ROC21 - SC02 - EMA/2020/46/TDA/L4.02
Implementation of controlled access to and distribution of medicinal products in European Union

Deliverable 2: Study Protocol

EU PE&PV research network

EUPAS1000000313

Version 2.0

March 10, 2025

To prevent information bias in the primary data collection, this protocol is uploaded in the HMA-EMA catalogue of RWD studies without Appendices

Implementation of controlled access to and distribution of medicinal products in European Union

Title	Implementation of controlled access to and distribution of medicinal products in European Union
Protocol version identifier	2.0
HMA-EMA Catalogue of Real World Data Studies number	EUPAS1000000313
Countries of study	Austria, Greece, Latvia, Netherlands, Portugal, Slovenia, Spain, Sweden
Medicinal products	Aspaveli® (pegcetacoplan), Fintepla® (fenfluramine), Revlimid® (lenalidomide), Soliris® (eculizumab), Spravato® (esketamine), Strimvelis® (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence), Uptravi® (selexipag), Yescarta® (axicabtagene ciloleucel)
Research objectives	The objectives of this project are to: 1. Identify and describe the processes for implementation of controlled access program (CAP) and controlled distribution system (CDS) at national level with focus on: a. Roles and responsibilities of key bodies and organisations involved in the implementation of CAP and CDS conditions and requirements; b. Established processes and timelines for implementing CAP and CDS conditions and requirements; 2. Based on a purposive sample of eight products, describe and analyse stakeholder experience with CAP and CDS with focus on: a. Feasibility of implementing specific conditions and requirements, by country, by medicinal product, by type of condition or requirement, by type of stakeholder (i.e., patient, carer, healthcare professional, marketing authorisation holder (MAH) and regulator); b. Criteria for determining successful implementation of CAP and CDS respectively; c. Perceived challenges for the healthcare system, by country, by medicinal product, by type of condition or requirement, by type of stakeholder (i.e., patient, carer, healthcare professional, MAH and regulator); Identify key enablers and barriers for adherence to CAP and CDS conditions and requirements at national level, by country, by medicinal product, by type of condition or requirement, by type of stakeholder (i.e., patient, carer, healthcare professional, MAH and regulator).

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2. List of abbreviations

AT	Austria
aRMM	Additional Risk Minimisation Measure
C	Coordinator
CAP	Controlled Access Programme
CDS	Controlled Distribution System
CP	Consortium Partners
CT	Coordinating Team
DMP	Data Management Plan
DPIA	Data Protection Impact Assessment
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU PAS	European Union Electronic Register of Post-Authorisation Studies
ES	Spain
FTE	Full Time Equivalent
GDPR	General Data Protection Regulation
EL	Greece (Elláda)
HCP	Healthcare Professional
LV	Latvia
MAH	Marketing Authorization Holder
NCA	National Competent Authority
NL	The Netherlands
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Portugal
RMM	Risk Minimisation Measure
SC	Steering committee
SI	Slovenia
SE	Sweden
SmPC	Summary of product characteristics
UK	United Kingdom
UU	Utrecht University
WP	Work package

3. Responsible parties

The Coordinating Team (CT) is composed by:

- Prof. dr. Marie L De Bruin, Research leader, Utrecht University, The Netherlands (lead)
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The project manager:

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- *The Netherlands - UU*: Dr. Christine Leopold, Assistant prof Utrecht University and backup: Prof dr Olaf H Klungel
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The Steering Committee (SC) is composed by:

- one representative per country and one alternate per country (back-up), see above;

- chair / vice-chair: SC and alternate.

The Coordinator of the EU PE&PV Research Network is:

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

4. Abstract

Title
Study protocol: Implementation of controlled access to and distribution of medicinal products in European Union (version 2.0)
ROC21 - SC02 - EMA/2020/46/TDA/L4.02 - EU PE&PV research network

Rationale and background
Controlled access programs (CAP) and controlled distribution systems (CDS) are imposed as the most stringent additional risk minimisation measures (aRMMs) within the EU pharmacovigilance legislation with the intent to minimise the highest safety risks.
In general, marketing authorization holders (MAHs) and national competent authorities (NCAs) have expressed concerns about national implementation of aRMMs, highlighting challenges arising from discrepancies in regulatory requirements and differences in national health systems as well as the need for coordination and alignment across various agencies.
The conditions and requirements for the control elements in CAP/CDS are outlined in the legally binding Annex II.D of the European Periodic Assessment Report (EPAR), but further detailing and adaptation to national health systems takes place during the implementation phase at Member State level. The actual implemented processes in which the control element is enforced may therefore vary across Member States. Currently, there is insufficient knowledge on how specific conditions and requirements of CAP/CDS are implemented across EU Member States.

Research question and objectives
The study aims to describe processes in and national experiences of implementing conditions of CAP and CDS at national level, with a specific focus on the *control* elements of these measures.

Specifically, the objectives of the study are to:

1. *Identify and describe the processes for implementation* of CAP/CDS at national level, including the roles and responsibilities of key bodies and organisations involved in the implementation of CAP/CDS conditions and requirements and established processes in eight EU Member States.
2. *Describe and analyse stakeholder experiences* based on a purposive sample of eight products, by focusing on the feasibility of and perceived facilitators and challenges in implementing the specific conditions and requirements.
3. *Identify key enablers and barriers* in implementing CAP/CDS conditions and requirements at national level.

Study design
A mixed-methods approach will be used including document analysis, a quantitative analysis of cross-sectional survey data, as well as a qualitative analysis of stakeholders' perceptions obtained in semi-structured interviews.
The methodology involves multiple components divided over three work packages (WPs): WP1 "Mapping the process of implementation", WP2 "Understanding stakeholder experiences" – including a cross-sectional survey (2a) and interviews with stakeholders (2b) – and WP3 "Identification of barriers and enablers at EU level". Findings will be

analysed by country, by medicinal product, by type of condition or requirement, and by type of stakeholder.

Population
Implementation of CAP/CDS conditions and requirements will be studied in Austria, Greece, Latvia, the Netherlands, Portugal, Slovenia, Spain, and Sweden, using eight centrally authorised medicinal products as examples.
WP1 will be based on desk research in each of the eight countries. For WP2a we will include key stakeholders, including the NCA, MAHs of the eight products, physicians, pharmacists, and other stakeholders involved in the national implementation of CAP/CDS. Based on the findings from WPs 1 and 2a, noteworthy cases that stand out will be selected for further detailed analysis through interviews in WP2b, where also patients/care givers are included. In WP3 we will synthesize findings from WPs 1 and 2.

Variables
In an overall country mapping for WP1, data collection will focus on the roles and responsibilities of involved stakeholders, as well as general timelines and processes of the implementation. In further product-specific mapping, variables will include local market availability of each product, details of the national CAP/CDS conditions, details on the stakeholders involved, and incentives to comply with the regulation. In WP2a, variables will include the respondent's experience with the national implementation and/or compliance with/use of the control elements, as well as their view on barriers and facilitators experienced. WP2b will elicit further detail on these variables from interviewees.

Data sources
WP1 will be based on desk review of publicly available data sources including key national regulatory documents and public statements on regulatory actions and (informal) consultation within the researchers' professional networks. WP2 will involve primary data collection from key stakeholders.

Study size
Implementation processes will be mapped in all eight countries and for all eight products. In WP2a we anticipate sending out 12-20 surveys per country, with the exact number depending on which stakeholders are involved in the national implementation of control elements and local availability of the products. For WP2b, we foresee 8-24 interviews per country.

Data analysis
The processes of implementation will be visualized in eight country flowcharts, and further product-specific flowcharts if appropriate. WP2a will employ descriptive statistics on pseudonymized data of the survey, and information received as free text will be translated to English and analysed through deductive and inductive content analysis. Transcripts of the semi-structured interviews from WP2b will be analysed through content analysis based on a close line-by-line reading of the responses and developing a conceptual coding scheme based on the major themes from the interview guide.

Milestones
Major milestones include "Data collection survey completed" (Jun 2025), "Cases for interviews selected" (Jun 2025) and "Interviews completed" (Oct 2025).

5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
N/A	13-1-2025	baseline	Version 1.0	N/A
1	24-2-2015	All sections	Version 1.1	Revisions following EMA/PRAC comments.
2	6-3-2025	All sections	Version 1.2	Minor revisions following EMA/PRAC comments and ethics review
3	10-3-2025	All sections	Version 1.3	Minor revisions following EMA review
4	10-3-2025	All sections	Version 2.0	Clean version after EMA approval, corrected page numbers and product availability table

6. Milestones and Deliverables

Milestones (M) and Deliverables (D)	**Planned date**
Start of project (Kick-off meeting)	Sep 12, 2024
D1: Preliminary study plan	Nov 12, 2024
M1: Data extraction template completed	Dec 2024
D2: Study protocol	Jan 13, 2025
M2: Stakeholder survey ready	Jan 2025
M3: Draft interview guide ready	Jan 2025
M4: Implementation process maps ready	Feb 2025
M5: Local ethical committee applications submitted	Apr 2025
DLP1: Survey respondents selected	Start of survey distribution
M6: Data collection survey completed	Jun 2025
M7: Cases for interviews selected, interview guides translated	Jun 2025
DLP2: Respondents for interviews selected	1 month before completion interviews
M8: Interviews completed, transcribed and translated	Oct 2025
M9: Barriers and enablers identified	Nov 2025
M10: Draft report written and agreed upon by consortium partners	Dec 2025
D3: Study report	Dec 12, 2025
M11: Draft manuscript written and agreed upon by CPs	Feb 2026
D4: Draft manuscript	Mar 12, 2026

7. Rationale and background

Post-marketing risk minimisation measures (RMMs) are crucial to provide patients with safe and effective medicines. Controlled access programs (CAP) and controlled distribution systems (CDS) are considered the most impactful tools for risk mitigation available within the EU pharmacovigilance legislation and are used only in specific situations, where the risks to be minimised clearly outweigh the additional burden put on involved stakeholders [1,2].

A CDS refers to a series of measures implemented to ensure that all steps in a medicinal product's distribution chain are followed as specified, down to the very moment the medicinal product concerned is prescribed and/or dispensed to the patient. With a CAP, certain conditions must be met before a medicinal product can be prescribed or dispensed to a patient. For instance, a special test or examination, a vaccine, an informed consent form, or the product in question can only be prescribed or dispensed by specific healthcare providers who are registered and authorised to do so [3]. In effect, it may be difficult to distinguish between a CDS and a CAP and terminology is often used interchangeably. As such, we will henceforth refer to CAP/CDS as a summary term for risk minimisation control tools (i.e. a subcategory additional risk minimisation measures (aRMMs)). Given that a CAP/CDS may consist of multiple components (e.g. a) written confirmation of vaccination and b) annual reminders to vaccinate), the distinct components within a CAP/CDS have been termed *control elements* (or *CAP/CDS conditions*) in this study. The tools needed to achieve the control elements, i.e. those tools intended for application in a healthcare setting, have been termed risk minimisation *control tools* (or in short *control tools* within this study) in the latest revision of GVP XVI (rev 3) [4].

In practice, CAP/CDS are relatively rare. Out of the 476 products authorised in the EU in the period 2006-2017, only 7 had a CAP and 6 had a CDS at authorisation. Adding such aRMMs after authorisation is even rarer (0 and 2 instances, respectively), as is their discontinuation [5].

In general, there is significant complexity to implementing aRMMs as they seek to modify knowledge and behaviour of a diverse range of individuals (i.e., patients, consumers, caregivers, and healthcare professionals) and often require adapted communication, educational materials and articulation with and within structures and organisations (i.e., health authorities, academic research centres, healthcare professional associations, and patient organisations) [6].

In a recent study, marketing authorization holders (MAHs) expressed concerns about the national implementation of aRMMs. They highlighted challenges arising from discrepancies in regulatory requirements issued by national competent authorities within the European Union and the United Kingdom (UK), complicating the effective dissemination and implementation of aRMMs for medicines [7].

National competent authorities (NCAs) within the EU have also highlighted challenges concerning national implementation. These primarily involve the need for coordination and alignment among various agencies at national level to ensure the effective dissemination and implementation of aRMMs, while also accommodating the diverse legal frameworks and healthcare systems across Member States [8].

CAP/CDS are often combined with educational programs to make healthcare professionals and patients aware of the risks and measures in place to prevent them. The 'control' component, however, makes CAP/CDS unique and distinct from other aRMMs. The conditions and requirements for these control elements are agreed at EU level and outlined in the legally binding Annex II.D of the European Periodic Assessment Report. The further detailing and adaptation to national health systems takes place during the implementation phase at Member State level. The actual implemented processes in which the control element is enforced may therefore vary across Member States. For example, in one country, the pharmacists may be made responsible for collecting patients' informed consent forms prior to dispensing a product, whereas in another country, the prescriber is supposed to do so before issuing a prescription.

Currently, there is insufficient information available on how specific conditions and requirements of CAP/CDS are implemented, both on a regulatory level and subsequently in healthcare, across EU Member States. This is an important knowledge gap, as these measures are imposed as the most stringent tools to minimise the highest risks. We therefore aim to provide insights in the feasibility and extent of implementation at national level throughout selected EU Member States.

8. Research questions and objectives

The study aims to describe processes in and national experiences of eight European countries (Austria (AT), Greece (EL), Latvia (LV), Netherlands (NL), Portugal (PT), Slovenia (SI), Spain (ES), and Sweden (SE)) of implementing conditions of marketing authorisation on aRMMs with an emphasis on CAP/CDS using eight centrally authorised medicinal products as examples (see 9.1.1). There will be specific focus on the control elements of CAP/CDS (risk minimisation control tools, also referred to in this study protocol as control tools), which makes them unique and distinct from other aRMMs. The findings could be used to inform recommendations for strengthening the role of EMA and NCAs in this respect as well as to assess the feasibility and added value of CAP/CDS as regulatory instruments.

The key research questions in this context are:

- How are EU level recommendations on CAP/CDS implemented in Member States?
- What are enablers and barriers for successful implementation of CAP/CDS programs?

Specifically, the objectives of the study are to:

4. **Identify and describe the processes** for implementation of CAP/CDS at national level with focus on the control element:
    a. Roles and responsibilities of key bodies and organisations involved in the implementation of CAP/CDS conditions and requirements;
    b. Established processes and timelines for implementing CAP/CDS conditions and requirements;
5. **Describe and analyse stakeholder experience** with the control elements of CAP/CDS based on a purposive sample of eight products, by focusing on:
    a. Feasibility of implementing specific conditions and requirements, by country, by medicinal product, by type of condition or requirement, by type of stakeholder (e.g., patient, healthcare professional, MAH and regulator);
    b. Criteria for determining successful implementation of CAP/CDS, respectively;
    c. Perceived challenges for the healthcare system, by country, by medicinal product, by type of condition or requirement, by type of stakeholder (e.g., patient, healthcare professional, MAH and regulator);
6. **Identify key enablers and barriers** in implementing CAP/CDS conditions and requirements at national level, by country, by medicinal product, by type of condition or requirement, by type of stakeholder (e.g., patient, healthcare professional, MAH and regulator).

9. Research methods

To investigate national processes of CAP/CDS implementation, a mixed-methods approach will be used including document analysis, a quantitative analysis of cross-sectional survey data, as well as a qualitative analysis of stakeholders' perceptions obtained in semi-structured interviews. Such a mixed-methods approach offers the advantage of gaining a holistic picture by "obtaining additional meanings from interviews to the prevalence of traits in a population obtained from surveys, which add depth and breadth to the study" [9].

The methodology involves three components which will be divided over three work packages (WPs, see Figure 1 below):

WP1: Mapping the process of implementation
WP2: Understanding stakeholder experiences
- **2a**: Cross-sectional survey
- **2b**: Interviews with stakeholders

WP3: Identification of barriers and enablers at EU level

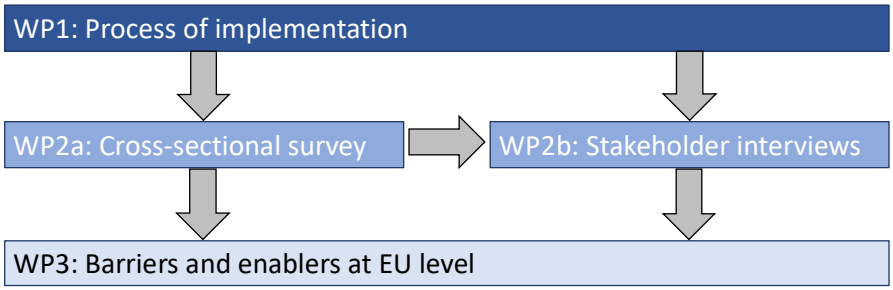

Figure 1 information flow between work packages

In the remainder of this protocol, we will distinguish different phases of the implementation pathway of RMMs: 1) regulatory implementation and 2) implementation of the CAP/CDS in healthcare [4]. To avoid ambiguity between these similarly worded phases, the latter will henceforth be referred to as 'integration in healthcare'. Dissemination of educational materials accompanying the CAP/CDS is considered a separate distinct phase in the implementation pathway, which is outside the scope of the current study.

Regulatory implementation refers to the process of translation of the CAP/CDS conditions (in Annex II.D of the EPAR) to the national healthcare systems and subsequent assessment and approval of the CAP/CDS by the national competent authorities. Integration in healthcare focuses on the use of the CAP/CDS in national healthcare systems and involves the practical operations of the different control tools by the involved stakeholders.

Table 1. Overview of included medicinal products and their availability in consortium countries.

Medicine name (INN)	Therapeutic area	Expected prescriber	Summary of key elements within CAP/CDS	Availability in consortium countries							
				AT	EL	LV	NL	PT	SI	ES	SE
Aspaveli (pegcetacoplan)	Hemoglobinuria, Paroxysmal	Haematologist	Written confirmation that patient has been vaccinated or receives additional antibiotics; annual reminders to vaccinate.	+	+	-	+	+	+	+	+
Fintepla (fenfluramine)	Epilepsies, Myoclonic	Paediatric neurologist	Controlled distribution to prevent off-label use; confirmation that prescribing physician has been informed of need for periodic cardiac monitoring.	+	+	-	+	+	+	+	+
Revlimid (lenalidomide)	Multiple Myeloma; Lymphoma, Mantle-Cell; Myelodysplastic Syndromes; Lymphoma, Follicular	Haematologist	Receipt of DHPC; Provision of Educational HCP Kit; Pregnancy Prevention Program, including risk awareness form, confirming patient is aware of potential serious side effects	+	+	+	+	+	+	+	+
Soliris (eculizumab)	Hemoglobinuria, Paroxysmal; Haemolytic uremic syndrome; myasthenia gravis; Neuromyelitis optica spectrum disorder	Haematologist, neurologist, nephrologist, paediatrician	Written confirmation that patient has been vaccinated or receives additional antibiotics; annual reminders to vaccinate.	+	+	+	+	+	+	+	+
Spravato (esketamine)	Depressive Disorder, Major	Psychiatrist	Product administration only under supervision of HCP in dedicated centre to prevent abuse; monitoring patient following administration.	+	+	+	+	+	+	+	+
Strimvelis*	Severe Combined Immunodeficiency (ADA-SCID)	Specialised paediatrician	Patient (or parent) has signed informed consent form, confirming they are aware of potential serious side effects; administration at specialised centre and by experienced physician.	+	+	-	+	-	-	+	+
Uptravi (selexipag)	Hypertension, Pulmonary	Cardiologist, pulmonologist	Identification and maintenance of a list of all prescribers; distribution of kits to identified prescribers to minimise risks of medication error; tracking of receipt of kits by prescribers.	+	+	+	+	+	+	+	+
Yescarta (axicabtagene ciloleucel)	Lymphoma, Follicular; Lymphoma, Large B-Cell, Diffuse, Primary mediastinal, High-grade	Haematologist	Ensuring immediate, on-site access to tocilizumab per patient prior to infusion; ensuring HCPs involved in treatment have completed the educational programme; ensuring HCPs are aware of need for tumour sample collection and testing following development of secondary malignancy of T cell origin.	+	+	-	+	+	-	+	+

*(autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence).

Note: the table provides a non-exhaustive overview of possible prescribers and should not be considered a restrictive list.

Note: A complete overview of control elements included in this study can be found in Appendix X.

AT = Austria, EL = Greece, HCP = healthcare professional, LV = Latvia, NL = Netherlands, PT = Portugal, SI = Slovenia, ES = Spain, SE = Sweden, + = available, - = not available.

9.1. Study design

9.1.1 WP1

To gain an understanding of the processes involved in the implementation of CAP/CDS, we will perform two mapping exercises; a) the first will provide a general overview of the implementation pathway and b) the second will give specific insight into the implementation pathway for each of the eight selected products (see Table 1).

a. *Overall mapping*: We will undertake a mapping of national implementation processes of CAP/CDS in eight selected European countries. Specifically, the mapping exercise will aim to provide a theoretical, structured overview of how the implementation of CAP/CDS is expected to take place in each country. This description is intended to provide a general overview of the national process of how conditions and requirements of a CAP/CDS are converted into national regulations and guidelines.

b. *Product-specific mapping*: The aim of this mapping exercise is to describe the eight national product-specific characteristics and implementation processes, and how they relate to the theoretical process as described under a).

The deliverable of this WP will consist of eight country-specific flowcharts detailing the national CAP/CDS implementation processes. The product-specific maps will be used to tailor the cross-sectional surveys and interviews in WP 2.

9.1.2 WP2a

To gain an understanding of the real-world national implementation of CAP/CDS processes, a cross-sectional survey among key stakeholders is planned. The aim of the survey is to characterize national implementation of the CAP/CDS conditions for the eight selected medicinal products across the eight participating EU countries.

A web-based cross-sectional survey for key stakeholders – not including patients and/or caregivers – will be used to retrieve information regarding the national implementation of CAP/CDS conditions for the eight medicinal products in the eight participating countries. An online methodology has a number of associated advantages, including covering a wide geographical spread and flexibility for respondents to complete the survey at a convenient time and allowing respondents to be completely honest without feeling like they are being questioned or judged by an interviewer.

The survey will focus on the control elements of the CAP/CDS as specified in the Annex II.D conditions for each of the eight medicinal products. A complete overview of control elements of CAP/CDS can be found in Appendix X. The survey will be divided into two parts: the first part will focus on the regulatory implementation of CAP/CDS conditions and the second part will focus on integration in healthcare (Figure 2).

The web-based survey will firstly contain identifying questions to characterize to which stakeholder group the respondent belongs. It will be adaptable to the respondent's role. This will be achieved by first questioning 1) whether and for which medicinal product(s) the respondent was involved in the regulatory implementation of the CAP/CDS conditions, and 2) whether and for which medicinal product(s) and their CAP/CDS the respondent had worked with or experience using in healthcare. Only the questions specific to context and

medicinal products as indicated by the respondent will appear to the respondent in our web-based survey, in order to keep the survey concise and user-friendly.

Figure 2 Overview of the implementation pathway of risk minimisation measures, including CAP/CDS conditions. This pathway distinguishes between 1) regulatory implementation of CAP/CDS conditions, 2) dissemination, and 3) integration in healthcare. The survey will focus on phase 1) regulatory implementation and 3) integration in healthcare. Within the latter phase, further dissemination [4] of the materials of the educational/safety advice tools or other materials related to the CAP/CDS will generally not be considered.

As no validated instruments exist, the web-based survey will be drafted based on expert knowledge, including information from WP1, and common principles extracted from implementation science frameworks [10-14]. The survey will have a predominantly quantitative set-up using 4-point Likert scale questions and will consist of closed-ended questions to allow for structured comparisons. The topics covered for each of the relevant medicinal product will include:

- the experiences and perceptions as to the ease of regulatory implementation of the control elements;
- barriers and facilitators related to the regulatory implementation of the control elements;
- the experiences and perceptions as to the integration and use of the control elements in healthcare;
- barriers and facilitators related to the integration and use of the control elements in healthcare.

Besides these closed-ended questions, the survey will also contain a single open-ended question for each medicinal product, allowing respondents to share further details on barriers and facilitators in the regulatory implementation of the control elements and integration of control elements in healthcare.

A tracking table of how the response options for surveyed barriers and enablers relate to the domains of the implementation science frameworks is available in Appendix XI.

9.1.3 WP2b

More insight into key stakeholders' perceptions – including patients and/or caregivers – about the facilitators and barriers for national implementation of CAP/CDS will be gained through semi-structured (telephone or online) interviews. The interviews will be conducted in all eight countries (see section 9.2).

The interviews with stakeholders will provide additional in-depth information about barriers and facilitators experienced by stakeholders both in the regulatory implementation phase and when integrating CAP/CDS into healthcare. When available, the preliminary results from the survey will be used to further develop the interview guide for the semi-structured interviews, i.e., the main version in English. The interview guide will be developed and reviewed by the coordination team and national teams. The interviews will

be held locally by national teams in their native language. Conducting interviews at national level gives interviewees the possibility to talk more openly in their own language and share information more easily.

The interview guide will cover topics such as: 1) reasons why implementing the CAP/CDS was challenging or not, 2) criteria and rationale behind enablers of implementation, and 3) the role of each stakeholder in the process and respective responsibilities towards challenges/enablers. One general interview guide will be prepared for each product for all stakeholders, with options to include more or less detail on specific CAP/CDS elements per stakeholder. The interview guide will contain some baseline questions about the stakeholder and then enquire about the stakeholder's experience with CAP/CDS followed by specific questions about the study products, and specific control elements. For specific stakeholders (e.g. patients), general experience with CAP/CDS may not be applicable. For this group it is likely that only product specific questions will be used.

9.1.4 WP3

To gain an in-depth understanding of barriers and enablers that contribute to expedient and viable implementation of CAP/CDS conditions and requirements identified in WPs 1, 2a and 2b, a structured overview will be presented across all included countries, as well as per country, per medicinal product, by type of CAP/CDS condition and per type of stakeholder group.

This will be done by tabulating of results and presenting data in tables, graphs and/or figures, as appropriate. The aim will be to draw conclusions on the key success factors as well as the key hurdles at national level for implementing CAP/CDS. To understand if there are product-specific or stakeholder-specific hurdles or success factors, separate analyses will be performed that will describe differences per medicinal product, per type of stakeholder and by control element. However, such a nuanced sub-analysis can only take place if the data collected allows it.

9.2. Setting

The enablers and barriers in the implementation of CAP/CDS will be studied in parallel in eight EU Member States. These include Austria (8.9m inhabitants), Greece (10.6m inhabitants), Latvia (1.9m inhabitants), the Netherlands (17.5m inhabitants), Portugal (10.3m inhabitants), Slovenia (2.1m inhabitants), Spain (47.4m inhabitants) and Sweden (10.4m inhabitants). Together these countries include an active population of around 109 million European citizens, distributed across the four different geographic regions (North, East, West, South) of the European Union.

The eight countries represent a mix of health systems, including social health insurance-based and national health systems, with variation in the roles and responsibilities of national, regional, and local stakeholders. Collecting data on the implementation of CAP/CDS in such a diverse group of countries will facilitate the provision of recommendations on CAP/CDS that are applicable throughout the EU.

9.2.1 WP1

The process mapping will be based on desk review of key national regulatory documents and public statements on regulatory action which specify timelines and processes of the CAP/CDS implementation. In a final step, 'verification' of the flowcharts is planned with

NCAs and/or MAHs to verify the correctness of the mapping per product (for details on recruitment see 9.2.2. below). This may be through informal, unstructured interviews or through written feedback. Although this verification step is intended to be held across all participating countries, its full realization will depend on stakeholders' willingness to participate.

9.2.2 WP2a

The target population of the survey includes national competent authorities, relevant individual physicians and pharmacists (potentially through their respective associations), and MAHs. Additional key stakeholders may be added based on the results of WP1. Patients and/or caregivers will not be targeted for the survey, but will be included in the interviews that follow (see 9.2.3).

There will be targeted recruitment of stakeholders to include those with relevant experience with the implementation of CAP/CDS and (one of) the eight products (or relevant generics/biosimilars). In general, we will approach all NCAs, all MAHs (including generic/biosimilar producers when applicable), individual HCPs through centres of expertise identified in WP1 or alternatively through relevant physician associations, and individual pharmacists through centres of expertise identified in WP1 or alternatively through the relevant pharmacist associations. The initial points of contact will be encouraged to forward the survey to colleagues who have experience with the product, to reach all key stakeholders and possibly broaden the target group. As such, the survey may be filled out by multiple respondents within the same organisation and/or stakeholder group. If recruitment through known contacts and further snowballing is incomplete, recruitment will be completed through contact information on public websites (and additional snowballing).

All stakeholders identified before first distribution of the survey in a respective country will be included in the survey (DLP1). The survey will not be reopened or redistributed when new stakeholders are identified in the (interim) analyses of WP2a. New stakeholders can only be incorporated in future study elements (i.e. WP2b interviews).

For a participant to be eligible for inclusion, the respondent needs to:

- belong to one of our previously defined stakeholder groups (NCA, MAH, physician, pharmacist) or in an otherwise identified group in WP1;
- have experience with at least one of the eight medicinal products (or generic/biosimilar when applicable) either relating to regulatory implementation of CAP/CDS conditions or integration and use of control elements in healthcare.

For physicians/pharmacists, experience is defined as having prescribed/dispensed the respective product in the last two years (orphan products), or in the last year only (non-orphan products).

Country-specific recruitment for the survey will take place as indicated in Appendix II, and may be expanded when new stakeholders are identified (see above). In short, country specific recruitment strategies will be tracked by mapping every stakeholder group of interest for each product in a respective country, whether they are relevant for the survey (WP2a) and/or the interviews (WP2b), which organization will be approached, the strategy to recruit (e.g. known personal contact, through general company email, etc), details of recruitment (date, name, reply, etc) and any comments.

9.2.3 WP2b

Based on the data collected in WP1 and WP2a, noteworthy cases will be identified. Noteworthy cases may stand out due to their ease or difficulty of implementation, heterogeneity of experiences across countries, or products otherwise worthy of a more in-depth analysis. The main aim is to select products with different degrees of ease of implementations between countries. This will allow us to reflect on the potential effect of differences in healthcare systems between countries on the implementation processes. Additionally, we aim to select a range of products for the interviews with different types of control tools. This will allow us to reflect on the ease of implementation of different types of control elements. For selection of noteworthy cases, we will apply a 3 step-approach:

1) Identification of potential noteworthy cases: results from the survey (WP2a) will be used to signal potential noteworthy cases. For each product and control tool, the average score on the Likert scale will be calculated and the distribution over the different categories will be displayed. Aggregation will be done to identify patterns across stakeholder types, countries, control tool types, and implementation phases. As a starting point to identify potential noteworthy cases, we will select: a) the questions with the 10% highest and 10% lowest average scores, b) consistent challenges (cases with consistent high scores[1] across all subgroups), c) consistent enablers (cases with consistent low scores[1] across subgroups) and d) outliers (cases that stand out in a minority of the subgroups). In addition, cases that stand out for other reasons after inspection of survey results may be added to the selection manually. Responses from open survey questions and knowledge from WP1 will also be used to inform this step.
2) Prioritisation and deduplication: all potential noteworthy cases from step 1 will be assigned a priority score, which will be based on factors such as seriousness of potential health consequences of a failure in the control element, population size at risk, etc. At this step the possibilities for interviews of one case to be combined with another will also be signalled (deduplication).
3) Final selection: a consensus meeting will be held with the leads at all participating consortium centres to select most suitable products per country based on the prioritized shortlist from step 2. This selection will take into account factors such as country-specific capacity, geographical spread of availability of products, possibilities to interview stakeholders about multiple products, etc.

The interviews will be held with prescribers, pharmacists, patients/caregivers, NCAs, MAHs and other relevant stakeholders who have experience with the selected products. The number of NCAs involved in the implementation pathway may vary by country, as well as the number of available patients or HCPs who have experience with the products. The mapping conducted in WP1 and WP2a will aid in clarifying which (types of) stakeholders are relevant for each CAP/CDS and/or product. Based on those results, the applicable stakeholder types will be listed for each product, at national level. The aim is to interview at least one[2] member from each relevant stakeholder group per noteworthy case in the selected country.

[1] The following scoring system is envisioned: very difficult = 4, difficult = 3, easy = 2, very easy = 1.
[2] For non-orphan products, three HCPs will be recruited per product.

Recruitment strategies for WP2b will be similar to those described for WP2a in section 9.2.2. For patients and caregivers, we plan to contact relevant disease-specific patient associations corresponding to the therapeutic indications of the medications under study to identify and invite individuals who have experience with the products and/or recruit patients via HCP at specialised point of care centres identified in WP1 and WP2a. Given the privacy and ethical implications, patient organizations and HCPs at specialised treatment centres will be requested to reach out to individual patients/caregivers on our behalf. An information letter which includes more details about the study and its goals, together with an permission form, will be attached to the invitation for the interview. Permission to participate and make recordings is sought in writing (signature), that is again confirmed at the beginning of the interview and recorded. As such, only with patients'/caregivers' explicit consent, contact details will be shared with the research team.

We will include all relevant stakeholders for a selected noteworthy case in the interviews, provided that they are identified not later than 1 month before all interviews need to be completed in a respective country (DLP2). As a result, additional stakeholders identified from the survey (WP2a) can be included in the interviews, or when identified during early interviews, when known before DLP2.

9.2.4 WP3

WP3 will synthesize the data collected in WP1, WP2a and WP2b.

9.3. Variables

9.3.1 WP1

The overall country flowchart will include a description of the relevant national bodies and organisations involved in the implementation process, including a description of their roles and responsibilities in the process (regional differences within a country will be described, when relevant), as well as key national regulatory documents and public statements on regulatory action which specify timelines and processes of the implementation (see Appendix IV).

The product-specific mapping (see Appendix V) will focus on details of the eight selected products and their alignment with the overall process by gathering insight on:

- the local market availability of the product and relevant generics/biosimilars (see Table 1), and – if not locally available – it will be investigated whether a scheme for obtaining the product from another Member State would make the product still available for a patient upon prescription;
- details of the CAP/CDS conditions through a description and a link to national documents;
- details on the stakeholders involved in the regulatory implementation and integration in healthcare;
- organisations responsible for enforcing the control elements of the CAP/CDS (e.g. legal enforcement towards MAHs and/or HCPs);
- incentives to comply with the regulation;
- the evaluation process to ensure CAP/CDS conditions have been implemented.

9.3.2 WP2a

In the web-based survey, variables of interest will include (see draft survey questions in Appendix I):

- The respondent's stakeholder group, including years of experience in such role;
- Other stakeholder groups that respondent has engaged with during the implementation of CAP/CDS conditions;
- The respondent's involvement in regulatory implementation of CAP/CDS conditions and/or integration in healthcare per medicinal product;
- Respondent's experience with the ease of regulatory implementation and/or integration in healthcare of the control elements (surveyed per control element per medicinal product; and overall per medicinal product);
- Respondent's view on barriers experienced during the regulatory implementation and/or integration in healthcare of the control elements (surveyed per medicinal product);
- Respondent's view on general facilitators experienced during the regulatory implementation and/or integration in healthcare of the control elements (surveyed per medicinal product).

9.3.3 WP2b

A pointer towards the interview guide is provided in Appendix VI. In the interviews, variables of interest will include:

<u>Section A: the stakeholder</u>

- Stakeholder type, position held;
- Experience with the product(s);
- Role in the implementation process;
- General experience with CAP/CDS (only for those experienced with more than one CAP/CDS product);

<u>Section B: product specific experience</u>

- Experience with implementation of CAP/CDS for the product;
- Experience with implementation of the specific control elements of the product;
- Product & control element-specific barriers;
- Product & control element-specific facilitators;

<u>Section C: general remarks</u>

- Any remaining remarks the interviewee wants to share on the topic.

9.3.4 WP3

The main outcome of this work package will be a structured overview of barriers and enablers for a successful implementation pathway of CAP/CDS. This will be based on descriptive data collected in WP1, WP2a and WP2b. Relevant variables will include countries, products, stakeholders and type of control tools.

9.4. Data sources

9.4.1 WP1

The mapping will be based on desk review of publicly available data sources. Additional data may be gathered through (informal) consultation within the researchers' professional networks.

9.4.2 WP2a

A template survey will be drafted in English by the UU team and reviewed by the consortium. This template will be translated by the National Teams to their local language. The National Teams will be responsible for translating the final survey through the translation protocol as provided in Appendix III. The same template survey will be used in all countries, meaning no country-specific questions are added to guarantee stringent cross-country comparability.

Prior to launching the survey, the web-based survey will be pilot tested in the Netherlands. The primary purpose of our pilot is to test the study design and contents of our proposed survey; i.e. whether participants are able to understand and complete the questions. The content of the questionnaire is developed in a manner to ensure content validity at the EU level. We do not expect the questionnaire's content to be interpreted differently across different countries/languages, as it is later adapted to reflect the country's language and situation. Furthermore, the validity of translations across all countries is ensured through back-to-back translations conducted by the panel of researchers involved at the national level. A single pilot test should suffice to uncover any weakness in the study's design, in line with a recently conducted study[3] on risk awareness and adherence across six EU countries.

In the pilot, two respondents similar to the target population will be asked to complete the survey. Additionally, they will be requested to provide feedback on the clarity, appropriateness and feasibility of the questions, as well as on the clarity of the subject matter, purpose and context of the study. The pilot may lead to improvements to the template survey.

Respondents should at least complete the identifying questions (see survey in Appendix I: questions 1-3) in order for their survey responses to be valid. Generally, respondents should complete all elements of a product-specific question in order for this question to be valid within the survey, i.e., the questions related to the ease of regulatory implementation or integration in healthcare, perceived barriers, and perceived facilitators. An exception to this is the first product-specific question, which is assessed per control element as well as for the overall program for each medicinal product. This question also remains valid if only scored for the overall program, without scoring individual control elements within the program. The open-ended questions are optional.

9.4.3 WP2b

In WP2b data will be obtained through primary data collection, including semi-structured interviews with healthcare professionals and other stakeholders.

[3] Impact of EU label changes and regulatory communication on SARS-CoV-2 adenovirus vector vaccines in context of thrombosis with thrombocytopenia syndrome (TTS): risk awareness and adherence (RiskAwareTTS). Available from https://catalogues.ema.europa.eu/node/3434/administrative-details.

The interview guide will be pilot tested in one country (NL) due to the study's tight timeline. The content of the guide will be developed in a manner to ensure content validity at EU level. We do not expect the guide's content to be interpreted differently across different countries/languages, as it will be adapted later to reflect the country's situation. Furthermore, the validity of translations of the guide across the 8 countries is ensured through back-to-back translations conducted by the panel of researchers involved at the national level. Bearing these aspects in mind, we consider that a single pilot testing should suffice to uncover any weakness in the design. Extending the pilot testing to other countries would result in an extension of the study timeline for another two months, as it would demand additional translations in all participating countries. This would also require additional funding to cover extra resources.

Pilot participants will be asked to comment on the following issues:

- Clarity of subject matter, purpose and context of the study;
- Readability of the questions/ language use;
- Pathway for the questions;
- Likelihood of odd or sensitive topics;
- Completeness of interview questions;
- Length of interview;
- Additional comments.

The comments received in the pilot will be incorporated in an updated version of the interview guide, which will then be shared with the consortium. Once the English version of the final guide is agreed upon by the consortium, national teams will adapt it to their own settings and translate according to protocol (Appendix III). At that stage, cross-checks will be done with WP1 and WP2a (interim) results to ensure that interview guides are aligned with the actual country-specific processes for the control elements of each CAP/CDS.

9.4.4 WP3

N/A.

9.5. Study size

9.5.1 WP1

For this exploratory, qualitative mapping exercise, no definitive sample size can be determined beforehand. For all 8 products of interest, mapping exercises will be initiated in each of the 8 participating countries where the product is available. In addition, a general mapping exercise of country specific processes is performed for each of the 8 countries.

9.5.2 WP2a

In this explorative survey, we anticipate to send out 12-20 surveys per country:

- 7 MAHs (one company is the MAH for two medicinal products);
- (One or) multiple respondents per NCA;
- At least one physician for each of the products[2];
- One or multiple pharmacists[2].

In countries where generics/biosimilars are available, additional surveys will be implemented as needed.

The actual number may vary per country, depending on which stakeholders are involved in the regulatory implementation of control elements (e.g., multiple NCAs per country, since different assessors were likely involved with different products), HCPs involved in the use of CAP/CDS in healthcare (allowing to survey the same stakeholder group about multiple products), and local availability of each product (i.e., some medicinal products are not marketed in some countries). The number will also depend on willingness of participants, particularly for the products indicated for very rare diseases with a single centre of expertise and a handful of patients in a country.

9.5.3 WP2b

We foresee 8-24 interviews to be held in each country. We expect each selected noteworthy case to have a minimum of 4 relevant stakeholders (patient or caregiver, physician, MAH, NCA), which can be up to 12 if a product has multiple indications, generic producers, or other stakeholders are involved (e.g. pharmacists, wholesalers), resulting in 8-24 interviews per country for the scenario where 2 selected cases per country are eligible. Other stakeholders may also be added based on WP1 and WP2a. Similar to WP2a, the actual number may vary per country, depending on which stakeholders are involved in the national implementation of control elements (e.g., multiple NCAs per country), HCPs involved in the use of CAP/CDS in clinical practice (allowing to survey the same stakeholder group about multiple products), and local availability of each product (i.e., some medicinal products are not marketed in some countries). The number will also depend on willingness of participants, particularly for the products indicated for very rare diseases with a single centre of expertise and a handful of patients in a country.

9.5.4 WP3

The population covered in the analyses on barriers and enablers in WP 3 includes representatives from 8 EU Member States, distributed across the four different geographic regions (North, East, West, South) of the European Union.

9.6. Data management

All pseudonymized data from WP2a (survey) will be hosted on a secure server (YODA) at Utrecht University, the Netherlands, and will be kept for 10 years. Interview data (WP2b) will be stored locally in the respective countries in line with national regulations. Dutch raw interview data (WP2b) will be stored within RIVM servers, secured/protected in accordance with RIVM standard operation procedures for data protection and the GDPR, and archived for 10 years. Raw data from other countries will be stored locally in each country (as mentioned above) and only pseudonymized summaries of the results will be stored on the servers from UU/RIVM.

9.6.1 WP1

Based on the responses as provided to the non-urgent information (NUI) request sent by EMA to all NCAs in early 2024, the UU team has developed an extraction template (e.g. in Excel) with uniform variables to be filled out by the National Teams (Appendix IV). The UU

team has developed a second generic data extraction template (see Appendix V) to collect basic information on each of the eight products. In addition, each national team will make use of their extensive knowledge of the key stakeholders and the set-up of the national health care system. Information will be documented in English.

9.6.2 WP2a

For WP2a, the surveys will be sent out using Qualtrics in all eight countries. Data from the surveys will be analysed using IBM SPSS Statistics Version 28 (IBM Corp., Armonk, N.Y., USA).

9.6.3 WP2b

For WP 2b, key informants will be asked about specific experiences with each product. Interview data will either be transcribed manually by the researcher, by a professional transcriptionist, or through AI transcribing software (if available in the native language). Processing of personal data will comply with the EU data protection legislation and in particular Regulation EU 679/2016 on General Data Protection. Each national team will hold a file containing the personal data (name, contact details and participant code).

The RIVM team has developed an extraction template (in Excel) with uniform variables to be filled out by the National Teams (Appendix VII).

Only duly anonymized data will be shared with the coordinating team. When anonymization is challenging due to limited number of persons pertaining to a key stakeholder role, no raw data from the interviews will be shared with the coordinating team. National teams will also be responsible for obtaining, compiling and archiving participants' permission forms. The coordinating team will provide a template for an permission form in English for interviewees.

9.6.4 WP3

N/A.

9.7. Data analysis

9.7.1 WP1

The processes of implementation will be visualized in eight country flowcharts, and further product-specific flowcharts, when appropriate.

9.7.2 WP2a

We will employ descriptive statistics on pseudonymized data of the survey. Data will be pseudonymized by assigning a unique identifier to the respondents and keeping a separate file with the pseudonymization key. Data analyses will be performed by evaluating each survey question individually using frequencies and proportions. Data will be analysed using IBM SPSS Statistics Version 28 (IBM Corp., Armonk, N.Y., USA).

All descriptive analyses will be conducted for each of the categories of control elements separately, aggregated per country and for all stakeholder groups. An overview of the

six control element categories are depicted in Table 2. A complete overview of the control elements of the CAP/CDS of study drugs and which control tools are applied can be found in Appendix X.

The information received as free text (from open-ended questions in the surveys) will be extracted by each National Team and translated to English. This will enable additional deductive and inductive content analysis. Two UU researcher will code together the first ten free text responses and prepare a joint agreement/draft a preliminary coding tree. Subsequently, for each country, one researcher will read through all responses and will organise them in several main categories and subcategories. Doubts will be discussed with a second researcher and arbitrated by a third researcher from the country in question for context, as needed. Additionally, two open text responses per medicinal product will be independently coded by a second researcher as a cross-check.

Table 2. Control tool categories.

Control tool category	Subcategories identified for the eight medicinal products
Healthcare professional qualification	Prescription limited to pre-registered physicians after receipt of prescriber kit/receipt of or completed educational materials/program
Healthcare facility accreditation	Treatment/administration at specialized/dedicated centre (including access to certain equipment/treatment of ADRs)
Traceability system (from manufacturing site till distribution/administration)	-
System for documented exchange of patient information between HCP	-
Check of patient certificates of medical interventions	Need for vaccination (or other medication) prior to administration; Negative pregnancy test as part of Pregnancy prevention program;
Other	Prevent off-label use, by written confirmation of indication; Administration under HCP supervision/observation after administration; Patient informed consent form. Signing of risk awareness for as part of a Pregnancy prevention program; Annual reminders for revaccination/treatment or other proof of distribution of educational materials (Informed on need to) Perform specified medical test/monitoring during/after treatment;

Control tool categories are based on the control tools provided in the GVP Module XVI (Rev 3) [4]. Note that no control tools related to 'Traceability system' and 'System for documented exchange of patient information' were identified for the eight medicinal products.

9.7.3 WP2b

Audio recordings will be transcribed verbatim. Each consortium member will be responsible for translating the interview guide, conducting the interviews, transcribing the interviews, and documenting the responses in the extraction template, including translating quotes where relevant. An extraction template will be developed by the RIVM to collect all relevant data from the interviews in a harmonized way.

The analysis of the semi-structured interviews in WP2b involves a content analysis based on a close line-by-line reading of the responses and developing a conceptual coding scheme (standardized coding framework) based on the major themes in the interview guide and common principles extracted from implementation science frameworks. Transcripts will be categorized by two coders in their native language following the common data extraction sheet developed by RIVM. However, before national analysis takes place, all coders from all countries will evaluate the categories used and agree to a single set of categories and codes. Analysis within WP2b will be performed nationally.

In a later stage, researchers meet (online) again to identify illustrative quotes, which have been translated by national teams as needed. This approach ensures that data is analysed as long as possible within the local context and language, ensuring accuracy of the findings.

9.7.4 WP3

Data collected in WP1, WP2a and WP2b will be integrated and presented as tables, graphs and/or figures, as appropriate. To categorise results, the coding scheme developed in WP2b using major themes in the interview guide and common principles extracted from implementation science frameworks will be used. Previously, implementation science frameworks, such as RE-AIM, PRECEDE-PROCEED, and CIFR have been used to study feasibility of risk mitigation strategies in the USA [15,16]. Furthermore, the International Risk Governance Framework could provide insights into the complex interactions and collaborations among stakeholders involved in implementing aRMMs in Europe. It would highlight the interconnectedness of MAHs, regulatory authorities, healthcare providers, and patients, and how they negotiate responsibilities and decisions in managing risks [17].

All analyses on key barriers and facilitators will be descriptive as the interviews and surveys will be the primary sources of information.

9.8. Quality control

9.8.1 General approach to quality management and control

The coordinator of the project consortium (UU) will be in charge of the overall project's quality management and control. To proof UU's experience in and its high standards of quality management and control, we are describing UU's quality management system and cite key facts.

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

Proof of UU's quality of research: In 2017 (evaluation period 2010-2015), the research quality of the Utrecht Institute for Pharmaceutical Sciences (UIPS) which includes the division of Pharmacoepidemiology & Clinical Pharmacology was assessed by an independent international peer review committee according to the Standard Evaluation Protocol 2015-2021 (SEP) for Research Assessment in the Netherlands. The overall conclusion of the committee was that the division was one of the top ten if not the top five worldwide and that excellent scientific work was being done, grounded in real-world problems and with a notable impact on the regulatory world, particularly in Europe. The scores received were all excellent for the Quality, Relevance to Society and Viability criteria. This report is available upon request.

A number of studies conducted by the EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network and the Utrecht University research group are registered in the HMA-EMA Catalogue of Real World Data Studies (e.g. EUPAS32405, EUPAS32408, EUPAS2382, EUPAS7730, EUPAS39757, EUPAS5383, EUPAS2561, EUPAS44970, EUPAS42504, EUPAS29798, EUPAS42467) and several have been awarded with the ENCePP Study Seal (e.g. EUPAS16014, EUPAS31001).

In addition, all consortium members will maintain several overarching quality assurance measures throughout the project. We will use existing guidelines for reporting of the results: QOREC will be used to report on qualitative findings and RIMES-SE to report the findings from implementation study analyses related to aRMM evaluation studies. Additionally, approaches to data collection and analysis will be shared among all members. Deliverables are peer-reviewed by an advisor (at least one member of the consortium that is not leading nor actively participating in the study).

A declaration of competing interests will be required from all those acting as principal investigators or co-investigators. These will be further presented to the Steering Committee who will then assess and act upon any potential conflict of interest. In addition, in line with ENCePP standards (European Medicines Agency 2018) we registered our study in the HMA-EMA catalogue of Real World Data Studies under number EUPAS1000000313.

9.8.2 Specific aspects of quality management and control

Tailored quality control: The coordinating team will rely on a peer-review model of consultation to inform and direct the study deliverables, using the timeline above to monitor and benchmark progress by which outcomes are assessed. In order to establish a quality control system specific to this study, we have identified key milestones (see section 6), which will attest to the efficient roll-out and continuity of the service. For the main documents of this study, an internal peer-review process (using version control on SharePoint) is foreseen, meaning that all consortium members are invited to review the data extraction templates, survey questionnaire, interview guide and the final reports as well as the manuscript.

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

Specific Task	**Standard Verifiable Indicators**
Kick-off meeting	Agenda Meeting Minutes

	Action Points Agreed Timeline
Development of template for mapping exercise (WP 1)	Country-specific flowcharts of processes
Development of product-specific data extraction template (WP 1)	Product-specific data extraction sheet
Development of online questionnaire (WP2a)	Online questionnaire
Development and pilot testing of interview guide (WP2b)	Pilot interview guide and final version of interview guide (national versions)
Recruitment of key informants	Number of stakeholders recruited per country
Drafting preliminary report	Preliminary Report
Review of draft report	Responses received
Drafting manuscript	First draft manuscript
Manuscript review	Responses received

Risk mitigation plan: to prevent the potential risk of delayed delivery or failure of the project, we are laying out a plan to mitigate these risks:

Potential risk	**Mitigation strategy**
Low response rate in the survey *(relevant for WP 2a*)	All our consortium members are well established researchers in their countries who have good ties with their national experts and stakeholders. With this network and the high relevance of EMA's request, we believe to reach a sufficiently high response rate. In addition, we will apply a tight schedule with frequent reminders and follow-up emails to reach a high response rate.
Loss of a consortium partner / coordinator *(relevant for all WP)*	We have set-up the project in a way that we have back-ups for all partners. The majority of partners have more than one expert working on this project. In addition, UU is the coordinator but we also designated RIVM as the co-coordinator to have an additional back-up and for quality assurance purposes.
Depletion of interviewee pool	Given that the pharmaceutical products subject to study are usually prescribed and administered in highly specialized care, we expect the pool of interviewees to be very small, especially in smaller countries. Although mitigation is difficult, we will be transparent in all of our recruitment efforts.
Delays in reviews of deliverables by EMA or Pharmacovigilance Risk Assessment Committee (PRAC)	In some cases, reviews by EMA or PRAC might not be delivered in line with the timing, as envisioned in the Gannt chart. This has an implication on whether the research team can

	adhere to the agreed deadlines. In this case, UU/RIVM will immediately communicate with EMA to request for an extension of the deadline of that deliverable due to external circumstances, but within the end date of the framework contract.
Late delivery of country-specific results *(relevant for all WPs)*	To avoid delays in country-specific results, we will work closely with the national teams to anticipate any delays. When a delay is foreseen we will first inform EMA, and secondly the UU/RIVM team will support the national team that experiences delays in which ever way is needed.

9.9. Limitations of the research methods

The first limitation is linked to the generalizability of the results of this study. This study aims to analyse specifications of eight medicinal products; hence the description of each case will be different and cannot be extrapolated to other CAP/CDS products. Although this project includes eight countries from various geographical regions in Europe, generalizability is not given due to the heterogeneity of European health care systems. To address this inherent limitation of case-study research, we selected 8 countries that represent different types of health care systems.

The second limitation is linked to a general methodological concern in qualitative data collection, which includes a lack of generalizability, contamination by researcher values, lack of rigid causality, and lack of precision in comparisons among groups [18], especially if national teams work in their own languages when collecting and analysing contextual data. To mitigate this concern, the researchers will incorporate methodological strategies to ensure the trustworthiness of the findings including the following points:

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

- Using mixed methods, whereby different methods and perspectives help produce a more comprehensive set of findings [19].
- The survey and interview will draw respondents from the same pool. These pools may be limited as the use of the CAP/CDS products may be scarce. There is a risk of depletion of respondents. The national teams will reduce bias by respondent validation, constant comparisons across participant accounts, representing deviant cases and outliers, independent analysis of the data by other researchers and comparison with the other national teams' researchers to the extent possible [20]. Meetings of national teams will be held regularly to align data collection, data analysis, and reporting of results.

9.9.1 WP1

For the process mapping, we anticipate that it might be difficult to obtain all relevant information given the lack of (publicly) available data on this topic. However, should the flowcharts not be fully completed based on desk review alone, we anticipate that the flowcharts could be finalized at later stage based on information obtained during WP2a and WP2b. Additionally, it might be challenging to conduct informal verification with the NCAs/MAHs. If verification for all flowcharts/products is not feasible due to national regulations, unwillingness to participate or any other factors, this step might be combined with the formal interviews planned in WP2b, when possible.

9.9.2 WP2a

For the survey, we have to acknowledge that there might be recall bias, particularly regarding regulatory implementation as we will include some products which were authorised more than a decade ago. Furthermore, non-responder bias inherent to the survey design can take place, whereby non-responders might differ substantially from the responders as to their views on the CAP/CDS implementation. An overview of biases that may occur and relevant mitigation strategies is provided in Appendix VIII.

9.9.3 WP2b

Similarly, recall and non-responder bias may also apply to this WP. Additionally, the exact selection criteria for the noteworthy cases cannot be established a priori and will depend on the information collected in WPs 1 and 2a. An overview of biases that may occur and relevant mitigation strategies is provided in Appendix VIII.

9.9.4 WP3

The identification of barriers and incentives is largely dependent on the data collected in WP1 and WP2. In that sense, given that the products being the object of study are not very widely used, the possibility of having to rely on a limited number of likely stakeholders and thus limited input and data collected does exist. Likewise, given the potentially large differences and experiences between products and countries, it may prove challenging to extract learnings about barriers and enablers that are widely generalizable.

9.10. Ethical aspects

The work performed in WPs 2a and 2b will need approval of local ethical committees in some of the participating countries or reference to approval in one of the other participating countries. Preparation of applications for ethical approval in each country will be initiated as soon as possible in the project, but this will be dependent on the approval of the study protocol by EMA. To facilitate faster submission for ethical approval the documents will be submitted in English when possible (to avoid delays due to translations). This allows for 2-6 months processing time at the national level. To deal with eventual delays, two extra months have been planned to accommodate extra time needed to conduct interviews (see Appendix IX).

10. Protection of human subjects

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

Throughout the project, results will be shared with EMA (see section 12). In the final report (deliverable 3), country specific results are to be reported to EMA, in line with the technical specifications. All the information will be submitted without any personal data for all stakeholders. However, as some products are used in a very limited number of patients and in specific settings or locations, both patients and physicians could be identifiable when reported on a country level. In such cases, the results will be confidentially reported to the EMA as an Annex to the study report. The main report will only contain aggregated, non-identifiable data (e.g. no categories with numbers ≤3). The report will be uploaded to the HMA-EMA Catalogue/Public domain, without the respective confidential supplement.

11. Management and reporting of adverse events/adverse reactions

Not applicable.

12. Plans for disseminating and communicating study results

The final report will be delivered on 12 December 2025 and a study manuscript on 12 March 2026. All these documents will be provided both as Word as well as a PDF file.

The study has been registered in the HMA-EMA Catalogue of Real World Data Studies (EUPAS1000000313).

The UU (NL) team will take the lead in drafting the study plan, the protocol, and the preliminary study report. The UU (NL) and the RIVM (NL) teams will jointly take the lead on drafting the preliminary manuscript. All deliverables will also be reviewed by all consortium partners, and by the EMA evaluation committee appointed for his study. Study results will be published in a peer reviewed journal as well as communicated to key informants participating in the study and their organisations at the end of the project.

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Annex 1. List of stand-alone documents

Appendix number	Document version	Date	Title
I	Version 2.0	Mar 2025	Draft of web-based survey (WP2a)
II	Version 1.0	Feb 2025	Template for country-specific recruitment (WP2)
III	Version 1.0	Dec 2024	Translation protocol (WP2)
IV	Version 1.1	Jan 2025	Data collection template for overall mapping of national implementation processes (WP1)
V	Version 1.0	Oct 2024	Data collection template for product-specific mapping (WP1)
VI	Version 2.0	Jan 2025	Pointers for interview guide (WP2b)
VII	Version 1.0	Dec 2024	Draft data extraction template (WP2b)
VIII	Version 1.0	Jan 2025	Biases and mitigation strategies
IX	Version 1.1	Dec 2024	Project schedule
X	Version 1.0	Feb 2025	Key elements of CAP/CDS of study products
XI	Version 1.0	Feb 2025	Tracking surveyed barriers/enablers to implementation science frameworks

Annex 2. ENCePP checklist for study protocols (revision 4)

Study title: Implementation of controlled access to and distribution of medicinal products in European Union

HMA-EMA Catalogue of Real World Data Studies number: EUPAS1000000313
Study reference number (if applicable): ROC21 - SC02 - EMA/2020/46/TDA/L4.02

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	X			App. VIII
1.1.2 End of data collection[5]	X			6
1.1.3 Progress report(s)			X	
1.1.4 Interim report(s)			X	
1.1.5 Registration in the EU PAS Register®	X			9.8.1
1.1.6 Final report of study results.	X			6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	X			8
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
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			8
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:

Qualitative study of descriptive nature, no a priory hypotheses to 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

[4] 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.
[5] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X			9
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:

Qualitative study of descriptive nature, no quantitative measures of occurrence and association assessed. Not studying exposure to medicinal products, so AE/ADR not relevant.

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		
	4.2.3 Country of origin	X			9.2
	4.2.4 Disease/indication		X		
	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:

Cross-sectional analyses of experiences and opinions any time before the assessment, no study time period restrictions or relevant duration of follow-up. Due to small number of eligible participants age and sex are not assessed to better ensure anonymity. Authorized indications for the 8 products of interest are known, but exact indication per participant is not assessed.

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			9.2.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)			X	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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:

Qualitative study of opinions and experiences, listed exposure details are not relevant.

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			9.3
6.2 Does the protocol describe how the outcomes are defined and measured?			X	
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	

Comments:

Qualitative study of opinions and experiences, listed outcome details are not relevant.

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			9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X			9.9

Comments:

Qualitative study of descriptive nature, no quantitative measures of occurrence and association assessed. Confounder adjustment not relevant.

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)			X	

Comments:

Qualitative study of descriptive nature, no quantitative measures of occurrence and association assessed. Effect modification not relevant.

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	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X			9.3
9.1.3 Covariates and other characteristics?	X			9.3
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			9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X			9.3
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	
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:

Qualitative study of opinions and experiences, listed exposure, outcome, covariate and linkage details are not relevant.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?			X	
10.2 Is study size and/or statistical precision estimated?	X			9.5

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	X			9.7
10.4 Are stratified analyses included?	X			9.7
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			9.4.2
10.8 Are relevant sensitivity analyses described?			X	

Comments:

Qualitative study of descriptive nature, no quantitative measures of occurrence and association assessed. Confounder adjustment and misclassification details not relevant.

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			9.6; 9.8; 10
11.2 Are methods of quality assurance described?	X			9.8
11.3 Is there a system in place for independent review of study results?			X	

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			9.9; App VII
12.1.2 Information bias?	X			9.9; App VII
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	
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			9.8.2

Comments:

Qualitative study of descriptive nature, no quantitative measures of occurrence and association assessed. Confounder adjustment not relevant.

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			9.10
13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?	X			10

Comments:

No ethical reviews have yet been performed.

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			10; 12
15.2 Are plans described for disseminating study results externally, including publication?	X			10; 12

Comments:

Name of the main author of the protocol: Prof. Dr. ML de Bruin

Date: 11/January/2025

Signature: 

Annex 3. Additional information