the study?	x	☐	☐	8.1 and 8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	x	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	x	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	x	

Comments:

Given the nature of the study, no hypotheses will be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	x	☐	☐	9.2
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	x	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	x	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	x	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	x	

Comments:

Given the nature of the study, no measures of occurrence, association and adverse reactions are described.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	x	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☐	☐	x	
4.2.2 Age and sex	x	☐	☐	9.9

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	x	☐	☐	9.1.2
4.2.4 Disease/indication	x	☐	☐	8.3 & 9.1.3
4.2.5 Duration of follow-up	☐	☐	x	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	x	☐	☐	9.2

Comments:

Data will only be collected from persons age 18 years and older. Given the nature of the study, there is no study time period and follow-up period defined.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	x	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	x	
5.3 Is exposure categorised according to time windows?	☐	☐	x	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	x	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	x	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	x	

Comments:

Given the nature of the study, these items are not applicable.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	x	☐	☐	9.4
6.2 Does the protocol describe how the outcomes are defined and measured?	x	☐	☐	9.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	x	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	x	

1603 Comments:

Given the nature of the study, 6.3 and 6.4 are not applicable.

1604

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	x	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	x	☐	☐	9.10
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	x	☐	☐	9.10

1605 Comments:

Given the nature of the study, 7.1 is not applicable

1606

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) I	☐	☐	x	

1607 Comments:

No sub-group analyses, but analyses will be stratified, see section 9.8

1608

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	x	☐	☐	9.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	x	☐	☐	9.2
9.1.3 Covariates and other characteristics?	x	☐	☐	9.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	x	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	x	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	x	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	x	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	x	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☐	☐	x	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	x	

Comments:

Given the nature of the study, 9.2, 9.3 and 9.4 are not applicable

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	x	☐	☐	9.8
10.2 Is study size and/or statistical precision estimated?	x	☐	☐	9.6 and 9.8
10.3 Are descriptive analyses included?	x	☐	☐	9.8
10.4 Are stratified analyses included?	x	☐	☐	9.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	x	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	x	
10.7 Does the plan describe methods for handling missing data?	x	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☐	☐	x	

Comments:

Given the nature of the study, not all questions are applicable.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	x	☐	☐	Annex 3G
11.2 Are methods of quality assurance described?	x	☐	☐	9.9 and Annex 3G
11.3 Is there a system in place for independent review of study results?	x	☐	☐	9.9

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	x	☐	☐	9.10
12.1.2 Information bias?	x	☐	☐	9.10
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	x	

Section 12: Limitations	Yes	No	N/A	Section Number
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	x	☐	☐	Among others: 9.2, table 6, 9.10

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	x	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	x	☐	☐	10.1
13.3 Have data protection requirements been described?	x	☐	☐	9.2 9.9 10

Comments:

An ethical review is foreseen in all participating countries. As questionnaires still have to be developed, it is not possible yet to apply for an METC assessment in some of the countries.

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	x	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	x	☐	☐	Section 12 and Annex 3H
15.2 Are plans described for disseminating study results externally, including publication?	x	☐	☐	Section 12 and Annex 3H

Comments:

Name of the main author of the protocol: Dr. Anne Brabers

Date:

Signature:

Annex 3A Gant chart of the study

Table 3A.1 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								■								■

		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
	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		
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, the focus will be on one of these.

Annex 3B Search strategy international literature

PubMed
Search string: “additional Risk Minimisation Measures” OR “aRMM” or “additional Risk Minimization Measures” or “additional Risk Minimisation Measure” or “additional Risk Minimization Measure”
No hits for “additional Risk Minimisation Measure” or “additional Risk Minimization Measure”
Research repeated with: “additional Risk Minimisation Measures” OR “aRMM” or “additional Risk Minimization Measures”

Search based on Mesh-terms:
Search string: ("Patient Safety"[Mesh] AND "Risk Management"[Mesh]) AND "Pharmacology"[Mesh]

Google Scholar
Search string "additional Risk Minimisation Measure" OR "additional risk minimisation measures" OR "additional Risk Minimization Measure" OR "additional risk minimization measures"

Embase
Search string “additional Risk Minimisation Measures” OR “aRMM” OR “additional Risk Minimization Measures” OR “additional Risk Minimisation Measure” OR “additional Risk Minimization Measure”

Additional search
Snowballing
Based on results of the literature extra papers can be included (so far one extra paper included)

Patient Alert Card
Search string: “Patient Alert Card”
In last 5 years in Pubmed

Checklists for HCPs
Search string: "prescriber checklist" OR "pharmacist checklist" OR “HCP checklist”: no results
Search string: "checklist" AND medicine[Mesh] AND (pharmacist OR prescriber)
In last 5 years in Pubmed

Educational materials for HCPS
Search string: "educational material" AND medicine[Mesh] AND (pharmacists OR prescriber)

Table 3B.1 Literature extraction form

Author	Year	Medicinal product	Country	Type of aRMM	Stakeholders/ research population	Dissemination methods	Research method/ data source	Results and Conclusions relevant for this study	Recommendations

Annex 3C Guiding document desk research

This document provides instructions for sub-contractors to perform the desk research in their own participating country.

1. Introduction

This document intends to provide an overview of the information that can be collected via desk research. Please complete the information for your country as requested in the sections below. We would appreciate if you return the document before **2 May 2025, by email**.

We drafted some tables for you to fill in, in the hope that this will be convenient to you. Feel free to add any information that you think is useful for the project.

For any question or unclarity, please contact Anne Brabers (a.brabers@nivel.nl) and/or Madelon Kroneman (m.kroneman@nivel.nl).

2. aRMM in your country

Could you please collect the available aRMM in your country for all of the included products in your national language(s) and report on the way the materials are disseminated to the users: by paper or digital or both. If available, please provide the link to the materials. If not, please store the materials somewhere for future reference. Please fill out the information in the table below.

Country name: …….

Medicinal Product	aRMM material	aRMM material found (yes/no)	Dissemination method D=digital P = paper DP = both UN=Unkown	URL
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			

3. Contact person NCA

To be able to organise the focus group for competent authorities, could you please find out who is the relevant contact person within the National Competent Authority in your country. It would be helpful if you can already inform this person that he or she will be approached by Nivel for this project.

Information regarding the NCA contact person	
Name of the organisation:	
Name of the proposed contact person:	
Email address of the contact person or functional mail address:	
Person is informed by me:	Yes/no

4. Grey literature search

In this section, we provide you the type of information we are looking for, to help harmonizing the search process.

What to search

Information on the dissemination method of aRMM and possible evaluations of these methods. Dissemination in this study refers to the physical dissemination of these materials: how do they reach the professionals and how are they handed over to patients. From a regulatory perspective little is known about the practical aspects and roles and responsibilities of the stakeholders involved in the dissemination processes at national level. The information should focus on understanding the processes based on the provided product-specific examples.

Where to search

Please search for grey literature using a search engine such as Google Scholar or similar. The search can also be performed at targeted websites, such as the following:

- Websites from the Competent Authorities
- Websites from patient organisations (see section 5 for some suggestions)
- Websites from relevant professional/medical organisations (see section 5 for some suggestions)
- Websites from pharmaceutical organisations or pharmacists associations
- Governmental websites, such as the Ministry of Health.

Please give an overview of all websites you visited.

We kindly ask you to provide a summary of the findings of your search, describing the dissemination process as detailed as possible (who is involved and in what form is it provided to physicians and/or handed over to patients).

Keywords

For the search, we propose to use the following keywords: “additional Risk Minimisation Measure” and “aRMM” translated in the language(s) of your country.

Reporting

Please fill out the following table for reporting on the search strategy:

Country name: ……

Website	Date visited	Name of organisation	Number of documents found

Please fill out the following table for reporting on the outcomes of the search:

Country name: ……

Substance and aRMM material	Title (national language)	Title (in English)	URL	Date of access

5. Relevant patient and professional organisations

Please fill out all relevant patient (table 8a below) and professional (table 8b below) organisations for you country.

Possible relevant patient organisations may address the following (groups of) diseases:

- Inflammatory Bowel Diseases, intestinal diseases
- Rheumatic diseases
- Multiple Sclerosis
- Epilepsy
- Macular degeneration, vision impairments, eye diseases
- Skin diseases
- Cardiovascular diseases

Relevant medical specialties are:

- Ophthalmology
- Gastroenterology
- Neurology
- Dermatology
- Cardiology

Table 8a **Overview of relevant patient organisations per country, per product.** Please add or amend the information. If information is not available in your country, please state: Not available.

Country	General	Xeljanz (rheumatism, gastroenterology)	Aubagio (multiple sclerose)	Lemtrada (multiple sclerose)	Eylea (macular degeneration)	Lixiana (anticoagulants)	Valproate containing products (epilepsy)	Retinoids containing products (acne and psoriarss)
NL								
FI								
IT								
HUN								
LIT								
ROM								

Table 8b **Overview of relevant professional organisations per country, per product.** Please add or amend the information. If information is not available in your country, please state: Not available.

Country	General	Xeljanz (rheumatism, gastroenterology)	Aubagio (multiple sclerose)	Lemtrada (multiple sclerose)	Eylea (macular degeneration)	Lixiana (anticoagulants)	Valproate containing products (epilepsy)	Retinoids containing products (acne and psoriasis)
NL								
FI								
IT								
HUN								
LIT								
ROM								

6. Number of users per medicinal product per country

Please check the information for your country (especially in the footnotes of the table) and add or amend the information accordingly. If information is not available in your country, please state: Not available. If possible add the source(s) in the footnote. We kindly request you to double check the information and to address the highlighted items for your country.

Table 6 Number of users per medicinal product per country

Country	Population	Xeljanz	Aubagio	Lemtrada	Eylea	Lixiana	Valproate containing products	Retinoids containing products
NL[1]	~18 million							
FL[2]	~5.5 million							
IT[3]	~58 million							
HUN[4]	~9.5 million							
LIT[5]	~3 million							
ROM[6]	~19 million							

1 Source:
2 Source:
3 Source:
4 Source
5 Source:
6 Source:

Annex 3D Interview guide and short questionnaire interviews MAHs

A shortened version of the interview guide will be sent to participants prior to the interview.

Part 1: INTRODUCTION (5-10 min)

Introduction

Thank you very much for your willingness to participate in this online interview. Before we start the interview, we will start with a short round of introductions. Then we will proceed with a short explanation of the purpose of this study and this interview.

[short round of introduction: note 'who' (function) is participating from each MAH]

Purpose of the study and the interview

Nivel (the Netherlands Institute for Health Services Research) and its partners (i.e. Syreon Research Institute, University of Eastern Finland, University of Naples Federico II, Vilnius University, Universitatea Babes-Bolyai and DESAN Research Solutions) are currently conducting a study investigating the dissemination of additional Risk Minimisation Measures (aRMM) for seven medicinal products in six European countries, namely The Netherlands, Finland, Italy, Hungary, Romania and Lithuania.

The objective of this study is to gain a better understanding of the current practice of disseminating aRMM for patients and healthcare professionals at national level, including any challenges encountered by the stakeholders involved in the actual dissemination process, which includes the marketing authorisation holder (MAH). This study will also investigate patients' and healthcare professionals' preferences and needs for aRMM, including for receiving these materials from MAHs. The focus of the study is on the physical dissemination of the aRMM. A secondary objective is to provide recommendations to regulators for regulatory decision-making on aRMM.

The study has been requested by the Pharmacovigilance Risk Assessment Committee (PRAC) to support regulatory decision-making around aRMM tools as described in Good Pharmacovigilance Practice (GVP) Module XVI.

The study uses a mixed-method approach, combining qualitative and quantitative methods. Besides this interview, we also conduct desk research, focus groups with staff from national regulatory agencies, healthcare professionals and patients, online surveys with healthcare professionals and patients, and a webinar with stakeholders from all EU/EEA member states to discuss the results of the study. The results will be included in a study report to be delivered to EMA in June 2026, and will be made publicly available after finalizing the study. Do you have some questions about the study?

Practical information

This interview will last 30-60 minutes, and you can indicate at any time that you want to stop. If you do not object, this interview will be recorded and transcribed by Teams. We will turn on the recording and transcription shortly, after which we will ask you to give permission for your participation and the recording of this interview. The recording and transcript will only be used to

transcribe the interview for thematic content analysis. We also use the transcript, for example, to include quotes (verbatim statements) made in the interview in the study report. Quotes will be reported in such way that the individual person who made the statement is not identifiable in the report. Besides these quotes, the study report will only contain aggregated, non-identifiable data and no product-specific evaluation of the effectiveness of aRMM will be performed. The recording will be deleted after approval of the study report. Do you have any questions about this interview or the research before we start?

[Answer]

Start recording and permission

We will now start the recording and transcription. Do you give permission:

1) To be interviewed, for this interview to be recorded and for the collection and use of video recordings?
2) That the recording and transcript will only be used to transcribe the interview for thematic content analysis. And, for example, to include quotes (verbatim statements) made in the interview in the study report. Quotes will be reported in such way that the individual person who made the statement is not identifiable in the report. Besides these quotes, the study report will only contain aggregated, non-identifiable data and no product-specific evaluation of the effectiveness of aRMM will be performed. The recording will be deleted after approval of the study report.

[Ask permission of the participant]

Part 2: DISSEMINATION PROCESS OF aRMM MATERIALS (15-20 min per material)

The following questions are about the dissemination process of aRMM materials in more detail. We will ask the following questions for each of the aRMM materials available for medicinal product [name] of your company.

We start with: [name aRMM material]

1. Can you give a short description of the dissemination **process** of [name aRMM material] for medicinal product [name] **by your company**?
    a. Does this process differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?

2. How do **HCPs** receive this aRMM material?
    a. Is it disseminated directly to HCPs, or disseminated through healthcare professional organisations or both? In case of directly to HCPs, how do you obtain the addresses of the relevant HCPs to reach them?
    b. Is it actively disseminated, or upon request (in case of a refill), or both?
    c. Does how HCPs receive this aRMM differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?
    d. Do you monitor /know to what extent HCPs indeed receive this aRMM? And if so, how do you monitor/know this? E.g. do you record/measure the receipt rate?
    e. Is this aRMM material available for download via your company, or other, website? And if so, is this a website with restricted access only for these HCPs or not? And if so, how do these HCPs get access?

[Note: Question 3 will only be asked if the aRMM material is a patient-targeted aRMM material!]

3. How do **patients** receive this aRMM material?
    a. Is it disseminated to HCPs (prescribers/pharmacists), or directly to patients (e.g. in the package or via a QR code on the package)?
    b. Is it actively disseminated? Can patients obtain it upon request?
    c. Does how patients receive this aRMM differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?
    d. Do you monitor /know to what extent patients indeed receive this aRMM? And if so, how do you monitor/know this? E.g. do you record/measure the receipt rate?
    e. Is this aRMM material available for download via your company, or other, website?

4. How do you ensure access to the aRMM material?
    a. For **HCPs**? (both paper-based and digital)
    b. For **patients** (both paper-based and digital) *[Note: only in case of patient-targeted aRMM material]*
    c. Does how access is ensured differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?

5. How do you ensure continuous availability of the aRMM material for HCPs/patients at the point of distribution (e.g. GP practice, hospital, pharmacy)?
    a. Do you have stockpiles? *[Note: only for paper based materials]*
    b. Do you monitor availability or stockpiles at the points of distribution to patients? *[Note: only in case of patient-targeted aRMM material]*
    c. Does how continuous availability is ensured differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?

6. Can you give an indication of the **frequency** with which the aRMM material is disseminated?
    a. If once, what are triggers to redistribute the aRMM material?
    b. What factors does the frequency of dissemination depend on? E.g. severity of the risk, long-term treatment, updated version because of newly discovered risks, exposure/sales of the product?
    c. Do you send reminders regarding electronically available materials?
    d. Does the frequency differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?

7. Can you describe the **key challenges** of disseminating this aRMM material?
    a. To all eligible **HCPs** who prescribe/dispense the product?
    b. To all eligible **patients** who are prescribed the product *[Note: only in case of patient-targeted aRMM material]*
    c. Do the challenges differ between the **countries** (included in our study)? And if so, what are the differences? And why are there differences?

[repeat all (sub)questions for all the available aRMM materials for the medicinal product]

8. Are there any other issues you encounter regarding the dissemination process that you would like to share?

Part 3: Closing (5-10 minutes)
I think I have gained a good insight in the dissemination process of aRMM materials from the perspective of your company.

Are there things that we have not yet discussed on this subject, that you think are important? Do you have any questions for me?

Thank you very much for participating in the interview. I will stop the recording.
[stop recording]

The recording has stopped. I would like to thank you again for your time and effort in participating in this interview.

Can we contact you by email if it occurs that we miss information or if something is not clear?

We will inform you after publication of the study report (around summer 2026).

Short list with factual questions for MAH before interviews

In which of the following countries included in our study is **[name medicinal product]** on the market? With "on the market" we mean that it is available for patients (possibly after a prescription by a healthcare provider). *(multiple answers possible)*

○ Finland
○ Hungary
○ Italy
○ Lithuania
○ Netherlands
○ Romania

We will tailor the questionnaire for each MAH in such a way that only the relevant aRMM materials are asked.

QUESTIONS FOR: PATIENT ALERT CARD/PATIENT EDUCATIONAL OR INFORMATION CARD/ PATIENT REMINDER CARD

What methods did your company use to disseminate the **patient alert card/patient educational or information card/patient reminder card** *(multiple answers possible)*?

○ By e-mail to (possible) prescribers *(how addresses are obtained will be asked in the interview)*
○ By e-mail to pharmacists *(how addresses are obtained will be asked in the interview)*
○ Made available on our website
○ Paper based send to prescribers and/or pharmacists
○ QR code on primary packaging or package leaflet
○ Via the package containing the medicinal product
○ Other, namely:… … …

To whom, or to which organisations, did you disseminate the **patient alert card/patient educational or information card/patient reminder card** *(multiple answers possible)*?

○ Patients directly, e.g. via the primary packaging or package leaflet
○ Patient organisations
○ Relevant prescribers and/or dispensers directly
○ Healthcare professional organisations (for physicians or pharmacists)
○ Other, namely:… … …

QUESTIONS FOR: PRESCRIBER GUIDE/ PRESCRIBER CHECKLIST/ EDUCATIONALMATERIALS/ RISK ACKNOWLEDGMENT FORM

What methods did your company use to disseminate **the prescriber guide/prescriber checklist/educational materials/risk acknowledgment form** to the relevant prescribers? *(multiple answers possible)*

○ By email to (possible) prescribers *(how addresses are obtained will be asked in the interview)*
○ Made available on our website
○ Send on paper to possible prescribers (*how addresses are obtained will be asked in the interview)*
○ Other, namely:… … …

To whom, or to which organisations, did you disseminate **the prescriber guide/prescriber checklist/educational materials/risk acknowledgment form** *(multiple answers possible)*?
○ Prescribing physicians directly *(how addresses are obtained will be asked in the interview)*
○ All physicians working in a relevant specialism *(how addresses are obtained will be asked in the interview)*
○ Healthcare professional organisations (for physicians or pharmacists)
○ Other, namely:... ... ...

QUESTIONS FOR: PHARMACIST CHECKLIST

What methods did your company use to disseminate the **pharmacist checklist** *(multiple answers possible)*?
○ By email to pharmacists *(how addresses are obtained will be asked in the interview)*
○ Made available on our website
○ Send on paper to pharmacists (*how addresses are obtained will be asked in the interview*)
○ Other, namely:... ... ...

To whom, or to which organisations, did you disseminate the **pharmacist checklist** *(multiple answers possible)*?
○ Dispensing pharmacists directly (how addresses are obtained will be asked in the interview)
○ All pharmacists (how addresses are obtained will be asked in the interview)
○ Healthcare professional organisations (for pharmacists)
○ Other, namely:... ... ...

Do you have anything to add with regards to the above questions?

Annex 3E Interview guide and short questionnaire focus group NCAs

A shortened version of the interview guide will be sent to participants prior to the focus group.

Part 1: INTRODUCTION (10-15 min)

Introduction

Thank you very much for your willingness to participate in this focus group. Before we start the focus group, we will start with a short round of introductions. Then we will proceed with a short explanation of the purpose of this study and focus group.

[short round of introductions: note 'who' (function) is participating from each NCA!]

Purpose of the study and the focus group

Nivel (the Netherlands Institute for Health Services Research) and its partners (i.e. Syreon Research Institute, University of Eastern Finland, University of Naples Federico II, Vilnius University, Universitatea Babes-Bolyai and DESAN Research Solutions) are currently conducting a study investigating the dissemination of additional Risk Minimisation Measures (aRMM) for seven medicinal products in six European countries, namely The Netherlands, Finland, Italy, Hungary, Romania and Lithuania.

The objective of this study is to gain a better understanding of the current practice of disseminating aRMM for patients and healthcare professionals at national level, including any challenges encountered by the stakeholders involved in the actual dissemination process. We would like to include your experience regarding the submission and approval of dissemination plans by MAHs. This study will also investigate patients' and healthcare professionals' preferences and needs for aRMM. The focus of the study is on the physical dissemination of the aRMM. A secondary objective is to provide recommendations to regulators for regulatory decision-making on aRMM.

The study uses a mixed-method approach, combining qualitative and quantitative methods. Besides this focus group, we also conduct desk research, online interviews with MAHs, focus groups with healthcare professionals and patients, online surveys with healthcare professionals and patients, and a webinar with stakeholders from all EU/EEA member states to discuss the results of the study. The results will be included in a study report to be delivered to EMA in June 2026, and will be made publicly available after finalizing the study. Do you have some questions about the study?

Practical information

This focus group will last 90-120 minutes, and you can indicate at any time that you want to stop. If you do not object, this focus group will be recorded and transcribed by Teams. We will turn on the recording and transcription shortly, after which we will ask you to give permission for your participation and the recording of this focus group. The recording and transcript will only be used to transcribe the focus group for thematic content analysis. We also use the transcript, for example, to include quotes (verbatim statements) made in the focus group in the study report. Quotes will be reported in such way that the individual person who made the statement is not identifiable in the report. Besides these quotes, the study report will only contain aggregated,

non-identifiable data and no product-specific evaluation of the effectiveness of aRMM will be performed. The recording will be deleted after approval of the study report. Do you have any questions about this focus group or the study before we start?

[Answer]

Start recording and permission

We will now start the recording and transcription. Do you give permission:

1) To participate in this focus group, for this focus group to be recorded and for the collection and use of video recordings?
2) That the recording and transcript will only be used to transcribe the focus group for thematic content analysis. And, for example, to include quotes (verbatim statements) made in the focus group in the study report. Quotes will be reported in such way that the individual person who made the statement is not identifiable in the report. Besides these quotes, the study report will only contain aggregated, non-identifiable data and no product-specific evaluation of the effectiveness of aRMM will be performed. The recording will be deleted after approval of the study report.

[Ask permission of each participant]

Medicinal products and aRMM materials included in this study

[The table below (we will also show this on slide) shows the included medicinal products and aRMM materials included in the study]

Medicinal Product Name	aRMM materials
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, Physician information pack, Patient reminder card
Lixiana (edoxaban)	Patient alert card, prescriber guide

Part 2: PROCESS AND FREQUENCY OF HOW aRMM ARE DISSEMINATED (30 min)

Objective (reminder for interviewer):

- Describe and analyse **the process and frequency (where appropriate) how aRMM materials are disseminated** in the six participating countries,
- **how patients and HCPs receive product-specific aRMM materials for the selected medicinal products**, 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.

1. Do you as NCA have an overview of the onward dissemination of aRMM materials within the **healthcare system** and **by HCPs to patients**?
    a. In general?
    b. More specific, for the seven medicinal products in this study?

c. Can you elaborate on the different dissemination methods for the product-specific aRMM materials for the selected medicinal products included in this study? *(Are there different dissemination methods within a single aRMM tool?)*

2. Do you oversee/monitor whether MAHs adhere to their MAH's national dissemination plans in general, and more specific for the seven medicinal products included in our study? And if so, how do you oversee/monitor this?

3. Do you oversee/monitor to what extent **HCPs** receive the aRMM materials in general, and more specific for the seven medicinal products included in our study? And if so, how do you oversee/monitor this?

4. Do you oversee/monitor to what extent **patients** receive the aRMM materials in general, and more specific for the seven medicinal products included in our study? And if so, how do you oversee/monitor this?

5. Do you think that more dissemination channels are required to assure receipt for HCPs and/or patients in general, and more specific for the seven medicinal products included in our study?

The following questions will be about guidelines regarding the dissemination of aRMM that are in place in your country.

6. In general, do you follow the guidelines, or are there cases that there are deviations from these guidelines in general, and more specific for the seven medicinal products included in our study? Do you have a procedure available for these situations? And if so, what is the reasons for deviations?

7. Within the guidelines, is guidance for MAHs concerning updating these aRMM materials included? And if yes, can you elaborate upon this?

Part 3: ACCES TO aRMM MATERIALS (30 min)

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.

1. When is access to the aRMM materials ensured according to NCAs in general, and more specific for the seven medicinal products included in our study?

2. How do you, from a regulatory point of view, ensure access to aRMM materials by the target population:
   a. For **HCPs** (e.g. prescribers/pharmacists)? Are there differences between the aRMM materials, and if so, which? Are there differences between the seven medicinal products, and if so which?
   b. For **patients**? Are there differences between the aRMM materials, and if so, which (for instance: materials disseminated via HCPs versus materials disseminated directly to patients)? Are there differences between the seven medicinal products, and if so which?

c. For **paper** based aRMM materials? Are there differences between the aRMM materials, and if so, which? Are there differences between the seven medicinal products, and if so which? How ensure stockpiling?
d. For **digital** based aRMM materials? Are there differences between the aRMM materials, and if so, which? Are there differences between the seven medicinal products, and if so which?

3. If aRMM materials are available through the NCA's website: How are these materials kept up to date on your website?

4. If aRMM materials are not available through the NCA's website: Are these materials available on websites of other stakeholders, such as professional associations or patient organisations, to your knowledge?

Part 4: KEY CHALLENGES (30-40 min)

Objective (reminder for interviewer):
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.

From a regulatory point of view, please reflect on:

1. What challenges and concerns do you identify with the dissemination of aRMM materials by MAHs in general *(e.g. monitoring adherence to MAH's plan)*? And more specific, for the seven medicinal products included in the study? Does this differ between type of aRMM materials?

2. Do you have suggestions for opportunities to support or improve the aRMM dissemination process? In general, and more specific for the seven medicinal products included in the study?

Part 4: Closing
I think I have gained a good insight in the dissemination process of aRMM materials from the perspective of national competent authorities.

Are there things that we have not yet discussed on this subject, that you think are important? Do you have any questions for me?

Thank you very much for participating in the focus group. I will stop the recording.
[stop recording]

The recording has stopped. I would like to thank you again for your time and effort in participating in this focus group.

Can we contact you by email if it occurs that we miss information or if something is not clear?

We will inform you after publication of the study report (around summer 2026).

Short list with factual questions for NCA before focus group

Please return this short questionnaire before the focus group, if possible. In case you have any questions, please contact dr. Anne Brabers (a.brabers@nivel.nl).

1. Could you, in the table below, indicate for each of the available aRMM materials per product the following information:
   - whether the product is on the market in your country?
   - whether the aRMM materials are available in your local language(s)?
   - whether the aRMM materials are available on your website?

Please make in the table the relevant answer category bold or tick the box/put an X before the answer category.

Medicinal Product Name	Is the product on the market in your country?	aRMM material	Available in local language(s)?	Is the material publicly available on your website (NCA website)?
Xeljanz (tofacitinib)	○ Yes ○ No	Patient alert card	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Guide for HCPs	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Prescriber checklist	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
Aubagio (teriflunomide)	○ Yes ○ No	Patient educational card	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Educational material for HCPs	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
Valproate containing medicinal products	○ Yes ○ No	Patient guide	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Patient card	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Healthcare professional guide	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Risk acknowledgement	○ Yes, in all local language(s)	○ Yes

Medicinal Product Name	Is the product on the market in your country?	aRMM material	Available in local language(s)?	Is the material publicly available on your website (NCA website)?
		form	○ In part of the local languages ○ No	○ No
Lemtrada (alemtuzumab)	○ Yes ○ No	Patient guide	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Patient alert card	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Healthcare professional guide	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Prescriber checklist	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
Eylea (aflibercept)	○ Yes ○ No	Patient information guide	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Physician information pack	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
Retinoids containing medicinal products	○ Yes ○ No	Prescriber checklist acknowledgement form	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Pharmacist checklist	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Patient reminder card	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
Lixiana (edoxaban)	○ Yes ○ No	Patient alert card	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No
		Prescriber guide	○ Yes, in all local language(s) ○ In part of the local languages ○ No	○ Yes ○ No

2. Do you have a guideline available in your country for market authorization holders (MAHs) for the dissemination of aRMM?
   0 Yes, one general guideline
   0 Yes, different guidelines
   0 No

3. If guidelines are available, please provide the link to the guidelines hereafter:

4. Do you have a guideline available in your country describing the roles and responsibilities of you as National Competent Authority (NCA) with respect to the dissemination of aRMM?
   0 Yes
   0 No

5. If a guideline is available, please provide the link to the guideline hereafter:

Do you have anything to add with regards to the above questions?

Annex 3F Questionnaires for patients, patient organisations, and healthcare professionals

PATIENT QUESTIONNAIRE DIS-aRMM STUDY

About this survey

This survey is about additional Risk Minimisation Measures (aRMM) for medicines. Medicines can have side effects. These are tested in studies before a medicine is marketed. The side effects are listed in the package leaflet. But sometimes additional measures are deemed necessary to ensure patient safety. aRMM measures are extra measures taken to reduce the risk of a medicine, such as preventing specific side effects or reducing their severity. aRMM materials provide information about these risks to the patient and/or healthcare provider, for example in the form of guides for healthcare providers and patients, patient cards or educational videos. aRMM materials are thus an addition to the regular product information, such as the package leaflet that comes with each medicinal product.

This survey aims to understand how these aRMM materials are shared with you (e.g. by your doctor or pharmacist). For example, we would like to know whether you have received aRMM materials from your healthcare provider for certain medicines. Completing the survey takes approximately 10 minutes.

Who can participate in the survey?

All people aged 18 and over, living in Finland, Hungary, Italy, Lithuania, Netherlands or Romania, using one of the following medicinal products prescribed:

- **Aubagio** (teriflunomide)
- **Eylea** (aflibercept)
- **Lemtrada** (alemtuzumab)
- **Lixiana** (edoxaban)
- **Xeljanz** (tofacitinib)
- **Oral retinoids containing medicinal products*** (can be used for skin conditions). *The survey is not applicable to retinoids containing medicinal products for topical use (use on the skin, e.g. cream, gel or cutaneous solution).*
- **Valproate containing medicinal products*** (can be used to treat epilepsy or bipolar disorders).

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

Who is conducting this survey?

In six European countries (Finland, Hungary, Italy, Lithuania, Netherlands and Romania), research institutes and universities are studying aRMM materials. This study was commissioned by the European Medicines Agency (EMA). EMA is responsible for the evaluation and supervision of medicines in the European Union. In *[name country]* the survey is carried out by *[name organisation]*, being a *[e.g. an independent research organisation]*.

Questions?
Do you have questions concerning the survey? Or are you not able to fill out the survey online? Please contact *[name local researcher]* via *[email/phone]*.

What happens with my answers?
Taking part in this survey is voluntary. You can stop filling out the questionnaire at any time. Completing the questionnaire will not affect the care you receive from your healthcare providers. All data collected through the survey will be processed in compliance with Regulation (EU) 2016/679 (General Data Protection Regulation). This means that your answers will be processed confidentially. This also means that the researchers do not know the name of who filled out the questionnaire. The results of the survey will be aggregated and included in a publicly available report. Furthermore, your answers may be used for similar research into how aRMM are shared with patients.

Do you, based on the information above, agree to participate in the study?
- ○ Yes
- ○ No → *Thanks for your interest in this survey. Unfortunately, you are not able to fill out the survey if you do not give consent to participate.*

1. Do you live in [Finland/Hungary/Italy/Lithuania/Netherlands/Romania]?
- ○ Yes
- ○ No → *Thanks for your interest in this survey. Unfortunately, you are not eligible to fill out the survey if you do not live in this country.*

2. What age category do you belong to?
- ○ Below 18 years old → *Thanks for your interest in this survey. Unfortunately, you are not eligible to fill out the survey if you are under age 18.*
- ○ 18 – 29 years old
- ○ 30 – 39 years old
- ○ 40 – 49 years old
- ○ 50 – 59 years old
- ○ 60 – 69 years old
- ○ 70 – 79 years old
- ○ 80 years or older
- ○ I'd rather not say

3. Which of the following describes you best?
- ○ Woman
- ○ Man
- ○ Other
- ○ I'd rather not say

4. Which of the following medicinal products do you use at this moment, or have you used in the past 12 months? *(Multiple answers possible)*

- ❑ Aubagio (teriflunomide)
- ❑ Eylea (aflibercept)
- ❑ Lemtrada (alemtuzumab)
- ❑ Lixiana (edoxaban)

- ❑ Xeljanz (tofacitinib)
- ❑ Oral retinoids containing medicinal products*
- ❑ Valproate containing medicinal products*
- ❑ None of these medicinal products → *Thanks for your interest in this survey. Unfortunately, you are not eligible to fill out the survey if you are not using one of these medicinal products.*

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

You indicate that you use *[name medicinal product Q4]*. For this medicinal product the following aRMM material(s) are available *[programming instruction: choose the relevant from the list below]*:

- Patient alert card / Patient reminder card / Patient educational card
  A patient card is a tool that patients carry with them that contains important information about a medicine, including the main risks and recommended actions. A patient card can take different forms, depending on the specific medicine. It is often a small, sturdy card that the patient can easily carry in his or her wallet or bag. The card can be printed, but is sometimes also offered in digital form to be printed at home.
- Patient guide
  A patient guide is a tool or document (e.g. a brochure or a leaflet), often educational, provided to patients taking a medicine to help them understand and minimize potential risks associated with that medicine.
- Risk acknowledgment form
  A risk acknowledgment form is a document used by the prescriber to ensure that a patient taking a medicine has been informed of and understands the potential risks associated with the medicine, for example those related to pregnancy. This form must be filled out by both the prescriber and the patient.

The following questions are about the *[name aRMM material]* for *[name medicinal product Q4] [Note: if two or three aRMM materials are available questions 5-12 will be repeated].*

5. Have you received the [name aRMM material]? *Multiple 'Yes' answers possible [Programming instructions: multiple answers possible, but No and I don't remember.. cannot be combined with each other and with the Yes answers]*

- ❑ No
- ❑ Yes, on paper from the prescribing doctor
- ❑ Yes, via a letter with a weblink or QR code to the *[name aRMM material]* from the prescribing doctor
- ❑ Yes, via an email with the *[name aRMM material]* as attachment from the prescribing doctor
- ❑ Yes, via an email with a weblink or QR code to the *[name aRMM material]* from the prescribing doctor
- ❑ Yes, on paper from the pharmacist that dispensed the medicinal product to me
- ❑ Yes, via a letter with a weblink or QR code to the *[name aRMM material]* from the pharmacist that dispensed the medicinal product to me

- ❑ Yes, via an email with the *[name aRMM material]* as attachment from the pharmacist that dispensed the medicinal product to me
- ❑ Yes, via an email with a weblink or QR code to the *[name aRMM material]* from the pharmacists that dispensed the medicinal product to me
- ❑ Yes, I downloaded it from the website of the pharmaceutical company of the medicinal product
- ❑ Yes, I downloaded it from another website, which website?:
- ❑ Yes, via the QR code on the medicine package or package leaflet
- ❑ Yes, it was included in the medicine package or attached to the outside of the package
- ❑ Yes, in another way, please describe:
- ❑ Yes, but I don't remember how I received it
- ❑ I don't remember if I received it

6. Did your healthcare provider discuss the [name aRMM material] with you?
Multiple 'Yes' answers possible
[Programming instructions: multiple answers possible, but No and I don't know cannot be combined with each other and with the Yes answers]

- ❑ No
- ❑ Yes, the doctor that prescribed the medicinal product to me
- ❑ Yes, the pharmacists that dispensed the medicinal product to me
- ❑ Yes, someone else, please describe (e.g. nurse):
- ❑ I don't know

7. Have you read the [name aRMM material]?

- o No
- o Yes, and I understood the information
- o Yes, but I had difficulties understanding the information
- o I don't know

[Programming instruction: In case respondent had difficulties understanding the information show question 8]

8. What made it difficult to understand the aRMM material? *(multiple answers possible)*

- ❑ Too much text
- ❑ Medical words I didn't know
- ❑ Small print/poor layout
- ❑ Not in my preferred language
- ❑ Conflicted with other information
- ❑ Too frightening/overwhelming
- ❑ Not relevant to my situation
- ❑ Something else, please describe:

9. How useful is the [name aRMM material] for you as patient?

- o Not useful at all

- o Not very useful
- o A bit useful
- o Useful
- o Very useful

[Note for programming the survey: For the patient alert card only:]

10. Do you carry the patient alert card with you?

- o Never
- o Sometimes
- o Mostly
- o Always
- o I don't know what a patient alert card is

[Programming instruction: In case respondent indicates never or sometimes to carry the patient card show question 11]

11. Why do you never or only sometimes carry the patient card with you? *(multiple answers possible)*

- ❑ Patient card is too large
- ❑ Patient card is not relevant to my situation
- ❑ I usually forget to carry the patient card
- ❑ I have read the patient card and I remember the information, so I don't need to carry it with me
- ❑ Something else, please describe: [ ]

[Note for programming the survey: For the risk acknowledgement form only:]

12. Have you filled out and signed the risk acknowledgment form together with your doctor?

- o No
- o Yes, together with my prescribing doctor
- o Yes, together with another healthcare provider, describe who: [ ]
- o I don't remember
- o I don't know what a risk acknowledgement form is

PREFERENCES FOR RECEIVING aRMM MATERIALS

The next questions are about how you prefer to receive aRMM materials in case they would be made available. The questions are about aRMM materials **in general**.

13. What are the most preferred ways for you to receive a patient card? Choose up to three options. *A patient card is a tool that patients carry with them that contains important information about a medicine, including the main risks and recommended actions. A patient card can take different forms, depending on the specific medicine. It is often a small, sturdy card that the patient can easily*

carry in his or her wallet or bag. The card may sometimes also be offered in digital form to be printed at home.

- ❑ On paper from prescribing doctor
- ❑ Letter from prescribing doctor with weblink or QR code to the patient card
- ❑ Email from prescribing doctor with the patient card attached
- ❑ Email from prescribing doctor with weblink or QR code to the patient card
- ❑ The prescribing doctor informs me verbally where the patient card can be downloaded
- ❑ On paper from pharmacist
- ❑ Letter from pharmacist with weblink or QR code to the patient card
- ❑ Email from pharmacist with the patient card attached
- ❑ Email from pharmacist with weblink or QR code to the patient card
- ❑ The pharmacist informs me verbally where the patient card can be downloaded
- ❑ Via the QR-code on the medicine package or package leaflet
- ❑ Included in the medicine package or attached to the outside of the package
- ❑ Through the website from the pharmaceutical company where I can download the patient card
- ❑ From a patient organisation
- ❑ In another way, please describe:

14. What is the most preferred way for you to receive a patient guide? Choose up to three options. *A patient guide is tool or document (e.g. a brochure or a leaflet), often educational, provided to patients taking a medicine to help them understand and minimize potential risks associated with that medicine.*

- ❑ On paper from prescribing doctor
- ❑ Letter from prescribing doctor with a weblink or QR code to the patient guide
- ❑ Email from prescribing doctor with the patient guide attached
- ❑ Email from prescribing doctor with a weblink or QR code to the patient guide
- ❑ The prescribing doctor informs me verbally where the patient guide can be downloaded
- ❑ On paper from pharmacist
- ❑ Letter from pharmacist with weblink or QR code to the patient guide
- ❑ Email from pharmacist with the patient guide attached
- ❑ Email from pharmacist with weblink or QR code to the patient guide
- ❑ The pharmacist informs me verbally where the patient guide can be downloaded
- ❑ Via the QR-code on the medicine package or package leaflet
- ❑ Included in the medicine package or attached to the outside of the package
- ❑ Through the website from the pharmaceutical company where I can download the patient guide
- ❑ From a patient organisation
- ❑ In another way, please describe:

15. Do you have any remarks regarding how you received the aRMM materials? For example, suggestions to improve the process?

This was our last question for this survey. We have one additional question on the next step in our study.

We would like to know more about how patients experience receiving the aRMM materials. We therefore organize a focus group about this topic. In a focus group, you talk about your experiences together with other patients. We would like to know whether you are willing to participate in this focus group. The focus group will be online or at a location. This will be decided later on. We will send you an invitation and you can decide upon participating or not after this invitation.
If yes, you will be contacted by a researcher from *[name research institute]*. The focus group is scheduled to take place at the end of 2025 or in the first months of 2026 and will last 90-120 minutes. The results will be included in a publicly available report. All personal data will be processed confidentially and in compliance with Regulation (EU) 2016/679 (General Data Protection Regulation) and relevant national data protection legislation. Your name and other personal information will never be displayed in the report in a way that can be traced back to you.

16. Are you interested in participating in a focus group? And if yes, do you agree that we will contact you?

- o Yes, I am interested to participate and you can contact me through the following email address and/or phone number:

We will only use this information to contact you for the focus group.

- o No

If countries due to ethics approval do not allow to ask for an email address and/or phone number, the following text can be included instead of question 16:

If you want to participate in the focus group, please contact *[name researcher]* via *[email address and/or phone number]*.

[Countries can add here additional information needed because of the GDPR or national legislation.]

PATIENT ORGANISATION QUESTIONNAIRE DIS-aRMM STUDY

About this survey
This survey is about additional Risk Minimisation Measures (aRMM) for medicines. Medicines can have side effects. These are tested in studies before a medicine is marketed. The side effects are listed in the package leaflet. But sometimes additional measures are deemed necessary to ensure patient safety. aRMM measures are extra measures taken to reduce the risk of a medicine, such as preventing specific side

effects or reducing their severity. aRMM materials provide information about these risks to the healthcare provider and/or patient, for example in the form of guides for healthcare providers and patients, patient cards or educational videos. aRMM materials are thus an addition to the regular product information, such as the package leaflet that comes with each medicinal product.

With this survey we would like to get insight in the dissemination process of aRMM materials from the perspective of **patient organisations**. With dissemination we mean the receiving of aRMM materials from the pharmaceutical company who holds the marketing authorisation (MAH) by healthcare providers as well as the distribution of aRMM materials by healthcare providers to patients. We would like to know whether you have a role in this process, for instance by making the materials available for your members or helping them in understanding the materials and actions to be taken to minimise risk. Furthermore, we would like to know whether you have identified challenges among your members in receiving these materials. Completing the survey takes approximately 15 minutes.

Who can participate in the survey?
Patient organisations from Finland, Hungary, Italy, Lithuania, Netherlands or Romania. We invite patient organizations focused on the conditions treated by the seven medicines listed below, as well as umbrella patient organizations, to complete the survey.

The following seven medicines are included in the study:

- **Aubagio** (teriflunomide)
- **Eylea** (aflibercept)
- **Lemtrada** (alemtuzumab)
- **Lixiana** (edoxaban)
- **Xeljanz** (tofacitinib)
- **Oral retinoids containing medicinal products*** (can be used for skin conditions). *The survey is not applicable to retinoids containing medicinal products for topical use (use on the skin, e.g. cream, gel or cutaneous solution).*
- **Valproate containing medicinal products*** (can be used to treat epilepsy or bipolar disorders).

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

Who is conducting this survey?
Within six European countries (Finland, Hungary, Italy, Lithuania, Netherlands and Romania), research institutes and universities are conducting research into aRMM materials. The European Medicines Agency (EMA) has commissioned this study. EMA is responsible for the evaluation and supervision of medicines in the European Union. In *[name country]* the survey is carried out by *[name organisation]*, being a *[e.g. an independent research organisation]*.

Questions?
Do you have questions concerning the survey? Or are you not able to fill out the survey online? Please contact *[name local researcher]* via *[email/phone]*.

What happens with my answers?

Taking part in this survey is voluntary. You can stop filling out the questionnaire at any time. All data collected through the survey will be processed in compliance with Regulation (EU) 2016/679 (General Data Protection Regulation). This means that your answers will be processed confidentially. This also means that the researchers do not know the name of who filled out the questionnaire. The results of the survey will be aggregated and included in a publicly available report. Furthermore, your answers may be used for similar research into the dissemination of aRMM.

Did you read all of the above mentioned and do you, based on this information, agree to participate in the study?

- o Yes
- o No → *Thanks for your interest in this survey. Unfortunately, you are not able to fill out the rest of the survey if you do not give consent to participate.*

1. Are you a representative from a patient organisation from [Finland/Hungary/Italy/Lithuania/Netherlands/Romania]?

- o Yes
- o No, but our organisation is a European-level patient organisation
- o No → *Thanks for your interest in this survey. Unfortunately, you are not able to fill out the rest of the survey if your organisation is not based in [mentioned country].*

2. What kind of patient organisation are you?

- o An umbrella organisation, not focusing on a specific condition *[Programming instruction: go to part B for umbrella organisations]*
- o A patient organisation focusing on (a) specific condition(s), namely:

3. Which of the following medicines are relevant for members of your patient organisation? *(multiple answers possible)*

- ❑ Aubagio (teriflunomide)
- ❑ Eylea (aflibercept)
- ❑ Lemtrada (alemtuzumab)
- ❑ Lixiana (edoxaban)
- ❑ Xeljanz (tofacitinib)
- ❑ Oral retinoids containing medicinal products*
- ❑ Valproate containing medicinal products*
- ❑ None of these medicinal products → *Thanks for your interest in this survey. Unfortunately, you are not eligible to fill out the survey if none of these medicinal products are relevant for your organisation.*

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

PART A FOR PATIENT ORGANISATIONS FOR WHICH ONE OF THE INCLUDED MEDICINAL PRODUCTS IS RELEVANT:

You indicated that the following medicinal product(s) are relevant for members of your patient organisation: [mention answers Q3].

For this medicine the following aRMM materials are available for patients:
[*programming instruction: choose the relevant materials from the list below. For each product we will include – if possible – the main safety concerns]:*.

- Patient alert card / Patient reminder card / Patient educational card
  A patient card is a tool that patients carry with them that contains important information about a medicine, including the main risks and recommended actions. A patient card can take different forms, depending on the specific medicine. It is often a small, sturdy card that the patient can easily carry in his or her wallet or bag. The card can be printed, but is sometimes also offered in digital form to be printed at home.
- Patient guide
  A patient guide is a tool or document (e.g. a brochure or a leaflet) provided to patients taking a medicine to help them understand and minimize potential risks associated with that medicine.
- Risk acknowledgment form
  A risk acknowledgment form is a document used by the prescriber to ensure that a patient taking a medicine has been informed of and understands the potential risks associated with the medicine, for example those related to pregnancy. This form must be filled out by both the prescriber and the patient.

The main safety warnings included in the aRMM materials can be viewed here.

A1. Does your organisation know that the above mentioned patient-targeted aRMM materials are available for [name medicine of Q3]?

- o No
- o Yes
- o I don't know

A2. Has your organisation received information about the above-mentioned patient-targeted aRMM materials for [name medicine of Q3]?

- o No
- o Yes, namely from (e.g. the pharmaceutical company, a professional organisation):
- o I don't know

A3. Has your organisation had a role in the dissemination of the above-mentioned aRMM materials to patients?

- o No
- o Yes. Please describe the role (e.g. making the materials available to members or helping them understand the materials and actions to be taken to minimise risks):
- o I don't know

A4. Does your organisation collaborate with others in the dissemination of the above-mentioned aRMM materials to patients? *(multiple yes answers possible)*

[Programming instructions: multiple answers possible, but No and I don't know cannot be combined with each other and with the Yes answers]

- ❑ No
- ❑ Yes, with healthcare providers
- ❑ Yes, with professional organisations
- ❑ Yes, with authorities
- ❑ Yes, with pharmaceutical companies
- ❑ Yes, with others, please describe:
- ❑ I don't know

A5. Has your organisation informed your members about the availability of the [name aRMM material] of [name medicine of Q3]? *(multiple yes answers possible) [Programming instructions: multiple answers possible, but No and I don't know cannot be combined with each other and with the Yes answers; and repeat question if more than one patient-targeted aRMM is available]*

- ❑ No
- ❑ Yes, through our paper-based newsletter
- ❑ Yes, through our digital newsletter
- ❑ Yes, through our social media accounts
- ❑ Yes, through emails to members
- ❑ Yes, through our website
- ❑ Yes, in another way, please describe:
- ❑ I don't know

A6. Is [name aRMM material] of [name medicine of Q3] available on the website of your organisation? *[Programming instructions: repeat question if more than one patient-targeted aRMM is available]*

- o No
- o Yes
- o I don't know

[REPEAT QUESTIONS A1 TO A6 FOR EACH PRODUCT THAT IS RELEVANT ACCORDING TO Q3]

PART B FOR UMBRELLA PATIENT ORGANISATIONS:

B1. In general, does your organisation receive information about aRMM materials for patients? Examples of patient-targeted aRMM materials are a patient alert card or a patient guide.

- o No
- o Yes, namely from (e.g. pharmaceutical companies, professional organisations):
- o I don't know

B2. In general, has your organisation had a role in the dissemination of aRMM materials targeted to patients? Examples of patient-targeted aRMM materials are a patient alert card or a patient guide.

- o No

- o Yes, Please describe the role (e.g. making the materials available to members or helping them understanding the materials and actions to be taken to minimise risks):
- o I don't know

B3. In general, does your organisation collaborate with others in the dissemination of patient-targeted aRMM materials? *(multiple yes answers possible) [Programming instructions: multiple answers possible, but No and I don't know cannot be combined with each other and with the Yes answers]*

- ❑ No
- ❑ Yes, with healthcare providers
- ❑ Yes, with professional organisations
- ❑ Yes, with authorities
- ❑ Yes, with pharmaceutical companies
- ❑ Yes, with others, please describe:
- ❑ I don't know

B4. Does your organisation inform your members about the availability of patient-targeted aRMM materials? *(multiple yes answers possible) [Programming instructions: multiple answers possible, but No and I don't know cannot be combined with each other and with the Yes answers]*

- ❑ No
- ❑ Yes, through our paper-based newsletter
- ❑ Yes, through our digital newsletter
- ❑ Yes, through our social media accounts
- ❑ Yes, trough emails to members
- ❑ Yes, through our website
- ❑ Yes, in another way, please describe:
- ❑ I don't know

B5. Are there patient-targeted aRMM materials available on the website of your organisation?

- o No
- o Yes
- o I don't know

PART C QUESTIONS FOR ALL PATIENT ORGANISATIONS:

C1. Do you see a role for patient organizations in the dissemination of aRMM materials? And if so, what kind of role do you see?

- o No
- o Yes. Please describe the role (e.g. making the materials available to members or helping them understanding the materials and actions to be taken to minimise risks):
- o I don't know

C2. Are you as patient organisation aware of any challenges regarding the dissemination process of aRMM materials? *It could be both challenges regarding the dissemination from pharmaceuticals companies to healthcare providers and from healthcare providers to patients. In addition, there may be certain patient groups that experience more challenges.*

- o No
- o Yes, please describe the challenges:
- o I don't know

The next questions are about how you think as patient organisation about the most preferred way for patients to receive aRMM materials. The questions are about aRMM materials in general.

C3. What is, according to your organisation, the most preferred way for patients to receive a patient card? Choose up to three options.
A patient card is a tool that patients carry with them that contains important information about a medicine, including the main risks and recommended actions to minimise risks. A patient card can take different forms, depending on the specific medicine. It is often a small, sturdy card that the patient can easily carry in a wallet or bag. The card may sometimes be offered in digital format to be printed at home.

- ❑ On paper from prescribing doctor
- ❑ Letter from prescribing doctor with weblink or QR code to the patient card
- ❑ Email from prescribing doctor with the patient card attached
- ❑ Email from prescribing doctor with weblink or QR code to the patient card
- ❑ The prescribing doctor informs the patient verbally where the patient card can be downloaded
- ❑ On paper from pharmacist
- ❑ Letter from pharmacist with weblink or QR code to the patient card
- ❑ Email from pharmacist with the patient card attached
- ❑ Email from pharmacist with weblink or QR code to the patient card
- ❑ The pharmacist informs the patient verbally where the patient card can be downloaded
- ❑ Via the QR-code on the medicine package or package leaflet
- ❑ Included in the medicine package or attached to the outside of the package
- ❑ Through the website from the pharmaceutical company where patients can download the patient card
- ❑ From a patient organisation
- ❑ In another way, please describe:

C4. What is, according to your organisation, the most preferred way for patients to receive a patient guide? Choose up to three options.
A patient guide is a tool or document (e.g. a brochure or a leaflet), often educational, provided to patients taking a medicine to help them understand and minimize potential risks associated with that medicine.

- ❑ On paper from prescribing doctor
- ❑ Letter from prescribing doctor with weblink or QR code to the patient guide
- ❑ Email from prescribing doctor with the patient guide attached

- ❑ Email from prescribing doctor with weblink or QR code to the patient guide
- ❑ The prescribing doctor informs the patient verbally where the patient guide can be downloaded
- ❑ On paper from pharmacist
- ❑ Letter from pharmacist with weblink or QR code to the patient guide
- ❑ Email from pharmacist with the patient guide attached
- ❑ Email from pharmacist with weblink or QR code link to the patient guide
- ❑ The pharmacist informs the patient verbally where the patient guide can be downloaded
- ❑ Via the QR-code on the medicine package or package leaflet
- ❑ Included in the medicine package or attached to the outside of the package
- ❑ Through the website from the pharmaceutical company where patients can download the patient guide
- ❑ From a patient organisation
- ❑ In another way, please describe:

C5. Do you have any remarks regarding the dissemination process of aRMM materials? For example, suggestions to improve the process?

This is the end of the questionnaire. Thank you for completing it.

HEALTHCARE PROVIDER QUESTIONNAIRE DIS-aRMM STUDY

About this survey

This survey is about the dissemination of additional Risk Minimisation Measures (aRMM) for medicines. aRMM are extra measures taken by the regulatory authority to reduce the risk of a medicine by preventing side effects or reducing their severity. aRMM materials provide information about these risks to healthcare providers and patients and the actions they should take to minimise them, for example in the form of guides for healthcare providers and patients, patient cards or educational videos. aRMM materials are an addition to the regular product information, like the package leaflet. With dissemination we mean the receiving of aRMM materials from the pharmaceutical company who holds the marketing authorisation (MAH) by healthcare providers as well as the distribution of aRMM materials by healthcare providers to patients.

This survey aims to understand how you receive these aRMM materials (e.g. from the pharmaceutical company) and how you share them with your patients. Completing the survey takes approximately 20-30 minutes.

Who can participate in the survey?

Healthcare providers prescribing or dispensing (in the last 12 months) one of the following medicinal products in Finland, Hungary, Italy, Lithuania, Netherlands or Romania:

- **Aubagio** (teriflunomide)
- **Eylea** (aflibercept)
- **Lemtrada** (alemtuzumab)
- **Lixiana** (edoxaban)
- **Xeljanz** (tofacitinib)
- **Oral retinoids containing medicinal products*** (can be used for skin conditions). *If you do not prescribe or dispense retinoids for oral use, but only for topical use (use on the skin, e.g. cream, gel or cutaneous solution), the survey is not applicable to you.*
- **Valproate containing medicinal products*** (can be used to treat epilepsy or bipolar disorders)

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

Who is conducting this survey?
In six European countries (Finland, Hungary, Italy, Lithuania, Netherlands and Romania), research institutes and universities are studying aRMM materials. This study was commissioned by the European Medicines Agency (EMA). EMA is responsible for the evaluation and supervision of medicines in the European Union. In *[name country]* the survey is carried out by *[name organisation]*, being a *[e.g. an independent research organisation (to be added if applicable)]*.

Questions?
Do you have questions concerning the survey? Or are you not able to fill out the survey online? Please contact *[name local researcher]* via *[email/phone]*.

What happens with my answers?
Taking part in this survey is voluntary. You can stop filling out the questionnaire at any time. All data collected through the survey will be processed in compliance with Regulation (EU) 2016/679 (General Data Protection Regulation). This means that your answers will be processed confidentially. This also means that the researchers do not know the name of who filled out the questionnaire. The results of the survey will be aggregated and included in a publicly available report. Your answers may be re-used for similar research about the dissemination of aRMM.

We advise you to fill out the survey on a computer and not on a mobile device. Please note that you **cannot** close the survey in your browser and return to your answers on a later moment in time.

Do you, based on the information above, agree to participate in the study?

- ○ Yes
- ○ No → *Thanks for your interest in this survey. Unfortunately, you are not able to fill out the survey if you do not give consent to participate.*

PART A. GENERAL QUESTIONS
[FOR BOTH PRESCRIBERS AND PHARMACISTS]

A1. Do you live in [Finland/Hungary/Italy/Lithuania/Netherlands/Romania]?

- Yes
- No → *Thanks for your interest in this survey. Unfortunately, you are not eligible to fill out the survey if you do not live in this country.*

A2. What is your profession?

- General practitioner / general practitioner in training
- Medical specialist /medical specialist in training
  - Neurologist
  - Ophthalmologist
  - Internist
  - Cardiologist
  - Rheumatologist
  - Gastroenterologist
  - Psychiatrist
  - Dermatologist
  - Hematologist
  - Oncologist
  - Other, namely…
- Pharmacist *[as not in all countries all three types may exist, an information balloon will be available with a short description of each type and respondents will be asked to tick the option that they feel describes their function best]*
  - Community pharmacist
  - Clinical pharmacist
  - Hospital pharmacist
  - Other, namely:
- Nurse
- Other, namely:

A3. What age category do you belong to?

- 18 – 29 years old
- 30 – 39 years old
- 40 – 49 years old
- 50 – 59 years old
- 60 – 69 years old
- 70 years or older
- I'd rather not say

A4. Which of the following describes you best?

- Woman
- Man
- Other
- I'd rather not say

A5. How many years of work experience do you have as a healthcare provider?

- < 5 years
- 5-10 years

- 11-15 years
- 16-20 years
- More than 20 years

➔ *PRESCRIBERS, NURSE AND OTHER HCPs FROM QA2 GO TO PART B.*
➔ *PHARMACISTS FROM QA2 GO TO PART C.*

PART B. DISSEMINATION OF aRMM MATERIALS
[QUESTIONS FOR PRESCRIBERS]

B1. Which of the following medicinal products have you prescribed in the past 12 months? *(multiple answers possible)*

- ❑ Aubagio (teriflunomide)
- ❑ Eylea (aflibercept)
- ❑ Lemtrada (alemtuzumab)
- ❑ Lixiana (edoxaban)
- ❑ Xeljanz (tofacitinib)
- ❑ Oral retinoids containing medicinal products*
- ❑ Valproate containing medicinal products*
- ❑ None of these medicinal products → *Thanks for your interest in this survey. Unfortunately, you are not eligible to fill out the survey if you have not prescribed one of these medicinal products.*

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

You indicate that you prescribed *[name medicinal product B1]*. For this medicinal product the following aRMM materials are available
[program instruction: choose the relevant materials from the list below. For each product we will include – if possible – the main safety concerns]:

- Guide for healthcare professionals/ Healthcare professional guide / physician information pack / healthcare professional educational material *Educational material (e.g. a brochure or leaflet) describing key risks, potential adverse drug reactions, and recommended actions for healthcare professionals to take to minimize those risks.*
- Prescriber checklist *A checklist used by healthcare professionals to ensure they are following the safety advice when prescribing certain medications. The checklist typically includes specific actions, considerations, or information that prescribers need to address before prescribing the medication.*
- Risk acknowledgement form *A risk acknowledgment form is a document used by the prescriber to ensure that a patient taking a medicine has been informed of and understands the potential risks associated with the medicine, for example those related to pregnancy. This form must be filled out by both the prescriber and the patient.*
- Patient alert card / Patient reminder card / Patient educational card
  A patient card is a tool that patients carry with them that contains important information about a medicine, including the main risks and recommended actions. A patient card can take different forms, depending on the specific medicine. It is often a small, sturdy card that the patient can easily carry in his

or her wallet or bag. The card can be printed, but is sometimes also offered in digital form to be printed at home.

- Patient guide
  A patient guide is a tool or document (e.g. a brochure or a leaflet) provided to patients taking a medicine to help them understand and minimize potential risks associated with that medicine.

The main safety warnings included in the aRMM materials can be viewed here.

The following questions are about the aRMM materials for *[name medicinal product ticked in QB1]*

B2. Are you aware of the availability of aRMM materials for [name product]?

- o No → *GO TO PART D*
- o Yes of the healthcare provider materials
- o Yes of the patient-targeted materials
- o Yes of both the healthcare provider and patient-targeted materials

B3. Have you received aRMM materials for [name medicinal product]? *Please provide an answer for each aRMM material in the respective columns. Multiple 'Yes' answers possible for each column.*
[Programming instructions: multiple answers possible, but No and I don't remember if I received it and Yes, but I don't remember how I received it cannot be combined with each other and with the Yes answers]

	aRMM material 1**	aRMM material 2	aRMM material 3	aRMM material 4
❑ No	❑	❑	❑	❑
❑ Yes, on paper from the pharmaceutical company	❑	❑	❑	❑
❑ Yes, via an email from the pharmaceutical company with the aRMM material as attachment	❑	❑	❑	❑
❑ Yes, via an email from the pharmaceutical company with a weblink or QR code to the aRMM material	❑	❑	❑	❑
❑ Yes, from a medical representative of the pharmaceutical company	❑	❑	❑	❑
❑ [a] Yes, I downloaded it from the website of the pharmaceutical company	❑	❑	❑	❑
❑ [b] Yes, I downloaded it from another website	❑	❑	❑	❑
❑ [c] Yes, from a professional association	❑	❑	❑	❑
❑ [d] Yes, from a colleague	❑	❑	❑	❑

❑ [e] Yes, in another way	❑	❑	❑	❑
❑ Yes, but I don't remember **how** I received it	❑	❑	❑	❑
❑ I don't remember **if** I received it	❑	❑	❑	❑

*** In each column one of the available aRMM materials for a specific product will be presented.*

B3a. *[To be asked if the respondent ticked a box in row [a]]* **You indicated that you downloaded the aRMM material for [name medicinal product] from the website of the pharmaceutical company. Please explain why you used this website:**

B3b. *[To be asked if the respondent ticked a box in row [b]*] **You indicated that you downloaded the aRMM material for [name medicinal product] from another website. What website did you use, and why did you use this website:**

B3c. *[To be asked if the respondent ticked a box in row [c]]* **You indicated that you received the aRMM material for [name medicinal product] from a professional organization. Please indicate which organization:**

B3d. *[To be asked if the respondent ticked a box in row [d]]* **You indicated that you received the aRMM materials from a colleague. In what way did you receive the material from your colleague?**

- o In a formal way (e.g. team meeting, newsletter, news board)
- o In an informal way (e.g. an informal interaction with colleagues)
- o In another way, namely:

B3e. *[To be asked if the respondent ticked a box in row [e]*] **You indicated that you received the aRMM material for [name medicinal product] in another way. Please describe how you received it and from whom:**

B4. You indicated that you received or are aware of the aRMM material(s) for [name product]. Do you have these on paper in stock in your healthcare facility? *(Multiple answers possible) [Programming instruction: I don't know cannot in combination with the other answers]*

- ❑ We have the patient-targeted materials on paper in stock
- ❑ We have the healthcare professional-targeted materials on paper in stock
- ❑ The patient-targeted materials are available for print on demand

- ❑ The healthcare professional-targeted materials are available for print on demand
- ❑ I don't know

B5. Do you know how to obtain a refill of aRMM material for [name product] (e.g. if stock runs out)? *(multiple yes answers possible)*
[Programming instructions: multiple answers possible, but No cannot be combined with the Yes answers]

- ❑ No
- ❑ Yes, I can contact the pharmaceutical company
- ❑ Yes, I can ask the medical representative of the pharmaceutical company
- ❑ Yes, I can download and print this from the website of the pharmaceutical company
- ❑ Yes, I can download and print this from the website of the national competent authority
- ❑ Yes, I can ask the pharmaceutical wholesale distributor
- ❑ Yes, in another way, namely: _____

B6. Have you read the aRMM materials for [name product]?

- o No
- o Yes, the patient-targeted materials
- o Yes, the healthcare professional-targeted materials
- o Yes, both the patient and healthcare professional-targeted materials
- o I don't remember

B7. Do you <u>discuss</u> the content of the aRMM materials with patients you prescribe [name product]?

	Patient card*	**Patient guide***	**Risk acknowledgement form***
❑ Yes, at **first** prescription with **all** patients	❑	❑	❑
❑ [a] Yes, at **first** prescription but only with **a selection** of patients	❑	❑	❑
❑ Yes, at **repeat** prescriptions with **all** patients	❑	❑	❑
❑ [b] Yes, at **repeat** prescriptions with **a selection** of patients	❑	❑	❑
❑ No, but I have made agreements with the **pharmacist** to discuss this with the patient	❑	❑	**Not applicable**
❑ No, but I have made agreements with the **nurse(s)** to discuss this with the patient	❑	❑	❑
❑ No, but I have made agreements with **another healthcare professional** to discuss this with the patient	❑	❑	❑
❑ [c] No, because of other reasons	❑	❑	❑

❑ [d] None of the above options apply	❑	❑	❑

** We will program an information balloon repeating the description of the aRMM materials. Only the relevant patient-targeted materials will be presented for each specific product.*

B7a. *[To be asked if the respondent ticked a box in row [a]]* **You indicated that you discuss the content of the aRMM material for [name medicinal product] at the first prescription only to a subset of patients. Please indicate which subset and why with this subset:**

B7b. *[To be asked if the respondent ticked a box in row [b]]* **You indicated that you discuss the content of the aRMM material(s) for [name medicinal product] at the repeat prescription only to a subset of patients. Please indicate which subset and why this subset:**

B7c. *[To be asked if the respondent ticked a box in row [c]]* **You indicated that you have other reasons to not discuss the content of the aRMM material(s). Please describe your experience:**

B7d. *[To be asked if the respondent ticked a box in row [d]]* **You indicated that none of the above options applied. Please describe your experience:**

B8. Do you <u>hand out</u> the patient-targeted aRMM materials to patients you prescribe [name product]?

	Patient card*	**Patient guide***	**Risk acknowledgement form***
❑ Yes, to **all** patients I prescribe this medicine	❑	❑	❑
❑ [a] Yes, but only to **a selection** of patients	❑	❑	❑
❑ No, but I have made agreements with the **pharmacist** to hand this out to the patients	❑	❑	**Not applicable**
❑ No, but I have made agreements with the **nurse(s)** to hand this out to the patient	❑	❑	❑
❑ No, but I have made agreements with **another healthcare professional** to hand this out to the patient	❑	❑	❑

❑ No, but I make the patient aware that it is included in the medicine package or attached to the package	❑	**Not applicable**	**Not applicable**
❑ No, but I ask the patient to use the weblink or QR code on the medicine package or the package leaflet for more information	❑	❑	**Not applicable**
❑ [b] No, because of other reasons	❑	❑	❑
❑ [c] None of the above options apply	❑	❑	❑

** We will program an information balloon repeating the description of the aRMM materials. Only the relevant patient materials will be presented for each specific product.*

B8a. *[To be asked if the respondent ticked a box in row [a]]* **You indicated that you hand out the aRMM material(s) for [name medicinal product] only to a subset of patients. Please indicate which subset and why only this subset:**

B8b. *[To be asked if the respondent ticked a box in row [b]]* **You indicated that you have other reasons to not hand out the aRMM material(s) for [name medicinal product]. Please describe your experience:**

B8c. *[To be asked if the respondent ticked a box in row [b]]* **You indicated that none of the above options applied. Please describe your experience:**

[Only if the HCP hands out the materials themselves (two yes answers previous question)]

B9. How do you hand out the patient-targeted aRMM materials to patients you prescribe [name product]? *(multiple answers possible)*

	Patient card*	**Patient guide***	**Risk acknowledgement form***
❑ On paper	❑	❑	❑
❑ Via an email with the aRMM material as attachment	❑	❑	❑
❑ Via an email with a weblink or QR code to the aRMM material	❑	❑	❑
❑ Via a letter with a weblink or QR code to the aRMM material	❑	❑	❑
❑ [a] In another way	❑	❑	❑

** We will program an information balloon repeating the description of the aRMM materials. Only the relevant patient materials will be presented for each specific product.*

B9a *[To be asked if the respondent ticked a box in row [a]]* You indicated that you hand out the aRMM material(s) in another way. Please describe your experience:

B10. Do you get an alert during the prescribing process that aRMM materials are available for [name product]? If so, how? *[programming instruction: No cannot be combined with the Yes answers]*

- ❑ No
- ❑ Yes, electronically through the electronic prescribing system
- ❑ Yes, in another way, namely:

B11. How useful are the aRMM materials for you as healthcare provider?

a) Patient-targeted materials:
- o Not useful at all
- o Not very useful
- o A bit useful
- o Useful
- o Very useful

b) Healthcare professional-targeted materials:
- o Not useful at all
- o Not very useful
- o A bit useful
- o Useful
- o Very useful

[REPEAT QUESTIONS B2 TO B11 FOR EACH PRODUCT THAT THE PRESCRIBER INDICATED TO HAVE PRESCRIBED IN THE PAST 12 MONTHS]

PART C. DISSEMINATION OF aRMM MATERIALS

[QUESTIONS FOR PHARMACISTS]

C1. Which of the following medicinal products have you dispensed in the past 12 months? *(multiple answers possible)*

- ❑ Aubagio (teriflunomide)
- ❑ Eylea (aflibercept)
- ❑ Lemtrada (alemtuzumab)
- ❑ Lixiana (edoxaban)
- ❑ Xeljanz (tofacitinib)
- ❑ Oral retinoids containing medicinal products*
- ❑ Valproate containing medicinal products*
- ❑ None of these medicinal products → *Thanks for your interest in this survey. Unfortunately, you are not able to further fill out the survey if you have not dispensed one of these medicinal products.*

**For the retinoids and valproate containing products we will program an information balloon where we include the list of (brand) names marketed per country.*

You indicate that you dispense *[name medicinal product C1]*. For this medicinal product the following aRMM materials are available *[program instruction: choose the relevant from the list below. For each product we will include – if possible – the main safety concerns]*:

- Guide for healthcare professionals/Healthcare professional guide / healthcare professional educational material *Educational material (e.g. a brochure or leaflet) describing key risks, potential adverse drug reactions, and recommended actions for healthcare professionals to take to minimize those risks.*
- Pharmacist checklist *A checklist used by healthcare professionals to ensure they are following safety advice when dispensing certain medications. The checklist typically includes specific actions, considerations, or information that pharmacists need to address before dispensing the medication.*
- Patient alert card / Patient reminder card / Patient educational card
  A patient card is a tool that patients carry with them that contains important information about a medicine, including the main risks and recommended actions. A patient card can take different forms, depending on the specific medicine. It is often a small, sturdy card that the patient can easily carry in his or her wallet or bag. The card can be printed, but is sometimes also offered in digital form to be printed at home.
- Patient guide
  A patient guide is a tool or document (e.g. a brochure or a leaflet) provided to patients taking a medicine to help them understand and minimize potential risks associated with that medicine.

The main safety warnings included in the aRMM materials can be viewed here.

The following questions are about the aRMM materials for *[name product ticked in QC1]*

C2. Are you aware of the availability of aRMM materials for [name product]?

- o No → *GO TO PART D*
- o Yes of the healthcare provider materials
- o Yes of the patient-targeted materials
- o Yes of both the healthcare provider and patient-targeted materials

C3. Have you received aRMM materials for [name product]? *Please provide an answer for each aRMM material in the respective columns. Multiple 'Yes' answers possible for each column.*
[Programming instructions: multiple answers possible, but No and I don't remember if I received it and Yes, but I don't remember how I received it cannot be combined with each other and with the Yes answers]

	aRMM material 1**	**aRMM material 2**	**aRMM material 3**	**aRMM material 4**
❑ No	❑	❑	❑	❑
❑ Yes, on paper from the pharmaceutical company	❑	❑	❑	❑
❑ Yes, via an email from the pharmaceutical company with the aRMM material as attachment	❑	❑	❑	❑

❑ Yes, via an email from the pharmaceutical company with a weblink or QR code to the aRMM material	❑	❑	❑	❑
❑ Yes, from a medical representative of the pharmaceutical company	❑	❑	❑	❑
❑ *[a]* Yes, I downloaded it from the website of the pharmaceutical company	❑	❑	❑	❑
❑ *[b]* Yes, I downloaded it from another website	❑	❑	❑	❑
❑ *[c]* Yes, from a professional association	❑	❑	❑	❑
❑ *[d]* Yes, from a colleague	❑	❑	❑	❑
❑ *[e]* Yes, in another way	❑	❑	❑	❑
❑ Yes, but I don't remember **how** I received it	❑	❑	❑	❑
❑ I don't remember **if** I received it	❑	❑	❑	❑

*** In each column one of the available aRMM materials for a specific product will be presented.*

C3a. *[To be asked if the respondent ticked a box in row [a]]* **You indicated that you downloaded the aRMM material for [name medicinal product] from the website of the pharmaceutical company. Please explain why you used this website:**

C3b. *[To be asked if the respondent ticked a box in row [b]*] **You indicated that you downloaded the aRMM material for [name medicinal product] from another website. What website did you use, and why did you use this website:**

C3c. *[To be asked if the respondent ticked a box in row [c]]* **You indicated that you received the aRMM material for [name medicinal product] from a professional organization. Please indicate which organization:**

C3d. *[To be asked if the respondent ticked a box in row [d]]* **You indicated that you received the aRMM materials from a colleague. In what way did you receive the material from your colleague?**

- o In a formal way (e.g. team meeting, newsletter, news board)
- o In an informal way (e.g. an informal interaction with colleagues)
- o In another way, namely:

C3e. *[To be asked if the respondent ticked a box in row [e]]* **You indicated that you received the aRMM material for [name medicinal product] in another way. Please describe how you received it and from whom:**

C4. You indicated that you received or are aware of the aRMM material(s) for [name product]. Do you have these on paper in stock in your healthcare facility? *(Multiple answers possible) [Programming instruction: I don't know cannot in combination with the other answers]*

- ❑ We have the patient-targeted materials on paper in stock
- ❑ We have the healthcare professional-targeted materials on paper in stock
- ❑ The patient-targeted materials are available for print on demand
- ❑ The healthcare professional-targeted materials are available for print on demand
- ❑ I don't know

C5. Do you know how to obtain a refill of aRMM material for [name product] (e.g. if stock runs out)? *(multiple yes answers possible)*
[Programming instructions: multiple answers possible, but No cannot be combined with the Yes answers]

- ❑ No
- ❑ Yes, I can contact the pharmaceutical company
- ❑ Yes, I can ask the medical representative of the pharmaceutical company
- ❑ Yes, I can download and print this from the website of the pharmaceutical company
- ❑ Yes, I can download and print this from the website of the national competent authority
- ❑ Yes, I can ask this to the pharmaceutical wholesale distributor
- ❑ Yes, in another way, namely: _____

C6. Have you read the aRMM materials for [name product]?

- o No
- o Yes, the patient-targeted materials
- o Yes, the healthcare professional-targeted materials
- o Yes, both the patient and healthcare professional-targeted materials
- o I don't know anymore

C7. Do you discuss the content of the aRMM materials with patients when you dispense [name product]?

	Patient card*	**Patient guide***
❑ Yes, at **first** dispensing with **all** patients	❑	❑
❑ *[a]* Yes, at **first** dispensing but only with **a selection** of patients	❑	❑
❑ Yes, at **each** dispensing with **all** patients	❑	❑
❑ *[b]* Yes, at **each** dispensing with **a selection** of patients	❑	❑

❑ No, but I have made agreements with the **prescriber** to discuss this with the patient	❑	❑
❑ No, but I have made agreements with **another healthcare professional** to discuss this with the patient	❑	❑
❑ *[c]* No, because of other reasons	❑	❑
❑ *[d]* None of the above options apply	❑	❑

** We will program an information balloon repeating the description of the aRMM materials. Only the relevant patient materials will be presented for each specific product.*

C7a. *[To be asked if the respondent ticked a box in row [a]]* **You indicated that you discuss the content of the aRMM material for [name medicinal product] at the first prescription only to a subset of patients. Please indicate which subset and why this subset:**

C7b. *[To be asked if the respondent ticked a box in row [b]]* **You indicated that you discuss the content of the aRMM material(s) for [name medicinal product] at the each prescription only to a subset of patients. Please indicate which subset and why this subset:**

C7c. *[To be asked if the respondent ticked a box in row [c]]* **You indicated that you have other reasons to not discuss the content of the aRMM material(s). Please describe your experience:**

C7d. *[To be asked if the respondent ticked a box in row [d]]* **You indicated that none of the above options applied. Please describe your experience:**

C8. Do you <u>hand out</u> the patient-targeted aRMM materials to patients when you dispense [name product]?

	Patient card*	**Patient guide***
❑ No, but I have made agreements with the **prescriber** to hand this out to the patient	❑	❑
❑ No, but I have made agreements with **another healthcare professional** to hand this out to the patient	❑	❑
❑ No, but I make the patient aware that this is included in or attached to the outside of the package	❑	**Not applicable**
❑ No, but I ask the patient to use the weblink or QR code on the medicine package or the package leaflet for more information	❑	❑
❑ *[a]*No, because of other reasons	❑	❑

❑ Yes, to **all** patients I dispense this medicine	❑	❑
❑ *[b]* Yes, but only to **a selection** of patients I dispense this medicine	❑	❑
❑ [c] None of the above options apply	❑	❑

** We will program an information balloon repeating the description of the aRMM materials. Only the relevant patient materials will be presented for each specific product.*

C8a. *[To be asked if the respondent ticked a box in row a]]* **You indicated that you have other reasons to not hand out the aRMM material(s) for [name medicinal product]. Please describe your experience:**

C8b. *[To be asked if the respondent ticked a box in row [b]]* **You indicated that you hand out the aRMM material(s) for [name medicinal product] only to a subset of patients. Please indicate which subset and why only this subset:**

C8c. *[To be asked if the respondent ticked a box in row [c]]* **You indicated that none of the above options applied. Please describe your experience:**

[Only if HCP hands out the materials themselves (two yes answers previous question)]
C9. How do you hand out the patient-targeted aRMM materials to patients when you dispense [name product]? *(multiple answers possible)*

	Patient card*	**Patient guide***
❑ On paper	❑	❑
❑ Via an email with the aRMM material as attachment	❑	❑
❑ Via an email with a weblink or QR code to the aRMM material	❑	❑
❑ Via a letter with a weblink or QR code to the aRMM material	❑	❑
❑ [a] In another way	❑	❑

** We will program an information balloon repeating the description of the aRMM materials. Only the relevant patient materials will be presented for each specific product.*

C9a. *[To be asked if the respondent ticked a box in row [a]]* **You indicated that you hand out the aRMM material(s) in another way. Please describe your experience:**

C10. Do you get an alert during the dispensing process that aRMM materials are available for [name product]? If so, how? *[programming instruction: No cannot be combined with the Yes answers]*

❑ No
❑ Yes, electronically through the electronic pharmacy dispensing system
❑ Yes, in another way, namely: [ ]

C11. How useful are the aRMM materials for you as healthcare provider?

c) Patient-targeted materials:
- o Not useful at all
- o Not very useful
- o A bit useful
- o Useful
- o Very useful

d) Healthcare professional-targeted materials:
- o Not useful at all
- o Not very useful
- o A bit useful
- o Useful
- o Very useful

[REPEAT QUESTIONS C2 TO C11 FOR EACH PRODUCT THAT THE PHARMACIST INDICATED TO HAVE DISPENSED IN THE PAST 12 MONTHS]

PART D PREFERENCES

QUESTIONS FOR BOTH PRESCRIBERS AND PHARMACISTS:

The next questions are about your preferences for the dissemination of aRMM materials. We are interested in the way you prefer to receive the materials from the pharmaceutical company as well as in the way you prefer to distribute the materials to your patients. The questions are about aRMM materials in general.

D1. How do you prefer to receive aRMM materials? *Choose up to three ways for each material (i.e. in each column)*

	Educational material for healthcare professionals*	**Healthcare provider checklist***	**Patient guide***	**Patient card***	**Risk acknowledgment form*/****
❑ On paper from the pharmaceutical company	❑	❑	❑	❑	❑
❑ Via an email from the pharmaceutical company with the aRMM material as attachment	❑	❑	❑	❑	❑
❑ Via an email from the pharmaceutical company with a	❑	❑	❑	❑	❑

weblink or QR code to the aRMM material					
❑ Via a letter from the pharmaceutical company with a weblink or QR code to download it	❑	❑	❑	❑	❑
❑ To download it from the website of the **pharmaceutical company**	❑	❑	❑	❑	❑
❑ To download it from the website of the **national competent authority**	❑	❑	❑	❑	❑
❑ To download it from the website of a **professional organisation**	❑	❑	❑	❑	❑
❑ Included in the medicine package or attached to the outside of the package	**Not applicable**	**Not applicable**	❑	❑	**Not applicable**
❑ Via a QR code on the medicine package or package leaflet	**Not applicable**	**Not applicable**	❑	❑	**Not applicable**
❑ In another way, namely:	❑	❑	❑	❑	❑

** We will program an information balloon repeating the description of the aRMM materials*

*** Only for prescribers*

D2. How do you prefer to hand out the aRMM materials to your patients? ***Choose up to three ways for each material (i.e. in each column)***

	Patient guide*	**Patient card***	**Risk acknowledgment form*/****
❑ On paper	❑	❑	❑
❑ Via an email with the aRMM material as attachment	❑	❑	❑
❑ Via an email with a weblink or QR code to the aRMM material	❑	❑	❑
❑ Via a letter with a weblink or QR code to the aRMM material	❑	❑	❑
❑ It should be included in or attached to the outside of the medicine package	❑	❑	**Not applicable**

❑ Via a weblink or QR code on the medicine package for patients	❑	❑	**Not applicable**
❑ Via informing patients they can download it themselves from the website of the **pharmaceutical company**	❑	❑	❑
❑ Via informing patients they can download it themselves from the website of **national competent authority**	❑	❑	❑
❑ Via informing patients that they can download it themselves from the website of a **patient organisation**	❑	❑	❑
❑ In another way, please describe:	❑	❑	❑

** We will program an information balloon repeating the description of the aRMM materials*

*** Only for prescribers*

D3. Do you experience any challenges in how you <u>receive</u> the aRMM materials from the pharmaceutical company?

- o No
- o Yes, challenges regarding: *(multiple answers possible)*
  - ❑ Delayed receipt of materials
  - ❑ Poor material quality/clarity
  - ❑ Lack of training on materials
  - ❑ Technical delivery problems
  - ❑ Other challenges, namely:

D4. Do you experience any challenges in how you <u>disseminate</u> the aRMM materials to your patients?

- o No
- o Yes, challenges regarding: *(multiple answers possible)*
  - ❑ Insufficient consultation time
  - ❑ Language/literacy barriers
  - ❑ Patient resistance
  - ❑ Patient anxiety
  - ❑ Remembering that aRMM materials exist for the product, remembering to handout these materials
  - ❑ Other challenges, namely:

D5. Do you have any remarks regarding the dissemination of aRMM materials? For example, suggestions to improve this process?

We would like to know more about how healthcare providers experience the dissemination process of aRMM materials. We therefore organize an **online** focus group about this topic. In this focus group, you discus with other professionals about your experiences with the dissemination process of aRMM materials. We would like to know whether you are interested to cooperate in this focus group. If yes, you will be contacted by a researcher from *[name research institute]*. The online focus group is scheduled to take place at the end of 2025 or in the first months of 2026 and will last 90-120 minutes. You can decide upon participation after this invitation. The results will be included in a publicly available report. All personal data will be processed confidentially and in compliance with Regulation (EU) 2016/679 (General Data Protection Regulation) and relevant national data protection legislation, ensuring that no identifying information will be published or shared without your explicit consent.

D5. Do you want to participate in a focus group? And if yes, do you agree that we will contact you?

- o Yes, I am interested in participating and you can contact me through the following email address:
- o No

If countries due to ethics approval do not allow to ask for an email address, the following text can be included instead of question D5:
If you are interested in participating in the focus group, please contact *[name researcher]* via *[email address and/or phone number]*.

[Countries can add here additional information needed because of the GDPR or national legislation.]

Annex 3G Data management plan

This data management plan follows the FAIR principles (Findability, Accessibility, Interoperability and Reusability). The aim is to make the data and research outputs: *i) Findable; ii) Accessible; iii) Interoperable and iv) Reusable.* In this data management plan first some general information about the data collection is described, thereafter it is described how we make our data findable, accessible, interoperable and reusable.

General information data collection

Here some general information about the data collection of this study is described.

How, when and where will the data be acquired?

Data for this study will be collected by desk research, interviews, focus groups, questionnaires and a webinar. All data will be collected in the period 1 March 2025 – March 31 2026. Data will be collected in the Netherlands, Finland, Italy, Hungary, Lithuania and Romania.

Data that will be produced:

This study uses a combination of **quantitative** and **qualitative** data. The following **new** data will be generated:

1) **Qualitative** data from the focus group with NCAs, the interviews with MAHs, the focus groups with patients and HCPs, and the webinar.
2) **Quantitative** data from the questionnaires among patient organisations, HCPs and patients.

In generating this new data Nivel and its six partners work together. Nivel has a collaboration agreement for this study with the institutes from the other five participating countries. DESAN and Nivel have a Service Level Agreement (SLA) describing the responsibilities of both parties regarding the collection of data through questionnaires, specifically privacy sensitive data and the quality control.

Expected size of the data:

1) **Qualitative** data:

We expect to have recordings of one focus group of 90-120 minutes with NCAs (6-12 participants), of 12 focus groups of 90-120 minutes with HCPs (8-10 participants per focus group), of 6 focus groups of 90-120 minutes with patients (8-10 participants per focus group), 11 interviews of 30-60 minutes with MAH's and one webinar of 90 minutes with 40-50 participants.
This part of the data collection will be around 3 GB in size.

2) **Quantitative** data:

Three data Stata questionnaire files for 1) patients, 2) HCPs and 3) patient organisations:
1) patients approximately (n= 300-600 patients (based on 50-100 patients per country));
2) HCPs approximately (n= 300-600 HCPs (based on 50-100 HCPs per country)); and
3) patient organisations (n=30-60 patient organisations (based on 5-10 patient organisations per country)).
This part of the data collection will be around 1 GB in size.

Hence, it is estimated that the total data storage will comprise less than 5 GB.

Data processing:
We will use Stata to analyse the data from the questionnaires. As described in more detail in section 9.8, the analyses will be done by two researchers. To analyse the data from the interviews, focus groups and webinar MaxQda or Excel will be used. Also here double coding of part of the transcripts is planned, as described in section 9.8 in more detail.

Data storage and back-up:
We will make use of our institution's standard facilities for storage and backup of the data. Data will be stored and being backed up in Nivel's secure data processing environments. Only authorized Nivel employees have access to the data. These authorized employees are bound by a non-disclosure agreement.

Datasets and audio recordings are stored in the secured environment on the datacentre of PQR (IT service provider). Access is reserved for authorized employees only. The data backup runs daily. The daily back-ups are incremental and stored at two different locations, the original data is hosted in the datacentre of PQR. This guarantees long term storage of the data, as well as sufficient storage space. Costs for lang term archiving are covered.

Data that contain privacy sensitive information will be stored separately, and destroyed after the project has ended apart from the recordings themselves which are stored at Nivel in conformity with Nivel regulations, without deadline.

Data sharing
Confidential data/documents (e.g. transcripts from focus groups) will only be shared between the institutes using a secured environment. In principle, SURFfilesender will be used by Nivel to send confidential data to the other institutes. SURFfilesender uses end-to-end encryption, which means that only the recipient can open the files with a password. The servers are also in the Netherlands, which means that they fall under Dutch and European privacy legislation. DESAN will use Cryptshare to share data (i.e. data from the questionnaires) with Nivel and the other institutes. Also Cryptshare is a secure email and file sending service that allows to send confidential information securely via email. It encrypts emails and attachments so that only the recipient can open them with a password.

Data security
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. The day-to-day coordinator (Brabers) is 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.

DESAN is ISO-27001 and ISO-20252 certified.

Version control

Researchers at Nivel maintain a digital logbook according to a fixed format, described in Nivel's quality guidelines and instructions. Within the guidelines also instructions for version control are included. For example, a date has to be included in the file name. Furthermore, old versions are set in a separate map "old", so that it is always clear what the most recent version is. For the preliminary plan and the protocol version numbering (e.g. version 1.0 or 2.0) alongside a date of the version will be used. By storing all documents belonging to the research into the secured Nivel environment and by using a clear version control, in the case of absence, project team members can replace each other or another researcher from Nivel's large pool of researchers can take over part of the research.

Making data findable

Firstly, the data will be made findable through publishing the results in an open access journal (Deliverable 4) and a study report (Deliverable 3) published on Nivel's website.
Secondly, the study is registered in the HMA-EMA Catalogues of RWD studies (registration number: EUPAS1000000524). In this register information about the study is included and an approved version of the protocol (Deliverable 2) will also be included.
Thirdly, the metadata as well as the anonymised data collected during the study will be stored in the DANS Data Station for Life Sciences. For the meta data the general Dublin Core scheme will be used. By deposing the anonymised collected data in the DANS repository, it is automatically assigned a Digital Object Identifier (DOI). This DOI serves as a persistent hyperlink, allowing researchers to reliably cite and access the data, even if the dataset's storage location change.

Making data accessible

We will make the anonymous collected data accessible through DANS Data Station for Life Sciences. Because it is expected that the manuscript (Deliverable 4) will be submitted at the end of the project, and it may take some time before this manuscript will be published, an embargo period of one year will be defined. Furthermore, the participants of the questionnaires are asked for their consent to reuse the data for similar research purposes, i.e. research performed into the dissemination of aRMM materials. Evaluation of the purpose of the reuse of the data will be done by the project leads before access to the data can be provided (Van Dijk and De Jong). Furthermore, an agreement between Nivel and the applicant that contains all the terms of use (e.g. purpose and security terms) must be signed.

At least the following collected data will be made available upon request:
-Datasets from the three questionnaires, and the syntaxes for questionnaire analyses;
-Research protocol;
-Questionnaires;
-Interview guides for interviews and focus groups;
-Search strings scientific literature search.

The transcripts from the interviews will not be made available upon request. The transcripts will be pseudonymized in such a way that obvious identifiers will be removed from the transcript, and participants will be given a number instead. However, it will be difficult to completely pseudonymize the transcripts because it may possible to identify persons or MAHs based on the answers they give during the interview. Therefore, the transcripts will not be made available upon request.

Making data interoperable

Data will be made interoperable by producing data and outputs in standard file formats. For example data from the questionnaires will be in .sav format (Stata). Text documents (like the questionnaires and the interview guides) will be in PDF format.

Making data reusable

As described, the data will be deposed in DANS to ensure long term archiving of the data. Furthermore, after the project, Nivel will store the data on a different server, where only the project leads (Van Dijk and De Jong) have rights to access. The data will be stored for a maximum of 10 years. Several quality checks will be done, for example, with regard to the data sets from the questionnaire, there will be a check for empty cases and for inconsistency in multiple choice questions. For the focus groups, for example, a second researcher will remind the interviewer to address (a) topic(s) which the interviewer forgot or has not addressed yet. In analysing both the quantitative and qualitative data, several measures will be taken to check the analysis (e.g. double coding and checking the syntax of the questionnaire analyses), as described in section 9.8.

Annex 3H Communication and publication plan

This plan lays out the communication and publication plan for the project and includes the following sections:

1. Objectives of the plan
2. Key audiences for communication
3. Publication Deliverables & Timeline
4. Communication products
5. Communication Governance and restrictions
6. Evaluation and updates

1 Objectives of the Communication and publication plan

- To ensure clear, timely, and effective communication of study progress, results, and implications.
- To disseminate study findings to target audiences in an accessible and engaging manner.
- To support transparency, scientific integrity, and public engagement.

2 Key Audiences

Table 3H.1 describes the audiences that need to be reached for the study as well as the channels used to reach them. Communication will be in English. Consortium partners will also disseminate content in their local languages via social media, institutional websites, and local news outlets.

Table 3H.1 Key audiences for communication and publications

Audience	Purpose of Communication	Mode/Channel*
EMA	Coordination, input, updates	• Monthly meetings • Correspondence
Scientific Community, including EMA	Share findings and methods	• *Study report* • *Open access manuscript* • Conference presentations • Social media
Policymakers, professional organisations, patient organisations	Inform about study outcomes	• Press release • *Study report* • Website content • News items • Social media
General Public	Inform about study outcomes	• Press release • Website content • News items • Social media
Participating Countries' Organizations	Amplify dissemination of survey and later on results, ensure local relevance	• Local websites • LinkedIn shares • Website content • Networking
Third Parties (media, stakeholders)	Dissemination after EMA review	• Website content • Press release

* *Mode/channels printed italics are publications*

3 Publication Deliverables & Timeline

The basis for communication is formed by the publications of the study. Table 3H.2 describes the planned publications including the timing and responsible parties.

Table 3H.2 Publications for the DIS-aRMM study

Deliverable	Content	Timing	Responsible Party	Notes
D1	Preliminary study plan	April 2025	Nivel	Internal & EMA
D2	Study protocol	June 2025	Nivel	Internal & EMA
D2.1	Data management plan	June 2025	Nivel	Annex 3G
D2.2	Communication Plan	June 2025	Nivel	This document
D3	Final study report	April 2026	Nivel	Shared publicly post EMA review
D4	Open access article	June 2026	Nivel	Submitted after EMA review Published after peer-reviewing in journal
News Item 1	Summary of D3	~April 2026	Nivel + EMA review	Published post-approval
News Item 2	Summary of D4	~June 2026	Nivel + EMA review	Published post-approval

4 Communication Products

The major communication products are listed in table 3H.3, including their format, target audience, channel and timing. Table 3H.4 describes the major communication products in more detail.

Table 3H.3 Major external communication products for the DIS-aRMM study

Product	Format	Target Audience	Channel	Timing
Press Release	1-page news-style	General Public, Media, Policymakers, professional organisations, patient organisations	Nivel + partner websites	After D3 & D4
Social Media	LinkedIn posts	Scientific community, General Public, Media, Policymakers, professional organisations, patient organisations	Social media platforms, mainly Linkedin	Post D3 & D4
Website News Item	News article with quotes	Scientific community, General Public, Media, Policymakers, professional organisations, patient organisations	Nivel + partner websites	Post D3 & D4
Networking	Engaging organisations through direct outreach (emails, phone calls, and events)	Professional organisations, patient organisations	Nivel + partner websites, personal contacting	From the start of the project

**All public-facing content will be reviewed by EMA before publication.*

Table 3H.4 Detailed information on communication products

Communication product	Content creation approach
Press release	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. An engaging quotation from a spokesperson will be included. 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 LinkedIn. This message will be written in simple yet engaging language, and will include relevant hashtags. The message will be shared across all six participating countries via their respective LinkedIn accounts.
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 it is suggested to also 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.

5 Communication Governance

Roles & Responsibilities

- Nivel Project Lead: Oversees all communication activities; responsible for content quality and coordination.
- Nivel Communication Officer: Supports design and readability of communication materials.
- Study Team (Nivel and partners): Provides content input, reviews drafts.
- EMA: Reviews content prior to public dissemination.

Internal Communication with EMA

- Monthly Meetings: First Tuesday of each month at 10:00.
- Meeting Minutes: Drafted and shared by Nivel post-meeting.
- Ad Hoc Teleconferences: Arranged as needed for urgent matters.
- Document Sharing: Draft protocols, survey tools, and communication materials shared for input before finalization.

Risk Communication

Any serious risks or issues impacting deliverables and communication products will be promptly escalated by Nivel to EMA through the project coordinator or co-lead. An action plan will be drafted promptly, and a responsible lead will be appointed by Nivel.

Communication Restrictions

- No public release of results or related products before PRAC review of the full study report (D3).
- All external communication (news items, press releases) will only proceed after coordination with EMA, including timing of the publication.

6 Evaluation & Updates

This communication plan will be reviewed and updated as needed.