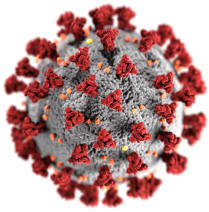
Cohort event monitoring to assess safety of COVID-19 vaccines using patient reported events, a protocol template from the ACCESS project

ACCESS

vACCine covid-19  monitoring readinESS

This protocol can be used by organizations for monitoring COVID-19 vaccines post-introduction. Please reference as

Meurs L, Kant A et al. Cohort event monitoring to assess safety of COVID-19 vaccines using patient reported events, a protocol template from the ACCESS project. EUPAS 38915

DISCLAIMER

This protocol has been accepted by EMA as a deliverable of the framework contract No EMA/2018/28/PE, taking into account the comments received from EMA. The protocol expresses the expertise of the authors and the ACCESS consortium as well as feedback received from EMA. It may not be understood or quoted as being made on behalf, or reflecting the position of the European Medicines Agency or one of its Committees or Working Parties

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Research question and objectives	Primary aim: - To generate incidence rates and to describe patterns (e.g. course and impact) of patient-reported AEFIs by COVID-19 vaccine brand on both the national and European level in near real time. Secondary aims: - to describe differences in AEFI patterns between different vaccine batches used across the participating countries, - to identify possible risk factors for AEFI The following questions should be answered: - What are the reported AEFIs, for each vaccine, in each country? - What are the frequencies of reported AEFIs for each vaccine, in each country? - What is the course of reported AEFIs (latency time, outcome, recovery time)? - What is the impact (medical assistance, hospitalisation, treatment, severity) of reported AEFIs? - Are there possible risk factors for AEFIs and AESIs
Country(-ies) of study	
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2. List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
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
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
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

Sponsor:	
name, degrees, job title	name, degrees, job title
name, degrees, job title	name, degrees, job title
name, degrees, job title	name, degrees, job title

Collaborating Institutions (by alphabetical order)	Study Sites	Key persons

4. Abstract

Title: Cohort event monitoring of COVID-19 vaccine safety in Europe using patient-reported outcomes: a template protocol from the ACCESS project

Version: 16

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Rationale and background: Intensive monitoring of adverse events following immunization (AEFI), 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 upcoming COVID-19 vaccines, a pan-European intensive monitoring system would be an important addition to existing spontaneous reporting systems for signal detection. This would enable the collection of patient-reported safety data in near real time such as the frequency, potential risk factors for AEFIs, and the characteristics like course and impact (medical assistance, hospitalisation, treatment, severity) of AEFIs.

Research question and objectives:
Primary aim:

- To generate incidence rates and to describe patterns (e.g. course and impact) of patient-reported AEFIs by COVID-19 vaccine brand on both the national and European level in near real time.

Secondary aims:

- to describe differences in AEFI patterns between different vaccine batches used across the participating countries,
- to identify possible risk factors for AEFIs.

The following questions should be answered:

- What are the reported AEFIs, for each vaccine, in each country?
- What are the frequencies of reported AEFIs for each vaccine, in each country?
- What is the course of reported AEFIs (latency time, outcome, recovery time)?
- What is the impact (medical assistance, hospitalisation, treatment, severity) of reported AEFIs?
- Are there possible risk factors for AEFIs and adverse events of special interest (AESIs)?

Study design: Prospective cohort study. 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, 6 and 8 weeks and 3 and 6 months after vaccination (from the first dose). The exact timing of the sending of the second 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 one questionnaire filled out after vaccination. Participants will be recruited before or at the moment of vaccination, which may differ per country and target group.

Variables:

- Vaccines, AEFIs, age, sex, height and weight, geographical area, medical history

Events: Adverse events that are reported after each dose of COVID-19 vaccination, by the patient. Incoming serious adverse events (SAEs) and AESIs or other events that need medical clarification will be assessed by a qualified assessor also with respect to contributing factors on intrinsic and extrinsic causality. If necessary, 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 would recommend to include at least 30,000 vaccine recipients in several countries per brand in total, which should allow for the detection of AEFIs with a frequency ≥1:10,000 on the European level based on the rule of three (Onakpoya 2018).

Data analysis: AEFI frequencies within the vaccinated cohort should be reported cumulatively every month, overall and for the different vaccine brands, doses and batches where available. The course of reported AEFIs (latency time, outcome, recovery time) and impact (medical assistance, hospitalisation, treatment, severity) should be assessed. Risk factor analyses should be performed for expected AEFIs and AESIs.

5. Amendments and updates

Date	Amendment	Justification	Protocol Section

6. Deliverables and Milestones

Milestone	Planned date	Submission date EMA

Template protocol submitted to EMA advisory board	30 November 2020	
Final protocol	30 November 2020	15 December 2020
Report on feasibility	30 November 2020	15 December 2020

7. Rationale and Background

7.1 Background

Research on vaccines against the novel coronavirus (SARS-CoV-2) is being conducted all over the world. Efforts are being made to accelerate the development of the vaccines. On October 29th 2020, 45 candidate vaccines were in clinical evaluation.[1]
In the available literature, different terms are used for proposed type of primary data collection in this template protocol – from (web-based) intensive monitoring, cohort event monitoring to participant-centred active surveillance of AEFIs. Torre *et al* and Cashman *et al* have recently reviewed intensive monitoring studies that have been published up to 2016. Currently, a cohort event monitoring is performed for Dengvaxia in Brazil, Mexico and the Philippines.[2]

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.[3] 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.

[1] www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
[2] www.who.int/news-room/q-a-detail/dengue-vaccines
[3] www.ema.europa.eu/en/documents/report/pandemic-report-lessons-learned-outcome-european-medicines-agencys-activities-during-2009-h1n1-flu_en.pdf

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.

AEFIs can comprise 5 different types[4]:

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 would be very useful for newly introduced vaccines or for 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 events, including those that are not medically attended. It generates more comprehensive safety data, e.g. on disease course and impact of the adverse events. Moreover, in contrast to spontaneously reported data, the denominator of the studied cohort is known (in real time) so that AEFI frequencies can be calculated, and directly compared to pre-licensure data. Finally, intensive monitoring is timelier and probably will be more sensitive to find unexpected AEFIs compared to secondary data.

8. Research question and objectives

Primary aim:

- To generate incidence rates and to describe patterns (e.g. course and impact) of patient-reported AEFIs by COVID-19 vaccine brand on both the national and European level in near real time."

Secondary aims:

- to describe differences in AEFI patterns between different vaccine batches used across the participating countries,
- to identify possible risk factors for AEFI

The following questions should be answered:

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

- What are the reported AEFIs, for each vaccine, in each country?
- What are the frequencies of reported AEFIs for each vaccine, in each country?
- What is the course of reported AEFIs (latency time, outcome, recovery time)?
- What is the impact (medical assistance, hospitalisation, treatment, severity) of reported AEFIs?
- Are there possible risk factors for expected AEFIs and AESIs?

9. Research methods

9.1 Study design

The study should be a prospective cohort study. The study should start when COVID-19 vaccination campaigns are implemented in one or more participating countries. Consequently, the monitoring system should be in place before the first doses are administered.

The way of recruitment should depend on the possibilities and infrastructure per country and can be advertised in different ways (e.g. through mainstream and social media, by health care providers, and employers). Recruitment can be done at the vaccination visit, physicians can recruit patients being vaccinated in-clinic, health care workers can be invited through registrations or their occupational health service. Or, if possible, the invitation for receiving the vaccine and the invitation for participating in the study should be sent simultaneously. Vaccine recipients should be directed (e.g. through a hyperlink or QR code on a leaflet with the study information) to the national study website where they can find further information about the study and where they can register. Vaccine recipients should provide informed e-consent and be surveyed with a web-based app (web app) or other tool available in the participating country. In all tools, the timing of data collection and core data should be the same (Figure 1). Participants should ideally register before they receive first dose in order to minimise preferential recruitment of vaccine recipients experiencing reactogenicity. Recruitment before vaccination may however not be feasible in all settings. To increase the number of participants that can be included into the cohort, recruitment should also be possible up to the 2nd day after vaccination.

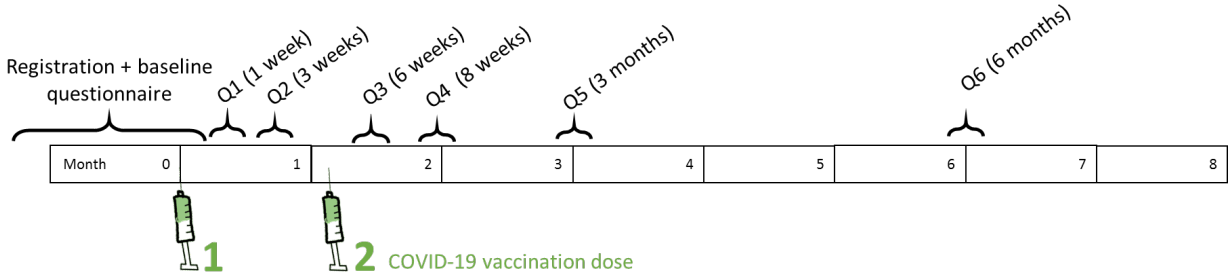


Figure 1: Timing of LIM questionnaires before and after COVID-19 vaccination
We here assume that the vaccine(s) that will be marketed have a 28-day vaccination interval. The exact timing of the questionnaires for 2 doses will depend on the immunisation schedule. Q refers to the different questionnaires after vaccination (e.g. Q1= questionnaire 1).

9.2 Setting

This study can be conducted in each of the European member states. The requirements are:

- harmonization of the timing of data collection and core data;
- willingness and ability to share results (pseudonymized data) every month;
- ability to recruit at least 500 participants (i.e. for countries with a relatively small population size);
- compliance with the General Data Protection Regulation (GDPR).

Inclusion criteria for participants:
Participants to be included should be vaccinated in one of the participating countries in 2021, and either the vaccine recipient or their proxy should:

- register for the study prior to vaccination or no longer than 2 days after COVID-19 vaccination
    - if vaccinated with a vaccine that requires multiple doses for complete vaccination, this should be at most 2 days after the first dose;
- be able to understand the language of the survey (which should at least be translated into the local official languages);
- be reachable 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 (global trade item number; GTIN): obtained via the vaccine recipient (e.g. number on vaccination certificate, or uploading photo) and/or via linkage with a vaccination register, if possible)
- Vaccine dose (if relevant)
- Vaccination date

9.3.2 Outcomes

Participants should be asked to report events 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). 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.

Solicited events
Closed dedicated questions (***solicited***):

- 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)

The solicited AEFIs are known to frequently occur. Additional events should be added to or deleted from the above list as more information from clinical studies becomes available.[5]

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

Assessors in the different participating countries should code unsolicited reported AEFIs into MedDRA lower level terms (in English), and determine whether AEFIs are serious (criteria of the Council for International Organizations of Medical Sciences; CIOMS criteria)[6].

Incoming SAEs or AESIs, and other events that need medical clarification should be assessed by a qualified assessor according to (inter)national guidelines (GVP) that also apply to spontaneous reports. Need for medical clarification should be assessed by a qualified assessor. Also, the assessor should describe the factors contributing to intrinsic and extrinsic causality (such as, but not limited to, causes for the event other than vaccination). If necessary, follow-up will be requested for verification and upgrading of the clinical documentation. If possible, Brighton Collaboration case definitions are followed.

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 detail of next of kin (if privacy regulations would allow this)
- Geographical area

[5] https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/
[6] https://cioms.ch/wp-content/uploads/2017/01/Group5_Pharmacovigilance.pdf

- 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 years).
- 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 should 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).

If possible in the country, depending on the availability and accessibility of vaccination registers, data on vaccine brand and batch number (GTIN code) should be collected through (automatic) linkage with this register.

9.5 Study size

The more countries participate in the study, the lower this limit of detection for (very) rare AEFIs would become. If 30,000 participants would be followed up in total, this would allow for the detection of rare AEFIs with a frequency of ≥1:10,000 on the European level. If 60,000 participants would be followed up in total, this would allow for the detection of rare AEFIs with a frequency of ≥1:20,000 on the European level (Eypasch et al. 1995).

At the same time, a sample size of 6,000 would enable an estimation of the frequency of common AEFIs with a confidence interval of maximally +/- 1.3% (using the formula for calculation of random error in simple random sampling: 95% CI = $p \pm z \cdot \sqrt{p \cdot (1-p) / n}$). This means that the precision would be +/- 1.3% for an AEFI frequency of 50%, and +/- 0,6% for a frequency of 5%.

9.6 Data management

The LIM web app can be provided to organizations for data collection in other countries. In this web-based app, after invitation, the vaccine recipient should register on a national research website as participant. It is recommended when possible in terms of resources, to also make the optional choice for phone based questionnaires possible.
Upon providing informed consent, participants should create a study account in order to receive the online questionnaires. 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. There, in the personal account, a baseline questionnaire is available. Further invitations to fill in subsequent questionnaires are e-mailed on the seventh day, as well as 3, 6 and 8 weeks and 3 and 6 months after vaccination (from the first dose). It is expected that most adverse events occur within 72 hours after vaccination. In addition, most of the well-known AEFIs recover within five days after vaccination. Therefore, the first questionnaire on AEFIs is available on the seventh day after vaccination to retrieve most information on recovery and reduce recall bias. Subsequent questionnaires serve to obtain information about AEFIs with later onset (Figure 1). In these questionnaires, also information should be obtained on course and outcome of previously reported AEFIs. The LIM system is smart in the sense that the questions on course and outcome will only appear for AEFIs from which the participant had not yet recovered when he or she filled in the previous questionnaire. Information on SARS-CoV2 infection and on COVID-19 disease should be collected in the last questionnaires (3 and 6 months after vaccination). If two doses of a vaccine are required, now it seems most likely that the second dose should be given after 28 days. In that case, reactogenicity of the second dose can be captured in the 6 weeks' questionnaire. Participants that do not complete the vaccination schedule (e.g. because of adverse events following the first dose) or skip a questionnaire should be continued to follow up (Figure 1).

Each country should have their own study website with one or more language sections. Data from all partners using the LIM web app will be stored in the Netherlands. Partners – and only they – should have access to the database of the automatically received questionnaires of participants in their own country (including identifying information) using the LIM admin section. For each country there also should be a LIM analysis database with pseudonymised data (Figure 2).

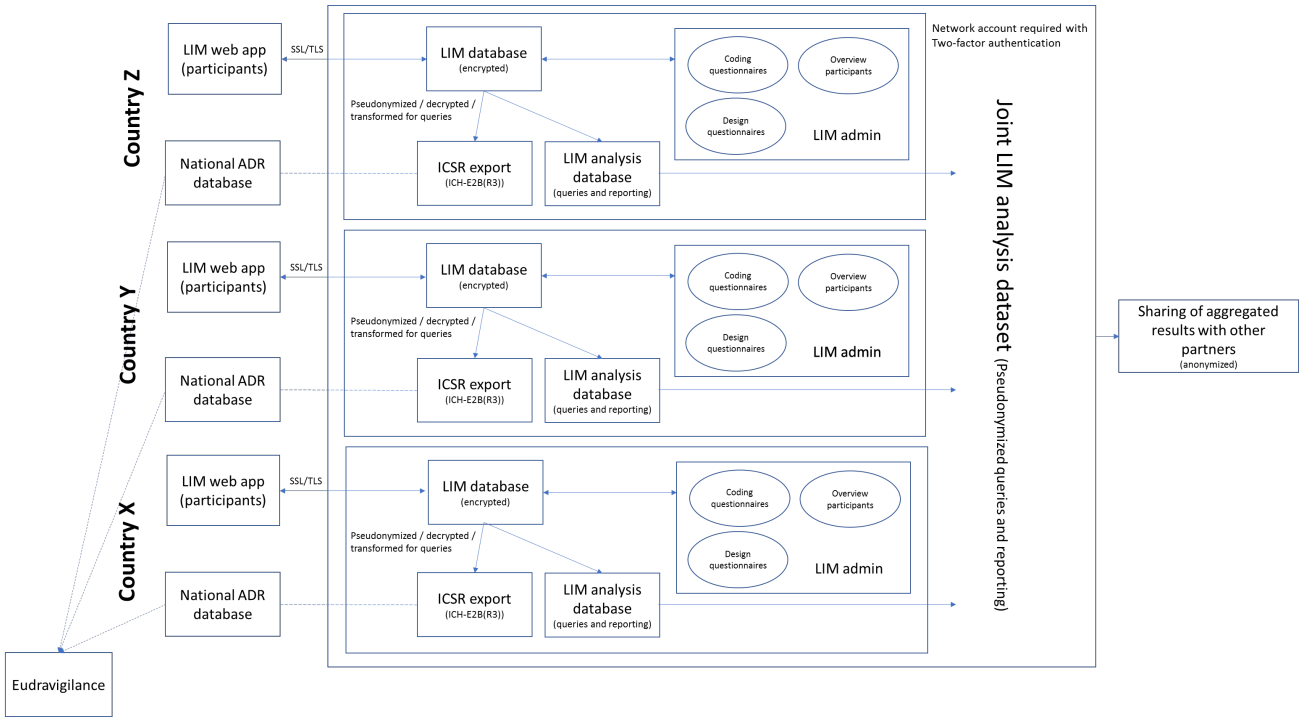


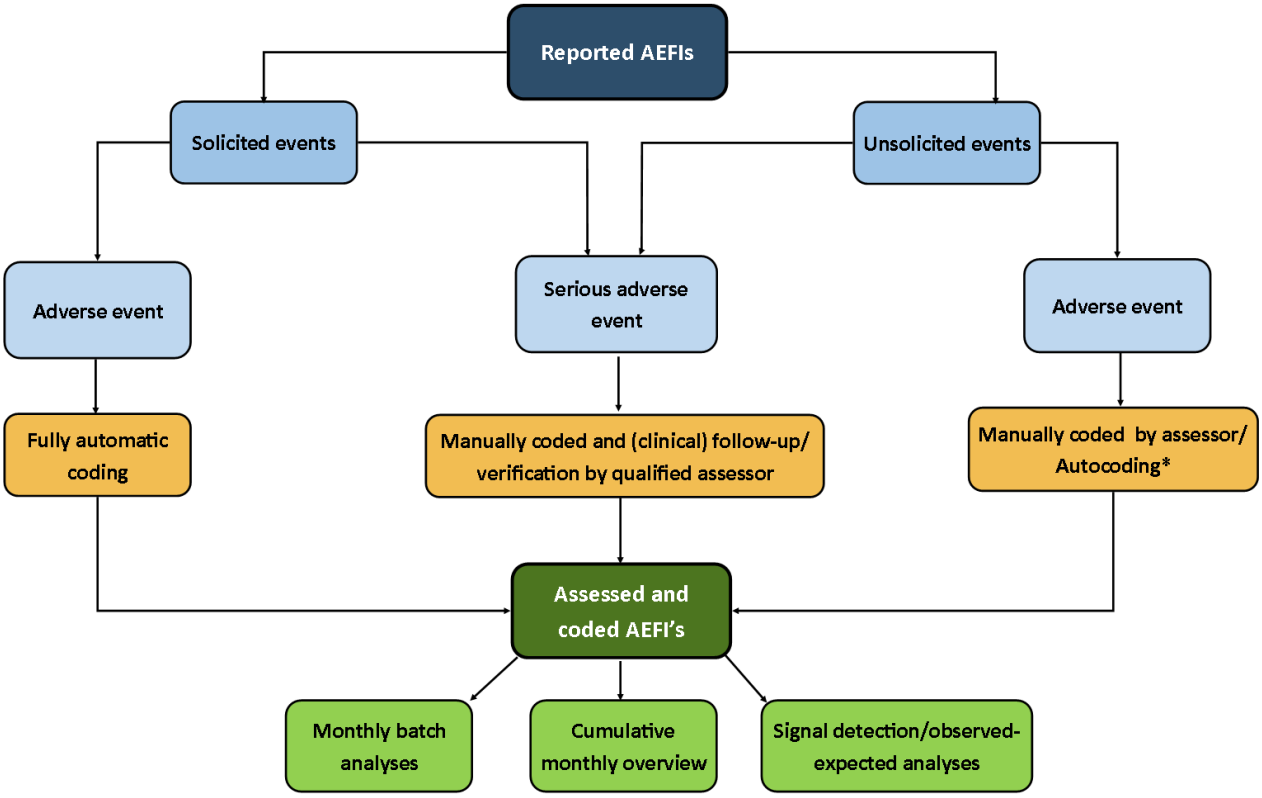
Figure 2: Data management of the LIM web app

In addition, data collection should be harmonized between countries using the LIM web app and countries using different tools that are appropriate for the collection of the core data at the same follow-up periods. These data should be pooled on aggregated level with data from countries not using the LIM app every month. Scripts should be developed and distributed for local deployment of data analysis. The aggregated results produced by these scripts should 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).

It is likely that the target population will change over time from priority population (health care workers and/or population with risk-elevating morbidity) to the more general population. The distribution of the vaccines will depend on the target groups and are likely to vary between countries (e.g. at the GP's, through occupational medical service, in hospitals and care homes, mass vaccination, pharmacies, municipal health offices) and over time. In all scenarios the prospective monitoring preferably should start at the moment the vaccination will start.

9.7 Data analysis

A description of the population at inclusion should 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. These metadata should be compared with the reported information. Also vaccine brand and batches that are reported by the participants need to be monitored whether the study population adequately reflects the source population. Furthermore, adherence to the recommended vaccination schedules should be monitored (including immunisation interval and mixing of vaccine brands and batches).



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

Figure 3. Flow chart of reported AEFIs and analysis

9.7.1 Overview

Various types of AEFIs can occur in the cohort of patients being vaccinated. These different AEFI categories require a different methodological approach (Figure 3). Most AEFIs that are reported in this cohort are probably expected and labelled, and also occurred during pre-licensure studies. They are likely to be causally associated with the vaccine under study (but not necessarily on the individual level). A second category consists of serious AEFIs that are 'unlabelled'. These AEFIs will be relatively rare and should therefore be captured as unsolicited events. These AEFIs might be anticipated due to experiences with other marketed vaccines, and are already highlighted as AESIs. However, also unexpected AEFIs that are not (yet) categorized as AESIs might occur.

A dedicated cumulative structured overview of all AEFIs per vaccine should be provided every month, which will be split into solicited and unsolicited AEFIs, and AESIs, by age group, at-risk conditions and concurrent use of other vaccines.

Characteristics like the frequency of reported AEFIs and seriousness, should be provided in the overview. These overviews should be analysed on a national level and on an international level, based on a pooled analysis of the aggregated data. The national overviews should be made available to national competent authorities (NCAs).

9.7.2 Expected AEFIs (all labelled)

The large majority of AEFIs that will be collected will be expected and already labelled AEFIs. The most common expected AEFIs should be captured as solicited events so that they can be fully automatically MedDRA-coded. This will improve data quality and facilitate timely data analysis. Less common expected AEFIs should be captured as unsolicited events. Assessors will assign MedDRA codes to these events as they are reported for the first time. At the same time, this process will create a library of patient-reported events with assigned MedDRA codes. From this library, MedDRA codes can be assigned automatically when the same event is reported again in the same language and country. This process of autocoding will similarly help to improve data quality and minimize time and resources needed for coding.
Incidence rates of expected AEFIs within the vaccinated cohort will be assessed every month overall, for different vaccine brands, age group, gender, and -where available- for batches.
Descriptive analysis should be performed per AEFI, and consist at least of the following: The distribution of the reported latency time should be visualised and summarized (e.g. mean with confidence interval). Similarly, the impact should be determined, by calculating the percentage (with confidence interval) of participants reporting different severity scores (on a 5-point scale). Furthermore, the percentage of participants that recovered from the event should be calculated. For the subgroup that recovered, the duration of symptoms should be visualized and summarized.
To interpret rates, a comparison might be made with the data observed in vaccinated groups from pre-licensure trials. When available, the observed incidence rates in the placebo and active arms should be compared to the reported frequency in the prospective cohort considering characteristics of the patient groups. Incidence rates should be standardized for the distribution of age and sex in the different study populations, if possible.
An association between vaccine and AEFI should be explored in more detail if a frequency substantially deviates (more than 25% expected frequency. An association (potential signal) should also be studied in detail at the discretion of the qualified assessor if other characteristics (e.g. latency time, duration, impact) are unexpected.

9.7.3 Unexpected AEFIs (unlabelled)

Besides expected, labelled events, also unexpected, unlabelled AEFIs can occur. These should be relatively rare and therefore captured as unsolicited events. These AEFIs should be assessed and coded by qualified assessors upon data entry into serious and non-serious. In addition, AESIs should be identified (see also 9.3.2 and 9.7.1). Incoming SAEs (including AESIs) and other events that need medical clarification should be assessed by a qualified assessor. The assessor should describe the factors contributing to intrinsic and extrinsic causality (such as, but not limited to, causes for the event other than vaccination). If necessary, follow-up will be requested by e-mail for verification and upgrading of the clinical documentation.

For AESIs, the observed frequency in the cohort should be compared with the age-specific incidence rates of AESIs in the ACCESS project[7,8]. If possible, incidence rates should be standardized for the distribution of age and sex in the different populations. An association (potential signal) should be explored in more detail if the observed number is higher than the expected (more than 10% increase) or in case other characteristics (e.g. the time to onset, duration, impact) are unexpected.
For the other unexpected AEFIs it can be decided, based on the overviews (9.7.1), to carry out a detailed analysis. Since clinical aspects should be decisive for this selection; depending on the reported AEFI, an observed versus expected ratio may be calculated depending on data available in literature.

9.7.4 Vaccine batch analysis

Since vaccines will be produced in batches, quality issues related to the production should be monitored. Every month, it should be assessed, based on pooled analysis of the aggregated data, whether there are COVID-19 vaccine batches with increased frequency of AEFIs related to reactogenicity (MedDRA terms to be decided upon) compared to the other COVID-19 vaccine batches of the same brand. In case of statistically significant differences, additional analyses should be carried out.

9.7.5 Interim and overall analyses

In addition to the monthly overviews, interim analysis might be done first on 10,000 participants with data up to 3 months after complete vaccination, per vaccine brand. The overall analysis should be performed on 30,000 participants with data up to 3 months after complete vaccination, per vaccine brand. The analyses are similar as described in paragraphs 9.7.1, 9.7.2, and 9.7.3 and should be conducted on a national as well as international level (based on a pooled analysis of the data). In addition, a multivariable risk factor analysis will be carried out on individual-level data to study potential risk factors for common AEFIs and – if possible, depending on case numbers – for AESIs. Potential risk factors include vaccine brand, immunizer, geographical area, age, sex, co-morbidity and (no) prophylactic intake of antipyretics.
To study the potential influence of selection bias, by preferential recruitment of vaccine recipients presenting with one or more AEFIs, a sensitivity analysis should be carried out per country. These analyses should include a calculation of incidence rates in vaccine recipients who registered no later than the day of the vaccination.
To study the potential influence of the population that is lost to follow up, another sensitivity analysis should be done (per country) to see if the outcomes are in line with those from the primary analysis and would lead to similar conclusions.

[7] https://brightoncollaboration.us/priority-list-aesi-covid/
[8] http://www.encepp.eu/encepp/viewResource.htm?id=37274

9.8. Quality control

The study should 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 AEFIs 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 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 SAEs may not be able to return the questionnaires and this may lead to an underestimation of the frequency of SAEs. 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.
- Since the AEFIs will be reported by patients and not by health care providers, there could be some misclassification. For (medically attended) SAEs, the necessary information to ascertain the SAE and to inform causality, will be collected via the participant's physician (if consent is provided for this). In addition, the participant has the possibility to directly upload medical documentation to the LIM web app (see Annex 1).
- Data on vaccine brand and batch numbers may be suboptimal (depending on possibilities per country). Since GTIN numbers will be available on secondary packaging only we recommend that patients make a picture of the package or of a barcode slip that is provided.
- Although background incidences should be made available for specific AESIs (based on electronic health record databases), other AEFIs may be observed in practice with unknown background incidences. This may be mitigated by conducting literature search or generating background rates ad hoc.
- AEFIs are monitored within a certain window of time. AEFIs with a long lag time may not be identified.
- Because only patients with internet, and capable of understanding the language may respond to web-based data collection, certain groups (e.g. elderly, illiterate, demented) which could experience a different safety profile may be underrepresented.
- The size of the study population may possibly not allow to detect rare events. Also, drop out/loss to follow-up may increase over time so that events with a long lag time may be difficult to capture.

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 at the 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 should 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 events/adverse reactions

The reported adverse events are potential adverse drug reactions (ADRs). Therefore, participating organizations, which are national competent authorities, should send all AEFIs to Eudravigilance according to GVP guidance. One ADR report should be created for each participant reporting one or more AEFIs. These reported ADRs should be exported from the database and converted to a ADR report according to national and EMA guidelines and formats. In this way, individual report should be transferred to EMA.

12. Plans for disseminating and communicating study results

The study protocol should be posted on the EU PAS register. Upon study completion and finalization of the study report, the results of this non-interventional study should be submitted for publication and posted in the EU PAS publicly accessible database of results. Publications should comply with the International Committee of Medical Journal Editors (ICMJE) guidelines.

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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 AEFI 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: …)

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 event after 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 AEFI (open question)
- Information collected for each reported AEFI:
    - 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 event? (if there were tests done, the outcomes of these tests will be asked, e.g. blood test or ECG)

- Was the adverse event treated? (including over the counter medication; ATC-coded locally)
- Impact of the event (5-point scale from not severe to very severe)
- Seriousness according to CIOMS (hospitalisation >24h; life-threatening situation; other medically important event). If ticked: open subquestions.
- Possibility to upload a picture of the event and/or documents such as a hospital discharge letter (participant should not be identifiable).

Q2: 3 weeks after dose 1

Old events:

- Outcome of each of the AEFIs 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 event? (if there were tests done, the outcomes of these tests will be asked, e.g. blood test or ECG)
- Was the adverse event treated? (including over the counter medication; ATC-coded locally)
- Impact of the event (5-point scale from not severe to very severe)
- Seriousness according to CIOMS (hospitalisation >24h; life-threatening situation; other medically important event). If ticked: open subquestions.
- Possibility to upload a picture of the event and/or documents such as a hospital discharge letter (participant should not be identifiable).

New events: Identical to Q1

Q3 & Q4: 6 & 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 event; disability). If ticked: open subquestions.

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