MASTER PROTOCOL

Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe

A contribution of COVIDRIVE, a public-private partnership
to estimate brand-specific COVID-19 vaccine effectiveness in Europe.

COVIDRIVE

Version 3.3

23 Dec 2021

CONTRIBUTORS and VERSION CONTROL

Contributing organisations to this Master Protocol

Organisation
P95
FISABIO
AstraZeneca
GSK
Janssen
Sanofi-Pasteur
Bayer

Abbreviations: FISABIO, Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana; GSK, GlaxoSmithKline.

Version control table for this master protocol

Version	Version date	Reason for new version
1.0	February 9, 2021	First draft
1.1	February 15, 2011	Addressing comments from AZ, SP-GSK, Janssen, Bayer, FISABIO
2.0	February 25, 2021	Sample size section, questions on ADL, risk taking behaviour. Information to collect on critical COVID-19 patients, master ICF
2.1	March 9, 2021	Addressing comments from AZ, SP-GSK, CureVac
2.2	March 15, 2021	Addressing comments from GSK, JnJ; and feedback from feasibility working group TC
3.0	April 23, 2021	Addressing comments ISC, EMA, ECDC
3.1	June, 2021	Minor correction to exposure definitions
3.2	June, 2021	Removing 'other hospital controls'
3.3	December, 2021	Amendments: • use the ECDC possible case definition for SARI instead of the more strict WHO case definition. • restructuring the order and organisation of the secondary and exploratory objectives without changing the content. • adding variables: - use of anti-SARS-CoV-2 antibody products or similar for pre-exposure prophylaxis, post-exposure prophylaxis and post symptom-onset but prior hospitalization. - full COVID-19 vaccination history including additional doses - symptoms related to the SARI case definition.

	• in addition to RT-PCR, also allowing confirmation of COVID-19 using RMA amplification systems with at least the same sensitivity as RT-PCR (e.g. TMA). • Improving sample size section Improving Annex 1 (VAED)

BACKGROUND OF THIS MASTER PROTOCOL

This master protocol describes a non-interventional study to estimate the effectiveness of COVID-19 vaccines against COVID-19 severe disease in Europe. The study is a multi-country, prospective hospital-based, case-control study with test-negative controls (test-negative case-control design, TNCC). This master protocol will be used to create Study Requestor-specific protocols that meet the requirements of the Study Requestor and to create site-specific protocols that reflect the data collection and requirements at the specific Study Sites.

This master protocol has been developed by the COVIDRIVE public-private partnership. Current COVIDRIVE members are FISABIO (Spain), P95 (Belgium), THL (Finland), AstraZeneca (UK), CureVac (Germany), Janssen (Belgium), Sanofi-Pasteur (France) and GSK (Belgium). Bayer contributed to this protocol on behalf of the CureVac-Bayer COVID-19 vaccine collaboration. The outline of this master protocol was developed in parallel to the writing of similar protocols by other initiatives (ECDC/WHO-EU, ACCESS). The COVIDRIVE outline and master protocol are subsequently harmonised with the ECDC/WHO-EU protocol to facilitate the comparison of study results. Comments received by the COVIDRIVE Independent Scientific Committee (ISC), the EMA and ECDC are reflected in version 2.3 and all subsequent versions of this protocol.

« This protocol is based on COVIDRIVE's Master Protocol. Several manufacturers are using this study to collect brand-specific vaccine effectiveness data. The main data collection is common across vaccine manufacturers. »

STUDY-SPECIFIC PROTOCOL

Brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe

Version [X.X]

[MM/DD/YYYY]

1 TITLE PAGE

« Text between square brackets [ ] are placeholders to be completed. Text between double angle quotation marks « » are instructions to be deleted afterwards. »

Abbreviated study title	[internal abbreviated study title]
Full study title	[internal full study title]
Study ID	[internal study ID]
EU PAS registry number	[number]
Protocol version	[number]
Date of protocol version	[date]
Active substance(s)	[name]
Medicinal product(s)	
Product reference	
Procedure number	
Indication(s)	
Marketing authorisation holder(s)	
Study requester(s)	[company or institution name(s)]
Study status	Non-interventional
Research question and objectives	***« Objectives to be selected/modified »*** Co-primary objectives: 1. To estimate brand-specific COVID-19 Vaccine Effectiveness (CVE) against hospitalisation due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose**. 2. To estimate brand-specific CVE against hospitalisation due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated**. Secondary objectives: See Section 13.2 Exploratory objectives: See Section 13.3.
Country(ies) of study	[name 1, name 2, …]
Protocol main author(s)	[name 1, name 2, …]

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organisation of the study and on condition that all such persons agree not to further disseminate it.

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5 ABBREVIATIONS

CVE	COVID-19 vaccine effectiveness
COVID-19	Coronavirus disease 2019
CIOMS	Council for International Organisations of Medical Sciences
CRS	COVIDRIVE Research Server
DMP	Data management plan
ED	Emergency department
EDTA	Electronic data transfer application
EMA	European Medicines Agency
EU	European Union
EU/EEA	European Union/European Economic Area
GDPR	General Data Protection Regulation
GEP	Good Epidemiological Practice
ICF	Informed consent form
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
LAR	Legally Acceptable Representative(s)
MAH	Marketing authorisation holder
NPI	Non-pharmaceutical interventions
NIP	National immunisation programmes
PAES	Post-authorisation efficacy study
QCAC	Quality Control and Audit Committee
RDP	Remote desktop protocol
RMP	Risk management plan
RT-PCR	Reverse transcription polymerase chain reaction
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SAP	Statistical analysis plan
sFTP	Secure file transfer protocol
TFL	Tables, figures and listings
TNCC	Test-negative case-control design
SOP	Standard operating procedure
VAED	Vaccine associated enhanced disease
WHO	World Health Organisation

6 RESPONSIBLE PARTIES

« Complete for study-specific protocols. »

6.1 Principal investigator

Name:
Organisation:
Address:
E-mail:

6.2 Study requestor(s)

Name:
Organisation:
Address:
E-mail:

Name:
Organisation:
Address:
E-mail:

6.3 Study sponsor

Name:
Organisation
Address
E-mail:

6.4 Study team

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

6.5 Study contributors (sites)

Organisation:
Address:
Name investigator:
E-mail:

Organisation:
Address:
Name investigator:
E-mail:

6.6 External partner(s)/committee(s)

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

Name, role:
Organisation:
Contribution:
E-mail:

7 ABSTRACT

Background

- .COVIDRIVE is a public-private partnership built upon the IMI-DRIVE project and adapting its tools and structure to the specificities of COVID-19 vaccine effectiveness (CVE). The IMI-DRIVE project was launched in 2017 to meet the regulatory requirement requesting all manufacturers with an influenza vaccine in Europe to provide European data on brand-specific seasonal influenza vaccine effectiveness [1].
- Since its emergence in 2019, SARS-CoV-2 has become a great challenge to public health.
- The first COVID-19 vaccines have received Marketing Authorisation and there are more COVID-19 vaccines to come.
- The considerations on the core requirements for the Risk Management Plan (RMP) for COVID-19 vaccines of the European Medicines Agency (EMA) states that "Vaccine effectiveness studies should be included and that is it recommended for the Marketing Authorisation Holder (MAH) to make use of existing EU efforts that could provide brand-specific data reliably and timely." The COVIDRIVE project fits this recommendation.
- COVIDRIVE developed the initial version of the study outline of this protocol in parallel to the development of similar protocols by other initiatives [2,3]. The current protocol and its amendments have been harmonised with the other protocols to facilitate results comparison, potential future data sharing or collaboration in Europe.

Research Question

To continuously monitor CVE against COVID-19 hospitalisations at the brand level using a network of hospitals across Europe.

Objectives

Co-primary:

1. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose.**
2. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated**.

« Objectives are to be selected, prioritised and modified by the Study Team. These objectives are to be interpreted as the evaluation of the effectiveness of primary vaccination with unvaccinated subjects as comparator group. Each unique combination of COVID-19 vaccine doses will be classified as primary or booster by expert consensus. The status of fully vaccinated will be similarly established. Objectives can differ between the study-requestor-specific protocols.»

Secondary: All secondary objectives are stratifications to the co-primary objectives.

1. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,**
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.
2. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated,**
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.

Exploratory: Exploratory objectives 1 and 2 are stratifications to the co-primary objectives.

1. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,**
    - by severity level [(1)].
    - by calendar time [(2)].
2. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated**,
    - by severity level [(1)].
    - by calendar time [(2)].
3. To estimate the brand-specific effect of COVID-19 vaccination *[been vaccinated with at least 1 COVID-19 vaccine dose - been fully vaccinated]* [(3)] on **length of hospital stay** (in days) due to laboratory-confirmed SARS-CoV-2 admission.
4. To study the potential occurrence of **vaccine-associated enhanced disease (VAED)** by describing the **clinical and laboratory features of critical COVID-19 disease** [(4)] cases, by **COVID-19 vaccine exposure status and time since vaccination.** [(5)]

[(1)] Three mutually exclusive categories: (a) hospital admission without ICU admission and without in-hospital death, (b) ICU admission without in hospital death and (c) in-hospital death.

(2) Calendar time at date of hospital admission as a proxy for changing genetic variants of the SARS-CoV-2 virus.

(3) The text between square brackets needs to be selected to match the exposure definitions from the co-primary objectives.

(4) Critical COVID-19 disease is defined as being admitted to Intensive Care Unit (ICU) due to laboratory confirmed SARS-CoV-2.

(5) It is postulated that the potential VAED risk may change with waning vaccine induced immunity, hence with time since vaccination as a proxy.

Study methods

Study design: A multi-country prospective hospital-based case-control study with test-negative controls (test-negative case-control study).

Data sources: A combination of primary and secondary data sources.

Study duration: Minimum 1 year with an expected study duration of 2 years.

Countries: Targeting several EU/EAA member states as well as the UK. Currently confirmed willingness to participate from study sites in Austria, Belgium, Croatia, Germany, Iceland, Italy, Luxembourg, Netherlands, Romania, Poland, Spain, Finland and the UK (1).

Study participants: Individuals presenting at the participating hospitals during the study period who 1) are hospitalized and meet the SARI case definition AND who 2) meet the following **inclusion criteria:**

- Ever eligible for COVID-19 vaccination following the regional/national immunization recommendations prior to hospital admission
- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR)

BUT who do NOT meet the following **exclusion criteria**:

- COVID-19 hospitalization within 3 months prior to the current admission. Hospital transfers are not considered as a prior hospitalization.
- Cannot be swabbed due to severe septum deviation, obstruction or other conditions that contra-indicate swabbing

Hospitalized person: SARI patients will be identified among patients admitted to the hospital with at least one overnight stay.

SARI case definition (possible COVID-19 case): A possible COVID-19 case is defined as a hospitalized person with **at least one** of the following symptoms;

- cough
- fever
- shortness of breath, OR
- sudden onset of anosmia, ageusia or dysgeusia

with symptom onset within the **last 14 days** prior to hospital admission as per ECDC definition [3].

Test-positive cases: study participants meeting the **SARI** case definition AND testing **positive** for at least 1 SARS-CoV-2 RT-PCR or similar molecular assays with specimens collected within 14 days prior to the day of hospital admission 2[(2)].

Test-negative controls: study participants meeting the **SARI** case definition AND testing **negative** for all SARS-CoV-2 RT-PCR or similar molecular assays with specimens collected within 14 days prior to the day at hospital admission[(2)].

Case-control ratio: When feasible and resource-saving, the number of controls sampled per calendar week will be restricted to maximum 3 times the number of cases sampled that same week.

(1) The list of countries will be extended as the network grows.

(2) Specimen collected between d-14 and d0 where d0 is the day at hospital admission (specimen collected within 24 hours upon arrival at the hospital).

Vaccine exposure

« Exposure outcomes to be aligned with study objectives. »

Vaccinated with at least one dose: vaccinated with **at least 1 dose** of the COVID-19 vaccine brand of interest > 14 days prior to SARI symptom onset.

Fully vaccinated: **fully vaccinated** with the COVID-19 vaccine brand of interest > 14 days prior to SARI symptom onset.

At least one additional COVID-19 vaccine dose: **any COVID-19 vaccine dose** with the brand of interest given **as last dose** > 14 days prior to SARI symptom onset to subjects who where previously fully vaccinated with any COVID vaccine(s) [(1)].

Recently vaccinated: vaccinated with any COVID-19 vaccine <= 14 days prior to SARI symptom onset [(2)].

Unvaccinated: did **not receive any COVID-19 vaccine dose.**

Other: additional vaccine exposure case definitions might be defined depending on the real-life use of the COVID-19 vaccines.

(1) For its secondary objective,the study-requestor may define specific exposure based on the number of COVID-19 vaccine doses, type(s) and brand(s) of the COVID-19 vaccine doses given prior to the last dose.

(2) Recently vaccinated patients will not be considered protected by the last vaccine dose. Their use will be specified in the statistical analysis plan.

Covariates

Covariates: Variables that are potential confounders and/or effect modifier and that will be collected at all sites include age, sex, history of medical diagnosis for selected morbidities of interest (asthma, lung disease, cardiovascular disease, hypertension, chronic kidney disease, type 2 diabetes, cancer, immunodeficiency), BMI, vaccination against pathogens causing COVID-19 like symptoms (influenza, pneumococcus), calendar time, previous SARS-CoV-2 infection and any use of monoclonal antibodies and other anti-SARS-CoV-2 antibody products as for either treatment or pre- or post-exposure prophylaxis prior to hospitalization.

Variables that will be potentially additionally collected at certain study sites include, socio-economic variables and/or ethnicity,precautionary health behavior, health care worker (HCW), long-term care facility residence and smoking history.

Sample size

A simulation based sample size calculation was performed. For a study conducted in 10 sites, an overall vaccination coverage of 50% to 90% in the study population, brand-specific vaccination proportions ranging from 5% to 75%, a case control ratio of 1:1, and an assumed CVE of 80% or 90%, having at least 2,210 SARI cases leads to an expected 95% CIs range ≤30%. It is expected that at least 10 study sites will be included in the study with a minimum of 400 SARI cases enrolled per 6 months per site.

The sample size requirements strongly depend on the case control ratio, overall vaccination coverage and share of the different vaccine brands. As such, the sample size requirements will be different for the different vaccine brands. In case the parameter settings used for these sample size calculations are very different from what is observed in the study, the sample size calculations will be updated accordingly.

Data collection and SARS-CoV2 testing

Vaccination status, brand information and date of vaccination(s) will be ascertained by consulting vaccination registries, vaccination cards or medical records (depending on the country and region). Batch information will be additionally collected when available.
RT-PCR (polymerase chain reaction) or another RMA amplification system with at least the same sensitivity as RT-PCR (e.g. TMA) will be required to confirm COVID-19 disease. Information on the SARS-CoV-2 genetic variants will be collected on all vaccine failures for brands of interest and a proportion of the unvaccinated cases sufficiently large to meet the study objectives.
After study enrollment, data will be collected directly from the patient or by consulting medical records. Information to be collected at minimum includes date of SARI symptom onset date, date of hospitalization, and information on the potential confounders.
Context information on national/regional immunization recommendations, SARS-CoV-2 genetic variant circulation and COVID-19 vaccine label information will be collected.

Statistical analysis

Descriptive analyses will be performed to describe the study population, the evolution of the SARS-CoV-2 dynamics and the COVID-19 vaccination coverage for the brands of interest.

For estimating brand-specific CVE in SARI patients the comparator group comprises of unvaccinated subjects.

Pooled brand-specific CVE estimates will be obtained through random-effects meta-analysis on the log-transformed site-specific estimates, where the latter are being obtained using logistic regression adjusting for the confounders above. Restricted maximum likelihood will be used to obtain the pooled meta-analyses estimates and 95% confidence intervals (CI). The modified Hartung-Knapp correction will be used to estimate the variance of the mean effect. The estimates and 95% CIs will then be back-transformed to obtain the pooled CVE estimates and 95% CI. Sensitivity analyses will be conducted when appropriate.

A full statistical analysis plan (SAP) will be developed prior to the conduct of the analysis.

Reporting

Progress reports will be prepared every two months. Interim analysis will be planned as appropriate. A final study report will be written for each of the individual COVID-19 vaccine brands of interest. In case the Study Requestor is a MAH, interim reports and final report will be submitted to EMA by the respective MAHs to meet regulatory requirements.

Data management

Data collected at study sites will be checked for quality and transferred to a dedicated, secured central server hosted by P95. If patient-level data transfer is not possible, alternative solutions will be sought. A data management plan (DMP) will be written prior to the start of the data collection. The DMP will describe all functions, processes, responsibilities and specifications for data collection, cleaning and validation.

Ethical considerations

The site-specific protocols will be submitted to relevant ethics committee(s) following local regulations. Informed consent will be obtained from all participants/guardians as specified by the national/regional ethics committee.

Study Limitations

- Low sensitivity and specificity of the RT-PCR test introduces stronger bias (towards underestimating the effectiveness) in the test-negative case-control design compared to the standard case-control design. This additional bias with the test-negative design increases with increasing SARS-CoV-2 positivity rates within the SARI patients. This potential bias might be mitigated/explored by shortening the time lag between symptom onset and taking the respiratory sample as the sensitivity of the RT-PCR tests decreases with increasing time lag [4].
- The SARS-CoV-2 positivity rates within the SARI patients varies over time and might be very high during certain calendar months, potentially making it difficult to obtain a sufficient number of controls that allow adjustment for time-varying confounding.
- Subjects at highest risk for severe COVID-19 disease are targeted for vaccination first and might have a higher propensity to self-select for vaccination compared to subjects at lower risk. When not properly controlled for, this will lead to a substantial underestimation of the vaccine effectiveness.
- Additional COVID-19 vaccines are being marketed and increasingly heterogeneous vaccination policies are being adopted in the various EU countries. This heterogeneity potentially leads to paucity of study patients with a certain vaccine exposure.
- The emergence of monoclonal antibodies and other anti-SARS-CoV-2 antibody products that impact the course of COVID-19 disease might affect the CVE estimates. Thus, confounders such as healthcare seeking behaviour and chronic conditions might impact both the likelihood of vaccination and of treatment.

Dissemination

This generic protocol and its significant amendments will be posted on the EU PAS register. Study reports, each for a specific vaccine brand, will be posted on the EU PAS register and will be published in peer reviewed open-source international journal(s).

Updates on study progress will be posted on the COVIDRIVE web site (covidrive.eu).

Funding

This generic protocol has been developed by the COVIDRIVE partnership, which has received funds from AstraZeneca, CureVac, Janssen, Sanofi-Pasteur and GSK, leveraging public health capacity from FISABIO and THL and existing infrastructure at P95. Other partners (vaccine companies or other institutes) might join the COVIDRIVE project at later stages.

The execution of the study will be funded by companies, which may join progressively. This specific funding will be transparently acknowledged in all communications.

COVIDRIVE partnership

COVIDRIVE is an open public-private partnership. Current members are FISABIO (Spain), P95 (Belgium), THL (Finland), AstraZeneca (UK), CureVac (Germany), Janssen (Belgium), Sanofi-Pasteur (France) and GSK (Belgium). The partnership aims to enable a continuous monitoring of brand- specific CVE in Europe.

Study status

Non-interventional

Study sponsor

P95

References

1. EMA. Guideline on Influenza Vaccines: Non-clinical and Clinical Module, 2016. European Medicines Agency. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module_en.pdf. Accessed: 2021-02-19.

2. ACCESS. Core protocol for SARS-CoV-2 vaccine effectiveness studies (test-negative design studies) a protocol from the ACCESS project, 2021. ACCESS project protocol under publication.

3. https://www.ecdc.europa.eu/sites/default/files/documents/Core-protocol-for-ECDC-studies-of-COVID-19-vaccine-effectiveness-against-hospitalisation-with-SARI.pdf

4. Miller, T.E., Garcia Beltran, W.F., Bard, A.Z., Gogakos, T., Anahtar, M.N., Astudillo, M.G., Yang, D., Thierauf, J., Fisch, A.S., Mahowald, G.K., Fitzpatrick, M.J., Nardi, V., Feldman, J., Hauser, B.M., Caradonna, T.M., Marble, H.D., Ritterhouse, L.L., Turbett, S.E., Batten, J., Georgantas, N.Z., Alter, G., Schmidt, A.G., Harris, J.B., Gelfand, J.A., Poznansky, M.C., Bernstein, B.E., Louis, D.N., Dighe, A., Charles, R.C., Ryan, E.T., Branda, J.A., Pierce, V.M., Murali, M.R., Iafrate, A.J., Rosenberg, E.S., and Lennerz, J.K. *Clinical sensitivity and interpretation of PCR and serological COVID-19 diagnostics for patients presenting to the hospital.* FASEB J, 2020. **34**(10): p. 13877-13884. DOI: 10.1096/fj.202001700RR.

8 AMENDMENTS AND UPDATES

Version	Version date	Reason for new version
V3.1	02 June 2021	Submitted to EU PAS on 02/08/2021 (EUPAS42328).
V3.2	June 2021	Removing 'other hospital controls'
V3.3	Dec 2021	Amendments: • use the ECDC possible case definition for SARI instead of the more strict WHO case definition. • restructuring the order and organisation of the secondary and exploratory objectives without changing the content. • adding variables: - use of anti-SARS-CoV-2 antibody products or similar for pre-exposure prophylaxis, post-exposure prophylaxis and post symptom-onset but prior hospitalization. - full COVID-19 vaccination history including additional doses - symptoms related to the SARI case definition. • in addition to RT-PCR, also allowing confirmation of COVID-19 using RMA amplification systems with at least the same sensitivity as RT-PCR (e.g. TMA). • Improving sample size section • Improving Annex 1 (VAED)

9 MILESTONES

« Modify milestones as appropriate »

Milestone	Planned date
<Registration Protocol in the EU PAS register>	[Date]
Start of data collection	[Date]
End of data collection	[Date]
<Study progress report 1>	[Date]
<Study progress report x>	[Date]
<Study progress report x>	[Date]
<Interim report 1>	[Date]
<Interim report x>	[Date]
<Interim report x>	[Date]
Final report of study results	[Date]
<Registration Results in the EU PAS register>	[Date]

10 INVESTIGATOR SIGNATURE PAGE

Study Title: [title]

Protocol number: [number]

I have read and I understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Epidemiological Practice (GEP), the ethical principles that have their origins in the Declaration of Helsinki and the General Data Protection Regulation (GDPR).

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the Study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the Study. I am aware that this protocol will need to be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Investigator:

_____
Print Name

_____ _____
Signature Date

_____
Print Name of Institution or Practice and Location

11 SPONSOR SIGNATURE PAGE

Study Title: [title]

Protocol number: [number]

Sponsor:

_____
Print Name

_____ _____
Signature Date

_____
Print Name of Institution or Practice and Location

12 RATIONALE AND BACKGROUND

In December 2019, an outbreak of respiratory disease caused by a novel coronavirus strain was reported in Wuhan City, Hubei Province, China. The novel coronavirus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), while the disease associated with it is referred to as COVID-19. The virus spread to different parts of China and an increasing number of countries worldwide and on 12 March 2020 the World Health Organisation (WHO) announced that the outbreak was characterized as a pandemic. Following the identification of SARS-CoV-2 and its global spread, large epidemics of COVID-19 occurred in Europe. In response, European countries implemented large-scale unprecedented nonpharmaceutical interventions (NPIs) such as closure of schools and national lockdowns. Data collected by the European Centre for Disease Prevention and Control (ECDC) from 31 countries showed on [19 March 2021] a total of [24,175,984] COVID-19 cases and [577,310] related deaths in the European Union/European Economic Area (EU/EEA) since the start of the pandemic [1].

The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. As of [10 March 2021], the following COVID-19 vaccines have been granted conditional marketing authorisation in the European Union (EU) by the European Medicines Agency (EMA): Comirnaty® from BioNTech/Pfizer on 21 December 2020, COVID-19 Vaccine Moderna on 6 January 2021, COVID-19 Vaccine AstraZeneca on 29 January 2021 and COVID-19 Vaccine Janssen on 11 March 2021 [2].

Despite the efficacy of the COVID-19 vaccines being thoroughly investigated during clinical trials, it is crucial to continue evaluating how well the vaccines prevent disease under real-world conditions once the COVID-19 vaccines are being used as part of the national immunisation programmes (NIPs). Questions that are typically unanswered by clinical trials and that remain to be evaluated by real-world effectiveness studies include amongst others the duration of vaccine protection and waning of immunity, effectiveness against disease by specific and newly emerging SARS-CoV-2 strains, effectiveness against severe COVID-19 disease and effectiveness in special risk groups such as immunocompromised, frail or subjects with chronic conditions or existing comorbidities..

Many of the ongoing and planned real-world effectiveness evaluations make use of existing programmes for the evaluation of the effectiveness of influenza vaccines. In Europe, the I-MOVE (Influenza – Monitoring Vaccine effectiveness in Europe) network of public partners joined forces and created the I-MOVE COVID-19 consortium [3]. COVIDRIVE, a public-private partnership launched in December 2020, is leveraging DRIVE, an existing vaccine effectiveness platform that provides yearly brand-specific influenza vaccine effectiveness estimates to the EMA. COVIDRIVE was launched to address the joint need to monitor COVID-19 vaccination programmes for public health institutes and assess brand-specific COVID-19 vaccine effectiveness for vaccines companies as part of their regulatory obligations. Current COVIDRIVE members are FISABIO (Spain), P95 (Belgium), THL (Finland), AstraZeneca (UK), CureVac (Germany), Janssen (Belgium) and Sanofi-Pasteur (France)/GSK (Belgium).

This protocol details a non-interventional study to estimate the effectiveness of COVID-19 vaccines against COVID-19 related hospitalisations through the COVIDRIVE partnership. Studying the effectiveness against COVID-19 hospitalizations is prioritized as COVID-19 hospitalizations are the main reason for national and regional governments to impose NPIs. Hence, having accurate and timely

information on how well the different COVID-19 vaccines protect and remain protective over time against hospitalizations is essential to successfully manage the pandemic. Considering the rarity of COVID-19 hospitalizations, clinical trials are not well suited to study this outcome and complementary real-world studies are required. Therefore, this protocol describes a prospective, multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design). Data will be collected through a wide network of hospitals located in several European countries and the UK. A hospital-based case control study is an efficient design well suited to study rare outcomes, potentially allowing for detailed medical information and additional data collection directly from the patient or healthcare provider.

In addition, the potential for vaccine-associated enhanced disease (VAED) will be studied as part of this vaccine effectiveness study as VAED relates to the efficacy/effectiveness outcomes. VAEDs are atypical and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same [4]. VAED is a theoretical concern for COVID-19 vaccines, based on observations from other respiratory viruses and from animal models of highly pathogenic coronaviruses [4]. Historically, VAED has been observed following administration of measles and RSV vaccines [5]. While the underlying potential mechanisms for VAED are unclear, VAED invariably involves a memory immune response primed by vaccination and appears to target the same organs as wild-type infections [4]. Given the lack of clinical findings, immunological assays or biomarkers of VAED that can differentiate severe breakthrough disease from VAED at this time, it is challenging if not impossible to assess VAED on an individual case basis. Instead, the assessment of this theoretical risk needs to be at a population level. As VAED is postulated to occur with low levels of neutralizing antibodies while the presence of non-neutralizing or poorly neutralizing antibodies still facilitate viral uptake, an association between VAED risk and time since vaccination may be observed if antibodies wane as was observed in Dengue-naïve individuals [6].

13 RESEARCH QUESTIONS AND OBJECTIVES

13.1 Co-primary objectives

1. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose.**

2. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated**.

« Objectives are to be selected, prioritised and modified by the Study Team. These objectives are to be interpreted as the evaluation of the effectiveness of primary vaccination with unvaccinated subjects as comparator group. Each unique combination of COVID-19 vaccine doses will be classified as primary or booster by expert consensus. The status of fully vaccinated will be similarly established. Objectives can differ between the study-requestor-specific protocols.»

13.2 Secondary objectives

« All secondary objectives are stratifications to the co-primary objectives.»

1. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,**
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.
2. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated,**
    - by SARS-CoV-2 genetic variants.
    - within populations of special interest (e.g. specific age groups, specific immunocompromised or chronic conditions, pregnant women).
    - by time since last COVID-19 vaccine dose.
    - by time between COVID-19 vaccine doses.

13.3 Exploratory objectives

« Exploratory objectives 1 and 2 are stratifications to the co-primary objectives.»

2. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in severe acute respiratory infection (SARI) patients who have been vaccinated with **at least 1 COVID-19 vaccine dose,**
    - by severity level [(1)].
    - by calendar time [(2)].
3. To estimate brand-specific CVE against hospitalization due to laboratory-confirmed SARS-CoV-2 in SARI patients who have been **fully vaccinated**,
    - by severity level [(1)].
    - by calendar time [(2)].
4. To estimate the brand-specific effect of COVID-19 vaccination *[been vaccinated with at least 1 COVID-19 vaccine dose - been fully vaccinated]* [(3)] on **length of hospital stay** (in days) due to laboratory-confirmed SARS-CoV-2 admission.
5. To study the potential occurrence of **vaccine-associated enhanced disease (VAED)** by describing the **clinical and laboratory features of critical COVID-19 disease** [(4)] cases, by **COVID-19 vaccine exposure status and time since vaccination.** [(5)]

[(1)] Three mutually exclusive categories: (a) hospital admission without ICU admission and without in-hospital death, (b) ICU admission without in hospital death and (c) in-hospital death.

[(2)] Calendar time at date of hospital admission as a proxy for changing genetic variants of the SARS-CoV-2 virus.

[(3)] The text between square brackets needs to be selected to match the exposure definitions from the co-primary objectives.

[(4)] Critical COVID-19 disease is defined as being admitted to Intensive Care Unit (ICU) due to laboratory confirmed SARS-CoV-2.

[(5)] It is postulated that the potential VAED risk may change with waning vaccine induced immunity, hence with time since vaccination as a proxy.

14 RESEARCH METHODS

14.1 Study design

This study is a multi-centre, multi-country, prospective hospital-based case-control study with test-negative controls (TNCC design).

A combination of primary and secondary data collection will be used to obtain the relevant data.

14.2 Study contributors (sites)

This is a multi-country, multi-centre study, with hospital sites in Europe. This study targets several EU/EAA member states as well as the UK. Currently confirmed willingness to participate from study sites in Austria, Belgium, Croatia, Germany, Iceland, Italy, Luxembourg, Netherlands, Romania, Poland, Spain, Finland and the UK. The participating studies sites are described in Table 1.

The participating study sites are either individual hospitals or hospital networks. Currently the network consists of up to 45 hospitals. Depending on the hospital, the data collection will be a prospective primary data collection or data will be retrospectively retrieved from the existing hospital databases and linked data.

For every participating study site, a site-specific protocol will be written describing details on patient flow, data collection, laboratory tests and genomic sequencing.

Table 1. Participating study sites.

Country	Hospital name	Site (location)	Hospital population	No. of hospital beds/ICU beds
« complete »				

14.3 Study population

The study population consists of individuals (patients), presenting at the participating hospitals during the study period, who

- meet the inclusion criteria (see Section 14.3.1) but who do NOT meet the exclusion criteria (see Section 14.3.3).

AND

- are hospitalized and meet the SARI case definition (see Section 14.6.2)

14.3.1 Inclusion criteria

Individuals (patients) need to fulfil the following inclusion criteria:

- Ever eligible for COVID-19 vaccination following the national/regional immunization recommendations prior to hospital admission

  AND

- Willing and able to provide informed consent, when applicable, obtained from the patient or from the patient's Legally Acceptable Representative(s) (LAR)

14.3.2 Exclusion criteria

- COVID-19 hospitalization within 3 months prior to the current admission. Hospital transfers are not considered as a prior hospitalization.
- Cannot be swabbed due to severe septum deviation, obstruction or other conditions that contra-indicate swabbing

14.4 Study period

« Modify as appropriate »

From Month 202X, with a minimum duration of 12 months and an expected duration of 2 years

14.5 Study outcomes

« Study outcomes to be aligned with study objectives. »

The outcome of interest for the primary analysis will be SARS-CoV-2 detection in patients hospitalized with SARI symptoms. SARS-CoV-2 infection should be laboratory-confirmed by Real-Time Polymerase Chain Reaction (RT-PCR) or another RMA amplification system with at least the same sensitivity as RT-

PCR (e.g. TMA). As the SARS-CoV-2 testing practices might change over time, the test requirement for confirmation of COVID-19 disease might be revisited. The impact of such revisions on the potential for disease misclassification will be considered.

The secondary outcomes include:

- Detection of SARS-CoV-2 genetic variants in patients hospitalized due to laboratory confirmed SARS-CoV-2.

The exploratory outcomes include:

- Hospitalisation due to lab-confirmed SARS-CoV-2 by level of severity: (i) hospital admission without ICU admission and without in-hospital death, (ii) ICU admission without in-hospital death and (iii) in-hospital death.
- Clinical and laboratory features of critical COVID-19 disease cases in patients hospitalized due to laboratory confirmed SARS-CoV-2. Critical COVID-19 disease is defined as being admitted to ICU.

14.6 Definitions

14.6.1 Hospitalized patient

Persons admitted to the hospital with overnight stay. In case of referral to another hospital, the date of hospital admission is defined as the date of first admission.

14.6.2 SARI (Severe Acute Respiratory Infection) patient (possible COVID-19 cases)

A possible COVID-19 case is defined as a hospitalized person with a suspicion of a respiratory infection with **at least one** of the following symptoms;

- cough
- fever
- shortness of breath, OR
- sudden onset of anosmia, ageusia or dysgeusia

with symptom onset within the **last 14 days** prior to hospital admission as per ECDC definition [7].

14.6.3 Test-positive case

A study participant who:

- meets the **SARI** case definition (see Section 14.6.2)

  AND

- tests **positive** for at least one SARS-CoV-2 RT-PCR or similar molecular assays with specimens collected between 14 days prior to and including the day of hospital admission. (Specimen collected between d-14 and d0 where d0 is the day at hospital admission and specimen is collected within 24 hours upon arrival at the hospital).

14.6.4 Test-negative control

A study participant that:

- meets the **SARI** case definition (see 14.6.2)

  AND

- tests **negative** for all SARS-CoV-2 RT-PCR or similar molecular assays with specimens collected between 14 days prior to and including the day at hospital admission. (Specimen collected between d-14 and d0 where d0 is the day at hospital admission and specimen is collected within 24 hours upon arrival at the hospital). Test-negative controls must have a negative result for the RT-PCR or similar molecular assay at hospital admission.

14.7 SARI patient identification

Depending on the study site, the SARI patient identification will be different. Hospitalized SARI patients will be identified prospectively (e.g. during consultation in the ED or during a pneumology consultation) or retrospectively by hospital database search or from respiratory samples sent to the virology laboratory.

«For every participating study site, the patient flow will be documented in detail.»

14.8 Exposure (COVID-19 vaccination)

14.8.1 Exposure definitions

« Exposure outcomes to be aligned with study objectives. »

1. Vaccinated with at least one dose: vaccinated with **at least 1 dose** of the COVID-19 vaccine brand of interest > 14 days prior to SARI symptom onset.
2. Fully vaccinated: **fully vaccinated** with the COVID-19 vaccine brand of interest > 14 days prior to SARI symptom onset.
3. At least one additional COVID-19 vaccine dose: **any COVID-19 vaccine dose** with the brand of interest given **as last dose** > 14 days prior to SARI symptom onset to subjects who where previously fully vaccinated with any COVID vaccine(s) [(1)].

4. Recently vaccinated: vaccinated with any COVID-19 vaccine <= 14 days prior to SARI symptom onset [2].
5. Unvaccinated: did **not receive any COVID-19 vaccine dose.**
6. Other: additional vaccine exposure case definitions might be defined depending on the real-life use of the COVID-19 vaccines.

[1] For its secondary objective, the study-requestor may define specific exposures based on the number of COVID-19 vaccine doses, type(s) and brand(s) of the COVID-19 vaccine doses given prior to the last dose.

[2] Recently vaccinated patients will not be considered protected by the last vaccine dose. Their use will be specified in the statistical analysis plan.

14.8.2 Exposure ascertainment

Information on all prior COVID-19 vaccine doses will be collected. Vaccination status, vaccination date, dose and vaccine brand information is required. When feasible, batch number will be collected. Depending on the study site, the source for exposure ascertainment will be different and may include; vaccination registry, medical records or vaccination cards. For every participating study site, the source documentation and its validity will be described in detail in the study site-specific protocol.

Patients that cannot be classified into one of the exposure categories (i.e. vaccination status is unknown) will be excluded.

Context information on national/regional COVID-19 immunization recommendations (priority groups by vaccine brand), SARS-CoV-2 genetic variant circulation and COVID-19 vaccine label information (including licensed age groups, contraindications, number of doses and timing between doses) will be collected.

14.9 Outcomes

14.9.1 Laboratory confirmed SARS-CoV-2

Respiratory specimens will be collected from those patients eligible for the study and as per routine clinical practice. Only study sites where laboratory confirmation is done by RT-PCR or another RMA amplification system with similar sensitivity are eligible to participate to the study. Nasopharyngeal or oropharyngeal swabs are recommended.

For every participating study site, the testing policy and laboratory methods will be described in detail in the site-specific protocol. Information as summarized in Table 2 will be collected.

Genomic sequencing will be performed using commercially available molecular kits. At every study site with a prospective data collection, 100% of the vaccinated SARS-CoV-2 positive cases (i.e. vaccine

failures) for the brands of interest and a random sample of the unvaccinated SARS-CoV-2 positive cases will be sequenced. The size of the random sample will be chosen to obtain a sufficient number of COVID-19 cases with the variant of interest allowing the estimation of variant-and brand-specific CVE with an expected 95% CI length ≤70% (See Section Sample size considerations).

Table 2. Key aspects of laboratory specimen collection and analysis

Site name	[to be inserted]
Sampling strategy	[all patients, selection of patients fulfilling certain criteria, …]
Type of respiratory sample	[nasopharyngeal swab, nasal swab, oropharyngeal swab, branchoalveolar lavage fluid, sputum, other (specify)]
Blood sample	[Yes or no]serum (for serology if collected)
Type of molecular laboratory test	[RT-PCR, multiplex PCR, transcription-mediated amplification (TMA) – LAMP-PCR, other (specify)]
Name of Molecular kit	[open]
PCR Ct value	[2-digit value] (optional)
PCR variant screening kit	[Positions screened in the S gene (501, 484, 417, 452, others)]
Full genome sequencing sampling strategy	[all, random sampling]
Full genome sequencing laboratory tests	[Illumina, Nanopore, other…]
Sequencing minimum nucleotide coverage	[value - minimun of 200 required]

14.9.2 Hospitalization due to laboratory-confirmed SARS-CoV-2: level of severity

The following three mutually exclusive categories will be considered to characterize the severity of the hospitalization due to laboratory confirmed SARS-CoV-2 disease:

1. Hospital admission without ICU admission and without in-hospital death
2. ICU admission without in-hospital death
3. In-hospital death

COVID-19 hospitalization that take place within 3 months of the first COVID-19 hospitalization will be considered to be part of the same episode.

14.9.3 Hospitalization due to laboratory-confirmed SARS-CoV-2: Length of hospital stay

Length of hospitalization stay is defined as the number of overnights spent at the hospital from hospital admission till hospital discharge or death.

COVID-19 hospitalization that take place within 3 months of the first COVID-19 hospitalization will be considered to be part of the same episode. The length of stays of the admission will be summed.

14.9.4 Critical COVID-19 disease

A critical COVID-19 disease case is defined as a COVID-19 disease case being admitted to ICU. The clinical and laboratory characteristics of the critical COVID-19 disease cases will be described (Annex 1).

14.10 Covariates

The covariates that will be collected in this study are summarized in Table 3. Some covariates are mandatory to collect for all participating study sites.

Table 3. Covariaties that will be collected for the study

Covariate	Description	Mandatory
Age at hospital admission	Calculated based on Date of Birth and Date of Admission	x
Sex	Male, female	x
Chronic conditions (see Annex 2 for definitions)		
Asthma	Binary	x
Lung disease	Binary	x
Cardiovascular disease	Binary	x
Hypertension	Binary	x
Chronic kidney disease	Binary	x
Type 2 diabetes	Binary	x
Cancer	Binary	x
Immunodeficiency (or organ transplant)	Binary	x
Pregnancy	Binary	x
Trimester	First, second, third	x
Body mass index (BMI)	Continuous	x
Smoking history	Never smoker, former smoker (smokefree for at least 28 days), current smoker	
Vaccination history influenza	Being vaccinated with at least one influenza vaccine within 12 months prior to SARI hospital admission.	x
Vaccination history pneumococcus	Year of vaccination	x

Long-term care facility residence	Binary	
Healthcare worker	Binary	
Healthcare worker with direct contact to COVID-19 patients	Binary	
Ethnicity [(1)]	Nominal	
Socio-economic variables [(1)]	Ordinal	
Precautionary health behavior (see Annex 3 for survey)	Participants will be asked about their precautionary health behavior (e.g. wearing face masks, using hand sanitizer, going to public places)	
Previous SARS-CoV-2 infection	Participants will be asked about prior COVID-19 tests and test results (Appendix 1)	x
Anti-SARS-CoV-2 antibody products or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior hospitalisation.	Binary, brand, start date treatment	
Anti-SARS-CoV-2 antibody products or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior hospitalization.	Binary, brand, start date treatment	
Anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset leading to the current hospitalisation	Binary, brand, start date treatment	

[(1)] Depending on the country/hospital site, this data might not be available.

14.11 Sample size considerations

14.11.1 Targeted sample size

14.11.1.1 Primary vaccination

For the analysis of interest, the number of required COVID-19 cases to obtain precise estimates were obtained using a simulation-based sample size calculation. The simulation study reflects the design of the current study; a multi-site TNCC study with data from different sites combined using a meta-analytical approach (see Section Data Analysis- Sample size calculations were performed with the number of equally sized sites being 10, the overall anticipated CVE being 80% or 90%, the control to case ratio being 3:1, 1:1 or 1:3, the overall vaccination coverage among controls being 60%, 80% or 90%, and the proportion of the vaccination coverage covered by the vaccine of interest being 5%, 10%, 25%, 50%, or 75%. For each combination of these parameters, the sample sizes for which the expected 95% CI range was ≤30%, were obtained. The technical specifications of the sample size calculations are given in Appendix 6.

For various CVE, total vaccination coverages, and different proportions of the total vaccination coverage covered by the brand of interest, the number of COVID-19 cases required to meet the CI criterion are summarized in Table 4. Excluding the 5% brand proportion but irrespective of the other considered parameter combinations, having at least 1,140 COVID-19 cases yields expected 95% CIs ranges ≤30%. The corresponding total number of SARI cases needed to be enrolled can be found in Table 5 and having at least 2,210 SARI cases yields expected 95% CIs ranges ≤30% for a control to case ratio of 1:1. As this sample size was obtained for the crude CVE instead of the adjusted CVE, it was decided to conservatively adjust the targeted sample size to 1.2 x 1,140 = 1,368 COVID-19 cases and 1.2 x 2,210 = 2,652 SARI cases.

Finally, in case the observed share of the different brands or the overall vaccination coverage rate observed in the study differs largely from the settings described, the sample size calculations will be updated accordingly. The sample size might also be updated in case vaccine effectiveness estimates against specific COVID-19 genetic variants are required.

Table 4. The required number of COVID-19 cases to allow the estimation of the CVE with an expected CI length ≤30%.

			Proportion of the total vaccination coverage covered by the brand of interest				
			5%	10%	25%	50%	75%
Anticipated crude CVE	Overall vaccination coverage	Control to case ratio	Required number of COVID-19 cases (unexposed + exposed any brand)				
80%	60%	1:3	2159	1099	470	248	185
80%	80%	1:3	1325	674	326	191	172
80%	90%	1:3	1045	592	370	288	308
90%	60%	1:3	1742	879	355	191	130
90%	80%	1:3	874	448	308	123	94
90%	90%	1:3	584	308	191	148	129

80%	60%	1:1	2258	1105	460	255	187
80%	80%	1:1	1297	666	330	211	172
80%	90%	1:1	1027	608	348	286	258
90%	60%	1:1	1702	855	363	190	128
90%	80%	1:1	874	440	208	127	93
90%	90%	1:1	582	343	203	148	128
80%	60%	3:1	2155	1134	464	264	180
80%	80%	3:1	1310	660	319	206	174
80%	90%	3:1	1122	594	368	288	267
90%	60%	3:1	1725	871	358	189	132
90%	80%	3:1	855	452	204	125	180
90%	90%	3:1	576	328	193	152	130

Table 5. The number of SARI cases to allow the estimation of the CVE with an expected CI length ≤30%.

			Proportion of the total vaccination coverage covered by the brand of interest				
			5%	10%	25%	50%	75%
Anticipated Crude CVE	Overall vaccination coverage	Control to case ratio	Required number of SARI cases (unexposed + exposed any brand)				
80%	50%	1:3	2879	1465	626	330	247
80%	70%	1:3	1767	899	435	255	230
80%	90%	1:3	1393	789	493	384	410
90%	50%	1:3	2323	1172	473	255	174
90%	70%	1:3	1166	598	410	164	126
90%	90%	1:3	778	410	255	197	172
80%	60%	1:1	4517	2210	921	510	374
80%	80%	1:1	2594	1332	659	422	345
80%	90%	1:1	2054	1217	697	572	517
90%	60%	1:1	3403	1710	726	380	255
90%	80%	1:1	1749	880	415	254	186
90%	90%	1:1	1163	686	406	295	255
80%	60%	3:1	8619	4534	1857	1054	720
80%	80%	3:1	5242	2641	1277	825	694
80%	90%	3:1	4489	2378	1473	1150	1067
90%	60%	3:1	6901	3484	1431	757	528
90%	80%	3:1	3419	1806	816	500	719
90%	90%	3:1	2304	1314	773	610	518

14.11.1.2 Primary vaccination, variants of interest

The sample size calculations for calculation of the brand specific CVE against variants of interest were done in the same manner as for the sample size calculations for the primary analysis with the exception that the required sample size had to lead to an expected range of the 95% CI ≤70%. The

required number of COVID-19 cases with the variant of interest ranged from 64 to 800. For the brand-specific analyses, the required number of COVID-19 cases with the variant of interest will be selected based on the observed vaccination coverage and brand proportions.

Table 6. The number of COVID-19 cases with the variant of interest to allow the estimation of the variant- and brand-specific CVE with an expected CI length ≤70%.

			Proportion of the total vaccination coverage covered by the brand of interest			
			10%	25%	50%	75%
Anticipated crude CVE	Overall vaccination coverage	Control to case ratio	Required number of COVID-19 cases with the variant of interest (unexposed + exposed any brand)			
80%	50%	1:3	476	191	134	80
80%	70%	1:3	274	134	94	75
80%	90%	1:3	250	169	130	116
90%	50%	1:3	488	191	110	134
90%	70%	1:3	255	124	134	64
90%	90%	1:3	214	125	95	75
80%	60%	1:1	472	203	108	84
80%	80%	1:1	276	146	92	73
80%	90%	1:1	258	164	128	120
90%	60%	1:1	506	209	114	80
90%	80%	1:1	244	128	82	68
90%	90%	1:1	208	128	93	84
80%	60%	3:1	476	198	110	84
80%	80%	3:1	270	134	94	89
80%	90%	3:1	250	166	129	127
90%	60%	3:1	492	206	109	102
90%	80%	3:1	334	126	83	66
90%	90%	3:1	215	126	94	80

14.11.2 Time to number of cases

The institute for Health Metrics and Evaluation (IHME) has developed a deterministic SEIR (susceptible – exposed – infectious – recovered) compartmental framework to predict SARS-CoV-2 infections, hospitalizations and deaths for over 380 locations worldwide (http://www.healthdata.org/covid)[8].

For study planning, the continuously updated IHME projected COVID-19 hospitalization rates will be used to predict the number of COVID-19 cases that is expected to be reached by a certain point in time, taking into account the catchment area of the study sites participating to the study. The number of vaccinated COVID-19 cases by brand are predicted by additionally accounting for the anticipated CVE and brand-specific vaccination coverage.

14.11.3 Case-control ratio

Including more than 3 controls per case does not lead to a notable increases in the precision of the estimates. When possible and resource-saving, the number of controls sampled per case by calendar week will be restricted. Restricting the number of controls might be possible for some sites where SARI patients can be enrolled after their SARS-CoV-2 status is known and before they are transferred to either the COVID-19 or non-COVID-19 area within the hospital. This will be described as part of the patient flow, when applicable.

14.12 Unfavourable COVID-19 positivity rate among SARI cases

The COVID-19 positivity rate among SARI cases will be closely monitored over time. Positivity rates that are too high or too low, result in an inefficient study requiring large sample sizes (SARI cases) to obtain limited precision of the vaccine effectiveness estimates. When the positivity rate is unfavourably high, changing the case capture definition (currently SARI) or enrolling other hospital controls (e.g. patients presenting to the emergency department for reasons other than SARI) will be considered. When the positivity rate is unfavourable low, the weekly number of controls per case will be restricted when possible.

14.13 Data management

Data collection, statistical analysis and preparation of the study report are activities firewalled from vaccine companies to avoid perception of undue influence on the study report and CVE results interpretation.

14.13.1 Data management at site level

Each study site is responsible for the data collection, data validation, and data management of their participant-level study data. Depending on the study site, the data collection and source documentation will be different. For every participating study site, the data flow and data management will be documented in detail, including data collection, validation, data entry and data cleaning processes.

All pseudonymized participant-level study data will be locally transformed to the study-specific common minimum dataset (see Annex 4). The study site will perform quality checks and process any findings accordingly, with sufficient documentation to ensure transparency and reproducibility. When the performed data quality checks are satisfactory the study site can upload the data. (Section 14.13.2).

14.13.2 Data transfer and management at central level

The study-specific common minimum dataset will be uploaded by the study sites to a dedicated secured central server, the COVIDRIVE Research Server (CRS). The server is hosted by P95, Koning Leopold III Laan 1, 3001 Heverlee, Belgium. P95 will act as Data Processor according to the General Data Protection Regulation (GDPR) 2016/679. The data flow from the study to the CRS and extraction of results from the CRS is described in Figure 1.

1. Each data site will upload the study-specific common minimum dataset through the COVIDRIVE Electronic Data Transfer Application (EDTA), a pass-word protected secure web-application using secure file transfer protocol (sFTP).

2. The CRS system administrator, a certified Data Protection Officer (DPO), checks whether the data are compliant to the protocol, statistical analysis plan (SAP) and privacy regulations.
    a. If the check is satisfactory, the system administrator releases the uploaded data to the study folder accessible to the data analysts (using Remote Desktop Protocol (RDP)) and performs a data lock (the data are only readable by the data analysts and cannot be changed).
    b. If the check is not satisfactory, the system administrator reports this to the study site responsible for the data.

3. The data analysts perform the required data transformations on the data released in the study folder as per the SAP.

4. When the data transformations are finalized, the data analysts flag the resulting output files to the system administrator for extraction out of the CRS. These output files only contain aggregated summary data such as figures, tables with number of events, or estimates.

5. The system administrator checks the resulting output files flagged for extraction for compliance to the SAP.
    a. If the check is satisfactory, the resulting files are extracted out of the CRS by the system administrator using sFTP.
    b. If the check is not satisfactory, the system administrator reports this to the data analyst and requests changes to get the data into compliance with the SAP.

6. After the resulting files are extracted from the CRS, they can be used as the basis for reports, web applications and publications as per the SAP.

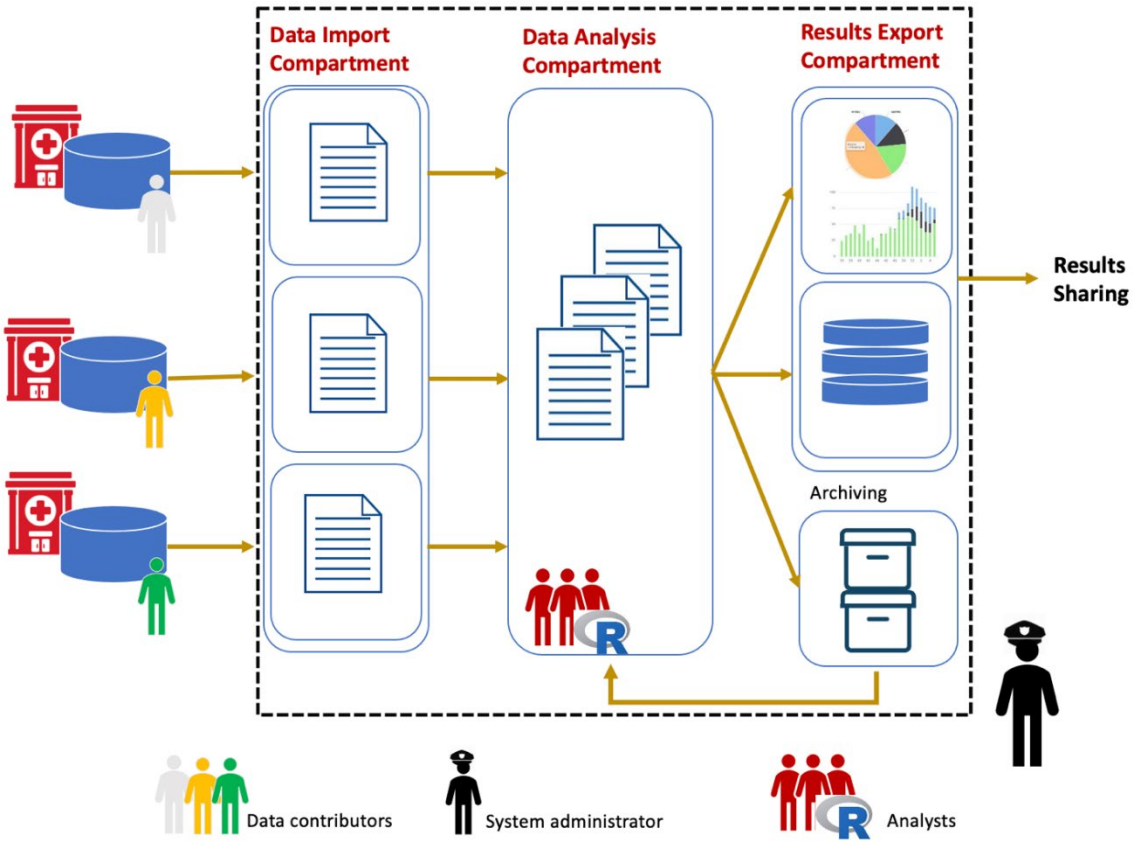

Figure 1. Data flow from study site to COVIDRIVE Research Server and beyond.

A data management plan (DMP) will be written prior to the start of the data collection to describe data management at the central level. The DMP will describe all functions, processes, responsibilities and specifications for data collection, data storage, quality checking, transfer, cleaning and validation.

14.14 Data analysis

A full SAP and mock report will be developed prior to the conduct of the analysis. The SAP specifies the statistical analyses to be conducted while the mock report, including tables, figures and listings (TFL) mock shells, specifies the presentation of the results.
All statistical analyses will take place in the Data Analysis Compartment of the CRS.

14.14.1 Description of SARS-CoV-2 dynamics and COVID-19 vaccine coverage

Context information will be provided by describing the evolution of the SARS-CoV-2 dynamics during the study period in the countries where the study sites are located. The circulating genetic variants will be described as well.

National (or regional) COVID-19 immunization recommendations over time will be described, along with the coverage of COVID-19 vaccination, overall and by brands of interest.

Table 7. Sources for context information on circulating genetic variants and national/regional COVID-19 immunization recommendations.

Genetic variants	
« Country 1 »	***« link »***
« Country 2 »	***« link »***
COVID-19 immunization recommendations	
« Country 1 »	***« link »***
« Country 2 »	***« link »***

14.14.2 Attrition diagram

For every study site, an attrition diagram will be created. The attrition diagram describes the number of records excluded from the statistical analyses, by reason of exclusion. For every study site, a bar chart of the distribution of vaccine brands will be created after exclusion criteria have been applied.

14.14.3 Descriptive analysis of demographics and baseline characteristics

For every study site and brand of interest, visualizations based on the final brand-specific data for analysis will be created including;

- number of controls and COVID-19 cases (possibly by genetic variants) over time
- distribution of covariates among cases and controls.

For every study site and brand of interest, a tabular summary based on the final brand-specific data for analysis will be created, describing the characteristics of cases and controls as predefined in the mock report. Similar visualizations and tabular summaries will be made for the combined data across study sites.

14.14.4 Statistical analyses

Site-specific CVE estimates by vaccine brand will be calculated and these will be pooled through a random effects meta-analysis. The main analysis will be based on this two-stage pooling methodology meaning that CVE estimates will be obtained for each site and subsequently pooled. An overview of the analysis workflow can be found in Figure 3.

The two-stage pooling approach has the advantage that it can easily integrate estimates from sites that cannot share patient-level data. Additionally, two-stage pooling approaches are easily understood by and communicated to researchers in the field who tend to be familiar with meta-analyses of aggregated data [9]. Finally, note that it has been shown that in most scenarios two-stage and one-stage pooling tend to lead to similar results [9-11]. To account for potential treatment effect heterogeneity a random effect will be incorporated into the model. Potential causes of such heterogeneity could include differences at the recruitment stage, local differences in the intensity of the epidemic, etc. The most important limitations of the random effects meta-analysis approach include a loss of power when there is no between-study heterogeneity as compared to a fixed-effects approach, a potential loss of power as compared to a one-stage pooling approach, and potential convergence issues when the outcome of interest is rare or the sample size of some sites is relatively small [11].

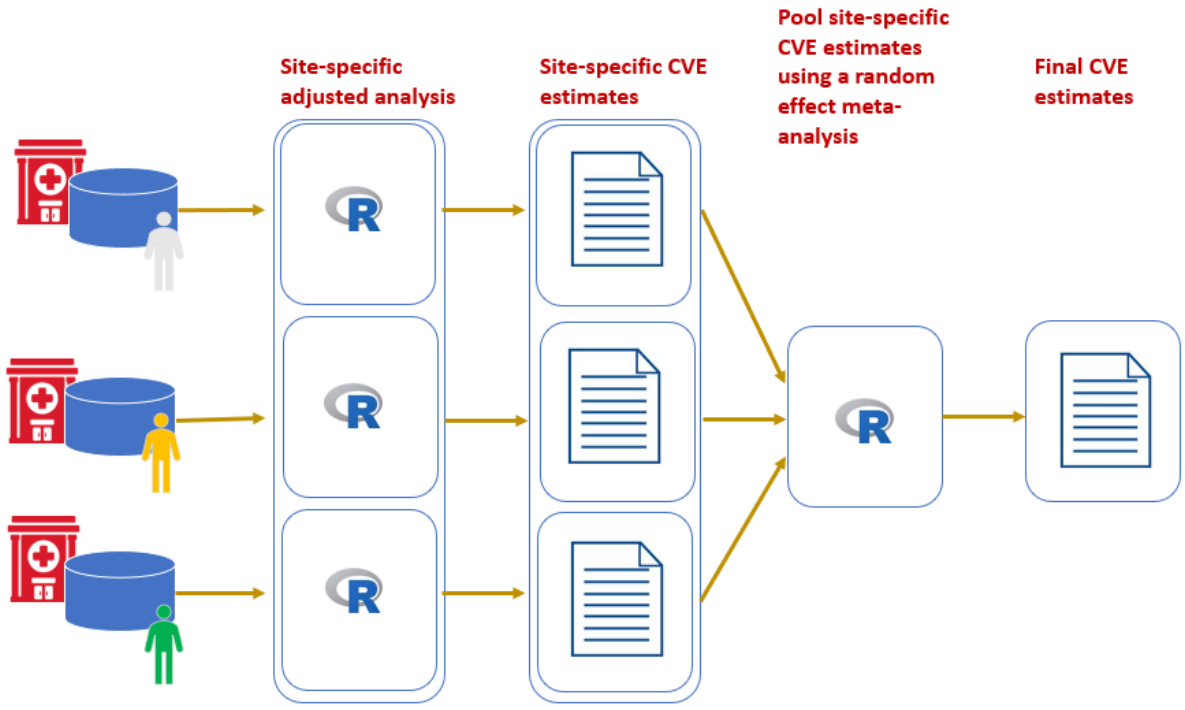

Figure 2. Analysis workflow from the site-specific datasets to the final CVE estimate.

14.14.4.1 Site-specific CVE

For every study site, the crude and confounder-adjusted brand-specific CVE against laboratory-confirmed COVID-19 disease will be estimated, as:

VE = (1 – OR) x 100%,

where *OR* denotes the confounder-adjusted odds ratio, comparing the odds of vaccination among COVID-19-positive study participants to the odds of vaccination among COVID-19-negative study participants.

Confounder-adjusted CVE estimates will be derived from multivariable logistic regression models. The analysis to estimate brand-specific CVE will account for the differences in approved indications, discarding from the analysis patients for which the vaccine brand of interest is not indicated. All CVE estimates will be adjusted for calendar time.

As COVID-19 status is part of the initial data collection, it is expected that exposure should be known for essentially all subjects. Data on exposure and especially the potential confounders, however, are likely to be missing for a proportion of the subjects. These data are often collected from existing medical records, vaccine registries, etc. which existed before the SARI episode and it seems reasonable to assume that whether the data is missing is independent of the COVID-19 status during the SARI episode. Assuming that the described missing data mechanism holds, performing a complete case analysis (CCA) will not lead to biased results. The primary analyses will therefore be a CCA, dropping records with missing information for the outcome, exposure of interest or the covariates. In case >20% of the cases and controls have missing covariate information CCA is likely to be inefficient and alternatives such as multiple imputation and augmented CCA will be explored. The smooth functions of age and symptom onset date will be modelled by penalized cubic regression splines and estimated using restricted maximum likelihood for smoothness selection [12]. Sensitivity analysis will be performed, such as on time between symptom onset and swab data and others as appropriate and as pre-specified in the SAP.

The analyses described above will be repeated for every objective.

14.14.4.2 Pooled CVE

Pooled brand-specific CVE estimates will be obtained through random-effects meta-analysis on the log-transformed site-specific estimates [13]. Restricted maximum likelihood will be used to obtain the pooled meta-analyses estimates and 95% confidence intervals (CI) [14]. The modified Hartung-Knapp correction will be used to estimate the variance of the mean effect [15]. The estimates and 95%CIs will then be back-transformed to obtain the pooled CVE estimates and 95%CI.

An indication for the heterogeneity among estimates from different study sites will be obtained by calculating I^2 according to Higgins et al [16]. For every meta-analysis performed, the potential impact of outliers and influential estimates on the pooled estimate will be evaluated. Studentized deleted

residuals *r* will be used to identify outliers in the meta-analysis. The standardized DFBETAs statistic will be used to identify influential estimates [17].

Multiple sensitivity analyses will performed. These sensitivity analyses will explore the effect of time between symptom onset and swab data, the use of a one-stage pooling method instead of the two-stage pooling methods, and others as appropriate and as pre-specified in the SAP.

15 QUALITY MANAGEMENT

15.1 Independent Scientific Committee

The Independent Scientific Committee (ISC) is composed of independent external experts (from organizations or institutions which are not partners of COVIDRIVE) with good expertise/experience relevant for COVID-19 vaccine effectiveness studies. They will give advice on the scientific study documents, and provide oversight to avoid perception of undue influence by vaccine companies.

15.2 Quality Control and Audit Committee

The Quality Control and Audit Committee (QCAC) of COVIDRIVE is composed of quality control and assurance experts from COVIDRIVE vaccine companies' partners. Their mission is to evaluate the quality of the study conduct, data reporting, the analysis and report (activities firewalled from vaccine companies) in order to ensure reliable data are delivered or when necessary, identify areas for improvement.

The QCAC provides quality management recommendations for Study Sites and oversees any audit at the study site level if needed; the audit is subcontracted to an external qualified consultants' auditor.

Because sites participating in COVIDRIVE are not subject to the specific quality mechanisms applicable to vaccine companies as per regulatory requirements, the QCAC seeks for reasonable and feasible mechanism to enhance the quality management. The QCAC aims to provide guidance and supports Study Sites to get the relevant study documentation and quality management system in place to ensure that reliable observational data are integrated into the study analysis and that activities are in place at site level to prevent, detect, correct and control potential errors.

15.3 Monitoring

Monitoring activities include:

- Before study start, the study site will be asked to complete a quality management questionnaire to inform the Study Team on all aspects of the study conduct, including a description of the installed data quality management system to ensure that reliable observational data are generated and that activities are in place at the site to prevent, detect, correct and control potential errors.
- Before study start, a site initiation visit (remote) will be organised by the Study Team.
- During study conduct, regular study site contacts will be organised to monitor study progress (number of cases and controls enrolled), to ensure regular data transfer to the COVIDRIVE Research Centre (CRC) and to discuss potential protocol deviations or other issues related to the study conduct.

The site investigators must permit, any external auditor mandated by the QCAC of the COVIDRIVE partnership or study requester, the IEC, auditors and representatives from regulatory authorities direct access to all study-related documents. Participant confidentiality will be protected at all times.

15.4 Data quality checks at central level

An automatic data quality check will be done during data upload to the COVIDRIVE Research Centre (CRC) via the Electronic Data Transfer Application (EDTA). The data quality checks relate to compliance with the study-specific common minimum data requirements (Annex 4), the presence of duplicated records, variable formats, implausible values, inconsistencies between variables and missing values. All uploaded data will be checked again for quality by the P95 team. When data quality issues will be found, the data site responsible person will be contacted, and the data will either be corrected or discarded from further analysis. After performing the data quality checks and implementing the corrective measures, the study inclusion criteria will be applied and records with missing data in the outcome and/or exposure information will be discarded.

For every site separately, a data quality report will be produced. These reports will contain a description of the results of the quality checks performed, the amount of data that was retained for analysis after applying the inclusion criteria and graphical summaries of the retained data. The data quality report will be send to the site for approval.

16 LIMITATIONS OF THE RESEARCH METHODS

The COVID-19 pandemic is unprecedented, unpredictable and poses challenges for the post-marketing evaluation of the COVID-19 vaccines. The following challenges and limitations for the real-world evaluation of the COVID-19 vaccines have been identified at the time of writing this protocol:

The sensitivity of the SARI case definition is imperfect and potential COVID-19 cases might not be included in the study. This will however not bias the CVE estimates unless vaccination affects the presentation of the SARI symptoms. Until now it is unknown whether COVID-19 vaccination induces a milder course of disease.

As for other epidemiological study designs, the results from TNCC study designs can be biased due to misclassification of disease status using diagnostic assays with imperfect sensitivity and specificity. Low sensitivity and low specificity are expected to bias the CVE estimates downwards with the bias resulting from low specificity being more substantial than the bias from low sensitivity [18]. To minimize misclassification bias, laboratory confirmation based on RT-PCR is required for the current study. The specificity of RT-PCR for the diagnosis of COVID-19 is high (>99.5%) while its sensitivity depends on various factors, including timing of sampling, type of specimen and sampling technique. In hospitalized patients, the clinical sensitivity of PCR decreased with days post symptom onset with >90% clinical sensitivity during the first 5 days after symptom onset and 70%-71% from Days 9 to 11 [19]. Also, the sensitivity is higher for lower respiratory samples than for upper respiratory tract samples [20], and a good sampling technique is required to obtain better results. To explore any potential bias due to disease misclassification, information on type of specimen will be collected and sensitivity analyses regarding time between symptom onset and swabbing will be performed. Guidance on collecting and handling specimens for the diagnosis of COVID-19 will be given as part of study staff training.

The SARS-CoV-2 positivity rates within the SARI patients varies over time with the observed positivity rates since the start of the COVID-19 pandemic ranging from 20% to 80% (FISABIO, personal communication), implying that the potential case to control ratio would vary from 1:4 to 4:1 depending on calendar time. Future SARS-CoV-2 positivity rates in SARI patients are difficult to predict as they depend on both the successfulness of the COVID-19 vaccination programmes and the circulation of other respiratory pathogens. In case-control studies, the ideal number of controls is typically 1 to 3 times the number of cases [21]. To allow optimizing the case-control ratio conditional on calendar time (with the latter being an important confounder in CVE studies), we allow for the possibility to 1) sample other hospital controls or modify the case capture definition in case the positivity rate would be high, and – when feasible and resource saving - to 2) restrict the number of controls per cases in case the positivity rate would be low.

Confounding is a substantial concern for real-world studies on the effectiveness of COVID-19 vaccines.

As a result of the huge demand for COVID-19 vaccines and initially limited vaccine supplies, most European countries prioritized the vaccination of elderly people, residents and personnel in long-term care facilities, healthcare workers, social care personnel and those persons with certain comorbidities

[22]. The presence of such vaccination priority groups is an important potential source of confounding in COVID-19 vaccine effectiveness studies. In addition, the uptake of vaccination may be highest among individuals who adhered most strongly to NPIs (i.e. subjects exhibiting precautionary health behaviour such as wearing face masks, using hand sanitizer, avoiding public places) and consequently have a lower propensity of natural infection and immunity. As naturally acquired immunity may be strongly protective against re-infection (~90%) [23], lack of precautionary health behaviour (~previous SARS-CoV-2 infection) might be an important potential confounder as well. An alternative bias mechanism might be that subjects feel protected once vaccinated and relax the precautionary health measures they were taken prior to vaccination. In addition, propensity towards vaccination in general might also act as a confounder when, for example, subjects more likely to be vaccinated against COVID-19 are also more likely to be vaccinated against influenza and/or against pneumococcal infection (e.g. as is the case for healthcare workers, risk groups and persons with a positive attitude towards vaccination). Joint vaccination against COVID-19, influenza and/or pneumococcal infection might bias the results of TNCC studies as such joint vaccination will affect both the probability that the subject becomes a case as well as the probability that the subject becomes a control. Another potential important confounder is ethnicity and socio-economic background. It is well established that some minority ethnic groups have a higher risk of confirmed SARS-CoV-2 infection and higher risk of developing critical COVID-19 disease given exposure, even after accounting for socio-economic variables [24]. When these groups are also less likely to be vaccinated, the vaccine effectiveness estimates will be overestimated. Finally, CVE studies are strongly subject to time-varying confounding as both the COVID-19 vaccination coverage and the SARS-CoV-2 infection pressure and virulence will co-vary over time.

An important potential effect modifier of the effectiveness of the COVID-19 vaccines is frailty. Frailty has been shown to affect older adults's responses to vaccines for infections such as influenza, shingles and pneumococcus (ref). Frailty is a multi-dimensional construct, with both psychical and psychosocial dimensions. Frailty is age- and disease associated, changes over time and is characterized by a strong inter-personal variation. There is currently no consensus on how to define and how to best measure frailty. Methods include questionnaires, performance measures, electronic health care database algorithms or any combination of these. As the study population of our study is the general population and given the complexity of measuring frailty, we do not measure frailty as such. Rather we will collect information on variables that are known to be strongly related to frailty, including age, BMI, long-term care facility residence and chronic conditions including cancer and immunodeficiency.

Finally, sample size estimations for brand-specific CVE estimates are challenging as they strongly depend on the SARS-CoV-2 attack rate and the brand-specific vaccination coverage, with both parameters being difficult to predict. Sample size requirements will further increase for estimating effectiveness against COVID-19 disease by genetic variants. Although our study covers a wide network of hospital across Europe, obtaining sufficient sample to obtain accurate estimates is a primordial challenge.

17 ETHICAL AND REGULATORY CONSIDERATIONS, RETENTION OF DATA AND OF BIOLOGICAL SAMPLES

17.1 Guiding Principles

To ensure the quality and integrity of research, this study will be conducted under the International Ethical Guidelines on Epidemiological Studies issued by the Council for International Organisations of Medical Sciences (CIOMS, 2009), Good Epidemiological Practice (GEP), the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations and guidelines.

This is an observational study without medical intervention or change in the clinical and diagnostic capacity. Therefore, there is no direct benefit to the participants. Nevertheless, there are important potential societal benefits derived from this vaccine effectiveness study. Effective COVID-19 vaccines are key to ending the pandemic and preventing potential future resurgence. Close monitoring of the effectiveness of COVID-19 vaccines is essential to guide decision-making regarding vaccine marketing approval, optimization of vaccination programmes and future COVID-19 vaccine development.

17.2 Ethics approval

The site-specific protocols will be submitted to relevant ethics committee(s) following local regulations and the declaration of Helsinki. Copies of the appropriate approvals will be collected from each site and archived according to the local regulations, but at least for 5 years.

The only exception is where the study is part of an ongoing routine program evaluation required by ministry of health or a requisite part of the public health institution's work, and would therefore fall outside the mandate for ethics committees. In these cases, a statement that no formal approval from ethics committee is required, is sufficient.

17.3 Informed consent

Written informed consent will be obtained from all participants/guardians as specified by the national/regional ethics committee. The following information should be specified in the informed consent form (ICF) (Annex 5): who is responsible for the study, aim of the study, nature of processed data, purposes of processing, purpose of the use of the data including potential future use of the data to advance knowledge on vaccines, recipients of possible data transfers, rights of the study participants, and consequences of not accepting the informed consent. Specific consent procedures may be needed for patients in poor health conditions (e.g. oral witnessed consent, consent by next of kin) or for children (assent). If informed consent will not be required, the reason will be stated.

17.4 Independent Ethics Committee/Institutional Review Board

Consistent with local regulations and prior to enrolment of participants at a given site, the study protocol together with its associated documents (e.g., ICF) will be submitted by the Study Site to the responsible IRB/IEC for its review. Participant enrolment will not start before the Study Site has obtained written confirmation of a favourable opinion/approval from the relevant central or local IRB/IEC. The Study Site will promptly and before first participant enrolment inform the Study Team that ethical approval has been granted. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to the Study Team.

Should the study be terminated early for any unanticipated reason, the Investigator will be responsible for informing the IRB/IEC of the early termination.

17.5 Participant's confidentiality

Data will be pseudonymised at the site-level prior to data transfer to the to P95. All parties will ensure protection of participant's personal data and will not include participant names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the countries, participants will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. Every effort will be made to protect participant confidentiality according to the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation; GDPR).

17.6 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Such protocol changes will be discussed and agreed upon with the Study Team prior to their implementation. Major (i.e., substantial, significant) amendments will usually require submission to the relevant institutional review board/ independent ethics committee (IRB/IECs) for approval or favourable opinion and to the relevant regulatory authorities, if applicable. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating study site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations.

17.7 Data re-use

Data can be re-used for additional analysis to advance the knowledge on infectious disease and their prevention or treatment following approval of their data request application by the COVIDRIVE Independent Scientific Committee (COVIDRIVE ISC) and under the following conditions:

- The data can only be used for relevant scientific research and as pre-defined in the data access application/protocol when approved by the COVIDRIVE ISC
- The data requestor will only be provided access to the data as needed for the purposes set out in the data access application/protocol approved by the COVIDRIVE ISC
- The data will remain at all times at the P95 server.

18 STUDY MANAGEMENT AND LOGISTICAL ASPECTS

This study will be performed by the study site investigator, with guidance, input, review and approval of the Study Team, including development of materials, recruitment, training and management of sites, electronic data capture and data management and analysis.

The Investigators and all study staff will conduct the study in compliance with the final version of this protocol. The rights, safety and well-being of the participants are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their tasks.

18.1 Study Investigators at hospital level

« Contact details to be inserted »

Each Investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the International Ethical Guidelines on Epidemiological Studies issued by the Council for International Organisations of Medical Sciences (CIOMS, 2009), Good Epidemiological Practice (GEP), the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations and guidelines.

2. Personally conduct or supervise the staff who will assist with the protocol.

3. Ensure that study-related procedures including study-specific (non-routine/non-standard panel) screening assessments are NOT performed on potential participants, prior to the receipt of written approval from relevant governing bodies/authorities.

4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.

5. Secure prior approval of the study and any changes by an appropriate IEC and competent authority.

6. Ensure that the IEC will be responsible for initial review, continuing review, and approval of the protocol.

7. Ensure that requirements for informed consent, as outlined in ICH-E6 (R2) 4.8 [25] and local regulations, are met.

8. Obtain valid informed consent from each participant and document the date of consent in the participant's medical chart. Valid informed consent is the most current version approved by the IEC.

9. Prepare and maintain adequate case histories of all persons entered into the study, including laboratory results, etc., and maintain these data for a minimum of 2 years, or upon agreement with the Sponsor. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

10. Allow possible inspection and copying by the regulatory authority of GEP-specified source documents.

11. Review and provide a signature as approval of the content of the epidemiological study report.

18.2 Training

Investigators and data collectors will be trained on the study protocol before the start of the study. They will receive the protocol, and study training material

«Training organisation and brief description of training content to be inserted»

18.3 Standard operating procedures (SOPs)

«Site-specific SOPs to be inserted»

18.4 Data capture

«Details on paper and/or electronic data capture systems to be inserted»

18.5 Retention

To enable evaluations and/or audits from regulatory authorities or others, the investigator agrees to keep documents and data relating to the study in an orderly manner in a secure Study file, which will be available for audits/inspections, for a period of 20 years after end of the study or longer according to local requirements and legislation. Documents to be archived include the participant enrollment log and the signed ICFs. In the event that archiving of the file is no longer possible at the site, the site/Investigator will be instructed to notify the Study Team. The Investigator must contact the Sponsor before destroying any study related documentation. It is the responsibility of the Sponsor to inform the study site of when these documents no longer need to be retained.

Biological specimen might be collected for future research. Retention, storage and access rights will be pre-defined and described as appropriate.

18.6 Discontinuation of study participation/Withdrawal from the study

Participation in the study is strictly voluntary. A participant has the right to withdraw from the study at any time and for any reason. All attempts should be made to determine the underlying reason for the discontinuation/withdrawal and, where possible, the primary underlying reason should be recorded. Data collected up to the time of consent withdrawal will be considered for the analysis.

18.7 Study termination

The Study Team reserves the right to terminate the study at a specific study site at any time. Reasons for terminating the study include but are not limited to the following:

- The study site does not respond to study management requests.
- Repeated protocol deviations/ poor protocol compliance.

19 REPORTING and DISSEMINATION OF RESULTS

19.1 Study protocol

The study protocol and final study report will be posted on the EU PAS register: (http://www.encepp.eu/encepp/studiesDatabase.jsp).

19.2 Management and reporting of adverse events/adverse reactions

This is a non-interventional epidemiological study for assessing the effectiveness of routine COVID-19 vaccination. The Study Sites conducting the study should follow local requirements as regards the submission of cases of suspected adverse reactions to the competent authority in the country where the reaction occurred.

19.3 Progress, interim and final reports

Progress reports will be provided every 2 months since enrolment of the first participant. Progress reports will provide an overview of the number of cases, number of controls, number of study participants vaccinated with any COVID-19 vaccine brand and number of study participants vaccinated with the COVID-19 vaccine brand of interest.

Interim analysis for a specific CVE objective will be performed as soon as a prespecified number of COVID-19 cases required for the brand-specific CVE estimates is reached. The progress reports will be used to monitor these required number of COVID-19 cases.

A final study report will be written for each of the individual COVID-19 vaccine brands of interest. When the Study Requestor is a MAH, the COVIDRIVE Independent Scientific Committee (ISC) will review the study report and the written comments by the vaccine company requestor. The ISC will provide recommendations for the integration of the vaccine company requestor comments. The interim and final reports will be submitted to the EMA by [Study Requestor] to meet regulatory requirements.

19.4 Publication

Study contributors (sites) may publish their own data independently from COVIDRIVE upon informing COVIDRIVE and acknowledgement of funding. Co-authorship will be defined following the ICMJE (International Committee of Medical Journal Authors) criteria and the Good Publication Practice (GPP). All publications will be open-access.

20 FUNDING

This study is partially funded by [Study Requestor].

The following study sites (hospitals) receive additional funding from other sources:

Study site (hospital)	Additional funding source

Study sites (hospitals) not listed did not receive additional funding. In those sites, the study is solely funded by [Study Requestor].

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ANNEX 1: VACCINE-ASSOCIATED ENHANCED DISEASE (VAED)

VAEDs are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen [1]. VAED has been observed in the past following administration of measles and RSV vaccines [2]. VAED is a theoretical concern for COVID-19 vaccines, based on observations from other respiratory viruses and from animal models of highly pathogenic coronaviruses [3]. While the underlying potential mechanisms for VAED are unclear, VAED always involves a memory response primed by vaccination and appears to targets the same organs as wild-type infections [3]. Particular concerns include the potential for (inactivated whole-virus) vaccines to elicit antibody-dependent enhancement (ADE) of infection or vaccine-associated enhanced respiratory disease upon SARS-CoV-2 infection[4], although neither has been observed in clinical trials so far. Studying VAED on an individual patient level is challenging, as no confirmatory tests to diagnose VAED exist, and distinguishing vaccine failure from VAED among vaccinees is difficult.

VAED may be studied on a population level by comparing the occurrence and presentation of severe disease among vaccinated and non-vaccinated patients. VAED through ADE is postulated to occur with low levels of neutralizing antibodies, and where non-neutralizing or poorly neutralizing antibodies increase the subsequent viral entry into cells, thereby intensifying the infection [5]. The effect of waning antibody titers after vaccination on ADE is unknown [6]. If neutralizing antibodies wane over time, an association between time since vaccination and the risk of developing severe disease may be observed. Therefore it is proposed to study CVE against different levels of COVID-19 disease severity by time since vaccination.

Further information on VAED including possible pathophysiologic pathways are described by Munoz et al. [3].

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The following form should be used to capture clinical and laboratory features of patients with critical COVID-19 disease admitted to the ICU.

Section A: clinical features

Please complete the tables below concerning the patient's condition during ICU admission:

During ICU admission, did the patient have any measurements at rest of:		**If yes, please provide the following details:**
a respiratory rate ≥ 30 per minute?	☐ No ☐ Yes	
an oxygen saturation of ≤ 93% on room air?	☐ No ☐ Yes	
a systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg?	☐ No ☐ Yes	
Fever ≥ 39.3°C? a respiratory rate ≥ 30 per minute?	☐ No ☐ Yes	Total number of days
a heart rate ≥ 125 beats per minute?	☐ No ☐ Yes	

During ICU admission, did the patient ever require:		**If yes, please provide the following details:**
non-invasive supplemental oxygen?	☐ No ☐ Yes	Total number of days:
respiratory ventilator support or ECMO?	☐ No ☐ Yes	Total number of days
Treatment with vasopressors?	☐ No ☐ Yes	Total number of days

During ICU admission, did the patient exhibit signs or symptoms of new/worsening dysfunction in any of the following categories?

Multiorgan failure?	☐ No ☐ Yes	
Gastrointestinal dysfunction? Acute hepatic dysfunction Acute liver failure	 ☐ No ☐ Yes ☐ No ☐ Yes	
Acute renal dysfunction? Acute renal failure? Renal replacement therapy?	☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes	
Neurologic dysfunction?		

Encephalopathy	☐ No	☐ Yes	
Convulsions/seizures	☐ No	☐ Yes	
Meningitis	☐ No	☐ Yes	
Altered level of consciousness	☐ No	☐ Yes	
Guillain-Barre Syndrome	☐ No	☐ Yes	
Stroke	☐ No	☐ Yes	
Other – specify:	☐ No	☐ Yes	
Respiratory dysfunction?	☐ No	☐ Yes	
Acute respiratory distress syndrome (ARDS)	☐ No	☐ Yes	
Pneumonia	☐ No	☐ Yes	If yes, radiological confirmation ☐ No ☐ Yes
Acute respiratory failure	☐ No	☐ Yes	
Dyspnea/tachypnea	☐ No	☐ Yes	
Other – specify:	☐ No	☐ Yes	
Acute cardiac injury?			
Myocardial infarction	☐ No	☐ Yes	
Arrhythmia (new onset)	☐ No	☐ Yes	
Ischemic Heart Disease	☐ No	☐ Yes	
Myocarditis, pericarditis	☐ No	☐ Yes	
Stress cardiomyopathy	☐ No	☐ Yes	
Microangiopathy	☐ No	☐ Yes	
Other – specify:	☐ No	☐ Yes	
Hematologic/Vascular disorders?	☐ No	☐ Yes	
Deep vein thrombosis	☐ No	☐ Yes	
Pulmonary embolus	☐ No	☐ Yes	
Cerebrovascular stroke	☐ No	☐ Yes	
Limb ischemia	☐ No	☐ Yes	
Vasculitis	☐ No	☐ Yes	
Thrombocytopenia	☐ No	☐ Yes	
Other – specify:	☐ No	☐ Yes	
Multisystem inflammatory syndrome	☐ No	☐ Yes	

Section B: laboratory features

Provide the clinically significant laboratory results for each day during ICU admission

Date of sampling	**dd/mm/yyyy**

Test Type/Name	**Clinically significant results?**	**Provide details for clinically significant results**
Creatinine	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Bilirubin	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Platelet count	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Lymphocytes (i.e.CD4, CD8 counts)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Cytokines	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Procalcitonin	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
C-reactive protein	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Ferritin	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Lactate dehydrogenase (LDH)	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
D-dimer	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
PT	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
PTT	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:

Test Type/Name	Clinically significant results?	Provide details for clinically significant results
INR	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
Fibrinogen	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
PaO2/FiO2	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
PaCO2	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
pH	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:
SpO2/FiO2	☐ Yes ☐ No ☐ Unknown	Results: Units: Reference range:

Section C: other measurements

Provide clinically relevant and significant laboratory, histopathological, and/or radiological results at ICU.

Test Type/Name	Clinically significant results?	Provide details for clinically significant results		
Histopathology/ immunopathology of organs involved	☐ Yes ☐ No ☐ Unknown	Date(s): Results:		
Diagnostic Imaging (Magnetic Resonance Imaging, Computed Tomography, Ultrasound, doppler, etc.)	☐ Yes ☐ No ☐ Unknown	Test	Date	Result
Other relevant results	☐ Yes ☐ No ☐ Unknown	Test	Date	Result w/units

ANNEX 2: CHRONIC CONDITIONS

Covariate		Definition
Chronic conditions		
	Asthma	• Any of the following diagnostic codes (ICD-10): J45, J46 • INCLUDING: predominantly allergic asthma, nonallergic asthma, status asthmaticus, acute severe asthma • EXCLUDING: acute severe asthma, chronic asthmatic (obstructive) bronchitis, chronic obstructive asthma, eosinophilic asthma, lung diseases due to external agents.
	Lung disease	• **Any of the following diagnostic codes (ICD-10):** A15-16, A19, A31.0, B33.4, E84.0, J40-44, J47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99 • **INCLUDING:** TB (pulmonary, miliary but not that of other systems), atypical mycobacteria, cystic fibrosis, COPD, bronchiectasis and other chronic sequelae of infections, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure. • **EXCLUDING:** acute respiratory infections, lung cancer, diseases of pulmonary circulation, pleural plaques without asbestos, previous uncomplicated pneumothorax.
	Cardiovascular disease	• **Any of the following diagnostic codes (ICD- 10):** A52.0, B37.6, I01-02, I05-09, I11.0, I13.0, I13.2, I20-25, I26-28, I30-43, I44- 46, I48, I49.0, I49.5, I50-52, I70-71, Q20-Q28 • **INCLUDING:** all conditions of heart & large vessels that are chronic or likely to have chronic sequelae. Cardiovascular syphilis, endo-, myo- and pericarditis, rheumatic fever, chronic rheumatic heart diseases, congenital malformations, hypertensive (renal) diseases with heart failure, ischaemic heart diseases, diseases of pulmonary circulation, atherosclerosis, cardiomyopathies, most conduction disorders, heart failure, aortic aneurysms & dissecation, other heart diseases and their complications. • **EXCLUDING:** uncomplicated hypertension, previous uncomplicated pulmonary embolism (with no lasting cardiac insufficiency), paroxysmal tachycardias, most cases of premature depolarization.
	Hypertension	• Any of the following diagnostic codes (ICD-10): I10, I11.9, I12, I13.1, I13.9, I15 • INCLUDING: essential (primary) hypertension, secondary hypertension

		• EXCLUDING: hypertensive heart/renal disease with (congestive) heart failure,
	Chronic kidney disease	• **Any of the following diagnostic codes (ICD- 10):** I12-13, M10.30, N00-19, N20.0, N25-27, N28.0, N28.9, Q63.9, Z90.5 • **EXCLUDING:** Clinically nonsignificant kidney cysts
	Type 2 diabetes	• **Any of the following diagnostic codes (ICD-10):** E11 • **INCLUDING:** Non-insulin dependent diabetes mellitus (adult-onset, maturity-onset, nonketotic, stable, type II, non-insulin-dependent diabetes of the young)
	Cancer	• **Any of the following diagnostic codes (ICD- 10):** C00-97, D37-48, Z85, Z92.3, Z92.6. • **INCLUDING:** All malignant neoplasms (both solid and haematologic) with potential to metastasize, either in treatment, active followup, or <5 years post curative treatment. • **EXCLUDING:** Benign & in situ neoplasms. Basal cell carcinomas. Any cancer previously treated with curative intent & in complete remission for ≥5 years.
	Immunodeficiency (or organ transplant)	• **Any of the following diagnostic codes (ICD-10):** B20-B24, D80–84, D89, Z94 • **INCLUDING:** HIV infections, immunodeficiencies & organ transplants. Or iatrogenic: ≥2 week systemic treatment, in the 3 months preceding symptom onset, with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, TNF-α blockers and other biological or cytostatic drugs with immunosuppressive effect. • **EXCLUDING:** Disorders of the immune system which do not lead to immunosuppression (e.g. some autoimmune conditions).

ANNEX 3: SURVEY ON PRECAUTIONARY HEALTH BEHAVIOUR

During the last three months,

It really bothers me when people sneeze without covering their mouths

0= strongly disagree
1= undecided
2= strongly agree

I avoid touching door handles and staircase railings at public locations

0= strongly disagree
1= undecided
2= strongly agree

I dislike wearing a face mask

0= strongly agree
1= undecided
2= strongly disagree

I want people's temperature to be taken before they enter public places

0= strongly disagree
1= undecided
2= strongly agree

I don't mind going to very crowded places

0= strongly agree
1= undecided
2= strongly disagree

I would self-isolate myself at home if needed
0= strongly disagree
1= undecided
2= strongly agree

I frequently use hand sanitizer and/or wash my hands after shaking someone's hand
0= strongly disagree
1= undecided
2= strongly agree

I avoid going to public places
0= strongly disagree
1= undecided
2= strongly agree

[1]Olapegba PO, Iorfa SK, Kolawole SO, Oguntayo R, Gandi JC, Ottu IFA, Ayandele O. Survey data of COVID-19-related Knowledge, Risk Perceptions and Precautionary Behavior among Nigerians. Data Brief. 2020 May 8;30:105685. doi: 10.1016/j.dib.2020.105685. PMID: 32391411; PMCID: PMC7206440.

ANNEX 4: STUDY-SPECIFIC COMMON MINIMUM DATASET

Nr	Variable name		Description	Additional info	Variable format	Values/coding	Mandatory
SITE IDENTIFICATION							
	idsite		Site identifier		Text	As described in the Study Plan	X
	country		Country identifier		Text	As described in the Study Plan	X
PATIENT IDENTIFICATION							
	idpatient		Patient identifier	Identifier also contains country and site identifier	Text	As described in the Study Plan	X
	sex		Sex		Numeric (categorical)	1=Male 2=Female X=Sex-neutral	X
	ageyears		Age in years at admission		Numeric		X
ADMISSION DATA							
	onsetdate		Date of first symptom onset		DD/MM/YYYY	Date within the study period	X
	admissiondate		Date of hospitalisation	First point of contact (arrival at Emergency Department)	DD/MM/YYYY	Date within the study period	X

	SARI		SARI patient		Numeric (categorical)	0=No 1=Yes 9999=No information	x
	fever		History of fever or measured fever >= 38°C		Numeric (categorical)	0=No 1=Yes 9999=No information	
	cough		cough		Numeric (categorical)	0=No 1=Yes 9999=No information	
	shortbreath		Shortness of breath		Numeric (categorical)	0=No 1=Yes 9999=No information	
	anos_dysg		Sudden onset of anosmia, ageusia or dysgeusia		Numeric (categorical)	0=No 1=Yes 9999=No information	
INCLUSION/EXCLUSION CRITERIA							
	vacc_eligible		Eligible for COVID-19 vaccination at time of hospitalization		Numeric (categorical)	0=No 1=Yes 9999=No information	
	comm		Communication with patient/Legally Acceptable Representative		Numeric (categorical)	0=No 1=Yes 8888=Not applicable	X
	consent		Consent/assent given		Numeric (categorical)	0=No 1=Yes 8888=Not applicable	X
	Consentwho1		If consent is given, who gives the consent?		Numeric (categorical)	0=Patient 1=Parents/tutor/guardian 8888=Not applicable	X
	Consentwho2		If consent is given, who gives the consent?	In case	Numeric (categorical)	0=Patient	X

				consent/assent needs to be given by both Parent/tutor/guardian and young patient		1=Parents/tutor/guardian 8888=Not applicable	
	consentdate		Date of consent given		DD/MM/YYYY	Date within the study period 8888 = Not applicable	X
	prior_hosp		COVID-19 hospitalization within 3 months prior to the current admission (excl hospital transfers).		Numeric (categorical)	0=No 1=Yes 9999=No information	
	contra_swab		Contra-indication for swabbing		Numeric (categorical)	0=No 1=Yes 9999=No information	
COVID-19 VACCINATION HISTORY							
	contra_vacc		Any contraindication for SARS-CoV-2 vaccination	Based on locally used criteria.	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccany1		Received of SARS-CoV-2 vaccination dose 1		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrand1		Vaccine brand dose 1		Text		X
	covvaccdate1		Date of SARS-CoV-2 vaccination dose 1		DD/MM/YYYY		X
	covvaccany2		Received SARS-CoV-2 vaccination dose 2		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrand2		Vaccine brand dose 2		Text		X

	covvaccdate2		Date of SARS-CoV-2 vaccination dose 2		DD/MM/YYYY		X
	covvaccany3		Received SARS-CoV-2 vaccination dose 3		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrand3		Vaccine brand dose 3		Text		X
	covvaccdate3		Date of SARS-CoV-2 vaccination dose 3		DD/MM/YYYY		X
	covvaccany4		Received SARS-CoV-2 vaccination dose 4		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrand4		Vaccine brand dose 4		Text		X
	covvaccdate4		Date of SARS-CoV-2 vaccination dose 4		DD/MM/YYYY		X
	covvaccanyx		Received SARS-CoV-2 vaccination dose x + 1 (additional dose numbers will be added following real-life use of COVID-19 vaccine doses)		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	covvaccbrandx		Vaccine brand dose x + 1		Text		X
	covvaccdatex		Date of SARS-CoV-2 vaccination dose x + 1		DD/MM/YYYY		X
	covvacsource		Source of the COVID-19 exposure information		Numeric (categorical)	1=registry 2=medical record 3= vaccine card 9999=No information	X
COMORBIDITIES/RISK FACTORS							

	asthma		Asthma	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	lungdis		Lung disease		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	cardiovasc		Cardiovascular diseases	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	x
	hypertens		Hypertension	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	liverdis		Chronic liver disease	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	rendisease		Chronic renal disease	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	type2diabetes		Diabetes	[diagnostic codes and definitions to be included after	Numeric (categorical)	0=No 1=Yes	X

				review of proposal in Annex 2]		9999=No information	
	cancer		Cancer	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	immuno		Immunodeficiency or organ transplant	[diagnostic codes and definitions to be included after review of proposal in Annex 2]	Numeric (categorical)	0=No 1=Yes 9999=No information	x
OTHER RISK FACTORS							
	pregnancy		Pregnancy	Any trimester at symptom onset.	Numeric (categorical)	0=No 1=Yes 9999=No information	X
	pregn_trim		Pregnancy trimester		Numeric (ordinal)	0=Not applicable 1=First trimester 2=Second trimester 3=Third trimester 9999=No information	X
	bmi		Body mass index		Numeric	10 to 55 or 9999=No information	X
	smoking		Smoking status (cigarettes, cigars, pipe, hookah, vaping, e-cigarettes). Not counting exclusively chewing tobacco or snus.	Never-smoker: <100 cigarettes during their lifetime. Ex-smoker: has smoked ≥100 cigarettes over lifetime but has stopped ≥3 months ago. Occasional smoker: has smoked	Numeric (categorical)	0=Never-smoker 1=Ex-smoker 2=Occasional smoker 3=Daily smoker 9999=No information	

				≥100 cigarettes over lifetime and has still smoked in the 3 months preceding symptom onset, but not daily. Daily smoker: has smoked ≥100 cigarettes over lifetime and smokes daily.			
	ltcf_res		Is the patient a long-term care facility resident		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw		Is the patient a healthcare worker		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw_patient		Is the patient a healthcare worker with direct contact to patients		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw_covid		Is the patient a healthcare worker with direct contact to COVID-19 patients		Numeric (categorical)	0=No 1=Yes 9999=No information	
	hcw_ltcf		Is the patient a healthcare worker working in long-term care facility		Numeric (categorical)	0=No 1=Yes 9999=No information	
	prev_covid		COVID-19 prior to current episode	I had a previous episode of COVID-19 more than 2 months	Numeric (categorical)	0= no 1= yes, clinical diagnosis only 2= yes, laboratory confirmed	

				ago			
PRECAUTIONARY HEALTH BEHAVIOR & VACCINATION ATTITUDE				***As measured through a precautionary health survey, by summing scores on questions detailed below***			
	prehb_sneeze		Sneeze	It really bothers me when people sneeze without covering their mouths	Numeric (categorical)	0= strongly disagree 1= undecided 2= strongly agree	
	prehb_touch		Touch	I avoid touching door handles and staircase railing at public locations	Numeric (categorical)	0= strongly disagree 1= undecided 2= strongly agree	
	prehb_mask		Face mask	I dislike wearing face mask because of the way it looks and/or feels	Numeric (categorical)	0= strongly agree 1= undecided 2= strongly disagree	
	prehb_crowd		Crowds	I don't mind going to very crowded places	Numeric (categorical)	0= strongly agree 1= undecided 2= strongly disagree	
	prehb_isolate		Self-isolate	I would self-isolate myself at home if needed	Numeric (categorical)	0= strongly disagree 1= undecided 2= strongly agree	
	prehb_sani		Hand sanitizer	I frequently use hand sanitizer and/or wash my hands after shaking someone's hand	Numeric (categorical)	0= strongly disagree 1= undecided 2= strongly agree	
	prehb_public		Public places	I avoid going to public places	Numeric (categorical)	0= strongly disagree 1= undecided	

						2= strongly agree	
LABORATORY							
	swabdate		Date of swabbing		DD/MM/YYYY	Date within the study period. In case of multiple tests with at least 1 positive test result within 14 days prior to hospital admission, take the swab date corresponding to the first positive test result. In case all test results are negative, take the earliest swab date within 14 days prior to hospital admission.	X
	virus1		Laboratory result: SARS-CoV-2		Numeric (categorical)	0=SARS-CoV-2 negative 1=SARS-CoV-2 positive 9999=No information	X
	virus2		Laboratory results: coinfection (in addition to SARS-CoV-2)		Numeric (categorical)	0=No coinfection 1=coinfection 9999=No information	X
	virus1_ext		Laboratory result: pathogen	Alternative to Q49 when multiple pathogens are tested	Numeric (categorical)	0=Negative 1=SARS-CoV-2 2= influenza 3 = RSV 4 = pneumococcus 5=Other virus 9999=No information	X
	virus2_ext		Laboratory result: In case of coinfection, second pathogen involved	Alternative to Q50 when multiple pathogens are tested	Numeric (categorical)	0=No coinfection 1=SARS-CoV-2 2= influenza 3 = RSV	X

						4 = pneumococcus 5=Other virus 9999=No information	
	sequenced		Tested for genetic variants		Numeric (categorical)	0=No 1=Yes 9999=No information	
	variant_pangolin		Pangolin lineage name		Alfanumeric (categorical)	Example, B.1.117	
	EPI_ISL_nr		GISAID identification number		Alfanumeric	Example, EPI_ISL_412974	
ADDITIONAL HOSPITALIZATION DATA							
	icu		ICU admission		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	death		In-hospital death		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	discharge_date		Date of discharge or death		DD/MM/YYYY	Date within the study period	X
OTHER VACCINATIONS							
	fluvacc		Being vaccinated with at least one influenza vaccine within 12 months prior to SARI hospital admission.		Numeric (categorical)	0=No 1=Yes 9999=No information	X
	fluvaccdate		Date of influenza vaccination		DD/MM/YYYY		X
	pneumovacc		Received any pneumococcal vaccination	Any time	Numeric (categorical)	0=No 1=Yes	X

						9999=No information	
	pneumovaccdate		Year of pneumococcal vaccination	Latest dose	YYYY		X
TREATMENTS							
	pre_prophylaxis_6mo		Having received anti-SARS-CoV-2 antibody products or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior to current hospitalization		Binary	0=No 1=Yes 9999=No information	
	pre_prophylaxis_brand		Brand of latest received anti-SARS-CoV-2 antibody product or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection		Text		
	pre_prophylaxis_date		Date of treatment start latest received anti-SARS-CoV-2 antibody product or other drugs indicated for pre-exposure prophylaxis for SARS-CoV-2 infection		DD/MM/YYYY		
	post_prophylaxis_6mo		Having received anti-SARS-CoV-2 antibody products or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection within 6 months prior to current hospitalization		Binary	0=No 1=Yes 9999=No information	
	post_prophylaxis_brand		Brand of latest received anti-SARS-CoV-2 antibody product or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection		Text		
	post_prophylaxis_date		Date of treatment start latest received anti-SARS-CoV-2 antibody product or other drugs indicated for post-exposure prophylaxis for SARS-CoV-2 infection		DD/MM/YYYY		
	post_symptom		Having received anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset leading to current hospitalisation		Binary	0=No 1=Yes 9999=No information	

	post_symptom_brand		Brand of received anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset prior leading to current hospitalisation		Text		
	post_symptom_date		Date of treatment start anti-SARS-CoV-2 antibody products or antiviral drugs indicated for treatment post-symptom onset leading to current hospitalisation		DD/MM/YYYY		

ANNEX 5: MASTER INFORMED CONSENT FORM

I. Study participant information for participation in an epidemiological scientific study

A study to measure the brand-specific COVID-19 vaccine effectiveness against severe COVID-19 disease in Europe:

A prospective, multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design) .

Dear Sir/ Madam,

You are being asked to take part in a medical-scientific study.

Participation is voluntary. In order to participate your written consent is required. You are receiving this letter because you have been hospitalized with a Severe Acute Respiratory Infection (SARI).

Before you decide whether you want to take part in this study, you will be information about the study. Please take your time to read the information below and ask the study doctor if you have any questions. You can also discuss it with your partner, friends or family.

1. General information

This study was designed by COVIDRIVE (a public-private partnership to estimate brand-specific COVID-19 vaccine effectiveness in Europe) and is being conducted in various hospitals in Europe. . Current COVIDRIVE members are FISABIO (Spain), P95 (Belgium), IABS-EU (France), THL (Finland), AstraZeneca (UK), CureVac (Germany), Janssen (Belgium) and Sanofi-Pasteur-GSK (France). The pharmaceutical industry will cover the costs of the current study

2. Background

In December 2019, an outbreak of respiratory disease in Wuhan City, Hubei Province, China. The novel coronavirus was named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2), while the disease associated with it is referred to as COVID-19. Following the identification of SARS-CoV-2 and its global spread, large epidemics of COVID-19 occurred in Europe. In response, European countries implemented large-scale unprecedented nonpharmaceutical interventions (NPIs) such as closure of schools and national lockdowns. Data collected by the European Centre for Disease Prevention and Control (ECDC) from 31 countries showed early February almost 20 000 000 COVID-19 cases and almost 500 000 related deaths in the European Union since the start of the pandemic. The development of safe and effective vaccines is key in containing the SARS-CoV-2 pandemic. At the end of 2020 the first COVID-19 vaccines have been granted conditional marketing authorization in the European Union (EU) by the European Medicines Agency (EMA), followed by more approvals in 2021.

3. Purpose of the research

The purpose of this study is to continue evaluating how well the COVID-19 vaccines prevent COVID-19 disease under real-world conditions once these vaccines are being used as part of the national immunization programs. Questions that are typically unanswered by clinical trials and that remain to be evaluated by real-world evidence studies include amongst others the long-term vaccine effectiveness, effectiveness against disease by specific and newly emerging SARS-CoV-2 strains, effectiveness against severe COVID-19 disease and effectiveness in special risk groups such as immunocompromised subjects. This knowledge is very valuable for public health decision-making on immunization strategies and for vaccine companies to decide on their clinical development programmes.

4. Type of Research intervention

This is a non-interventional study to estimate the effectiveness of COVID-19 vaccines against COVID-19 related hospitalizations through the COVIDRIVE partnership. The study is a prospective, multi-centre, hospital-based, case-control study. Data will be collected through a wide network of hospitals located in more than 10 different European countries.

Definitions:

Non-interventional: Means that no interventions (such as blood sampling, imaging, …) other than those part of your standard care are needed for the study.

Prospective means that the study will collect data which will become available during your current hospital admission. Some data like your age, gender, vaccination history, and medical history information will also be collected.

Case-control study: the study is based on a group of patients with a positive COVID-19 test ('cases') and a group of persons with a negative COVID-19 test ('controls').

5: What will be expected of you

The study does not require additional visits or assessments other than those required in normal clinical practice for a patient with your condition. The study doctor or nurse may ask you some questions or will provide you with a short questionnaire to measure your precautionary health behavior in the context of the pandemic.

Your responsibilities as a study participant include the following:

- Tell the truth about your medical history, vaccination history and current conditions,
- Complete the questionnaires upon request of the study doctor,
- Agree to be contacted by the study team as necessary, by telephone or through writing.
- Allow your GP to be contacted by the study team to obtain additional information required for this study.
- Tell the study doctor about any problems you have during the study.

- If you have to withdraw from the study, tell the study doctor

1. If you do not want to participate, or would like to stop participating in the study

The decision whether or not to participate in this study will not have any negative impact on the quality of care or the relationship with the treating study doctor(s).

You are participating in this study on a voluntary basis and you have the right to withdraw your consent for any reason. You do not need to state a reason for this. Please contact your study doctor, if you wish to withdraw your consent. If you withdraw your consent, the data collected up to the time of your cancellation will be retained. This is to guarantee the validity of the study. No new information will be collected.

6. Confidentiality: Use and storage of your data and body material

Use and storage of your data

In order to get the answers we need for the study described in this document, we need to collect personal information about you and your health. The data collected can be reused for additional analysis and for purposes related to investigate respiratory infectious diseases and the prevention of these diseases.

This includes:

- your age and gender,
- your medical history (including any chronic conditions, previous Sars-CoV-2 infection), your body mass index (BMI), your smoking history, if you are pregnant your due date),
- results of the tests and examinations you will have for your current condition,
- your vaccination history,
- a measure of precautionary health behaviour in the context of the pandemic,
- whether you are a long-term care facility resident,
- whether you are a healthcare worker and if so, if you are in direct contact with SARS-CoV-2 patients.

The collection, transfer and processing of personal data from patients participating in this study will be done in accordance with [the country law of dd-Mm-YYYY] the protection of natural persons with regard to the processing of personal data and the European General Data Protection Regulation (GDPR), effective from May 25, 2018. Your pseudonymized data will be stored on a dedicated and secured central server. This server is hosted by P95 and is located in 2 different locations in Europe (main location and back-up location). COVIDRIVE will keep your data for 10 years after study end.

We will do everything we can to ensure that no one except the study doctor and study staff know who you are. We do this by pseudonymizing your personal information and using a code instead of your name; only your study doctor and study staff will have the key to the code.

In order to check the quality of the study, your non-coded personal data or information from your medical file relevant to this study may be inspected by people other than the study staff. This access takes place under the supervision of the researcher and these persons are bound by professional secrecy or by means of a confidentiality agreement. This may include:

- personnel designated by the client (Monitors and Auditors) and people or organizations who provide services to or collaborate with the client. However, they will never pass on your name and contact details to the client.
- inspectors from the competent Health Authorities from around the world
- an independent audit group
- persons appointed by the Ethics Committee.

Use and storage of biological samples

A respiratory sample will be taken, processed and stored as part of the standard care, to determine the whether you have been infected with SARS-CoV-2 or another pathogen. This sample will be analyzed as part of the study.

The sample will not be destroyed immediately after use. It will be stored in order to perform new assessments related to the research questions. Since scientific progress in infectious respiratory diseases is constant, we would like to, with your consent, retain the remainders of the sample for a maximum of 3 years for purposes of genomic characterization of the pathogen.

7. Your Rights if you decide to participate

You may also withdraw at any time without giving any reason, even if you have previously agreed to participate. Your decision will not affect your relationship with the investigator or your treating physician, or the quality of your future medical care

You have the right to ask the researcher which data is collected about you and what it is used for in this study. You have the right to;

- Access and check this data
- To receive the collected personal data
- Ask for correction if they are incorrect
- Restrict the processing of your data
- Oppose the processing of your personal data
- Withdraw your consent to the processing of personal data . Your personal data already collected prior to your withdrawal will be retained to avoid misinterpretation of study results

8. Benefits and risks for participation in this study

Since this is a non-interventional study, and all study analysis and medical procedures are part of the standard medical care for your condition, **your participation in this study does not pose any health risk.**

Participation in this study will not bring you any personal benefits. If you participate you will contribute to a better understanding about COVID-19 disease and the vaccine effectiveness of the new COVID-19 vaccines (which will help us to understand how good these vaccines work).

COVIDRIVE is responsible for your personal information. All results resulting from the research described in this document are property of the sponsor. More information about the confidentiality of your data can be found in section 7.

9. Sharing the results

After study closure a description and the results of this study will be published in specialised medical journals. A copy of the scientific publication can be obtained from the study doctor or the study staff. A description of the study will also be available on www.covidrive.eu and the EU PAS Register. The information that will be made publicly available will not include information that can identify you.

10. Do you have any questions

If you have any questions please contact the study doctor or study nurse. If you have any complaints about the study, you can discuss this with your study doctor, if you would rather not do that, you can contact the complaints committee at your hospital.

[contact details study doctor]

[Contact details Study nurse]

[Contact details complaints committee of the hospital]

II. Adult Informed Consent

Research title: **A study to measure the brand-specific Covid-19 vaccine effectiveness against severe covid-19 disease in Europe:**

A prospective, multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design)

I declare that,

- I have been informed of the nature, purpose, duration, possible benefits and risks of the study and that I know what is expected of me. I have read the information document and its annexes.
- I have had enough time to think about this and to talk to a person of my choice, such as my doctor or a family member.
- I have been able to ask any questions that came to mind and I have received clear answers to my questions.
- I understand that my participation in this study is voluntary and that I am free to discontinue my participation in this study without affecting my relationship with the therapeutic team in charge of my health.
- I understand that data will be collected about me during my participation in this study and that the study doctor and the sponsor ensure the confidentiality of this data in accordance with Belgian law.
- I agree to the processing of my personal data in accordance with the modalities described in the section on ensuring confidentiality also consent to the transfer to and processing of my encrypted data in countries other than Belgium.
- I agree that my personal data may be used and shared by the sponsor and other researchers for future research, as described in this document, provided that such processing is limited to the context of the study mentioned here for a better understanding of the disease and its prevention or treatment.
- I agree that my doctor or other health care professionals will be contacted if necessary to obtain additional information about my health.
- I have received a copy of the Participant Information and Informed Consent.

I, the undersigned, agree to participate voluntarily in the study

First Name (Study Participant)	Family Name (study Participant)
Your Signature	Date of signature

If a witness / interpreter is present. Witness / Interpreter

I have been present throughout the process of providing information to the participant and I confirm that information about the objectives and procedures of the study has been adequately provided, that the participant is likely to have understood the study and that participation in the study is voluntary.

First Name (witness / interpreter)	Family Name (witness / interpreter)

Capacity of the Witness

Your Signature	Date of signature

If a Legal Authorized Representative of the study participant is present

I have been present throughout the process of providing information to the participant and I confirm that information about the objectives and procedures of the study has been adequately provided, that the participant is likely to have understood the study and that participation in the study is voluntary.

First Name (Legal Authorized Representative)	Family Name (Legal Authorized Representative)

Your Signature	Date of signature

Attending study doctor

I, the undersigned treating study doctor / authorized representative, declare that I have provided the necessary information regarding this study orally as well as a copy of the information document to the participant.

I confirm that no pressure has been placed on the participant to get him / her to agree to participate in the study and I am willing to answer any additional questions.

First Name (study doctor /authorized representative)	Family Name (study doctor /authorized representative)
Your Signature	Date of signature

III. Child Informed Assent and Parent Informed Consent

Research title: A study to measure the brand-specific Covid-19 vaccine effectiveness against severe covid-19 disease in Europe:

A prospective, multi-centre, hospital-based, case-control study with test-negative controls (test-negative case-control design).

Child

I declare that,

- This study has been explained to me (how long the study takes, why this study is done, all risks and discomforts and what is expected of me).
- My mom, dad or the person taking care of me knows about this study and they want me to be in it if I want to. I have had enough time to think about taking part in this study and I could also talk to others if I wanted to (for example friends, other family member, treating doctor, …).
- I could ask all my questions.
- I understand that I can choose to participate or to not participate in this study and I know that I can stop whenever I like.
- I understand that information about me will be collected and that it will be treated confidentially.
- I understand that I should tell my mom, dad or the person taking care of me and the study doctor immediately if I think any harm is caused to me.
- I agree to my treating doctor(s) being informed of my participation in this study.
- I understand that I need to cooperate in this study and follow the instructions of the study doctor or study team.

First Name (Study Participant)	Family Name (study Participant)
Your Signature	Date of signature

I declare that,

- I have been informed of the nature, purpose, duration, possible benefits and risks of the study and that I know what is expected of my child. I have read the information document and its annexes.
- I have had enough time to think about this and to talk to a person of my choice, such as my doctor or a family member.
- I have been able to ask any questions that came to mind and I have received clear answers to my questions.
- I understand that my child's participation in this study is voluntary and that I am free to discontinue my child's participation in this study without affecting my and my child's relationship with the therapeutic team in charge of my health.
- I understand that data will be collected about my child during my participation in this study and that the study doctor and the sponsor ensure the confidentiality of this data in accordance with Belgian law.
- I agree to the processing of my child's personal data in accordance with the modalities described in the section on ensuring confidentiality also consent to the transfer to and processing of their encrypted data in countries other than Belgium.
- I agree that my child's personal data may be used and shared by the sponsor and other researchers for future research, as described in this document, provided that such processing is limited to the context of the study mentioned here for a better understanding of the disease and its prevention or treatment.
- I agree that my child's doctor or other health care professionals will be contacted if necessary to obtain additional information about my child's health.
- I have received a copy of the Participant Information and Informed Consent forms.

I, the undersigned, agree that my child participates in the study

First Name (Legal Authorized Representative: Mother/Father/ guardians)	Family Name (Legal Authorized Representative: Mother/Father/ guardians)
(Legal Authorized Representative: Mother/Father/ guardians)	
Your signature	Date of signature

If a witness / interpreter is present. Witness / Interpreter

I have been present throughout the process of providing information to the participant and their parent/guardian and I confirm that information about the objectives and procedures of the study has been adequately provided, that the participant and their parent/guardian are likely to have understood the study and that the study is voluntary.

First Name (witness / interpreter)	Family Name (witness / interpreter)

Capacity of the Witness

Your Signature	Date of signature

Attending study doctor

I, the undersigned study doctor / authorized representative, declare that I have provided the necessary information regarding this study orally as well as a copy of the information document to the participant and their parent/guardian.

I confirm that no pressure has been placed on the participant or their parent/guardian to get him / her to agree to participate in the study and I am willing to answer any additional questions.

First Name (study doctor/authorized representative)	Family Name (study doctor /authorized representative)
Your Signature	Date of signature

ANNEX 6: SAMPLE SIZE CALCULATIONS, TECHNICAL SPECIFICATIONS

Sample size calculation

To guide the study design and site selection, several sample size calculations were performed. The goal of the sample size calculations was to ensure that the study will be able to obtain precise CVE estimates. As analytical sample size formulas for the two-stage pooling methodology are not readily available a simulation approach was utilized.

Aims and objectives

The goal of this simulation study is to calculate the required sample size which ensures the estimation procedure yields an expected length of the 95% confidence interval (CI) of the CVE ≤30%.

Data generation workflow

In TND studies generally the OR and the CVE are related as follows: $OR_{overall} = 1 - \frac{CVE}{100}$.
In each simulation run, a dataset is constructed by combining data generated for each of the individual sites. We will denote the total number of sites with k and the total sample size as N, additionally it is assumed that each site consists of the same number of subjects, i.e. $\frac{N}{k}$. Note that one of the goals of the budget allocation and site-selection has been to have a similar number of subjects for each site. Nonetheless, it is possible that the number of subjects recruited or the vaccination coverage differs strongly among the different sites, in case large discrepancies are observed, the sample size calculations will be accordingly updated. The case control ratios will be denoted as r and the overall vaccination coverage among the controls as c.

To incorporate the expected study heterogeneity, for each study site a study-specific odds ratio (OR_{site}) was generated from a log-normal distribution with a median of $1 - \frac{OR_{overall}}{100}$ and variance on the log scale of 0.05. The value of the variance parameter on the log scale was selected to be 0.05 as it introduced an amount of between-site heterogeneity which seemed relatively large as compared to what we expect to see (see Figure 4), note that decreasing the value of this parameter lead to a decrease in the sample size requirements.

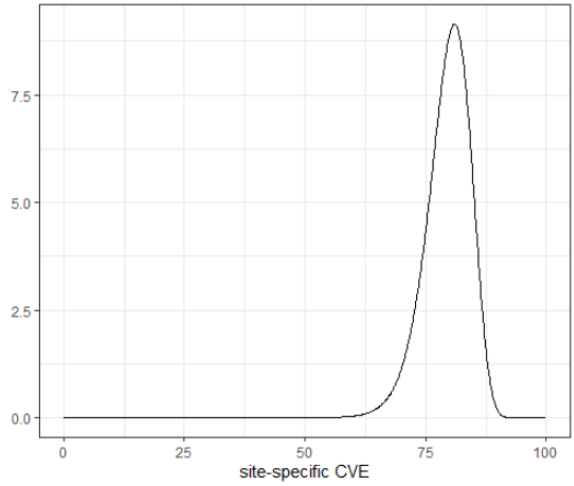

Figure 3. Probability density function of the distribution for the site-specific CVE assuming an median overall CVE of 80%.

For each of the $\frac{N}{k} \times \frac{r}{1+r}$ controls, the exposure status was then generated from a Bernoulli distribution with a success probability equal to c. For each $\frac{N}{k} \times \frac{1}{1+r}$ of the cases, the exposure status was then generated from a Bernoulli distribution with a success probability equal to $\frac{OR_{site}}{OR_{site}+\left(\frac{1}{c}-1\right)}$.

Inserting these probabilities in the formula of the OR gives us:

$$\frac{\frac{P(treatment\,|case)}{1-P(treatment\,|case)}}{\frac{P(treatment|control)}{1-\,P(treatment|control)}} = \frac{\frac{\frac{OR_{site}}{OR_{site}+\left(\frac{1}{c}-1\right)}}{1-\frac{OR_{site}}{OR_{site}+\left(\frac{1}{c}-1\right)}}}{\frac{c}{1-c}} = OR_{site}$$

Confirming that the underlying odds ratio of this simulation scheme is equal to the site-specific OR.

For each vaccinated subject, a dummy variable representing the vaccination brand was generated using a Bernoulli distribution based on the brand-specific vaccination proportion.

Scenarios to be investigated

The simulation study was performed assuming for each combination of the following study characteristics:

1. Total number of cases (N): ranging from 100 to 3000
2. Number of sites (k): 10, 20
3. Median overall CVE (CVE): 80%, 90%
4. Control:case ratio of (r): 1:3, 1:1, 3:1
5. Overall vaccination coverage among the controls (c): 50%, 70%, 90%
6. Brand-specific vaccination proportion: 10%, 25%, 50%, 75%, and 100%

Estimates and data obtained for each simulation

For each simulated dataset an estimate of the CVE and the corresponding 95% CI is obtained using the following two-stage procedure:

- The site-specific log OR of the treatment effect is calculated using a logistic regression model with the vaccination status as the outcome and the disease status as a covariate.
- The site-specific log OR estimates are combined using a random-effects meta-analysis model. More particularly, the log OR estimates are combined using the Sidik-Jonkman estimator to obtain an estimate of the overall log OR and the corresponding 2-sided 95% confidence interval.
- The pooled log OR and the corresponding confidence interval are then back-transformed to obtain an estimate and 95% CI of the median overall CVE.
- The overall CVE estimate and the length of the CI are stored for each simulation.

Number of simulations performed

For each combination of the study characteristics of interest 100 simulations were performed. 100 simulations were performed as empirically this was seen to lead to Monte Carlo confidence intervals with a range small enough for our purposes while limiting the computational burden.

Summary measures of the simulation study

For each combination of the study characteristics, the expected range of the 95% CI is defined as the mean range of the confidence interval obtained from the 100 simulations. 95% Monte Carlo confidence intervals were constructed based on the respective Monte Carlo standard errors observed in the simulations.