

Covid-Vaccine-Monitor

Study protocol for Cohort Event Monitoring of safety of COVID-19 vaccines in special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection)

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2. List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 2019
CVM	Covid-Vaccine-Monitor
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ECVM	Early-Covid-Vaccine-Monitor
GTIN	Global Trade Item Number
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

3. Responsible parties

Collaborating Institutions (by alphabetical order)	Study Sites	Key persons
Ireland	Rotunda Hospital Dublin	
Italy	University of Verona/ Pharmacovigilance Regional Centre of Veneto and ilmiovaccinoCOVID19 collaborating group (Veneto and Tuscany Region, INSPIRE, AOU G.Martino Messina, Italian College of General Practitioners (SIMG), CRO – National Cancer Institute Aviano, Florence University Perinatal Research Laboratory, AOUP Palermo, ARNAS Civico Palermo, University of Bologna, Local Health Unit of Bologna, Local Health Unit of Ferrara, University of Catanzaro, Pharmacovigilance and pharmacoepidemiology Regional Centre of Campania, Pharmacovigilance Regional Centre of Sicily, Local Health Unit of Caserta, Italian Society of Pharmacology (SIF), National Association of Rheumatic patients (ANMAR), Local Health Unit of Messina, University of Foggia, Pharmacovigilance Regional Centre of Emilia-Romagna)	
Portugal	CLPP Vaccines Network	
Romania	University of Medicine and Pharmacy ‘Iuliu Hatieganu’ Cluj-Napoca	
Slovakia	Medical faculty of Pavol Jozef Safarik University SLOVACRIN)	
Spain	Institut Universitari d’Investigació en Atenció Primària (IDIAP Jordi Gol)	
Switzerland	University of Bern	
The Netherlands	Pharmacovigilance Centre LAREB, University Medical Center Utrecht	

Sponsor: N/A

This protocol is based on the protocol as a deliverable to contract No EMA/2018/28/PE (SC05, Lot 4) and has been amended as a deliverable of the framework contract No EMA/2018/23/PE (SC01, Lot 3) both with the European Medicines Agency

4. Abstract

Title: Cohort Event Monitoring of safety of COVID-19 vaccines in special populations (pregnant and lactating women, children and adolescent, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection)

Version: 2.0

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Rationale and background: Intensive monitoring of adverse reactions following immunization (AEFI) with COVID19 vaccines or cohort event monitoring has been performed on (sub)national levels. However, the exact data collection and analysis methods, study populations, and vaccines monitored varied. For the already marketed and upcoming COVID-19 vaccines, a pan-European cohort monitoring system is an important addition to existing spontaneous reporting systems for signal detection. This is of particular importance in fragile populations (e.g., immunocompromised) who may be at higher risk of developing vaccine-related adverse reactions as well as in those patients' categories that have not been included in COVID-19 vaccine premarketing clinical studies (e.g., pregnant and lactating women, children and adolescents). This will enable the collection of patient-reported safety data to generate incidence rates of vaccine-related adverse reactions in those special cohorts.

Objectives:

Primary aim

To generate and compare incidence rates of patient-reported adverse reactions of different COVID-19 vaccines across the participating countries in pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection

Secondary aim

Within each special cohort of vaccinees to identify potential predictors of the most frequently reported adverse reactions related to different COVID-19 vaccines.

Study design: Prospective cohort study in special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection). In different countries, on the national level, data will be prospectively collected, directly from a cohort of vaccine recipients. The common core data from different countries will be pooled, stratified by special cohort and analysed at the European level. The study is set up as a cohort monitoring for a duration of up until 6 months from the first dose vaccination date (except for pregnant women who will be followed up until 1.5 month after the pregnancy end).

Vaccine recipients should be asked to fill in questionnaires at baseline, and 1 and 3 weeks after the first dose (and eventually the second dose), and 3 and 6 months after first dose vaccination. The exact timing of the sending of the third questionnaire will depend on the vaccination interval between two doses. As regards pregnant women a specific “End of Pregnancy” questionnaire will be additionally sent within 1.5 months from the estimated delivery to collect information on outcomes related to pregnancy and new-born.

Study population: Pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection who received COVID-19 vaccines first dose within 48 hours, consenting to participate and with a baseline questionnaire as well as questionnaires filled out after vaccination at multiple time points. Participants will be recruited before or at the moment of vaccination (as mentioned earlier within 48 hours from first dose vaccination at latest), which may differ per country and target group. There is the possibility of recruiting participants receiving a COVID-19 vaccine booster in the future, namely those who have already received a complete cycle of vaccination.

Variables: Vaccine brand and batch number, ADRs, age, sex, height and weight, geographical area, medical history including information on comorbidities and concomitant diseases (e.g., diseases or drugs affecting the immune system, history of allergy and SARS-CoV-2 prior infection, etc.). In addition, for pregnant women: baseline variables for pregnancy (e.g., gestity, parity, previous pregnancy complications, ongoing pregnancy due date, etc.) and outcomes of pregnancy and new-born (pregnancy complications, end of pregnancy week, delivery mode, pregnancy outcomes and neonatal outcomes).

ADRs: Suspected short- and medium/long-term adverse reactions that are reported after each dose of COVID-19 vaccination (as both solicited and unsolicited events) by the participant. All serious adverse reactions will be assessed by a qualified assessor, taking into account all information including possible uploads of documents by participants or comments on these events. When consent has been given by a participant, follow-up will be requested by e-mail for verification and upgrading of the clinical documentation grade. Otherwise, serious ADR assessment will be carried out by regional center of pharmacovigilance or local pharmacovigilance responsible person, in agreement with national pharmacovigilance legislation. Outcomes of pregnancy and new-born will also be explored in pregnant women.

Data sources: Safety data can be directly reported by vaccine recipients in their local language using the Lareb Intensive Monitoring (LIM) web app or the ResearchOnline web app, which have been both built

specifically for patient-reported outcomes using exactly the same structure. As regards pregnancy monitoring, only ResearchOnline will be used as collecting additionally information on pregnancy. Collected data from European countries using LIM/ResearchOnline web app can be stored in dedicated central databases.

Study size: We aim to include overall up to 60,000 vaccine recipients belonging to the special cohorts from 8 European countries, with a maximum of up to 30,000 pregnant and lactating women, up to 10,000 children, up to 20,000 immunocompromised, up to 10,000 persons with history of SARS-CoV-2 infection, and up to 5,000 with a history of allergies.

Data analysis: For each special cohort, adverse reaction incidence rates will be reported overall and stratified and compared across different vaccine brands, gender, age groups, and countries.

5. Amendments and updates

Date	Amendment	Justification	Protocol Section
N/A			

6. Deliverables and Milestones

Milestones and deliverables	Planned date
Contract signature	6 Apr 2021
Start of project	6 Apr 2021
D1 Study plan*	6 May 2021
D2 Study protocol(s)*	7 Jun 2021
Study start	7 July 2021
D3 Monthly interim statistical report 1* on dashboard	30 Sep 2021
D3 Monthly interim statistical report 2* on dashboard	29 Oct 2021
D3 Monthly interim statistical report 3* on dashboard	30 Nov 2021

D3 Monthly interim statistical report 4* on dashboard	31 Dec 2021
D3 Monthly interim statistical report 5* on dashboard	31 Jan 2022
D3 Monthly interim statistical report 6* on dashboard	28 Feb 2022
D3 Monthly interim statistical report 7* on dashboard	31 Mar 2022
D4.1 Interim report*	6 Apr 2022
D3 Monthly interim statistical report 8* on dashboard	29 Apr 2022
D3 Monthly interim statistical report 9* on dashboard	31 May 2022
D3 Monthly interim statistical report 10* on dashboard	30 Jun 2022
D3 Monthly interim statistical report 11* on dashboard	29 Jul 2022
D3 Monthly interim statistical report 12* on dashboard	31 Aug 2022
D3 Monthly interim statistical report 13* on dashboard	30 Sep 2022
D3 Monthly interim statistical report 14* on dashboard	31 Oct 2022
D3 Monthly interim statistical report 15* on dashboard	30 Nov 2022
D3 Monthly interim statistical report 16* on dashboard	30 Dec 2022
D3 Monthly interim statistical report 17* on dashboard	31 Jan 2023
D3 Monthly interim statistical report 18* on dashboard	28 Feb 2023
D3 Monthly interim statistical report 19* on dashboard	31 Mar 2023
D4.2 Final report*	6 Apr 2023
D5 Manuscript*	6 Apr 2023

* Deliverable to be submitted to EMA

7. Rationale and Background

7.1 Background

As reported in the Early-Covid-Vaccine-Monitor (ECVM) protocol (EUPAS39798), the European Medicine Agency's (EMA) mission is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

COVID-19 vaccines in the European Union (EU) are evaluated by EMA via the centralised procedure, based on a rolling review. While a large number of COVID-19 vaccines are still progressing in clinical development, four vaccines (from Pfizer/BioNTech, Moderna, AstraZeneca, Janssen) have been granted conditional marketing authorisation. While more vaccines are expected to be authorised during 2021 and 2022, large-scale vaccination campaigns are being rolled out across the EU.

During the 2009 pandemic, major lessons learned were a need for improved collaboration within Europe, and a common approach for the collection of safety data and data-sharing.¹ This would contribute to improved signal detection and timely evaluation of safety signals in a forthcoming pandemic. The large scale of the 2009 worldwide H1N1 pandemic vaccination programme prompted several countries to improve and expand their vaccination safety monitoring procedures. Indeed, various intensive monitoring studies were performed in different countries. The results of two intensive monitoring studies on 2009 pandemic influenza vaccination in Europe were published (Harmark et al. 2011; Mackenzie et al. 2012). Upon the experience with the H1N1 vaccination programmes, the intensive monitoring system was developed further to monitor seasonal influenza vaccination in the Netherlands (van Balveren-Slingerland, Kant, and Harmark 2015), and has been used since (cf. Lareb Intensive Monitoring (LIM) system). For the design of an intensive monitoring system for COVID-19 vaccination at the European level, we are building upon these experiences.

In order to complement spontaneous reporting systems for signal detection (routine pharmacovigilance) and other initial safety monitoring activities such as pharmaco-epidemiological studies conducted or planned by different stakeholders, the Agency procured an early safety monitoring study through its framework contracts (ECVM) which is conducted by the EU PE&PV research network and VAC4EU. The study includes subjects in groups prioritised for vaccination in seven EU Member States (Germany, Croatia, the Netherlands, Belgium, Luxembourg, Italy, France) and the UK. An extension of the ECVM project (Covid Vaccine Monitor – CVM) was approved (EUPAS39798).

The CVM project aims to enlarge the ECVM study in a target number of at least 8 additional EU Member States to further inform the benefit-risk profile of all COVID-19 vaccines in the EU as immunisation campaigns are expanding, targeting larger population groups.

¹www.ema.europa.eu/en/documents/report/pandemic-report-lessons-learned-outcome-european-medicines-agencys-activities-during-2009-h1n1-flu_en.pdf

7.2 Rationale for the study

Clinical trials prior to licensing collect key information on Adverse Events of Special Interest (AESIs) and Adverse Events Following Immunization (AEFIs) and often include selected persons.

Certain groups, such as pregnant/lactating women or children and adolescents have not (at least initially) included in the pivotal COVID-19 vaccines clinical trials. Therefore, available risk management plans from currently authorized vaccines show the lack of information on the safety and effectiveness of COVID-19 vaccines in special populations who have not been vaccinated in the first phases.

During the rollout of vaccines, larger and more diverse populations (including those at higher risk of developing AESIs and/or AEFIs as well as those initially not included in COVID-19 vaccine premarketing clinical studies) are expected to be vaccinated, which means that a lot can be learned.

Also, a limited number of vaccine batches are monitored prior to registration, so there is always the risk of a batch-related safety problem.

AEFIs can comprise 5 different types:²

1. Vaccine product-related reaction.
2. Vaccine quality defect-related reaction.
3. Immunization error-related reaction.
4. Immunization anxiety-related reaction.
5. Coincidental event.

Licensure of a vaccine that is rolled out to a large population in a short time requires not only regular spontaneous reporting but also cohort event monitoring to obtain more in-depth information on the safety of the vaccines.

In addition to existing spontaneous reporting systems, a large-scale cohort event monitoring system on special populations (i.e., pregnant and lactating women, children and adolescents, immunocompromised, people with a history of allergy, and people with prior SARS-CoV-2 infection) allows for the monitoring of marketed COVID19 vaccines in categories of persons that have not been included in pivotal clinical trials in the EU. This approach is complementary to spontaneous reporting systems as well as observational studies using healthcare databases in several ways. In particular, it is better suited to capture the more frequent adverse reactions, including those that are not medically attended.

Despite the lack of published evidence about the safety and efficacy of the vaccines in people who were immunocompromised (e.g., those with autoimmune disorders, receiving radiotherapy and/or chemotherapy treatments or other types of immunosuppressive medications, and undergoing transplant), all countries in the EU have started at an early stage of the vaccination campaign the administration of

² <https://apps.who.int/iris/handle/10665/206144>

COVID19 vaccines in this patients' group according to the "prioritisation of target groups for vaccination" strategies provided by the European Centre for Disease Prevent and Control (ECDC) (<https://www.ecdc.europa.eu/en/publications-data/covid-19-vaccination-and-prioritisation-strategies-eueea>). This prioritisation of fragile people was due to their higher risk of COVID19-related mortality and of showing severe symptoms. For instance, people with HIV were found to be a high-risk group for SARS-Cov-2 associated mortality, with an adjusted HR of 2.30 (1.55-3.41), meaning that people with HIV have two times the risk of dying from SARS-Cov-2 infection compared with people without HIV (Bhaskaran et al, 2021).

Regarding the special population group involving pregnant and lactating women, there is now cumulating evidence from the real world setting that Pfizer and Moderna's vaccines are safe to use during pregnancy (Shimabukuro et al, 2021), but this requires further investigation. It is particularly important to vaccinate pregnant women as they are known to be at increased risk of hospitalization and have a 3-fold adjusted relative risk of needing intensive care (10.5 vs 3.9/1000 cases) and mechanical ventilation (2.9 vs 1.1/1000 cases) compared with age-matched nonpregnant individuals. Current data (which may be biased due to right censoring) show that pregnant women who contracted SARS-COV-2 infection during pregnancy had higher risk of caesarean delivery (1.57 [95% CI, 1.30-1.90]), postpartum haemorrhage (2.04 [95% CI, 1.19-3.47]), hypertensive disorders of pregnancy (1.64 [95% CI, 1.21-2.23]), and preterm birth (3.53 [95% CI, 2.42-5.15]) (Bianchi et al, 2021).

Concerning children, only recently the EMA approved the use of the COVID-19 vaccine Comirnaty in children aged 12-15 (<https://www.ema.europa.eu/en/news/first-covid-19-vaccine-approved-children-aged-12-15-eu>). The effects of Comirnaty were studied in 2,260 children aged between 12 and 15 years, resulting in a favourable safety profile, high immune response, and effective protection against COVID-19 (Frenck et al, 2021).

Outpatients with a history of allergy are another category of patients for whom concerns on COVID19 vaccine safety have been shown. Post-marketing evidence showed that mRNA vaccines were associated with an increased risk of severe allergic reactions (1 per 100,000 doses vs. 1.4 per million doses with conventional vaccines) in general and having a history of allergies was documented as a risk factor (https://www.ema.europa.eu/en/documents/presentation/presentation-how-safety-new-covid-19-vaccines-will-be-monitored-sstraus-prac_en.pdf). Likewise, Vaxzevria (previously AstraZeneca) vaccine is recommended in subjects with history of allergy under close medical supervision (https://www.ema.europa.eu/en/documents/overview/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-medicine-overview_en.pdf

While most of the approved vaccines consist of the administration of two doses of vaccines, the large majority of the EU countries have taken the decision to administer a single dose of vaccine to people with prior SARS-CoV-2 infection. This population group, after receiving one dose of the BNT162b2 mRNA COVID-19 vaccine, can produce high levels of antibodies against the spike protein, which may be related to enhanced antibody response and a potentially higher adverse reactions risk (<https://www.medrxiv.org/content/10.1101/2021.01.29.21250653v1.full.pdf>).

Based on these premises, there is the urgency to conduct careful post-marketing active surveillance to assess the short- and long-term safety (and benefits) of COVID-19 vaccines in those special populations. In particular, considering the recent recommendation on vaccinating pregnant women, it is utterly important to monitor both maternal and neonatal outcomes following immunisation. The results generated by this prospective monitoring study will complement the results from other sources, such as the V-safe Surveillance System in the United States, which collects information about ADRs and the health status of the general population, including pregnant women (CDC, 2021). In addition, the recent approval of vaccination in children/adolescents requires intense post-marketing surveillance.

8. Goal and objectives

8.1 Goal

The CVM project aims to collect data on adverse drug reactions in specific target populations for COVID-19 vaccines in a target number of at least 8 additional EU Member States to further inform the benefit-risk profile of all COVID-19 vaccines in the EU as immunisation campaigns are expanding, targeting larger population groups this study extends the ongoing work as proposed in the ECVM protocol (EUPAS39798).

8.2 Objectives

The specific objectives include:

Primary aim

To generate and compare across different COVID-19 vaccines the incidence rates of patient-reported COVID-19-related adverse reactions in pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection.

Secondary aim

Within each special cohort to identify potential predictors of the most frequently reported adverse reactions related to different COVID-19 vaccines.

9. Research methods

9.1 Study design

The study is set up as a cohort event monitoring in special populations for a duration of six months after vaccination and will be implemented in 8 EU and non-EU Member States (Ireland, Italy, Netherlands, Portugal, Romania, Slovakia, Spain, and Switzerland).

This protocol is based on the protocol of the Early-Covid-Vaccine-Monitor (ECVM) (EUPAS39798), which focuses on Cohort Event Monitoring of safety of COVID-19 vaccines in the general population for six months (<http://www.encepp.eu/encepp/viewResource.htm?id=40288>). Modifications were made to address pregnancy and an additional modality for online data collection.

In the ECVM study, with the exception of two (Germany and Croatia) of the eight participating countries, data is collected through a LIM app, and at baseline, it is possible to identify special subpopulations. In general, subpopulations from some of the ECVM participating countries will therefore be included in the analysis of this study.

It was decided to add a subset of questions to the existing questionnaires in order to better identify and characterize these special group participants (see Annex 1: extra questions for identification of special groups).

For the pregnancy population, detailed questions have been included in the baseline questionnaires and a follow-up questionnaire for the end of pregnancy was added to the newly developed ResearchOnline web app. Data collection for the pregnancy population will therefore follow this protocol.

The following table shows the participating countries, their contribution to this protocol, and the web app that is going to be used for data collection.

Table 1 - Participating countries and their contribution to special cohorts investigated in CVM project for special population and the data collection tool.

Country*	Cohort					Tool
	Pregnant and lactating women	Immuno-compromised	Children and adolescents	Patients with history of allergy	Prior SARS-COV-2 infection	
The Netherlands		X		X	X	LIM web app
Italy	X	X	X	X	X	ResearchOnline (only pregnancy) – LIM web app for other cohorts
Ireland	X					ResearchOnline
Switzerland	X					ResearchOnline
Spain	X		X		X	ResearchOnline
Portugal	X	X	X	X		ResearchOnline

Romania	X	X	X		X	ResearchOnline
Slovakia	X	X	X	X	X	ResearchOnline

*Toulouse and Lyon regional centre for pharmacovigilance (France) is evaluating participation in a later phase based on the agreement with the Agence nationale de sécurité du médicament et des produits de santé which funded a similar project on COVID19 vaccine monitoring in pregnancy.

Participants must be invited to participate in the study before vaccination, when they are invited to have the vaccine administered or, at the latest, on the day of vaccination. This invitation will be sent in an email (when participants are invited or when the appointment for vaccination is confirmed) as a link or as a website on social media or a website/QR-code on a flyer or poster at the vaccination locations. Participants can register to participate in the study up until a maximum of 48 hours after vaccination.

Vaccinees will be asked by e-mail or via a reminder through an app to fill up to seven online questionnaires which will be sent out to them at set times. Data will be collected on exposure (vaccine brand, batch, date of vaccination), vaccinee demographics and comorbidities (age, gender, medical history), and outcome: adverse reactions and SARS-CoV-2 infection occurrence as a proxy of lack of effectiveness.

For serious adverse reactions or other adverse reactions that need medical clarification, clinical follow-up will be performed with the consent of the participant. Based on national pharmacovigilance (PV) legislation and organization, as data on ADRs will be transferred to the national reporting system, regional pharmacovigilance centers, as well as local pharmacovigilance officers, may be involved in the follow-up of serious adverse reactions as routinely done.

Information will also be sought through phone contacts in pregnant women not completing the “End of pregnancy” questionnaire, provided that they gave consent to be contacted also via phone. No contact will be made for those not providing consent.

To get accurate data on the reported adverse reactions, the questionnaires will be scheduled to capture both short-term and long-term reactions. It is expected that most adverse reactions occur within 72 hours after vaccination. In addition, most of the well-known adverse reactions recover within five days after vaccination. Therefore, the first questionnaire on adverse reactions will be available on the seventh day after vaccination, to retrieve the first reactions as accurately as possible (Figure 1 – Q1 and Q3). The second questionnaire after vaccination will capture adverse reactions with a later onset and obtain more information on recovery of previously reported reactions (Figure 1 – Q2 and Q4). Subsequent questionnaires serve to obtain information about adverse reactions with an even later onset and information on a possible SARS-CoV2 infection and on COVID-19 disease (Figure 1 – Q5 and Q6). The schedule is chosen ahead of the start of the study and is based on the most likely period between two doses. Depending on the chosen schedule, the three questionnaires Q3, Q4, and Q5 will shift with the aim to capture the period directly following the second vaccination. Participants receiving a single dose vaccine will receive questionnaires with the same schedule as those receiving the two doses of a vaccine.

For pregnant women, a specific “End of Pregnancy” questionnaire will be sent within 45 days after the estimated delivery to collect information on outcomes related to pregnancy and new-born.

Since the Q5 and Q6 may overlap with the end of pregnancy, these will not be administered, instead, an end of pregnancy questionnaire will be administered, which will include questions about medium/long-term adverse reactions following first dose vaccination as well as on SARS-COV-2 infection occurrence in between the last filled questionnaire and end of pregnancy questionnaire. Since participants may receive the second dose of their COVID-19 vaccine at a different moment than the predetermined schedule, the most important aspect is that all partners collect vaccinations dates and the start dates of the reported ADRs. With this information, time-to-onset for all ADRs can be calculated, irrespective of the scheduling of questionnaires. Participants who skip a questionnaire will not be able to continue their participation for the full six months, they will automatically be indicated as lost to follow-up.

The figure below shows the questionnaires' schedule for participants receiving the COVID-19 vaccine based on a 3 weeks interval between doses 1 and 2.

Schedule 1 with 2 doses (roughly 3 weeks between dose 1 and 2)

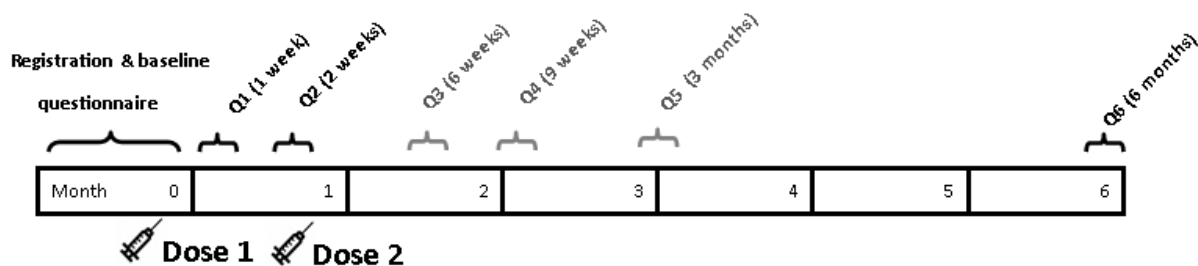


Figure 1 – Questionnaire schedule based on 3 weeks interval between dose 1 and dose 2

Safety data can be directly reported by vaccine recipients in their local language using the Lareb Intensive Monitoring (LIM) web app (built by LAREB) and the ResearchOnline web app, built by the University Medical Centre Utrecht (UMCU) team, respectively.

ResearchOnline is a web app that has been developing specifically for the patient-reported outcome for the CVM study. It is based on the already existing LIM web app used for the ECVI study. The way questions are asked, the content of the questions, and the questionnaire schedule will not differ between the two web apps.

The Countries participating in the Covid-Vaccine-Monitor study will use ResearchOnline, while the Netherlands, and Italy that participated already in the ECVI and agreed to contribute to the CVM study will use LIM web app.

Since the questionnaires have been updated for pregnant women, only ResearchOnline can be used to include pregnant women.

9.2 Setting

9.2.1 Inclusion criteria

Participants to be included should be vaccinated in one of the participating countries in the period ranging from February 2021 (in Countries already starting prospective monitoring in ECVI) until August 2022.

The vaccine recipient or their proxy should:

- register for the study prior to (the first) vaccination or no longer than 48 hours from first dose of COVID-19 vaccination or booster dose (when this becomes reality) be able to understand the language of the survey (translated into the local official languages)
- be able to register and participate by e-mail;
- provide informed consent (translated into the local official languages and adapted according to the Country-specific laws). Regarding children informed consent of the parents or the legal representative will be sought. The informed consent must be given if the person wishing to participate in the project is under 16 or 18 years of age, depending on the Country-specific law.

9.2.2 Study population

Target groups are pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy and people with prior SARS-CoV-2 infection vaccinated against SARS-CoV-2 infection, providing informed consent.

People in the target groups will have the following characteristics:

- Pregnant/lactating women: pregnant women at any point of pregnancy at the moment of vaccination, which will depend on national vaccination campaign, and during the breastfeeding period
- Children: persons 0-18 years of age. Parents or legal representative are expected to enter the data on behalf of their children, as needed, based on national legislation.
- Immunocompromised subjects:
 - subjects with immune system compromised due to diseases such as HIV/AIDS, transplants, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, psoriasis, psoriatic arthritis), leukaemia/lymphoma;
 - and/or subjects currently taking drugs affecting their immune system (e.g., myelosuppressive chemotherapy, glucocorticoids, anti-rheumatics drugs, monoclonal antibodies interfering with immune system)

- Subjects with history of allergy including hay fever, dust mite allergy, allergy to animals, food allergy, allergy to insect bites, allergy to medication or vaccine, etc.
- Subjects with prior SARS-CoV-2 infection: people who had a suspected/diagnosed SARS-CoV-2 infection (whether confirmed or not-confirmed by a test) any time prior to the first dose vaccination.

9.3 Variables

In general, data will be collected on exposure (vaccine brand, batch, date of vaccination), vaccinee demographics and clinical characteristics (comorbidities, concomitant diseases, information for characterizing special cohorts, etc.), and outcome (i.e., adverse reactions and lack of efficacy). Information on pregnancy will be mainly collected at baseline. As regards variables at different gestational ages (in addition to 1-4 FU questionnaires investigating short-term adverse reactions following 1-2 vaccination doses). For the end of pregnancy questionnaire information on key variables during pregnancy (in between first vaccination dose and end of pregnancy) as well as pregnancy- and neonatal-related outcomes will be collected.

Suspected adverse reactions occurring after each dose of COVID-19 vaccination will be collected. Incoming serious adverse reactions will be verified by the local pharmacovigilance responsible, based on national pharmacovigilance legislation. For adverse reactions requiring medical clarification, a clinical follow-up will be performed, provided that the participant has given consent to be contacted.

Participants will be asked to report suspected adverse reactions after vaccination at multiple follow-up time points.

The data collection system (ResearchOnline web app or LIM app for ECVI partners) will remind participants to fill in the questionnaire at these time points by sending automated e-mails (as well as one or more reminder e-mails). It is furthermore important to clearly explain to the participants that they need to contact their own physician if they have questions about their symptoms or if they are worried about the symptoms. Vaccinees who may not be able to fill electronic questionnaires can delegate the task to caregivers/family members.

A dedicated questionnaire after the end of pregnancy will be sent to pregnant women within 45 days from the estimated date of delivery. At the time of registration, we will collect the phone numbers of pregnant women and their consent to be contacted via phone by dedicated persons from participating centres, in case of lack of response to the “End of pregnancy” questionnaire. We take this measure as we expect a high proportion of loss to follow-up after delivery.

The list of variables related to pregnancy was carefully chosen based on the already existing COVIPREG project. In addition, a dedicated pregnancy-specific working group involving experts in perinatal research has been set up.

9.3.1 Exposure data

- *Vaccine brand & batch number* (if available) obtained via the vaccine recipient (e.g. number on vaccination certificate, or uploading photo)
- *Vaccine dose number*
- *Vaccination date*
- Vaccine switch from first to second dose will be collected: data on the second dose, including the name of the vaccine received and the day it was received, are asked in questionnaire number 3. In case the participant selected they have not yet received the vaccine in Q3, second dose-related questions will be asked in the next questionnaires (Q4, Q5, and Q6). Therefore, information regarding any vaccine switch from first to second dose as well as the information about the interval between the two doses can be collected in Q3-6.

Vaccinee demographics and clinical characteristics

The following information will be collected upon enrolment (same as in ECVM, but more details on item 5)

1. Age
2. Height and weight (to calculate body mass index - BMI)
3. Contact details of next of kin (if privacy regulations allow this)
4. Geographical area
5. **Maternal morbidity & obstetric history (see below)**
6. Previous SARS-CoV2 infection and COVID-19 disease (closed questions, incl. date and severity)
7. History of anaphylaxis or anaphylactoid reactions & allergies
8. Presence of conditions/treatments that alter immune response
9. Additional information to determine country-specific target population for vaccination: health care worker, (informal) caregiver, resident of nursing home, ...
10. Current co-medication and previous, other vaccinations (within previous 2 weeks).
11. Immunizer (e.g. GP, occupational health service, municipal health authority)
12. Vaccination site (e.g. right/left arm/leg)
13. Antipyretics intake around time of vaccination
14. Prior vaccination with COVID-19 (once booster vaccinations are started)

Additional baseline variables on Maternal morbidity & obstetric history

The following information will be collected for pregnant women:

- Gestity
- Parity
 - Number of previous C-Section if parity ≥ 1

- Number of previous vaginal delivery parity ≥ 1
- Number of previous early miscarriage (<14 weeks) if gestity ≥ 1
- Number of previous late miscarriage (≥ 14 weeks) if gestity ≥ 1
- Number of previous terminations of pregnancy if gestity ≥ 1
- Number of previous stillbirth if gestity ≥ 1
- Maternal medication
- Previous pregnancy complications (preeclampsia, intra uterine growth restriction, foetal malformation, preterm birth, postpartum haemorrhage, other)
- Maternal use of recreational Drugs
- Maternal use of Tobacco
- Maternal use of Alcohol
- Ongoing pregnancy due date*

*pregnancy due date can be calculated by the pregnant woman, who is generally aware of her last menstrual period

9.3.2 Outcome data

Solicited adverse reactions (as in ECVI protocol) (EUPAS39798)

Closed dedicated questions (solicited):

1. Injection site reaction (redness, warmth, pain, itch, hematoma, swelling, induration)
2. Fever/feverishness
3. Shivering/chills
4. Headache
5. Nausea
6. Myalgia/muscle pain
7. Arthralgia/joint pain
8. Malaise
9. Fatigue

These solicited adverse reactions are known to occur frequently. In addition, also COVID-19 positive test and/or (severity of) symptoms will be specifically assessed in Q5-Q6.

Unsolicited adverse reactions

In addition, it will be asked whether any other suspected adverse reactions occurred (open question/unsolicited). The later follow-up periods should serve to monitor suspected adverse reactions with a longer lag time and to assess the course of previously reported adverse reactions (i.e., outcome, duration of symptoms).

Assessors in the different participating countries will code unsolicited reported adverse reactions into MedDRA lower-level terms (in English), and determine whether they are seriously based on the criteria of the Council for International Organizations of Medical Sciences (CIOMS) criteria.

Reported adverse reactions which are considered serious based on the above mentioned CIOMS criteria and other adverse reactions that need medical clarification will be assessed in agreement with national PV legislation.

Pregnancy and neonatal outcomes

After the end of pregnancy, a dedicated questionnaire will be sent to the woman to collect key information on pregnancy and neonatal outcomes.

- Pregnancy complications (abnormal first trimester screening if enrolment before screening, multiple gestation, preeclampsia, intra uterine growth restriction, oligohydramnios, polyhydramnios, foetal malformation, spontaneous preterm birth, iatrogenic preterm birth, foetal lung maturation, postpartum haemorrhage, other)
- End of pregnancy weeks (since Last Menstrual Period)
- Delivery mode (vaginal birth, C-section)
- Pregnancy outcomes (livebirth, late miscarriage ≥ 14 weeks, early miscarriage < 14 weeks, Termination of pregnancy, stillbirth, other)
- Neonatal outcomes (sex, weight, height, physical examination abnormality, death, ICU admission, feeding method at discharge, other)

9.4 Data sources

Data on vaccination (both doses or booster doses where relevant), outcomes, and other variables will be directly reported by the vaccine recipient. Vaccine recipients that are not able to participate themselves (e.g., children) can participate via a proxy (e.g., family member), that is expected to enter all the data.

To collect complete data reporting, some of the fields in the questionnaires were made compulsory. Questionnaires will be validated by dedicated and PV-trained persons who will correct and code all the information provided by the vaccinees. The dedicated personnel can also contact the vaccinees in case of inconsistency of the collected information or lack of important information, provided that the participant has given the consent to be contacted. A number of quality checks will be implemented to verify the accuracy of the questionnaires' data collection. Invalid/Incomplete questionnaires will be excluded from the analyses.

9.5 Study size

9.5.1 Goals for minimum number of inclusions

Unless the vaccination campaign status is too advanced, each participating country will attempt to include at least 1,000 vaccinees in total, independently from the special cohorts. We aim to include overall up to 60,000 vaccine recipients belonging to the special cohorts from 8 European countries, with a maximum of

up to 30,000 pregnant women, up to 10,000 children, up to 20,000 immunocompromised, up to 10,000 persons with history of SARS-CoV-2 infection, and up to 5,000 with a history of allergies.

Study size of recruitment will depend on underlying national population, national vaccination rate and phase of vaccination campaign at the moment the study will start (e.g., immunocompromised patients have been already vaccinated all over Europe). In addition, as indicated in section 9.5.2 in some countries there are contacts with target groups organization or healthcare professional networks providing care to special cohorts, which may help recruitment of specific categories of vaccines.

9.5.2 Recruitment by country

In general, in WP1 country-specific approaches for recruiting special cohorts will be adopted either by contacting target groups a priori or instructing the personnel working at the vaccination centres participating in the study on how to recruit vaccinees belonging to special cohorts at the moment of medical history collection right before the vaccination. Each Country provided information on how they intend to recruit their participant:

Ireland

In Ireland, a maternity hospital setting coordinating a network of academic Irish Maternity units will be involved to help promoting and recruiting specifically pregnant women for this project, based on the available resources needed for undertaking the project's activities undertaking this work.

Ireland has approximately 60,000 births per annum across 20 maternity units. Pregnant women with risk factors are currently vaccinated and a national recommendation has been made to offer vaccination to all pregnant women between 14- and 36-weeks' gestation. These women will be offered the vaccine shortly.

Italy

In Italy a large network of multi-regional pharmacovigilance centres, academic centres and local health units covering around 100 vaccination centres have been set-up with the aim of facilitating the recruitment of special cohorts. Posters, flyers and video promoting the project will be showed in the included vaccination centers. In addition, Italian Society of Pharmacology and Italian College of General Practitioners will send dissemination material via email and social networks. In particular, SIMG will distribute flyers to around 8,000 GP practicing in Italy. National Association of rheumatic patients will be involved to recruit specifically those immunocompromised patients. By this time almost all immunocompromised people have been vaccinated also in Italy. As such, this Association will help out eventually to recruit immunocompromised patients at the time of booster vaccination. Such a network called "IlmiovaccinoCOVID19" collaborating group is already closely collaborating with the Italian Drug Agency regarding the data transfer from web app database to the national reporting system database. The project has been presented to all the regional PV centres and contribution of the local PV responsible persons for checking duplicated and update follow-up reports has been clarified. Regarding pregnancy monitoring specifically, also Florence University Perinatal Research Laboratory ("PeaRL") will be involved. PeaRL is a joint laboratory constituted by the Department of Neurosciences, Psychology, Drug Research and Child Health and the not-for-profit Foundation for Perinatal Health Research "CiaoLapo" that is able

to involve civil society and stakeholders in clinical research in the field of mental and physical health in pregnancy, breastfeeding and in general in the perinatal period, with particular reference to drug and vaccination safety during pregnancy.

Portugal

In Portugal, a network of pharmacovigilance centre will be able to contribute to the recruitment of all cohorts except for the one related to patients with previous SARS-COV-2 infection. Participants' recruitment will be facilitated through involvement of several vaccination centres, which are disseminated throughout the country. Specifically for patients with history of allergies, it will be used a research collaboration with a team of allergologists that is already in place.

Romania

In Romania partners participating to the project will address special cohorts to be vaccinated through patients' organizations (e.g., previous online surveys of immunocompromised patients have been carried out), social media groups (e.g., pregnant women, prior COVID-19 patients, high-school children), general practitioners (GPs), as it is foreseen that certain GP offices will be involved in vaccination). In addition, they will contact official authorities involved in vaccination to get their support (including flyers distribution at vaccination centers), as soon as the study will be officially rolled out.

By this time almost all immunocompromised people have been vaccinated in most of EU Countries. As such for this cohort data from European Countries already participating to ECVM using the LIM web app and that already started with the monitoring will be included as well. In addition, those patients may be included also in case of booster vaccination in the next year or by the end of 2021.

Slovakia

In Slovakia cohorts will be recruited through vaccination centres established as part of the National Vaccination Strategy in Slovakia. Registration for vaccination is electronic via the portal of National Health Information System and people are ordered for vaccination according to currently open groups copying the national strategy. Before the vaccination itself, people in the vaccination centre fill in a questionnaire, on the basis of which it is possible to identify vaccinees belonging to the special cohorts. Contribution to the recruitment of vaccinees for all special cohorts will be provided. Children will be identified directly at the vaccination centre and the parent/legal representative will be informed about the possibility to participate in the study. At the same time, patients will be selected through specialized physicians, copying specific cohorts who will inform about the possibility to participate in the study. The study team will be in close contact with all stakeholders.

Spain

In Spain, activities will be coordinated by the Institut Universitari d'Investigació en Atenció Primària (IDIAP Jordi Gol). From their network of primary health centres recruitment of the following categories into the project will be specifically sought as described below:

- midwives of the primary care system will be involved for pregnant women recruitment;

- for children/adolescents it is not yet defined when the vaccination campaign will start. Nevertheless, in their primary care system there are paediatricians that will be in charge of the vaccination of children (≤ 14 years old);
- In addition, collaboration will be sought with PROHEPIC team monitoring a cohort of patients with prior COVID19.

Switzerland

The COVI-preg network already monitoring the safety of vaccination in pregnancy in Switzerland will be used to recruit women. This network will allow to recruit women through maternities at the university hospitals, obstetricians, in the ambulatory setting and vaccination centres.

COVIPREG and ORCHESTRA projects contribution

In addition to Country-specific approaches, COVIPREG and Orchestra networks will be used to recruit patients.

- COVIPREG is based on multi-country networks of midwife and gynaecologist centres who will be actively involved in the recruitment of pregnant women receiving COVID-19 vaccination. Surveys are filled out by a health professional, such as a midwife or a gynaecologist. The variables that are going to be collected for pregnant women are comparable to the ones collected in COVIPREG. Considering that the questionnaires will be filled directly by the pregnant women, questions were adapted to reach a lay population. The contribution of the coordinator of the Swiss project was essential in the draft of the pregnancy questionnaire.

Based on expertise and the questionnaire already available in COVIPREG, pregnancy specific baseline questionnaires plus end of pregnancy questionnaire have been prepared for this study. In addition, some of the centres participating in COVIPREG will contribute to recruit pregnant women also for CVM (e.g., Switzerland, Ireland and possibly France).

- ORCHESTRA has been enrolling cohorts of fragile patients for COVID19 monitoring in several EU and non-EU Countries. Based on the vaccination phase and the country, dissemination material about the CVM project will be shared by Orchestra coordinating centre and partners with special cohorts that they are following (immunocompromised patients such as HIV or oncologic patients or COVID19 patients) if not yet vaccinated. Otherwise, the same will apply the next year, in case of booster vaccination. In addition, collaborative efforts will be put for recruiting pregnant women by involving maternal and child centres mainly (but not exclusively) in Italy.

As for Italy, there is an active and intensive collaboration between the leaders of the ORCHESTRA and CVM WP1 projects. H2020 ORCHESTRA collaborators from the University of Verona and University of Bologna are going to contribute by disseminating the project and the web app across two Italian Regions (Veneto and Emilia Romagna, Italy), targeting vaccinated fragile cohorts (mainly HIV, hematological, oncological, solid organ transplant).

They will also contribute with the dissemination of the project and the web app among COVID patients in case of vaccination and/or booster vaccination.

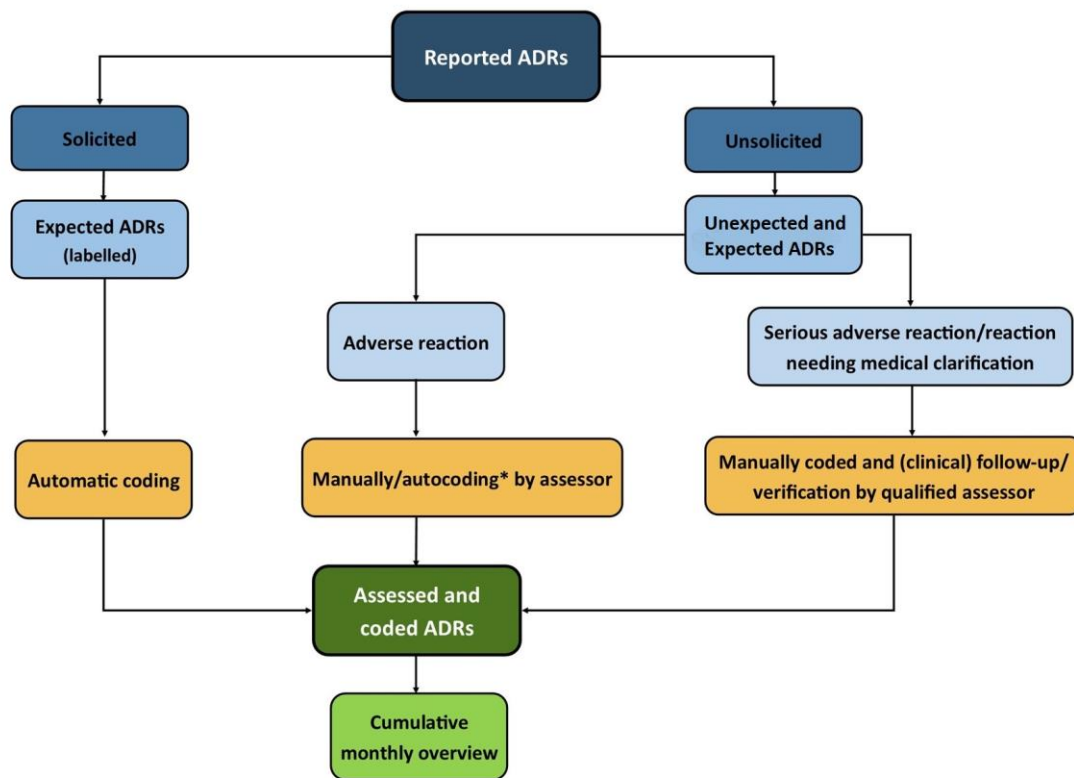
9.6 Data management

The ResearchOnline and the LIM web apps will be used for data collection for this protocol. Once patients have been invited to participate, via an e-mail or via flyers, they will register themselves and create a study account on a website designed specifically for this study, for each country.

Participants can register for the study up to 48 hours from the first dose of COVID-19 vaccination and are asked to log in on their account on the website. They will also be able to download the LIM/ResearchOnline web app to their smartphones where they can access their questionnaires online and receive reminders to fill in questionnaires. In their personal account, a baseline questionnaire will be available. According to the schedule, as described above, further invitations to fill in subsequent questionnaires are e-mailed on the 1 and 3 weeks after the first (and eventually the second) dose vaccination, as well as 3 and 6 months after the first dose vaccination in the scenario that the time period between vaccine doses is three weeks. Each country will have its own study website with one or more language sections in the LIM web app, while in ResearchOnline unique website with specific language sections will be available.

The large majority of adverse reactions that will be collected will be expected and already labelled adverse reactions. The most common expected adverse reactions will be captured as solicited so that they can be fully automatically MedDRA-coded. This will improve data quality and facilitate timely data analysis. Less common expected and unexpected adverse reactions will be captured as unsolicited. Assessors will assign MedDRA codes to these reactions as they are reported for the first time. This process of assigning MedDRA codes to unsolicited reactions by an assessor will create a library. In this library, the participant reported text will be linked to the MedDRA code most likely chosen by an assessor. From this library, MedDRA code suggestions can be assigned automatically for future reported unsolicited reactions in the same language and country. This process of auto coding will similarly help to improve the data quality and minimize the time and resources needed for coding.

The following figures (**Figure 2** and **3**) show the adverse reactions coding process and how data are managed in the ResearchOnline web app.



*autocoding: a library of previously assigned codes linked to reported ADRS is built, which will automatically code when the same ADR is reported again

Figure 2 – Reported ADRs coding system

Data from all partners using the LIM/ResearchOnline web app will be stored in centralized databases. Partners will have access to the database of the automatically received questionnaires of participants in their own country. Both the admin section and the LIM/ResearchOnline analysis database of each country contain identifying information but can only be accessed by the partners of that country. The LIM/ResearchOnline questionnaires will also pseudonymised and transformed into ICSR reports in an R3 format (or older version such as R2B, if needed), as described in **Figure 3**. This ICSR data can only be accessed and downloaded by the country that this data belongs to. For each partner working with a National Competent Authority (e.g., regional PV centre), these reports need to be sent to the national reporting system and ultimately to the EudraVigilance system (GVP module VI). As the case for spontaneous reports to EudraVigilance, these reports need to be checked for duplicates. This process of sending ICSR reports and duplicate checks is the responsibility of each country, based on national PV regulation.

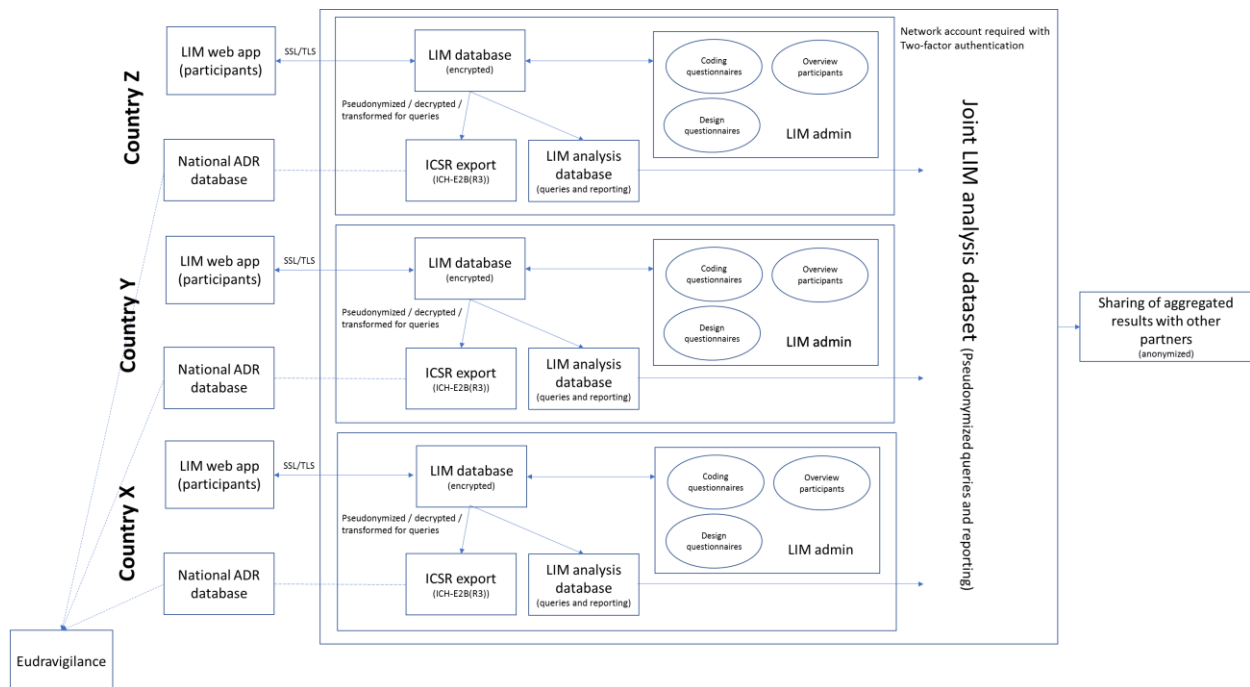


Figure 3 - Data management of the LIM web app (the same applies to ResearchOnline web app)

Data in the LIM/ResearchOnline database will also be anonymised and pooled to be shared with all partners and analysed. Scripts will be centrally developed and distributed for local deployment of data analysis. The aggregated results produced by these scripts will then be centrally uploaded for pooled analysis.

9.7 Data analysis

9.7.1 Main analysis

A description of the population at inclusion will be made by participating partners, comprising of the number of patients included in the cohort, distribution of gender, age categories, and country. In particular, periodically (every two weeks initially and adjusted as needed) reports on the updated country-specific number of recruited vaccinees and the rate of loss to follow-up for each special cohort will be shared with all the participating partners to customize recruitment strategies if needed.

In addition, for each ADR special cohort, a dedicated cumulative structured overview of numbers and incidence of all adverse reactions per vaccine will be provided, overall, and also stratified by vaccine brand, country, gender, and age group. For each adverse reaction, cumulative incidence with its 95% confidence interval (CI) will be reported by COVID-19 vaccine brand and dose. All the analyses will be presented for each special cohort separately. Overviews of aggregated data will be made available in a dashboard on a monthly basis, and an interim analysis with formal comparisons will be conducted periodically, testing differences in incidence rates between brands. A statistical analysis plan for the comparisons will be developed with WP4 (methods group), since we observe strong channelling due to targeted rollout

strategies and risk minimization strategies that countries take following the recent safety concerns with the AstraZeneca and Janssen vaccines. The ECDC overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA (ECDC, Technical Report, 29 March 2021) will be used to identify different implementation strategies in the different countries. A comparison of incidence rates of AE between vaccine brands will therefore need to be controlled for these subgroup characteristics in case these are also associated with the AE of interest. We will use standard epidemiological methods to obtain adjusted estimates (e.g., matching, standardization, weighting).

9.7.2 Sensitivity analyses

Cohort event monitoring is based on solicited and unsolicited adverse vaccine events (suspected to be related to the vaccine). A comparison of observed event rates with expected (background) event rates will be biased due to selective reporting of observed events in the cohort. These events will by definition be related to exposure. Even when comparing different vaccine brands, selective reporting due to for instance media attention related to a specific AE and specific vaccine brand (e.g., AstraZeneca and Thrombosis with Thrombocytopenia Syndrome), may lead to differential (selective) reporting of AEs between vaccine brands. The observed adverse vaccine reaction incidence rates based on the prospective cohort study will be compared with the observed adverse event incidence rates in EHR datasets from ACCESS or participants in CVM. This will be done for adverse events that can be captured well by EHR datasets only. This will give an estimate of the potential overestimation of incidence rates in the prospective cohort – by attributing events to vaccines that can be coincidental- and provide background information for the comparison of observed-to-expected vaccine adverse event rates. We will conduct separate analyses for solicited and unsolicited vaccine adverse events.

The impact of potential selection bias due to the higher chance of subjects experiencing an adverse reaction shortly after vaccination to register will be explored by excluding subjects with an AE before the enrollment date.

9.8. Quality control

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008 – available at: <https://www.pharmacoepi.org/resources/policies/guidelines-08027/>) and according to the ENCePP code of conduct (European Medicines Agency 2018). All partners have experience in conducting pharmaco-epidemiological research and researchers trained in pharmacoepidemiology do the research.

Workshops were organised for all project partners to harmonize MedDRA coding of ADRs as well as data analysis.

Each country will translate the English version of the frontend of the LIM/ResearchOnline web app to the local language(s). A back-translation to English should be prepared from each of these language versions for specific parts of the questionnaire to validate that the content has not changed during translation. Even though very similar questionnaires have previously been validated and used in the LIM/ResearchOnline

web app, questionnaires should be piloted before implementation to assess user functionality and user friendliness (in the different languages).

9.9. Limitations of the research methods

Due to the nature of the study design, several limitations of the study should be taken into account.

- Participants experiencing serious adverse reactions may not be able to return the questionnaires and this may lead to an underestimation of the frequency of these serious adverse reactions.
- Participants or their proxy may register for the study up to 2 days after vaccination. This may introduce selection bias since subjects experiencing an adverse reaction shortly after vaccination may be more likely to register.
- Since the adverse reactions will be reported by patients and not by health care providers, there could be some misclassification. For (medically attended) adverse reactions, the vaccinee's physician may be contacted to obtain more information, if needed and if consent is provided. In addition, the participant has the possibility to directly upload medical documentation to the LIM/ResearchOnline web app (see Annex 1).
- Because the study is based on primary data collection of patient-reported data there is the risk of misclassification of both exposure and outcome.
- Data on vaccine brand and batch numbers may be suboptimal (depending on possibilities per country).
- Adverse reactions are monitored within a certain window of time. Adverse reactions with a long lag time may not be identified.
- Because only patients with internet, a personal e-mail address, and capable of understanding the language may respond to web-based data collection, certain groups (e.g., elderly, illiterate, and cognitively impaired), which could experience a different safety profile, may be underrepresented.
- The size of the study population may possibly not allow the detection of rare reactions. Also, drop out/loss to follow-up may increase over time so that ADRs with a long lag time may be difficult to capture. In particular, the loss to follow-up may concern pregnant women, because of the questionnaires' timelines and sensitive questions.
- Many unknown factors surrounding availability of vaccines and the impact it has on national vaccine strategies call for regular interim checks to assess inclusions.
- Almost all immunocompromised people have been vaccinated in most of the EU Countries at the time this protocol has been drafted, reducing the chance of recruiting this group of people. However, there is the possibility of including this specific cohort once they will receive the second cycle of vaccination, starting from approximately the end of 2021. The safety risk profile may differ between first ever vaccinees and vaccinees receiving a booster dose, and this will be taken into account in the analysis.
- A Longer follow-up would allow collecting more information about long-term ADRs; however, it is unrealistic to expect vaccinees to fill questionnaires beyond 6 months after so many follow-up questionnaires. An amendment can be submitted later on to Ethical Committees for monitoring the booster vaccination which might be considered as a prolongation of the follow-up.

- Some elderly participants from the immunocompromised, prior SARS-CoV-2 infection or history of allergy targets groups could potentially be excluded from this study as they might not be able to fill the questionnaires through the web app because of their limited experience with technology. Therefore caregivers/family members might need to fill the questionnaires for them. This can be particularly challenging if the elderly participant is institutionalized (e.g., long-term care facilities residents). However, those categories of persons have been already almost fully vaccinated by this time and are likely to have minor impact on the project. This limitation will be eventually taken into consideration for the analysis of data of elderly vaccinees recruited at the booster vaccination.
- We expect that for most of the vaccinees with a prior SARS-COV-2 infection the diagnosis was confirmed by a positive test due to the massive use of diagnostic tests for such an infection. Nevertheless, if the sample size allows it, a sub-group analysis comparing adverse reaction frequency of patients with prior SARS-COV-2 infection that was confirmed by a positive test vs. those with the suspected infection will be performed.

10. Protection of human subjects

Participation is voluntary and only participants providing informed consent (example in Annex 2) should be included in the study. The study should be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements, ethical approval and the guiding principles of the Declaration of Helsinki.

Participants have to give an informed consent upon registration. On the study website, background information about the study and a statement regarding the protection of the privacy of the patients involved is mentioned. Each country will have a dedicated website to allow for differences between countries. Patients can withdraw from the study at any time for any reason, without disclosing this reason for withdrawal.

11. Management and reporting of adverse reactions

Participating organizations, which are national competent authorities, should send all reported adverse reactions to EudraVigilance according to GVP guidance. One report should be created for each participant reporting one or more adverse drug reactions. Follow-up information on adverse reactions will be added to the existing report for each participant. These reported ADRs should be exported from the database and converted to an ADR report according to national and EMA guidelines and formats. In this way, ICSRs will be transferred to EudraVigilance. Duplicate checks need to be conducted by each country before transfer to EMA.

12. Plans for disseminating and communicating study results

The study protocol will be posted on the EU PAS register. Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication and posted in the EU PAS publicly accessible database of results. Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines. A dashboard for monitoring of results will be created as part of the study, and will be made publicly available after EMA agrees.

13. References

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Annex 1: Core data collection

If possible, participants should register before vaccination. They would fill in a short registration form on the study website to receive an e-mail and activate their study account. A study identification number will be assigned to each participant, and for each questionnaire the date of completion will be stored in the database.

Registration form (on the study website; compulsory)

- Participant is a proxy vs vaccine recipient (i.e. whose e-mail address is used for the study?)
- Informed consent (Example in Annex 2)
 - If 12-16 years, or adult unable to fill in the questionnaire: Both vaccine recipient and proxy need to provide informed consent
- Previously received a COVID-19 vaccine?
 - If this was ≤ 2 days ago: complete follow-up on ADRs can still be done for that dose.
- E-mail address & password (to be chosen by the participant)

Baseline questionnaire (compulsory)

- Gender
- Age (e.g. calculated based on date of birth)
- National identification number, if the data can be linked to a vaccination register
- Geographical area (e.g. local health unit)
- Planned vaccination date
- Medical history (current conditions) and pregnancy (closed questions):
 - Impaired immune function (e.g. due to disease or due to treatment)
 - Lung disease (including chronic obstructive pulmonary disease and asthma)
 - Liver disease
 - Neurological disease or injury (including epilepsy)
 - Psychiatric condition (including depression)
 - Cardiovascular disease
 - Hypertension
 - Kidney disease
 - Diabetes
 - Malignancy / cancer
 - Allergy (y/n) with subquestion (checkbox): pollen (hay fever), dust mites, animal (e.g. cat), food (e.g. egg), insect bites and stings, medication, other (namely:...)
 - Other disease:...
 - Pregnancy (subquestion on gestational age)
 - None of the above
- Health care worker/ informal caregiver (y/n)? If yes sub question (radio button): medical doctor, pharmacist, nurse, other paramedical (e.g. midwife, physiotherapist), informal caregiver, other (namely:...)

- Previous infection with SARS-CoV-2 / COVID-19 disease (yes, confirmed with a test; yes but no test; probably but no test; no)?
 - Date of symptom onset
 - Severity (asymptomatic, cold-like symptoms, considerable symptoms without hospitalisation, hospitalized due to symptoms)
- Height (in cm)
- Weight (in kg)
- Current medication (including over the counter medication; ATC-coded locally)
- Vaccinations (other than COVID-19 vaccine) in the past 2 years (namely: ...)

Extra questions for identification of special groups

- Have you ever experienced an allergic reaction in the past after receiving a vaccine (of any kind)?
- Have you ever had any allergic reaction (e.g. anaphylactic shock) that has required emergency treatment or A&E admission?
- Did you take any medication (e.g., antihistamines or corticosteroids) before COVID-19 vaccination to prevent vaccine-related allergy?
 - Please specify: _____
- Are you immunocompromised due to any medical conditions (e.g., HIV/AIDS, transplants, autoimmune diseases, leukaemia/lymphoma)?
 - HIV/AIDS
 - Transplantation
 - Leukaemia/lymphoma
 - Autoimmune diseases
 - Other, please specify: _____
- Do you currently take any medications that affect your immune system (e.g., chemotherapy, glucocorticoids, anti-rheumatics)?
 - No
 - Yes, Please specify: _____
- Will or have you stopped your medication in the period immediately preceding or following the COVID-19 vaccination?
 - No
 - Yes, I have stopped/will stop my medication preceding my COVID-19 vaccination
 - Yes, I have stopped/will stop my medication following my COVID-19 vaccination
 - Yes, I have stopped/will stop my medication both in the period preceding and following my COVID-19 vaccination

Extra baseline questions for pregnant women

- When is your baby due? (You can work this out by counting 40 weeks from the first day of your last period)
 - Dd/mm/20yy (example: 15/March/2022)
- How many weeks pregnant are you? _____ weeks
- Are you pregnant with more than one baby? (Yes / No / Not sure or don't know yet / Prefer not to say)
- During this pregnancy or before this pregnancy, have you experienced or been treated for any of the following conditions? (Please tick Yes or No for each condition)
 - Diabetes (Yes, during this pregnancy/ Yes, before this pregnancy / No)
 - High blood pressure (hypertension) (Yes, during this pregnancy / Yes, before this pregnancy / No)
 - Blood clots (thrombosis) (Yes, during this pregnancy / Yes, before this pregnancy / No)
 - Obesity (Yes, during this pregnancy / Yes, before this pregnancy / No)
- Before this pregnancy, how many times have you been pregnant? _____ times (force the 0 to 10)
- Please indicate the number of babies born full term (after 39 weeks). _____ babies born full term
- Please indicate the number of babies born preterm (born alive before 39 weeks of pregnancy) _____ babies born preterm
- Have you ever had a caesarean section (this is when the baby is removed by an incision-cut in the mum's belly)? (yes, no, prefer not to say, not sure)
- Please, specify how many times you had a caesarean section. _____ times
- Have you ever experienced a stillbirth before (loss of your baby after 20 weeks of pregnancy)? (yes, no, prefer not to say, not sure)
- Please, specify how many times you experienced a stillbirth. _____ times
- Have you ever experienced a miscarriage? (yes, no, prefer not to say, not sure)
- Please, specify how many times you experienced a miscarriage. _____ times
- Have you ever had an ectopic pregnancy (pregnancy growing outside of your uterus)? (yes, no, prefer not to say, not sure)

Additional component to baseline questionnaire – if already vaccinated

- COVID-19 vaccination date
- Immunizer (e.g. GP, employer, municipal health authority, etc.)
- Vaccination site (arm which one...)
- Antipyretics intake (if applicable, as prophylaxis)
- Vaccine brand (GTIN code) and batch number: It should be ensured that the vaccine recipients receive this information themselves, e.g. through a vaccination certificate that is obtained at the point of vaccination, in a vaccination booklet that is updated at the point of vaccination, and/or - less preferable - that they can look it up in a digital account (e.g. linked with the vaccination

register). The participant can then either report the name of vaccine brand or the GTIN, or upload a photo (e.g. of the barcode or GTIN) to the LIM web app.

- In addition, this information should be derived from a vaccination register to improve data quality / completeness.

Verification of vaccination on planned vaccination date (dose 1)

- Have you received the vaccination?
 - If yes:
 - COVID-19 vaccination date
 - Immunizer (e.g. GP, employer, municipal health authority, etc.)
 - Antipyretics intake (if applicable, as prophylaxis)
 - Vaccine brand (GTIN code) and batch number: It should be ensured that the vaccine recipients receive this information themselves, e.g. through a vaccination certificate that is obtained at the point of vaccination, in a vaccination booklet that is updated at the point of vaccination, and/or - less preferable - that they can look it up in a digital account (e.g. linked with the vaccination register). The participant can then either report the name of vaccine brand or the GTIN, or upload a photo (e.g. of the barcode or GTIN) to the LIM web app.
 - In addition, this information should be derived from a vaccination register to improve data quality / completeness.
 - If no:
 - New planned date
 - This same questionnaire will be sent on the new planned date

Q1: 7 days after dose 1

- Have you experienced an adverse reaction vaccination (y/n)? If yes:
 - Injection site reaction on the right side (closed question)
 - Sub-question (closed) on symptoms (redness, warmth, pain, itch, haematoma, swelling, induration)
 - Closed subquestion to assess extensive limb swelling (if swelling and/or redness are ticked)
 - Injection site reaction on the left side (closed question)
 - Subquestion (closed) on symptoms (redness, warmth, pain, itch, haematoma, swelling, induration)
 - Closed subquestion to assess extensive limb swelling (if swelling and/or redness are ticked)
 - Fever (closed question) - sub question on highest temperature that was measured:
 - Category:
 - 37.5 – 37.9 degrees Celsius
 - 38.0 – 40.4 degrees Celsius

- 40.5 – 42.0 degrees Celsius
 - Higher than 42 degrees Celsius
 - Not measured
 - Temperature as continuous variable (1 decimal)
- Chills (closed question),
- Headache (closed question),
- Nausea (closed question),
- Myalgia / muscle pain (closed question),
- Arthralgia / joint pain (closed question),
- Malaise (closed question),
- Fatigue (closed question),
- Other ADR (open question)
- Information collected for each reported ADR:
 - Latency (i.e. date of onset as well as in seconds, minutes, hours, days after vaccination)
 - Outcome (recovered, recovering, not recovered)
 - If recovered: duration of symptoms (date as well as in seconds, minutes, hours, days after onset)
 - Visited a medical doctor/GP because of the adverse reaction? (if there were tests done, the outcomes of these tests will be asked, e.g. blood test or ECG)
 - Was the adverse reaction treated? (including over the counter medication; ATC-coded locally)
 - Impact of the reaction (5-point scale from not severe to very severe)
 - Seriousness according to CIOMS (hospitalisation >24h; life-threatening situation; other medically important reaction). If ticked: open sub-questions.
 - Possibility to upload a picture of the reaction and/or documents such as a hospital discharge letter (participant should not be identifiable).

Q2: 3 weeks after dose 1

Old adverse reactions:

- Outcome of each of the ADRs from which the participant had not (yet) recovered in the previous questionnaire (recovered, recovering, not recovered)
 - If recovered: duration of symptoms (date as well as in seconds, minutes, hours, days, weeks after onset)
- Visited a medical doctor/GP because of the adverse reaction? (if there were tests done, the outcomes of these tests will be asked, e.g. blood test or ECG)
- Was the adverse reaction treated? (including over the counter medication; ATC-coded locally)
- Impact of the adverse reaction (5-point scale from not severe to very severe)
- Seriousness according to CIOMS (hospitalisation >24h; life-threatening situation; other medically important adverse reaction). If ticked: open sub-questions.
- Possibility to upload a picture of the adverse reaction and/or documents such as a hospital discharge letter (participant should not be identifiable).

New adverse reactions: Identical to Q1

Q3 & Q4: 5 & 8 weeks after dose 1

Identical to Q2, and in addition, it includes the following questions:

- Have you received a second dose of the vaccination?
 - If yes:
 - COVID-19 vaccination date
 - Immunizer (e.g. GP, employer, municipal health authority, etc.)
 - Antipyretics intake (if applicable, as prophylaxis)
 - Vaccine brand (GTIN code) and batch number: It should be ensured that the vaccine recipients receive this information themselves, e.g. through a vaccination certificate that is obtained at the point of vaccination, in a vaccination booklet that is updated at the point of vaccination, and/or - less preferable - that they can look it up in a digital account (e.g. linked with the vaccination register). The participant can then either report the name of vaccine brand or the GTIN, or upload a photo (e.g. of the barcode or GTIN) to the LIM web app.
 - In addition, this information should be derived from a vaccination register to improve data quality / completeness.
 - If not: reason for not taking it or for delay? (practical reason, because of the experienced side effects of the first dose, other)

Q5: 3 months after dose 1

Identical to Q3 & Q4, and in addition, it includes the following questions:

- Infection with SARS-CoV2 / COVID-19 disease since vaccination? (yes, confirmed with a test; yes but no test; probably but no test; no)?
 - Date of symptom onset
 - Severity (asymptomatic, cold-like symptoms, considerable symptoms without hospitalisation, hospitalized due to symptoms)

Q6: 6 months after dose 1

Identical to Q5, except that 2 questions are adapted as follows:

- Infection with SARS-CoV2 / COVID-19 disease since the last questionnaire? (yes, confirmed with a test; yes but no test; probably but no test; no)?
 - Date of symptom onset
 - Severity (asymptomatic, cold-like symptoms, considerable symptoms without hospitalisation, hospitalized due to symptoms)

“End of Pregnancy” questionnaire: 45 days after due date

Your pregnancy and delivery (Pregnancy outcome)

- Did you delivered your baby? (Yes / No, I experienced a stillbirth (loss of your baby after 20 weeks of pregnancy / No, I had a miscarriage (loss of your baby before 20 weeks of pregnancy) / No, please specify)
- How many weeks pregnant were you when you had your baby? (the time from the first day of your last menstrual period)? _____ weeks
- Have you been diagnosed with any of the following conditions during your pregnancy?
 - Gestational diabetes (yes, no)
 - High blood pressure (hypertension) (yes, no)
 - Blood clots (thrombosis) (yes, no)
 - Obesity (yes, no)
 - Preeclampsia (yes, no)
 - Intra uterine growth restriction (yes, no)
 - Abnormal foetal doppler (yes, no)
 - Threatened preterm labor (yes, no)
 - Placenta praevia (yes, no)
 - Premature Rupture of Membranes (yes, no)
 - Placental abruption (yes, no)
 - Other, please specifiy (yes, no)

About your baby (Neonatal outcome)

- What is your baby’s gender? (Male/Female)
- Please, tell us your baby weight at birth if known (___Kg, or ___ pounds)
- And her/his height at birth if known (___cm, ___feet___inches)
- Has your baby died in his first two weeks of life? (yes, no, do not)
- Has your baby experienced any of the following conditions? Please tick all that apply
 - neonatal intensive care unit admission for any reason
 - physical birth defect (missing or malformed part of the body)
 - infection (such as infection of the lungs, eye infection, diarrhoea, white/yellow patches in the mouth)
 - hypoglycaemia (the level of sugar in the blood is too low)
 - Physical injury at birth, that is the result of being born
 - Breathing problems at birth (baby was breathing too fast or too slowly at birth)
 - feeding problems at birth (baby had difficulty eating in the first two weeks of life)
 - Hypothermia (difficulty to keep its body temperature)
 - Jaundice (the colour of the skin was/is yellow)
 - Other conditions you would like us to know about _____
- To fill in only if answered No to Q 1.1 in the “End of Pregnancy” questionnaire. You answered that you experienced a stillbirth. If you would like to share what happened please fill in the blank space

Annex 2: Example of informed consent

Either the vaccine recipient and/or their proxy should will provide their e-mail address and fill out the questionnaires. Consequently, there should be different version of the informed consent. Furthermore it is important to note that this example informed consent needs to be adapted to the local standards and requirements.

Purpose of this research

The purpose of this research is to gather information on health complaints which arise after vaccination with the corona vaccine. Furthermore a comparison of the reported complaints will be made between the different corona vaccine. To expand any existing knowledge on the corona vaccine, it is important to gather information on possible health complaints in a structured manner.

Who can participate?

- You are above 16 / 18 years old
- You / Your child (who you will fill in the questionnaires for) will soon receive the first corona vaccine or received the first corona vaccine no more than 2 days ago

Informed consent

Obligatory questions in this registration form are marked with an asterisk (*).

In order to participate in this study we need your consent. Furthermore, you will be asked to provide some general details. As soon as the informed consent has been sent, you will receive an e-mail with an activation link. Once this link has been clicked, the participation is confirmed and definitive. You will receive the first questionnaire which can be filled in immediately. The activation link is valid for a maximum of 48 hours.

For questions, please contact the study team at [name organisation] via [email organisation] or [telephone number organisation].

- I have read the privacy statement and the information regarding this research. Any and all questions I had were answered by contacting [name organisation]
- I understand that participation is voluntary. Furthermore, I understand that I can decide at any moment to stop my participation in this research and do not need to give a reason for my decision.
- I understand that all information will be treated with strict confidentiality.
- I give permission for my data to be used for the purpose of this research, namely to gather information and expand knowledge on possible symptoms which can occur after receiving the corona vaccine. It is important for [name organisation] to know precisely which vaccine was given in order to compare the reported symptoms between the given corona vaccines. Gaining more insight in the relevant medical history of participants, reported symptoms, the nature of these symptoms, the course of these symptoms, possible risk factors and the consequences related to health.

- I understand that my e-mail address will only be used for registration and communication with [name organisation]
 - I understand that my data with the exception of personal data such as e-mail address, postal code and date of birth could be used for European research. Several European countries will perform similar research. Results of this research will be compared to each other.
 - I am 16 /18 years or older
- Hereby I (as parent/guardian) agree with the processing of the data of my child as described above.

Sometimes extra information about reported symptoms is necessary. In this case we would like to be able to contact you. By doing so we are able to have complete and reliable data on the medical situation which is essential for this research.

I give permission (as parent/guardian) to be contacted for extra information about the reported symptoms.

- Yes
- No

Annex 3: List of stand-alone documents

Number	Document reference number	Date	Title
1	<i>DMP Covid-Vaccine-Monitor_in_special_interest_groups_(WP_1).docx</i>	2 Jun 2021	<i>Data Management Plan: Covid-Vaccine-Monitor in Special Interest Groups</i>
2	<i>DMP Covid-Vaccine-Monitor_(WP_5).docx</i>	2-Jun-2021	<i>Data Management Plan: Covid-Vaccine-Monitor</i>
3	<i>CVM DPIA DRAFT version 0.2.docx</i>	26 May 2021	<i>Data Privacy Impact Assessment: Covid-Vaccine-Monitor</i>
4	<i>CVM DPIA DRAFT English.xlsx</i>	26 May 2021	<i>Data Privacy Impact Assessment Questionnaire</i>
5	<i>SLIM DPIA DRAFT version.docx</i>	26 May 2021	<i>SLIM Data Privacy Impact Assessment</i>
6	<i>SLIM DPIA Dutch.xlsx</i>	26 May 2021	<i>SLIM Data Privacy Impact Assessment Questionnaire</i>

Annex 4: WPs collaboration and timelines scheme

ROC20 Covid-Vaccine-Monitor

