Covid-Vaccine-Monitor

Study protocol for Cohort Event Monitoring of safety of COVID-19 vaccines

Version 2.1

25 August 2021

Title	Cohort Event Monitoring of safety of COVID-19 vaccines
Date of last version of protocol	25-08-2021
EU PAS register number	
Active substance	NA
Medicinal product	NA
Product reference	NA
Procedure number	NA
Marketing authorisation holder(s)	NA
Research question and objectives	Primary aim: - To generate incidence rates of patient-reported ADRs of COVID-19 vaccine brand in near real time. Secondary aim: - to describe differences in ADR incidence rates between different vaccine batches used across the participating countries
Country(-ies) of study	Belgium Croatia France Germany Italy The Netherlands United Kingdom
Authors	Monika Raethke (Lareb, The Netherlands) Agnes Kant (Lareb, The Netherlands)
Contributors	Françoise Wuillaume (FAMHP, Belgium) Martine Sabbe (FAMHP, Belgium) Željana Margan Koletić (HALMED, Croatia) Nikica Mirošević Skvrce (HALMED, Croatia) Morana Pavičić (HALMED, Croatia) Barbara Kovačić (HALMED, Croatia) Ivana Ljubičić (HALMED, Croatia) Nicolas Thurin (Université de Bordeaux, BPE, France) Cécile Droz-Perroteau (Université de Bordeaux, BPE, France) Brigitte Keller-Stanislawski (PEI, Germany)

	Ugo Moretti (University of Verona, Italy) Gianluca Trifirò (University of Verona, Italy) Miriam Sturkenboom UMC Utrecht, the Netherlands Joan Fortuny, RTI-HS Xabier García de Albéniz, RTI-HS Alejandro Arana, RTI-HS Estel Plana, RTI-HS Olaf Klungel (Utrecht University, the Netherlands)

1. Table of contents

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
The Netherlands	Pharmacovigilance Centre LAREB	
Italy	University of Verona	
France	University of Bordeaux	
United Kingdom	DSRU	
Germany	Paul Ehrlich Institute (PEI)	
Croatia	HALMED	

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

Version: 2.2

Main authors:
M. S. Raethke, Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands
Dr. A.C. Kant, Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Rationale and background: Intensive monitoring of adverse reactions, 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. A pan-European cohort monitoring system is an important addition to existing spontaneous reporting systems for signal detection. This will enable the collection of patient-reported safety data in near real time and generate incidence rates of ADRs.

Research question and objectives:
Primary aim:
- to generate incidence rates of patient-reported ADRs of COVID-19 vaccine brand in near real time.

Secondary aim:
- to describe differences in ADRs incidence rates between different vaccine batches used across the participating countries

Study design: Prospective cohort study in the general population. In different countries, on the national level, data should be prospectively collected in near real time, directly from a cohort of vaccine recipients. The common core data from different countries will be pooled and analysed at the European level. Vaccine recipients should be asked to fill in questionnaires at baseline, 1, 3, 5 and 8 weeks and 3 and 6 months after vaccination (from the first dose). The exact timing of the sending of the third questionnaire will depend on the vaccination interval between two doses.

Population: Recipients of COVID-19 vaccines in participating countries 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, which may differ per country and target group.

Variables:
- Vaccine brand, vaccine batch number, ADRs, age, sex, height and weight, geographical area, medical history

ADRs: Suspected adverse reactions that are reported after each dose of COVID-19 vaccination, 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.

Data sources: Safety data can be directly reported by vaccine recipients in their local language using the Lareb Intensive Monitoring (LIM) web app, which has been built specifically for patient-reported outcomes. Reported data from European countries using this LIM app can be stored in a dedicated central database. Data can also be collected nationally with non-LIM intensive monitoring tools/apps and countries can store and code data locally and share at regular intervals.

Study size: We include at least 60,000 vaccine recipients in several countries in total.

Data analysis: ADR incidence rates within the vaccinated cohort will be reported cumulatively, overall and for the different vaccine brands, gender, age group, 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

On December 21st, 2020, the first SARS-CoV-2 vaccine was granted conditional marketing authorisation by the EMA. On December 27-28-29 the first vaccination campaigns started in the majority of EU member states. Spontaneous reporting systems are already in place to signal any possible ADRs resulting from the novel vaccines. In addition to existing spontaneous reporting system, cohort event monitoring systems are being put into place to obtain in-depth information of the safety of the vaccines. It will generate more comprehensive safety data, e.g., on incidence, disease course and impact of the adverse reactions.

During the 2009 pandemic, major lessons learned were a need for improved collaboration within Europe, and a common approach for collection of safety data and data-sharing.[1] This would contribute to improved signal detection and timely evaluation of safety signals in a next 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.

7.2 Rationale for the study

Clinical trials prior to licensing collect key information on Adverse Events of Special Interest (AESI) and Adverse Events Following Immunisation (AEFIs) and often include selected persons. During rollout of vaccines, larger and more diverse populations will be vaccinated, which means that a lot can be learned. Certain groups, e.g., those with high-risk co-morbidities or pregnancy, have not been included in pivotal clinical trials. Also, a limited number of vaccine batches are monitored prior to registration, so there is always the risk of a batch-related safety problem.

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

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.
A large-scale cohort event monitoring system allows for the monitoring of newly introduced vaccines or new target groups, in addition to existing spontaneous reporting systems and healthcare database studies (i.e., secondary data), as it is complementary to these systems in several ways. First of all, it is better suited to capture the more frequent adverse reactions, including those that are not medically attended. It generates more comprehensive safety data, e.g., on disease course and impact of the adverse reactions.

8. Research question and objectives

Primary aim:

- to generate incidence rates of patient-reported ADRs by COVID-19 vaccine brand in near real time.

Secondary aim:

- to describe differences in ADR incidence rates between different vaccine batches used across the participating countries,

9. Research methods

9.1 Study design

The study is set up as a cohort event monitoring for a duration of six months after vaccination and will be implemented in several European countries.

The initial study was set up as a cohort event monitoring for the duration of eight months for the Early COVID Vaccine Monitor (ECVM) project but due to an extension, the project will run for an extra 16 months under the COVID Vaccine Monitor (CVM) project. Combined the two projects will take place within two

[2] https://apps.who.int/iris/handle/10665/206144

years, with inclusions starting from 1 February 2021 onwards until the minimal amount of inclusions has been reached.

This protocol is based on protocol of the Early-Covid-Vaccine-Monitor (ECVM), Specific Contract No 05 implementing Framework Contract No EMA/2018/28/PE (Lot 4) which focuses on Cohort Event Monitoring of safety of COVID-19 vaccines in the general population for six months.

The CVM project, which encompasses the extension of the ECVM project, also includes a focus on special groups such as pregnant women, children, the immunocompromised or those who have a history of severe allergy. Due to the fact that participants taking part in the ECVM also include those who belong to these special groups, it was decided to add a subset of questions to the existing ECVM protocol and questionnaires in order to identify these special group participants. With this minor adjustment, it is possible to not only include special groups in the new CVM project but also in the existing ECVM project. The additional questions are only added for those partners also contributing to the special groups of the ECVM/CVM projects. The study and analyses of these special groups is described in a separate protocol.[3]

The following table shows the participating countries and their contribution to the ECVM and CVM projects.

Table 1: participating countries and their contribution to the ECVM and CVM projects.

Country	ECVM	CVM	Special groups (immunocompromised and with allergy history)
Netherlands	X	X	X
Belgium[a]	X		X
Italy	X	X	X
France	X	X	
UK	X	X	X
Germany	X	X	
Croatia	X	X	X

[a] Belgium is not part of the CVM participating countries, but its collected data from the ECVM study might be partially considered and visualize on the CVM dashboard.

[3] 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), protocol submitted to EMA on the 7th of June 2021

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 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 two days after vaccination.

Vaccinees will be asked by e-mail or via a reminder through an app to fill in the 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. For serious adverse reactions or other adverse reactions that need medical clarification clinical follow-up will be performed with consent of the participant.

To get accurate data on the reported adverse reactions, the questionnaires should 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 a two-dose vaccine.

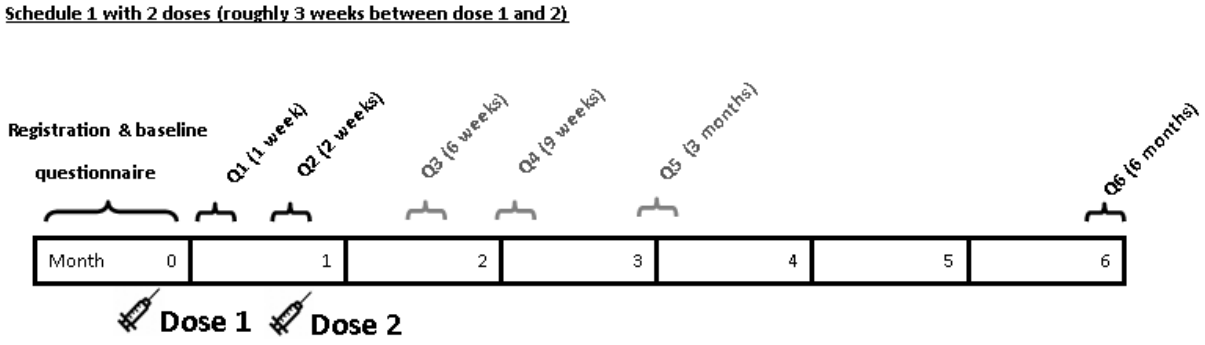


Figure 1: Questionnaire schedule based on 3-week interval between dose 1 and dose 2.

Partners not using the LIM web app have questionnaire scheduling based on the agreements in the ACCESS protocol. Due to the fact that 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 data on the vaccination date and the start date of the adverse reaction in order to calculate time to onset.

Participants who skip a questionnaire will not be able to continue their participation for the full six months, they will be automatically indicated as lost to follow-up by the LIM web app. In case participants with a status of lost to follow-up would like to share information of already started questionnaires and events it is possible to have these questionnaires updated. But they cannot receive new questionnaires.

9.2 Setting

Participating countries

Table 2: participating countries.

Country	Partner	Which app?
The Netherlands	Pharmacovigilance Centre LAREB	LIM app
Italy	University of Verona	LIM app
France	University of Bordeaux	LIM app
United Kingdom	DSRU	LIM app
Germany	Paul Ehrlich Institute (PEI)	Phone app
Croatia	HALMED	Educational tool

Inclusion criteria

Participants to be included should be vaccinated in one of the participating countries in the period February onwards until the minimal amount of inclusions has been reached.
The vaccine recipient or their proxy should:

- register for the study prior to (the first) vaccination or no longer than 2 days after COVID-19 vaccination;
- be able to understand the language of the survey (which should at least be translated into the local official languages);
- be able to register and participate by e-mail;
- provide informed consent (which should at least be translated into the local official languages).

9.3 Variables

9.3.1 Exposure

- Vaccine brand and batch number of each dose: obtained via the vaccine recipient (e.g., number on vaccination certificate, or uploading photo) and/or via linkage with a vaccination register (for example The Netherlands, Belgium) with a personal identification number.
- Vaccine dose number (if relevant).
- Vaccination date.

9.3.2 Outcomes

Participants will be asked to report adverse reactions after vaccination at multiple follow-up time points (Figure 1). The LIM system 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). Furthermore, the participants will

be made aware that they need to contact their own physician if they have questions about their symptoms or if they are worried about the symptoms.

Closed dedicated questions:

- Injection site reaction (redness, warmth, pain, itch, haematoma, swelling, induration)
- Fever/feverishness
- Shivering/chills
- Headache
- Nausea
- Myalgia / muscle pain
- Arthralgia / joint pain
- Malaise
- Fatigue
- COVID-19 positive test and/or (severity of) symptoms (at 3 and 6 months after vaccination)

These adverse reactions are known to frequently occur.

Other adverse reactions:
In addition, it will be asked whether any other adverse reactions occurred (open question / unsolicited). The later follow-up periods should serve to monitor adverse reactions with a longer lag time and to assess the course of previously reported adverse reactions (i.e., outcome, duration of symptoms).
For each reported adverse reaction, date of onset/time to onset, outcome, duration of symptoms (if recovered), severity/impact of the symptoms (including medical assistance & hospitalization) will be asked.

Assessors in the different participating countries will code the reported adverse reactions into MedDRA lower level terms (in English), and determine whether they are serious based on the criteria of the Council for International Organizations of Medical Sciences; CIOMS criteria.[4]

Reported adverse reactions which are considered serious based on the above mentioned CIOMS criteria and other adverse reactions that need medical clarification should be assessed by a qualified assessor. If necessary, follow-up will be requested for verification and upgrading of the clinical documentation. If possible, Brighton Collaboration case definitions will be followed.

[4] https://cioms.ch/wp-content/uploads/2017/01/Group5_Pharmacovigilance.pdf

9.3.3 Measured covariates

Following information should be collected upon enrolment (full description in Annex 1):

- Age and gender,
- Height and weight (to calculate body mass index (BMI),
- Contact details of next of kin (if privacy regulations would allow this)
- Geographical area
- Presence of chronic disease (impaired immune function, lung disease, liver disease, neurological disease or injury, psychiatric condition, cardiovascular disease, hypertension, kidney disease, diabetes, malignancy, allergies, or other disease)
- Pregnancy (incl. gestational age)
- Previous SARS-CoV2 infection and COVID-19 disease (closed questions, incl. date and severity)
- Additional information to determine country-specific target population for vaccination: health care worker, (informal) caregiver, resident of nursing home, …
- Current co-medication and previous, other vaccinations (within previous 2 weeks).
- Immunizer (e.g., GP, occupational health service, municipal health authority)
- Vaccination site (e.g., right/left arm/leg)
- Antipyretics intake around time of vaccination

9.4 Data sources

Data on vaccination (both 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 and/or elderly population) can participate via a proxy (e.g. family member).
Depending on the availability and accessibility of vaccination registers, data on vaccine brand and batch number will also be collected from this register.

9.5 Study size

Goals for minimum number of inclusions

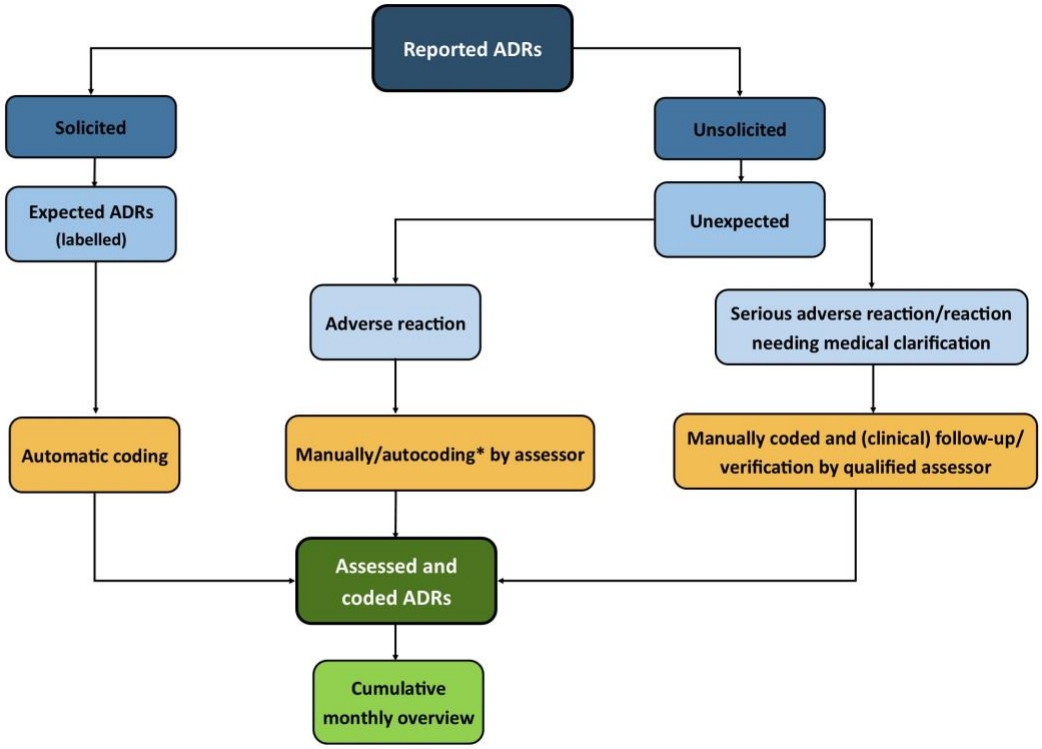
Table 3: Goals for minimum number of inclusions.

Country	Partner	**Goal minimum inclusions ECVM**	**Goal minimum inclusions CVM**	**Start inclusions**
The Netherlands	Pharmacovigilance Centre LAREB	5000	12.000	February 2021
Belgium	Federal Agency for Medicines and Health Products (FAHMP)	2000	-	May 2021
Italy	University of Verona	2000	4.000	May 2021
France	University of Bordeaux	2000	4.000	May 2021
United Kingdom	DSRU	1000	2.000	May 2021
Germany	Paul Ehrlich Institute (PEI)	5000	15.000	February 2021
Croatia	HALMED	1000	2.000	February 2021
Total		**18.000**	**39.000**	

9.6 Data management

The LIM web app will be used for data collection in six of the participating countries. 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 and including the second day after vaccination and are asked to log in on their account on the website. They will also be able to download the LIM web app to their smart phones where they can access their questionnaires online and receive reminders to fill in questionnaires. In their personal account, a baseline questionnaire will be available. Further invitations are sent via e-mail according to the schedule as described in paragraph 9.1. to fill in subsequent questionnaires are e-mailed on the seventh day, as well as 3, 5 and 8 weeks and 3 and 6 months after vaccination (from the first dose) in the scenario that the time period between vaccine doses is three weeks. Each country will have their own study website with one or more language sections.

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 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 data quality and minimize time and resources needed for coding.



*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: Flow chart of reported ADRs and analysis.

Data from all partners using the LIM web app will be stored in the Netherlands. Partners will have access to the database of the automatically received questionnaires of participants in their own country using the LIM admin section and a LIM analysis database. Both the admin section and the LIM analysis database of each country contain identifying information but can only be accessed by the partners of that country. The LIM questionnaires will also pseudonymised and transformed into ICSR reports in an R3 format (Figure 3). This ICSR data can only be accessed and downloaded by the country that this data belongs to. If a partner is an NCA or working with an NCA, these reports need to be sent to the EudraVigilance system (GVP module VI). As is the case for spontaneous reports to EudraVigilance, these reports need to be checked for duplicates. This process of sending ICSR reports and duplicate check are the responsibility of each country.

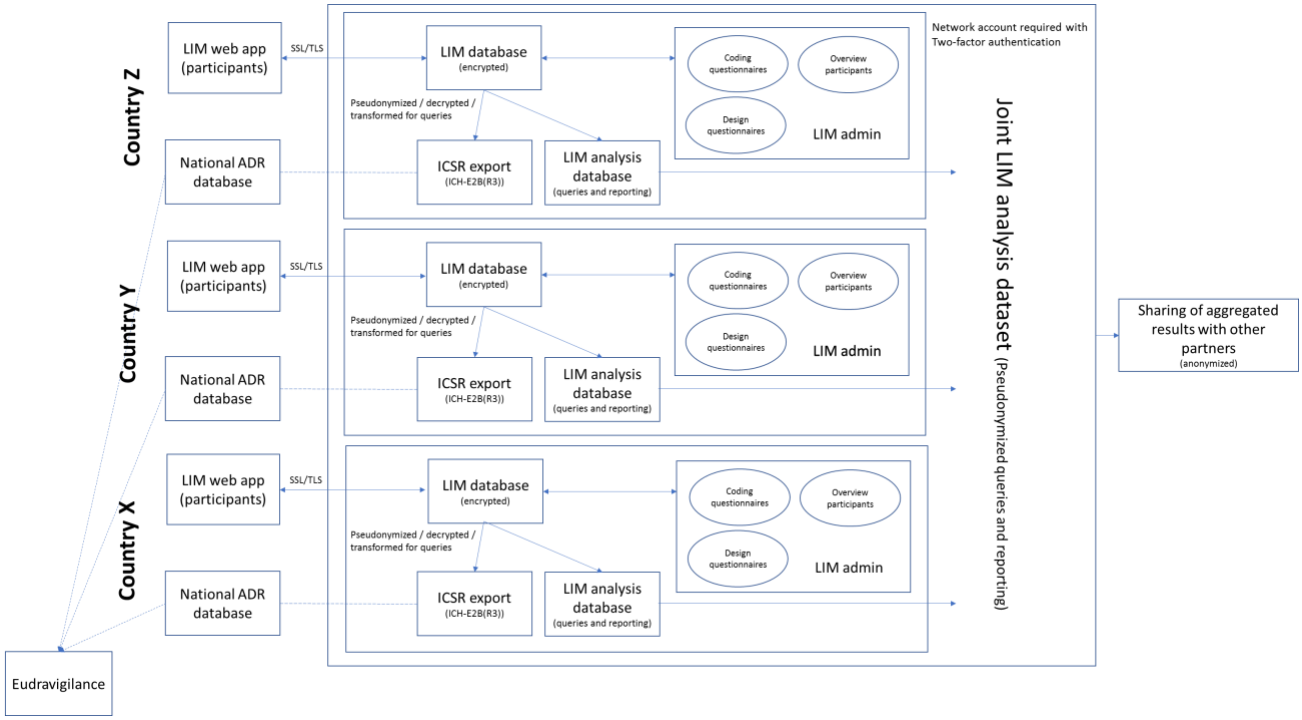


Figure 3: Data management of the LIM web app.

Data in the LIM database will also be anonymised and pooled to be shared with all partners, both LIM web app collected data and data from other apps, and analysed. This data will be harmonized between the six countries using the LIM web app and the two countries using different tools for the collection of the core data at the same follow-up periods. These data will be pooled on aggregated level. 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. In order to be able to perform stratified analyses on this data, countries not using the LIM web app need to use the same definitions for strata of interest (e.g., with different indications for vaccination, according to age, and/or previous exposure to SARS-CoV2).

9.7 Data analysis

Main analyses:

A description of the population at inclusion will be made by participating parties, comprising of the number of patients included in the cohort, distribution of gender, age categories (to be defined), country and additional core data as described in the Annex 1.

In addition, the dynamics of national vaccine distribution should be described, including at least vaccine coverage and target groups for vaccination. Furthermore, adherence to the recommended vaccination schedules should be monitored (including immunisation interval and mixing of vaccine brands and batches).

A dedicated cumulative structured overview of numbers and incidence rate of all adverse reactions per vaccine will be provided, overall, and also stratified by vaccine brand, country, gender and age group. For each ADR, incidence rate with its 95% confidence interval (CI) will be reported by COVID-19 vaccine brand

and dose. Overviews of aggregated data will be made available in a dashboard. Age/sex standardised incidence rates will be calculated to account for different vaccination strategies across age/sex groups by vaccine brand in the different countries.

A statistical analysis plan for the comparisons will be developed with WP4 (methods), since we observe strong channelling due to targeted roll out 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 and 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).

Sensitivity analyses:
Cohort event monitoring is based on solicited and unsolicited adverse vaccine events (suspected to be related to 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), this 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 (WP3) from the participating countries. 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 which 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 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) and according to the ENCePP code of conduct (European Medicines Agency 2018). All partners have experience in conducting pharmacoepidemiological research and researchers trained in pharmacoepidemiology do the research.
Workshops should be 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 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 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. If privacy regulations allow this, next of kin should be contacted for a random sample of non-responders, to assess whether loss to follow-up is selective.
- 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 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.
- 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 to detect 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.
- Many unknown factors surrounding availability of vaccines and the impact it has on national vaccine strategies call for regular interim checks to assess inclusions.

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

Harmark, L., F. van Hunsel, E. Hak, and K. van Grootheest. 2011. 'Monitoring the safety of influenza A (H1N1) vaccine using web-based intensive monitoring', *Vaccine*, 29: 1941-7.

Mackenzie, I. S., T. M. MacDonald, S. Shakir, M. Dryburgh, B. J. Mantay, P. McDonnell, and D. Layton. 2012. 'Influenza H1N1 (swine flu) vaccination: a safety surveillance feasibility study using self-reporting of serious adverse events and pregnancy outcomes', *Br J Clin Pharmacol*, 73: 801-11.

van Balveren-Slingerland, L., A. Kant, and L. Harmark. 2015. 'Web-based intensive monitoring of adverse events following influenza vaccination in general practice', *Vaccine*, 33: 2283-88.

Annex 1: Proposal 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 (closed question; e.g. NUTS2 or 3 area)
- 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-CoV2 / 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

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)
        - 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)
    - 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 subquestions.
    - 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

<u>Old adverse reactions:</u>

- 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)
- Seriousness according to CIOMS (hospitalisation >24h; life-threatening situation; other medically important adverse reaction; disability). If ticked: open sub-questions.

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

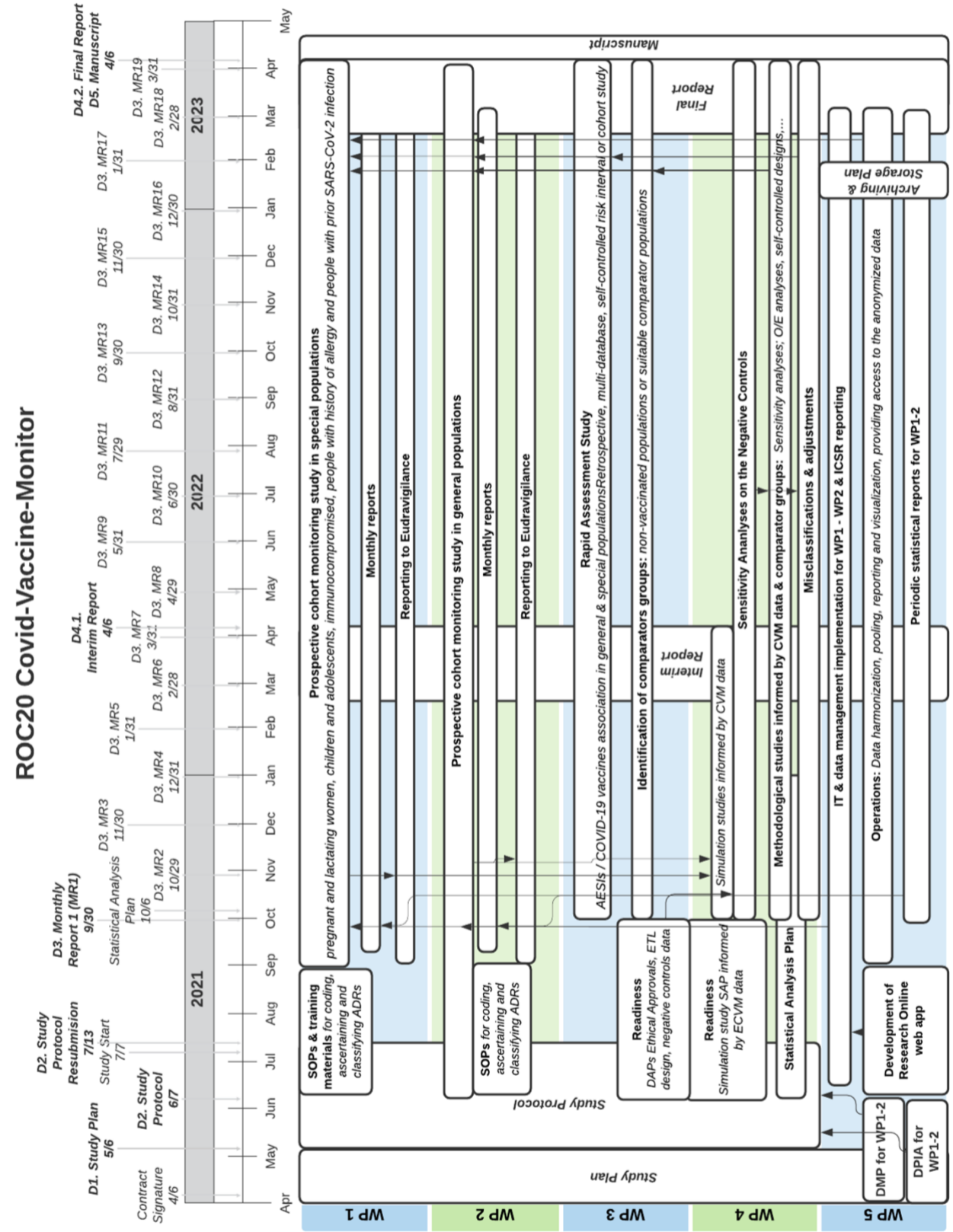
  - Hereby I (as parent/guardian) agree with the processing of the data of my child as described above.

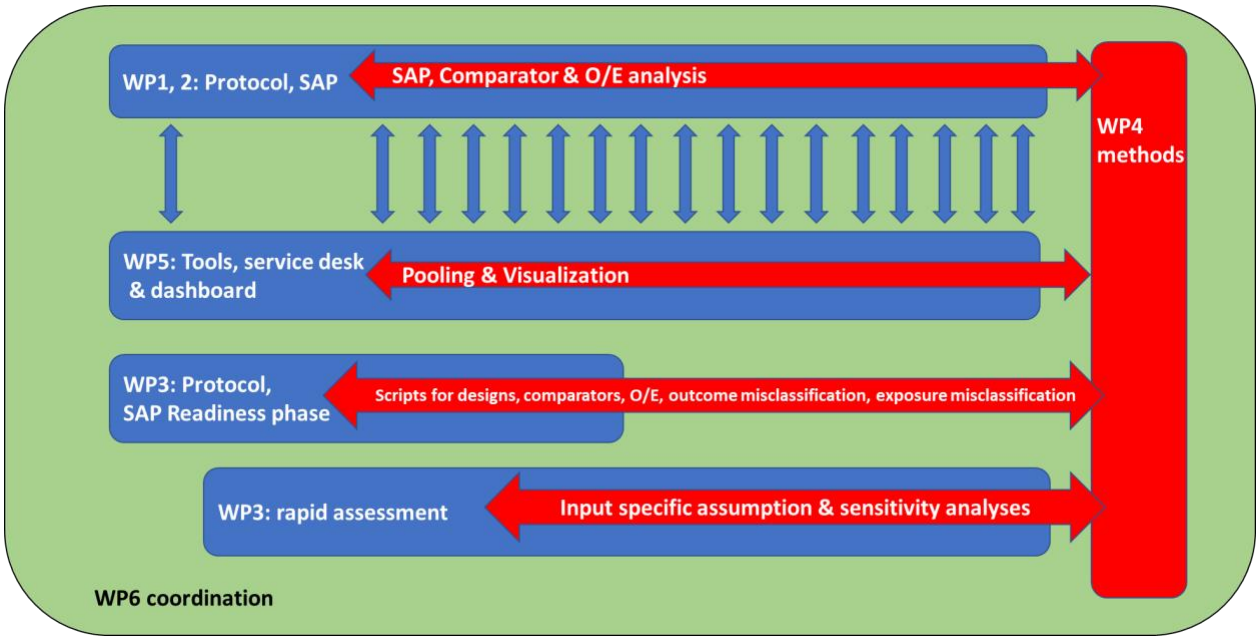
Sometimes extra information about reported symptoms is necessary. In this case we would like to be able to contact you. By doing so we are able to have complete and reliable data on the medical situation which is essential for this research.

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

- Yes
- No

Annex 3: WPs collaboration and timelines scheme




WP1, 2: Protocol, SAP
SAP, Comparator & O/E analysis
WP4 methods
WP5: Tools, service desk & dashboard
Pooling & Visualization
WP3: Protocol, SAP Readiness phase
Scripts for designs, comparators, O/E, outcome misclassification, exposure misclassification
WP3: rapid assessment
Input specific assumption & sensitivity analyses
WP6 coordination