PROTOCOL REFERENCE information

Title	Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2.
Protocol version identifier	4.0
Current date of the protocol	24 January 2024
EU PAS register number	EUPAS105009
International non-proprietary name (INN)	Moderna vaccines targeting SARS CoV-2 (Elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran)
Medicinal product	Spikevax, Spikevax bivalent
Product reference	EMEA/H/C/005791
Procedure number	MEA 0065 – P910
Marketing authorisation holder(s)	European Union: Moderna Biotech Spain, S.L. Calle del Príncipe de Vergara 132 Plt 12 Madrid 28002 Spain
Joint PASS	No
Research question and objectives	The overarching goal of this study is to describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2. This study plans to investigate the natural course in terms of morbidity and to identify the relevant prognostic factors using the following study objectives. Primary objectives: 1 To identify possible risk factors for myocarditis and pericarditis following Moderna vaccination targeting

	SARS-CoV-2, including demographic characteristics, medical history, and vaccination characteristics. 2. To characterize the clinical course of myocarditis and pericarditis of varying origin, including myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis or pericarditis not associated with vaccinations targeting SARS-CoV-2, and to identify prognostic factors in the course of myocarditis and pericarditis. Secondary objectives: 1. To identify whether there are differences in the clinical course and risk factors between myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis and pericarditis not associated with vaccinations targeting SARS-CoV-2. 2. If severe cases or cases with sequelae are identified, to identify risk factors for severe myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.
Countries of study	Four countries (Denmark, Norway, Spain, United Kingdom).
Authors	Prof. Diederick E. Grobbee, MD, PhD Dr. David S.Y. Ong, MD, PhD, PharmD Julius Clinical Research Broederplein 41-43 3703 CD Zeist The Netherlands

Marketing authorisation holder(s)

Marketing authorisation holder(s) (MAH)	Moderna Biotech Spain, S.L. Calle Monte Esquinza 30 28010 Madrid Spain
MAH contact person	PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD Moderna Tx 200 Technology Square Cambridge, MA 02139 United States

1. Table of contents

2. List of abbreviations

Abbreviation	Explanation
ACCESS	vACCine COVID-19 monitoring readinESS
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CDM	Common data model
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
DAP	Database access provider
DSRU	Drug Safety Research Unit
ECMO	Extracorporeal membrane oxygenation
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EEA	European Economic Area
GDPR	General Data Protection Regulation
GVP	Guideline on good pharmacovigilance practices
HR	Hazard ratio
ICD-9CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICPC	International Classification of Primary Health Care
ICU	Intensive care unit
IVIG	Intravenous immunoglobulins
MAH	Marketing Authorisation Holder
mRNA	Messenger ribonucleic acid
OR	Odds ratio
PASS	Post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation	Explanation
SE	Standard error
SNOMED	Systematised Nomenclature of Medicine
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TVEM	Time-varying effect model
UK	United Kingdom
US	United States
VAC4EU	Vaccine Monitoring Collaboration for Europe
WHO	World Health Organisation

3. Responsible parties

Centre	Role	Address	Main Contact Person
Moderna Tx	Sponsor	Moderna Biotech Spain, S.L. Calle Monte Esquinza 30 28010 Madrid Spain	PPD PPD PPD PPD PPD PPD PPD PPD PPD PPD
Julius Clinical Research	Lead Operating Center	Julius Clinical Research Broederplein 41-43 3703 CD Zeist The Netherlands	Rob Schneijdenberg Senior Project Manager rob.schneijdenberg@juliusclinical.com
Julius Clinical Research	Lead Scientific Center	As above	Prof. Diederick E. Grobbee, MD, PhD Chief Scientific Officer Dr. David S.Y. Ong, MD, PhD, PharmD Scientific Officer

Signatory Approval

Reviewed and Approved

PPD	Signature	PPD	Date
PPD	Signature	PPD	Date

4. Abstract

Title: Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2.

Short title: Myocarditis and pericarditis after mRNA-1273

Protocol date & version: 24 January 2024, version 4.0

Coordinating investigator: David Ong, Julius Clinical, the Netherlands

Rationale and background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign has been implemented in Europe. The mRNA-1273 vaccine, currently known as Elasomeran, and the more recent omicron-containing bivalent booster vaccine, currently known as imelasomeran, combine Moderna's mRNA (messenger ribonucleic acid) delivery platform with the stabilised SARS-CoV-2 spike immunogen.

Cases of myocarditis and pericarditis have been observed following vaccination with mRNA vaccines targeting SARS-CoV-2, including Elasomeran. Most of these cases have occurred within 14 days following vaccination, more often after the second dose and in younger men aged 18 to 39. This increased risk has been described in several observational studies to date. Although most cases of vaccine-associated myocarditis and pericarditis have been described as mild, additional data are needed to document the inflammation's clinical course and longer-term outcomes of these events. Follow-up research can also serve to identify possible risk factors for both the occurrence and severity of myocarditis and pericarditis.

Research question and objectives

The overarching goal of this study is to describe the clinical course, outcomes and risk factors for myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2. We will investigate the clinical course in terms of morbidity and to identify the relevant prognostic factors using the following study objectives:

Primary objectives:

1. To identify possible risk factors for myocarditis and pericarditis following Moderna vaccination targeting SARS-CoV-2, including demographic characteristics, medical history, and vaccination characteristics.

2. To characterize the clinical course of myocarditis and pericarditis of varying origin, including myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis or pericarditis not associated with vaccinations targeting

SARS-CoV-2, and to identify prognostic factors in the course of myocarditis and pericarditis.

Secondary objectives:

1. To identify whether there are differences in the clinical course and risk factors between myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis and pericarditis not associated with vaccinations targeting SARS-CoV-2.

2. If severe cases or cases with sequelae are identified, to identify risk factors for severe myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.

Study design:

The study will include two distinct designs to answer the primary and secondary objectives.

Case Cohort: To assess risk factors for development of post-vaccine myocarditis and pericarditis, a case-cohort of recipients of Moderna vaccination targeting SARS-CoV-2 will be defined in each participating database. This set will be used to investigate the first primary objective.

The Case-Cohort design requires (1) all cases of myocarditis and pericarditis who previously had received Moderna vaccination targeting SARS-CoV-2 (2) a random subsample of the original cohort ('subcohort'), selected independently of the definition of cases.

Cohort: To characterize the clinical course, outcomes, and risk factors for severe disease, a cohort of myocarditis cases (with and without prior exposure to Moderna vaccination targeting SARS-CoV-2) will be studied. Severe disease will be a composite endpoint based on the diagnosis of acute coronary syndrome, acute myocardial infarction, heart failure, atrial fibrillation/flutter, ventricular arrhythmias/cardiac arrest, pulmonary embolism or deep venous thrombosis, stroke outcomes, peripheral arterial embolism, hospital readmission, Intensive Care Unit (ICU) admission or death.

The cohort set will be used to investigate the second primary objective and both secondary objectives.

Population:

For the case-cohort design, the cohort is the group of individuals with at least one dose of a Moderna vaccination targeting SARS-CoV-2. Inclusion criteria are at least one year of enrolment in the applicable database prior to the index vaccine dose and without myocarditis events within 6 months prior to receiving a Moderna vaccination targeting SARS-CoV-2. Cases are individuals meeting the criteria of myocarditis or pericarditis. Moreover, cases should be able to meet the adjudication criteria according to the Brighton Collaboration Case Definition for possible, probable, or definite myocarditis or pericarditis.

For the cohort design, individuals meeting the criteria of myocarditis or pericarditis, with at least one year of enrolment in the applicable database prior to the index myocarditis or pericarditis event will be included. Cases of myocarditis and pericarditis will be excluded if these individuals have no record of a Moderna vaccine targeting SARS-CoV-2 but a record of another vaccine targeting SARS-CoV-2 within 30 days prior to the onset of myocarditis or pericarditis. Within the cohort design, all cases following vaccination are adjudicated according to the Brighton Collaboration Case Definition. A 1:1 matched sample of the cases not following vaccination matched based on sex and age will also be adjudicated. Only cases that meet the adjudication criteria for possible, probable, or definite myocarditis or pericarditis are included.

Endpoints:

Objective	Endpoint	Analysis Set
Primary		
To identify possible risk factors for myocarditis and pericarditis post-Moderna vaccination targeting SARS-CoV-2, including demographic characteristics, medical history, and vaccination characteristics.	Myocarditis or pericarditis within 30 days after Moderna vaccination targeting SARS-CoV-2.	Case-cohort
To characterize the clinical course of myocarditis and pericarditis of varying origin, including myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis or pericarditis not associated with vaccinations targeting SARS-CoV-2, and to identify prognostic factors in the course of myocarditis and pericarditis.	Clinical outcomes within 30 days of myocarditis' or pericarditis' onset, • Acute coronary syndrome or acute myocardial infarction; • Heart failure; • Atrial fibrillation/flutter; • Ventricular arrhythmias/cardiac arrest; • Pulmonary embolism or deep venous thrombosis; • Stroke outcomes; • Peripheral arterial embolism; • Hospital readmission; • ICU admission; and/or • Death. Long term outcome (90 day, 6 months or 12 months depending on availability of data),:	Cohort

	• Acute coronary syndrome or acute myocardial infarction; • Heart failure; • Atrial fibrillation/flutter; • Ventricular arrhythmias/cardiac arrest; • Pulmonary embolism or deep venous thrombosis; • Stroke outcomes; • Peripheral arterial embolism; • Hospital readmission; • ICU admission; and/or • Death.	
Secondary		
To identify whether there are differences in the clinical course and risk factors between myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis and pericarditis not associated with vaccinations targeting SARS-CoV-2.	Clinical outcomes within 30 days of myocarditis' or pericarditis' onset,: • Acute coronary syndrome or acute myocardial infarction • Heart failure • Atrial fibrillation/flutter • Ventricular arrhythmias/cardiac arrest • Pulmonary embolism or deep venous thrombosis • Stroke outcomes • peripheral arterial embolism • Hospital readmission • ICU admission • Death Long term outcome (90 day, 6 months or 12 months depending on availability of data: • Acute coronary syndrome or acute myocardial infarction; • Heart failure; • Atrial fibrillation/flutter; • Ventricular arrhythmias/cardiac arrest;	Cohort

	• Pulmonary embolism or deep venous thrombosis; • Stroke outcomes; • Peripheral arterial embolism; • Hospital readmission; • ICU admission; and/or • Death.	
If severe cases or cases with sequelae are identified, to identify risk factors for severe myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.	Severe myocarditis or pericarditis within 30 days after Moderna vaccination targeting SARS-CoV-2, as well as severe myocarditis or pericarditis in the longer term.	Cohort

Variables:

Exposures: The main variable of interest is vaccination with any dose of Moderna vaccination targeting SARS-CoV-2. In both the Moderna vaccination-exposed case-cohort analysis and the myocarditis/pericarditis cohort, myocarditis and pericarditis cases (each separately) will be described as recently exposed to Moderna vaccination targeting SARS-CoV-2 if at least one dose of a Moderna vaccine was received within 30 days prior to the onset of myocarditis/pericarditis. Individuals with exposure more than 30 days prior to onset of myocarditis/pericarditis will be considered to have past exposure, and individuals with no history of Moderna vaccination targeting SARS-CoV-2 will be considered unexposed.

Outcomes: Myocarditis and pericarditis cases will be confirmed based on adjudication criteria according to the Brighton Collaboration Case Definition. Possible, Probable and Definite cases will be included. If feasible, cases with a severe clinical course or long-term sequelae will be identified as a subgroup analysis. Covariables: Risk factors will be explored, including demographic characteristics (e.g., age, sex, geography), lifestyle factors (e.g., tobacco use, substance use, level of physical activity), medical history (including chronic conditions, recent acute events such as infection including COVID-19, cardiac history), and recent medication/vaccination use.

For cases following administration of Moderna vaccination targeting SARS-CoV-2, characteristics of vaccination will also be explored, including: product, dosing interval; dose number; primary series versus booster dose; homologous versus heterologous schedule; and, co-administration with other vaccines.

Data sources:

This study is planned as analysis of routinely collected health data in five secondary automated electronic data sources in four countries (Denmark, Norway, Spain, and the United Kingdom [UK]). The data access providers (DAPs) are selected based on availability of the required routinely collected data, including information on vaccine brand and frequency of data updates, in cooperation with the established VAC4EU association. As feasible, linkage to medical records is planned for case confirmation and if applicable, collection of data on risk factors and outcomes not available in structured data. Local laws and regulation will apply for case validation and data collection.

Study size:

Considering the type of investigation, a traditional sample size calculation cannot be provided. Given that the number of cases is expected to be limited, and the number of possible risk factors for post-vaccine myocarditis (including demographic characteristics, lifestyle factors, medical history, and vaccination characteristics) under investigation, all individuals that meet the criteria for the outcome will be selected as cases, and four times as many controls will be sampled to improve statistical efficiency. The number of myocarditis cases will drive the number of risk factors that can be investigated with adequate power in this study. The nature of this study will therefore be observational and exploratory.

Derived from literature, it is assumed that the incidence of myocarditis and pericarditis is approximately 0.4-4.0 per 100,000 individuals. Based on the inclusion of subjects of the DAPs for Denmark, Norway, Spain and UK, we expected a total size of 27-270 cases for each outcome separately. Based on preliminary results, however, the expectation was adjusted to 40-160 cases of myocarditis and 100-280 cases of pericarditis for the cohort design per DAP. For the Moderna vaccination-exposed case-cohort design, a study size of 100-400 is expected for myocarditis, and 250-700 for pericarditis per DAP.

Data analysis:

In the Moderna vaccination-exposed case-cohort design, all cases of myocarditis, pericarditis and the control population will be described with respect to demographic characteristics, lifestyle factors or proxy variables of lifestyle factors (depending on the availability in each database), medical history and vaccination history. The control group will be a sample of the cohort of Moderna vaccination-exposed individuals aligned with the distribution to cases based on the month and year of documented Moderna vaccination targeting SARS-CoV-2 receipt.

A predictive modelling approach will be used to identify risk factors for development of myocarditis or pericarditis within the Moderna vaccination-exposed population.

In the cohort design, all cases of myocarditis and pericarditis will be described in terms of demographic characteristics, lifestyle factors or proxy variables of lifestyle factors (depending on

the availability in each database), medical history and vaccination characteristics. Clinical course of the myocarditis/pericarditis event will be described for these cases. To identify differences in risk factors for myocarditis/pericarditis with a severe clinical course or long-term sequelae, the different variables of demographic, lifestyle factors, medical history and vaccination characteristics at the time of Moderna vaccination targeting SARS-CoV-2 will be assessed. Outcomes and identified follow-up care will also be characterized. If sequelae or unusually severe cases are able to be identified, cases with and without sequelae will be compared within the exposed and unexposed groups.

Descriptive statistics and statistical model results will be presented, and details of these will be provided in the SAP.

As primary analysis, the case-cohort and the cohort analyses will be performed for all Moderna vaccinations targeting SARS-CoV-2 combined. If feasible, the case-cohort and cohort analyses will also be performed separately for different variants of the Moderna vaccine (e.g., Spikevax and the Spikevax bivalent Original/Omicron BA.1 and Original/Omicron BA.4/BA.5 vaccines separately) as subgroup analyses.

Milestones:

Data collection will start March 2023 (pending timelines for endorsement of the protocol) and continue through the second quarter of 2024. Upon data transformation by DAPs, the final analytical dataset will be available 31 August 2024 with a final study report planned by June 2025. Interim analysis reports are planned every twelve months. Progress reports are planned every six months.

5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1.0	26-APR-22	NA – Initial version	NA – Initial version	NA – Initial version
2.0	11-AUG-22	Section 1,4,5,6,7,8,9, and 13	1: Table of Contents updated 4: Abstract updated to reflect all protocol updates 5: Amendments and Updates: updated to summarize changes	EMA feedback obtained on initial version

Number	Date	Section of study protocol	Amendment or update	Reason
			6: Milestones: updated to reflect current timelines 7: Rationale and Background: Updated in line with EMA feedback 8: Research Question and Objectives: updated in line with EMA feedback 9: Research Methods: updated in line with EMA feedback, defined study population, end of data collection, calculation of case estimation, description of analytical principles and limitations of the research method 13: References: updated reference list	
2.1	29-AUG-22	Throughout	The exposure of interest has been revised from the original strain vaccine (elasomeran) to also include the omicron-containing bivalent vaccine (imelasomeran). Subgroup analyses have been added to consider each exposure separately as data allow.	EMA request
3.0	25-JAN-23	Title, and section 3,4,6,7, 9 and 13	Title: adjusted to reflect the incorporation of different variants of the Moderna vaccine targeting SARS-CoV-2 4: Abstract adjusted to reflect the inclusion variants of the	EMA feedback obtained on Version 2.1

Number	Date	Section of study protocol	Amendment or update	Reason
			Moderna vaccine targeting SARS-CoV-2 in the study. 6: Date of study interim report 1 changed 7: Rationale and background: Updated in line with EMA feedback 9: Research methods: Updated in line with EMA feedback and to incorporate the inclusion of different variants of the Moderna vaccine targeting SARS-CoV-2. 13: Updated reference list	
		Throughout	Minor administrative and cosmetic updates have been incorporated throughout the document for clarity. Moreover, several changes to the study methods were incorporated. These changes are all minor and are not expected to lead to changes in project outcomes. For instance: - Case validation will be based on criteria according to the Brighton Collaboration Case Definition instead of the CDC case definition. - Inclusion criteria for the cohort design have been redefined. That is, individuals are now also	Other changes not requested by EMA. The decision to use criteria according to the Brighton Collaboration Case Definition instead of the CDC case definition was made following VAC4EU's preference for the former of the two.

Number	Date	Section of study protocol	Amendment or update	Reason
			included if they received a non-Moderna vaccination targeting SARS-CoV-2 within the 30 days prior to myocarditis or pericarditis onset, as long as they also received a Moderna vaccination in the same time window and meet the other inclusion criteria. - For the main analyses, a Cox regression methodology will be used instead of a logistic regression. - Handling of missing data is now done in a different manner.	
3.1	22-MAY-23	9.2.2, 9.2.3 Inclusion and exclusion criteria	• Updated language to clarify inclusion and exclusion criteria using text suggested by the EMA.	EMA feedback obtained on Version 3.0
		9.1 Study design	• Added text to clarify end of study period	Other changes not requested by EMA
		Throughout	• Updated contact list details.	Other changes not requested by EMA

Number	Date	Section of study protocol	Amendment or update	Reason
4.0	24-JAN-24	Throughout	• Minor cosmetic and textual updates have been incorporated for clarity	Update for clarification
		9.2.1 Study period	• Updated text to clarify the definition of the End of Data collection	Update for clarification
		9.2.2 Inclusion criteria; 9.3.2 Outcomes	• Updated to reflect a novel approach for case validation in the cohort study design	Reducing the total number of cases to be adjudicated due to feasibility reasons.
		9.5 Study size	• Updated study size calculation to reflect new insights and preliminary results	EMA feedback received on version 3.1
		9.7.2 Main analyses	• For the case-cohort main analyses, conditional logistic regression will be performed instead of Cox analyses	In response to feedback from US FDA on version 3.1
		9.9 Limitations of the research methods	• Added text to clarify potential limitations related to the case validation and the sampling of cases for validation	Updated in line with the novel approach for case validation proposed in Section 9.2.2

6. Milestones

Milestone	Planned date*

Protocol Final	24 January 2024
Registration in the EU PAS register	Following EMA endorsement of the study protocol
Start of data collection	31 March 2023
End of data collection	31 August 2024
Study interim report 1 (written progress report, no data analysis)	30 August 2022
Study interim report 2 (written progress report, no data analysis)	31 January 2023
Study interim report 3 (written progress report, no analysis)	30 June 2023
Study interim report 4 (interim analysis 1, including preliminary analysis on study objectives)	31 January 2024
Study interim report 5 (written progress report, no analysis)	30 June 2024
Study interim report 6 (interim analysis 2, including preliminary analysis on study objectives)	31 January 2025
Final report of study results	30 June 2025

* Subject to data queues by data custodians; refer to Section 12 "Plans for disseminating and communicating study results" for planned contents of the interim reports

7. Rationale and background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and has led to a global pandemic. A mass vaccination campaign has been implemented in Europe.[1,2]

Rare cases of cardiac inflammation, i.e., myocarditis and pericarditis, have been observed following vaccination with mRNA vaccines targeting SARS-CoV-2, including the Moderna vaccine.

Most of these cases have occurred within 14 days following vaccination, more often after the second dose and in younger men.

Myocarditis is an inflammatory disease of the myocardium (heart muscle) and may be due to any one of numerous etiologies, including infectious pathogens, toxins, drugs, and autoimmune disorders.[3] The condition may resolve spontaneously or with supportive care, but it may also be associated with heart failure, dilated cardiomyopathy, cardiogenic shock, and arrhythmias. The most common etiology of myocarditis, especially among younger people, is viral infection including SARS-CoV-2. Younger men are typically at higher risk. Pericarditis is an inflammation of the pericardial layers and is the most common form of pericardial disease. Causes may be infectious or non-infectious, but most cases remain idiopathic. Similar to myocarditis the clinical course is typically mild with most cases making a full recovery.

The EU Risk Management Plan (RMP) for Moderna vaccines targeting SARS-CoV-2 lists myocarditis and pericarditis as important identified risks. Missing information includes use in pregnancy and while breastfeeding (to be addressed in a separate protocol), long-term safety, use in immunocompromised subjects, interaction with other vaccines, use in frail subjects with unstable health conditions and chronic co-morbidities (e.g., chronic obstructive pulmonary disease, diabetes, chronic neurological, disease, cardiovascular disorders), and use in subjects with autoimmune or inflammatory disorders.[4]

On 09 July 2021, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that myocarditis can occur in very rare cases following vaccination with the two current mRNA vaccines targeting SARS-CoV-2[5]. This conclusion was reached after an in-depth review of 145 cases of myocarditis in the European Economic Area (EEA) among people who received Comirnaty and 19 cases among people who received the Moderna vaccine. PRAC also reviewed reports of 138 cases of pericarditis following the use of Comirnaty and 19 cases following the use of the Moderna vaccine. The PRAC concluded that the cases primarily occurred within 14 days after vaccination, more frequently after the second dose, with young age, and male sex identified as potential risk factor for occurrence. Among those with myocarditis, advanced age and concomitant diseases were risk factors for subsequent mortality. As PRAC qualified this adverse event of special interest (AESI) as 'very rare', an updated product information will list myocarditis as side effects with very rare frequency and health care professionals are advised that the cases may need specialist care.[6] Although vaccine trials are usually large, they may not detect rare adverse events. In addition, there is a high safety standard applied to a preventive agent administered to individuals in their usual state of health.

Population-based descriptive studies have addressed the occurrence of myocarditis after mRNA-based vaccination targeting SARS-CoV-2. In Denmark, 21 persons among a half million individuals who received the Moderna vaccination targeting SARS-CoV-2 developed myopericarditis within 28 days from vaccination date[7]. The Moderna vaccination targeting SARS-CoV-2 was associated with a significantly increased risk compared to unvaccinated individuals. In another study passive surveillance reporting in the US showed that rates of myocarditis were highest after the second

vaccination dose of mRNA-based vaccines.[8] In the latter study 490 myocarditis cases following Moderna vaccination targeting SARS-CoV-2 were reported to the Vaccine Adverse Event Reporting System. As both studies merely focused on short-term follow-up and myocarditis is a rare adverse event, larger international studies with longer follow-up time are needed.

The association between mRNA-based vaccination targeting SARS-CoV-2 and the increased risk for the development of myocarditis or pericarditis has already been well established in previous studies. However, it is important to further assess using other characteristics which individuals who received mRNA-based vaccinations targeting SARS-CoV-2 are at the highest risk of developing myocarditis.

Although most cases of vaccine-associated myocarditis and pericarditis have been described as mild[7,9], additional data are needed to characterize the natural history and long-term outcomes of these events and characterize risk factors for both occurrence and severity.

8. Research question and objectives

The overarching goal of this study is to describe the risk factors, clinical course and outcomes for myocarditis and pericarditis temporally associated with Moderna vaccination targeting SARS-CoV-2.

We want to investigate the clinical course in terms of morbidity and to identify the relevant prognostic factors using the following study objectives.

8.1 Primary objectives

1. To identify possible risk factors for myocarditis and pericarditis following Moderna vaccination targeting SARS-CoV-2, including demographic characteristics, medical history, and vaccination characteristics.

2. To characterize the clinical course of myocarditis and pericarditis of varying origin, including myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis or pericarditis not associated with vaccinations targeting SARS-CoV-2, and to identify prognostic factors in the course of myocarditis and pericarditis

8.2 Secondary objectives

1. To identify whether there are differences in the clinical course and risk factors between myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis and pericarditis not associated with vaccinations targeting SARS-CoV-2

2. If severe cases or cases with sequelae are identified, to identify risk factors for severe myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2

Confirmed cases are those that meet clinical adjudication criteria for myocarditis or pericarditis based on review of clinical data. The adjudication process will use a structured questionnaire that adapts the Brighton Collaboration Case Definition[10] to those elements available in the clinical data available for validation, and will be both informed by expert cardiologist advice and documented in a separate medical record adjudication plan prior to the initiation of case review. Within the cohort study, not all cases undergo validation. All cases following vaccination are included in the validation process, as well as a 1:1 age and sex matched sample of cases not following vaccination.

Final definitions of the level of data details, study variables and detailed descriptions of analyses methods and presentations will be provided in the Statistical Analysis Plan (SAP), which will be developed with clinical and statistical input from all relevant parties involved and the participating database experts.

9. Research methods

9.1 Study design

To answer the objectives, this study will use an Moderna vaccination targeting SARS-CoV-2-exposed case-cohort design and a myocarditis cohort study design (Figure 1).

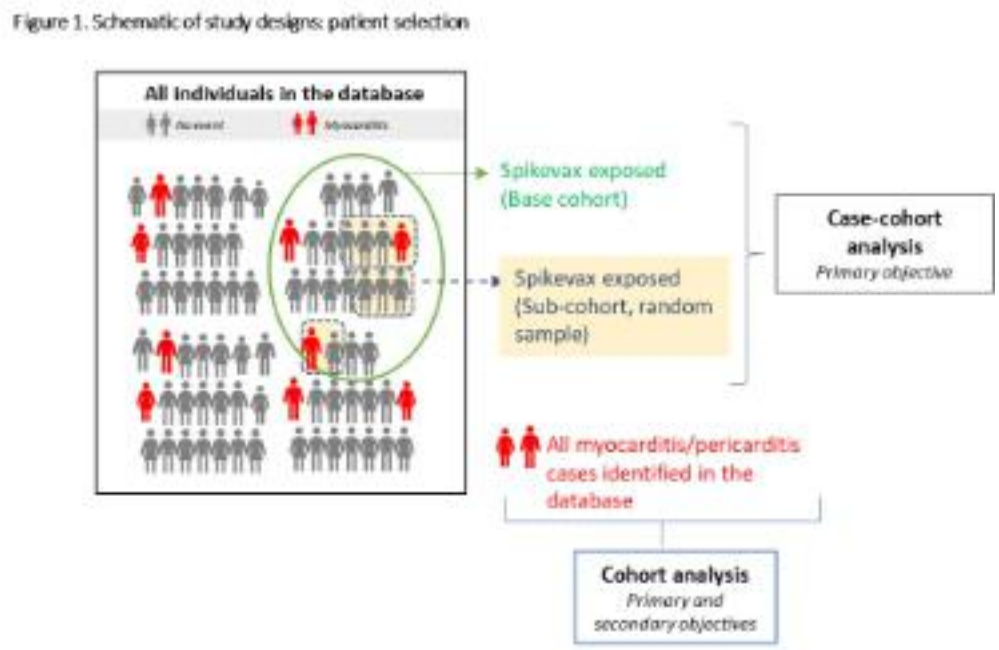
The case-cohort design will be used to assess risk factors other than Moderna vaccination targeting SARS-CoV-2 for the development of myocarditis and pericarditis in recipients of the Moderna vaccine targeting SARS-CoV-2, to understand which characteristics increase or decrease the risk for the development of myocarditis and pericarditis after vaccination (i.e., t0). This may contribute to risk assessment and identification of individuals who do not have an increased risk on myocarditis or pericarditis.

The cohort design will be used to describe prognostic factors for a (severe) clinical course in patients with myocarditis or pericarditis regardless of vaccination status. As most myocarditis and pericarditis cases are mild in disease severity, it is clinically relevant to identify the individuals who are at increased risk for severe clinical outcomes as early as possible, in order to provide appropriate care in a timely manner. These severe outcomes are acute coronary syndrome, acute myocardial infarction, heart failure, atrial fibrillation/flutter, ventricular arrhythmias/cardiac arrest, pulmonary embolism or deep venous thrombosis, stroke outcomes, peripheral arterial embolism, hospital readmission, ICU admission or death. Therefore, information available at the onset of myocarditis or pericarditis (i.e., t1) could be used to predict the clinical course including long-term outcomes (i.e., t2).

The cohort design will also be used to address both secondary study objectives. Within the cohort of myocarditis/pericarditis cases, clinical course and risk profiles will be compared between patients with myocarditis/pericarditis recorded after vaccination targeting SARS-CoV-2 and patients with myocarditis/pericarditis unrelated to vaccine administration. Moreover, risk factors for severe myocarditis/pericarditis will be investigated within this cohort.

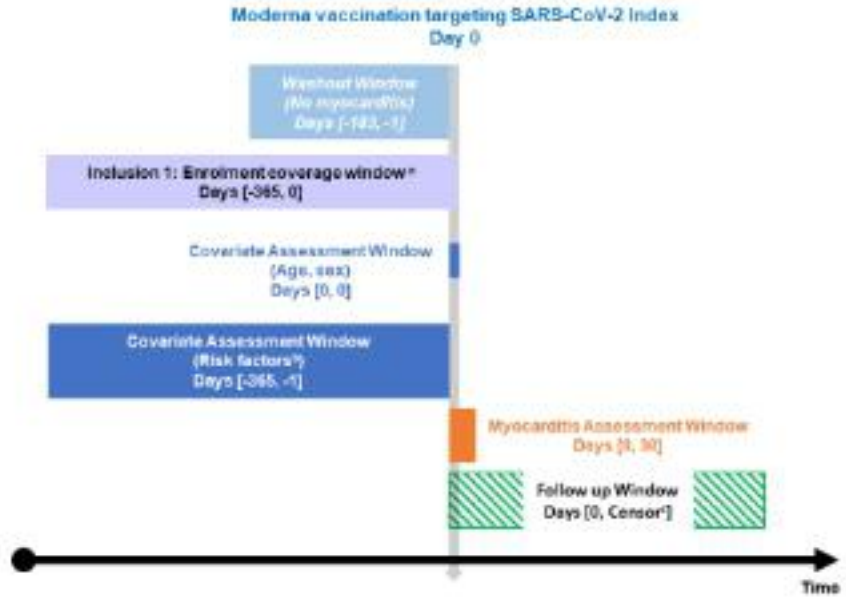
Recipients of Moderna vaccination targeting SARS-CoV-2 and cases of myocarditis and pericarditis will be identified between January 2021 (date of the earliest approval of Moderna vaccines targeting SARS-CoV-2 in Europe) and the end of the study period (defined as most recent data availability at the time of the End of Data collection).

Figure 1 Overview of the Study Designs



a. In the case-cohort design all myocarditis/pericarditis cases are selected among individuals who received Moderna vaccination targeting SARS-CoV-2. The controls will be sampled from the exposed cohort, sampled to align with the distribution of cases based on month and year of documented vaccination receipt. For the cohort design, all myocarditis and pericarditis cases from the available databases will be selected.

Figure 2 Case-cohort design

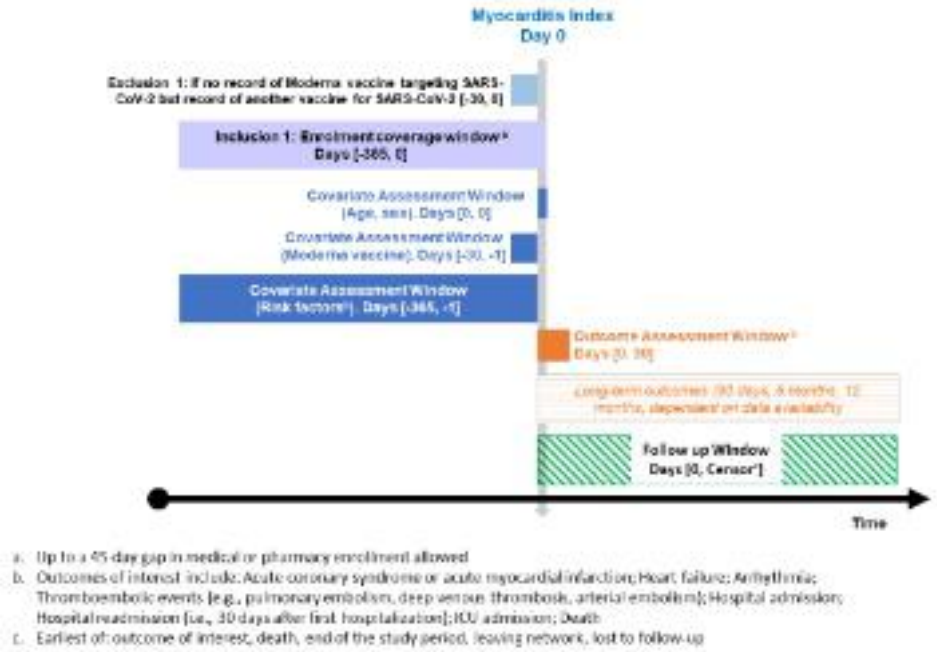


a. Up to a 45-day gap in medical or pharmacy enrollment allowed
b. Risk factors may include demographic characteristics, lifestyle factors, medical history, and vaccination characteristics
c. Earliest of: outcome of interest (myocarditis), death, end of the study period, leaving network, lost to follow-up

**If 2 doses within 90 days: index on first dose. If more than 90 days since last dose: re-indexing.*

*** A <45 day gap for changes in insurance is not expected for European Union (EU) Data Access Providers (DAPs).*

Figure 3 Cohort design



a. Up to a 45 day gap in medical or pharmacy enrollment allowed
b. Outcomes of interest include: Acute coronary syndrome or acute myocardial infarction; Heart failure; Arrhythmia; Thromboembolic events (e.g., pulmonary embolism, deep venous thrombosis, arterial embolism); Hospital admission; Hospital readmission (i.e., 30 days after first hospitalization); ICU admission; Death
c. Earliest of: outcome of interest, death, end of the study period, leaving network, lost to follow-up

** A <45 day gap for changes in insurance is not expected for EU DAPs.*

9.1.1 Moderna vaccination targeting SARS-CoV-2-exposed case-cohort

To assess risk factors for development of post-vaccine myocarditis and pericarditis, a cohort of Moderna vaccination targeting SARS-CoV-2 recipients will be defined in each participating database. This set will be used for the first primary objective.

For the case-cohort design, individuals with at least one dose of Moderna vaccination targeting SARS-CoV-2 will be used to define a cohort of Moderna vaccination recipients. Cases are those individuals who develop myocarditis or pericarditis any time during the follow-up after Moderna vaccination targeting SARS-CoV-2. The controls will be sampled from the exposed cohort, such that they align with the distribution of cases based on the month and year of documented Moderna vaccination receipt.

9.1.2 Cohort design

To characterize the risk factors, clinical course and outcomes for severe disease, a cohort of myocarditis and pericarditis cases (with and without prior exposure to the Moderna vaccine targeting SARS-CoV-2) will be studied. This set will be used for the second primary objective and both secondary objectives.

For the cohort design, eligible cases of myocarditis and pericarditis will be described in terms of demographic characteristics, medical history and vaccination history. The clinical course and long-term outcomes including sequelae will be described and quantified.

9.2 Setting

This study will include information from multiple databases, utilizing routinely collected health and administrative data of four European countries: Denmark, Norway, Spain (2 databases), and the United Kingdom (UK). The study databases are representative of the source population in each country (see Annex 3 for details). Both the case-cohort design and the cohort design will draw on data from all five databases.

Briefly, in Denmark and Norway, the registries have full population coverage with respect to the available routinely collected data. The regional databases in Spain (SIDIAP and FISABIO) are representative with respect to background rates and demographic distributions of the underlying regional populations (Catalonia and Valencia, respectively). The CPRD is broadly representative of the UK population.

9.2.1 Study period

Recipients of Moderna vaccination targeting SARS-CoV-2 (regardless of age) will be identified starting 06 January 2021 (date of the earliest approval of Moderna vaccination targeting SARS-CoV-2 in Europe). The data on which the full analytical dataset will be available (End of Data collection) is 31 August 2024. Prior to the full analytical dataset being available and cases being identified, data will require extraction, transformation, and quality checks by each of the participating DAPs. In each country, the observation will start on the date of country-specific availability of the Moderna vaccine targeting SARS-CoV-2.

9.2.2 Inclusion criteria

For the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort design, a cohort will first be defined including individuals of all ages with (1) at least one dose of Moderna vaccination targeting SARS-CoV-2 administered during the study period, (2) at least one year of enrolment in the applicable database prior to the index vaccine dose to allow for ascertainment of baseline covariables and potential risk factors, and (3) no myocarditis or pericarditis events within 6 months prior to Moderna vaccination receipt. Myocarditis and pericarditis cases are defined when adjudication criteria according to the Brighton Collaboration Case Definition[10] for possible, probable or definite myocarditis or pericarditis is fulfilled. Cases and controls are defined as mentioned in Section 9.1.1.

In the cohort design, all cases following vaccination, and only a sample of cases not following vaccination will undergo adjudication. In the analyses, individuals will be included if they: (1) have been adjudicated and meet the adjudication criteria according to the Brighton Collaboration Case Definition for possible, probable or definite myocarditis or pericarditis, and (2) have at least one year of enrolment in the applicable database prior to the index myocarditis or pericarditis event to allow for ascertainment of baseline covariates and potential risk factors.

For both the case-cohort as the cohort design, individuals with administrative codes for myocarditis or pericarditis will be identified in each data source. Following this initial screening, selected cases will be confirmed based on review of clinical data (based on criteria according to the Brighton Collaboration). The selection will include all cases of myocarditis and pericarditis following Moderna vaccination targeting SARS-CoV-2, as well as an age- and sex- matched sub-sample of other cases.

9.2.3 Exclusion criteria

Individuals not meeting criteria outlined in Section 9.2.2 are excluded from the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort and myocarditis/pericarditis cohort analyses, respectively. For the cohort design an additional exclusion criterium is applied: Persons with no record of a Moderna vaccine targeting SARS-CoV-2 but record of another vaccine for SARS-CoV-2 within 30 days prior to index date of myocarditis or pericarditis event will be excluded. Individuals who have evidence of myocarditis or pericarditis in structured data (e.g., ICD-10 codes) where review of clinical data is not performed due to sampling, or is incompatible with adjudication criteria according to the Brighton Collaboration Case Definition for myocarditis or pericarditis will be described but will not be included as cases in primary analyses. In the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort design, non-confirmed myocarditis/pericarditis cases will be censored at the onset of the false positive myocarditis/ pericarditis diagnosis.

9.3 *Variables*

Availability and definition of specific variables varies by data source, and full information will be sought in collaboration with the DAPs where possible. All data-source specific variable definitions and country-specific data availability will be specified in the SAP.

9.3.1 Exposure

In the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort analysis, multiple risk factors are considered as exposures of interest. In the cohort analysis, multiple prognostic factors are also considered as exposures of interest. See Section 9.3.3 for further details.

In both the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort analysis and the cohort analysis, myocarditis and pericarditis cases will be described as recently-exposed if at least one dose of Moderna vaccination targeting SARS-CoV-2 was received within 30 days prior to the onset of myocarditis/pericarditis. Individuals with exposure more than 30 days prior to onset of myocarditis will be considered to have past exposure, and individuals with no history of Moderna vaccination targeting SARS-CoV-2 will be considered unexposed.

For both Moderna and other vaccinations targeting SARS-CoV-2, it is possible to ascertain the vaccine brand and/or applicable vaccine characteristics from the available data. Exposure to each dose in the order received (e.g., first dose, second dose, booster dose) or any dose of Moderna

vaccination targeting SARS-CoV-2 will be considered. Characteristics of vaccination will also be explored as feasible based on available sample size, including but not limited to dosing interval, dose number, primary series vs booster dose, homologous vs. heterologous schedule, and co-administration with other vaccines.

9.3.2 Outcomes

The primary outcome of the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort is myocarditis and pericarditis, which will be analysed combined and separately. For individuals with diagnosis codes for myocarditis/pericarditis within 30 days of exposure, medical records will be reviewed to verify whether they comply with adjudication criteria according to the Brighton Collaboration Case Definition for possible, probable and definite cases.

The cohort analysis of myocarditis and pericarditis cases will include several clinical outcomes such as the hospital readmission and mortality (see Table 1 for details). Outcomes measured will include major adverse clinical outcomes, structural or functional cardiac abnormalities, and patient reported outcomes and functional assessments. Required medication or related cardiac procedures during and following hospitalization, and cardiac or other hospitalization events will be described across the follow-up period. Presence and findings from ambulatory monitoring will also be described during the follow-up period.

Table 1 Study objectives and endpoints

Objective	Endpoint	Analysis Set
Primary		
To identify possible risk factors for myocarditis and pericarditis post-Moderna vaccination targeting SARS-CoV-2, including demographic characteristics, medical history, and vaccination characteristics.	Myocarditis or pericarditis within 30 days after Moderna vaccination targeting SARS-CoV-2.	Case-cohort
To characterize the clinical course of myocarditis and pericarditis of varying origin, including myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis or pericarditis not associated with vaccinations targeting SARS-CoV-2, and to identify prognostic factors in the course of myocarditis and pericarditis.	Clinical outcomes within 30 days of myocarditis' or pericarditis' onset: • Acute coronary syndrome or acute myocardial infarction; • Heart failure; • Atrial fibrillation/flutter; • Ventricular arrhythmias/cardiac arrest; • Pulmonary embolism or deep venous thrombosis;	Cohort

	• Stroke outcomes; • Peripheral arterial embolism; • Hospital readmission; • ICU admission; and/or • Death. Long term outcome (e,g., 90 day, 6 months or 12 months depending on availability of data): • Acute coronary syndrome or acute myocardial infarction; • Heart failure; • Atrial fibrillation/flutter; • Ventricular arrhythmias/cardiac arrest; • Pulmonary embolism or deep venous thrombosis; • Stroke outcomes; • Peripheral arterial embolism; • Hospital readmission; • ICU admission; and/or. • Death.	
Secondary		
To identify whether there are differences in the clinical course and risk factors between myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2, and myocarditis and pericarditis not associated with vaccinations targeting SARS-CoV-2.	Clinical outcomes within 30 days of myocarditis' or pericarditis' onset: • Acute coronary syndrome or acute myocardial infarction • Heart failure • Atrial fibrillation/flutter • Ventricular arrhythmias/cardiac arrest • Pulmonary embolism or deep venous thrombosis • Stroke outcomes • peripheral arterial embolism • Hospital readmission • ICU admission • Death	Cohort

	Long term outcome (90 day, 6 months or 12 months depending on availability of data): • Acute coronary syndrome or acute myocardial infarction; • Heart failure; • Atrial fibrillation/flutter; • Ventricular arrhythmias/cardiac arrest; • Pulmonary embolism or deep venous thrombosis; • Stroke outcomes; • Peripheral arterial embolism; • Hospital readmission; • ICU admission; and/or • Death.	
If severe cases or cases with sequelae are identified, to identify risk factors for severe myocarditis and pericarditis associated with Moderna vaccination targeting SARS-CoV-2.	Severe myocarditis or pericarditis within 30 days after Moderna vaccination targeting SARS-CoV-2, as well as severe myocarditis or pericarditis in the longer term.	Cohort

Additionally, the acute phase of care for the initial myocarditis episode will be described with respect to the following characteristics:

- Highest level of care (outpatient, emergency department visit, inpatient, intensive care unit)
- Length of stay in the hospital

9.3.3 Covariables

The key covariables described for both the Moderna vaccination targeting SARS-CoV-2-exposed case-cohort and the myocarditis cohort will include variables that include information from one year or two years before until the day of Moderna vaccination (in the case-cohort design) or until the day of myocarditis/pericarditis onset (in the cohort design), such as the following, depending on what the different DAPs have collected: country of residence, calendar time, age, sex, selected comorbidities (e.g., diabetes mellitus, hypertension, obesity, cerebrovascular disease, cardiac history, chronic lung disease, chronic kidney disease, chronic liver disease, history of cardiac inflammation, autoimmune disorders, immunocompromise, substance use disorders, history of cancer), Charlson Comorbidity Index (CCI), relevant medical treatments (e.g., chemotherapy or

radiation for cancer, systemic immunomodulator therapy, immunosuppression, plasmapheresis, intravenous immunoglobulins (IVIG), systemic steroids, cardiotoxic medications), history of COVID-19 infection, other vaccinations targeting SARS-CoV-2, and other vaccinations (e.g., influenza, hepatitis B). Health care utilisation will be measured by the frequency of inpatient, outpatient, intensive care unit (ICU), emergency room (ER), and primary-care encounters. For the Moderna vaccination targeting SARS-CoV-2, characteristics of utilization will be described, including doses received, formulation (if additional options become available during the study period). As available, lifestyle factors such as smoking status, activity level, and other factors may be assessed.

It may be possible that not all information is available for each DAP, and some data may need to be searched in clinical background databases. Full definitions, including timeframes and codes will be provided in the Statistical Analysis Plan (SAP). Annex 3 provides a summary of availability of different data types from in the participating databases. The SAP will include an elaboration on the variables available from each data partner.

9.3.4 Subgroups

The feasibility of performing subgroup analyses will be strongly driven by available sample size.

In the case-cohort design a subgroup analysis will be performed in the following subgroups: young children (<12 years), adolescents (12-17 years), young adults (18-24 years), male and female.

In the cohort design of all myocarditis/pericarditis cases, a subgroup analysis will be performed in the following subgroups: Moderna vaccination targeting SARS-CoV-2-exposure status (Recently exposed, Past exposure, Never exposed), SARS-CoV-2 infection status (Recent infection, Past infection, Never infected) prior to myocarditis/pericarditis onset.

As feasible, stratified analyses by different variants of the Moderna vaccine targeting SARS-CoV-2 will be presented for both the case-cohort and the cohort designs. First, descriptive analyses in the above subgroups will be presented. Subsequent multivariable analyses will only be performed in subgroups that are sufficiently large in size. Details will be further elaborated in the SAP.

9.4 Data sources

This study will be based on electronic, routinely collected data in four European countries (listed alphabetically): Denmark, Norway, Spain, and the UK. The participating databases cover the underlying countries' population fully or partially. Table 2 provides an overview of the data sources in each country. Additional description of the participating data sources is provided in Annex 3. Most databases and DAPs have contributed to the ACCESS protocol and are considered fit for purpose through that contribution or other previous experience in vaccine studies. The data access providers have committed to cooperate on addressing the study objectives.

Table 2 Summary of the data sources by country

Country	Denmark	Norway	Spain	Spain	UK
Data access partner	Aarhus University	University of Oslo	IDIAP	FISABIO	DSRU
Type of data	Record linkage	Record linkage	Record linkage & GP	Record linkage & GP	GP medical record and linked datasets
Data source name	Danish registries	Norwegian registries	SIDIAP	VID	CPRD
Size of data in 2019	5.8 M	5.4 M	5.8 M	5M	16 M
Diagnosis coding	ICD-10	ICD-10CM/ICPC	ICD-10CM	ICD-9CM/ICD-10/ICD-10CM	MEDCODE IDs/ICD-10 (for some linked datasets)
Hosp. discharge diagnoses	Yes	Yes	Yes	Yes	Yes
Intensive care unit (ICU) admission	Yes	Yes	No	Yes	Yes
Extracorporeal membrane oxygenation (ECMO) use	Maybe	Maybe	No	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes
Emergency unit visit diagnoses	Yes	Yes	Yes	Yes	Yes
Outpatient specialist visit diagnoses	Yes, hospital outpatient specialist clinics	Yes	Yes, referrals to specialists	Yes	Yes
Primary care diagnoses	No	Yes	Yes	Yes	Yes
COVID-testing	Routine testing only during early pandemic	Routine testing only during early pandemic	Routine testing only during early pandemic	Routine testing only during early pandemic	Routine testing only during early pandemic
Medicines dispensing outp.(pharmacy)	Yes	Yes	Yes	Yes	No
Medicines inpatient	Some	Yes, but not accurate	No	Yes	No
Medicines prescribing	No	No	Yes	Yes	Yes
COVID-19 Vaccine brand	Yes	Yes	Yes	Yes	Yes

In addition to the structured data available in these databases, medical record data will be reviewed to confirm myocarditis and pericarditis case characteristics.

In the SAP the exact variables that are required to answer all research questions will be defined, resulting in a data instance, which is a document that contains information about which data point can be found in which data source for every DAP and in which CDM table this will be stored.

The data instance is created in collaboration with the DAP. Extracting the data is done by the DAPs, following the data instance, and results in the CDM tables that contain all the data points that are required for the study.

The CDM tables are evaluated by the so-called Level-checks, which are provided by the University Medical Center Utrecht (UMCU). The Level-checks result in a quality report. The VAC4EU association coordinates this process, however, the PI is responsible for the quality of the CDM tables. After all the Level-checks have been performed and the data has been validated by the PI, the remaining part of the ETL process takes place, which results in data being submitted to a centralized platform where all results can be analysed.

9.5 Study size

Table 3 shows the total number of doses administered in each participating country as of April 2022.

Table 3 Total doses of Moderna vaccination targeting SARS-CoV-2 administered in the participating countries as of April 2022

Moderna vaccination targeting SARS-CoV-2 doses administered as of April 2022		Moderna vaccination targeting SARS-CoV-2 recipients in Data source
Denmark	1,350,690	675,345
Norway	3,293,800	1,646,900
Spain	27,721,800	SIDIAP: 1,386,090
		FISABIO: 3,107,305
UK	951,198	28,536
TOTAL:	33,317,488	6,844,176

Source: ECDC https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab and Moderna

Considering the type of investigation, a traditional sample size calculation cannot be provided. Given that the number of cases is expected to be limited, and the number of possible risk factors for post-vaccination myocarditis (including demographic characteristics, lifestyle factors, medical history, and vaccination characteristics) under investigation, all individuals that meet the criteria for the outcome will be selected as cases, and four times as many controls will be sampled to improve statistical efficiency.[11] This sampling will be done 1,000 times to limit biases. The number of myocarditis/pericarditis cases will drive the number of risk factors that can be investigated with adequate power in this study. The nature of this study will be observational and exploratory.

Derived from literature[7,8,12,13] it is assumed that the incidence of myocarditis is approximately 0.4-4.0 per 100,000 vaccinated individuals. Based on the inclusion of subjects of the Data Access Providers (DAPs) for Denmark, Norway, Spain and UK (see Table 3), 27-274 myocarditis cases were to be expected. Similar incidence estimates were to be expected for pericarditis[7, ,12,]. However, preliminary results suggest that 20-80 cases of myocarditis are expected for each of the DAPs, leading to an expected total study size of 100-400 myocarditis cases in the case-cohort analysis. For pericarditis, the expected number of cases is 50-140 per DAP, which corresponds to a total expected study size of 250-700.

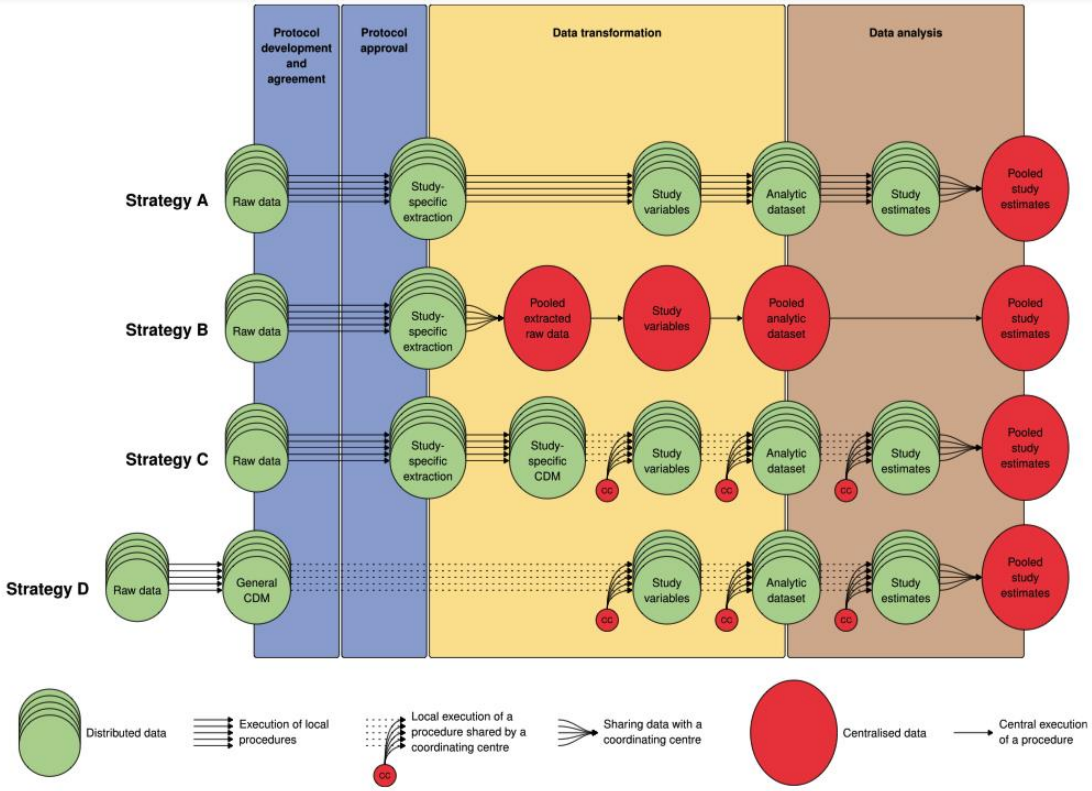
For the myocarditis/pericarditis cohort analysis, based on preliminary outputs it is estimated that there will be approximately 40-160 cases of myocarditis studied, and 100-280 cases of pericarditis.

The estimated numbers of myocarditis and pericarditis indicate that the study should be feasible for the intended two main analyses.

9.6 Data management

This study, which will be conducted based on this common protocol, will use the Vaccine monitoring Collaboration for Europe (VAC4EU, https://vac4eu.org/) research environment based on a common protocol, common SAP, and a common data model (CDM). The work will be conducted using a distributed network of the participating DAPs, all of whom have experience with and have contributed to the ACCESS project. The work will proceed according to Model C (Figure 4): each DAP will extract the data required for the study and transform their local patient level data into a CDM. It is proposed to use the ConcePTION CDM, which is publicly available.[14] Extraction, transformation, and loading (ETL) design and instructions are available, as well as tools to check the quality of the data for the AESI estimated and utilised for the ACCESS background rate protocol. A common program to run quality checks, data transformation, and analysis will be prepared, verified and distributed to all DAPs. Results and summary estimates resulting from the programs will be returned to the coordinating centre for analysis and reporting. The full approach will be developed and described in the SAP.

Figure 4 Options for multi-database studies in Europe



9.7 Data analysis

Full details of the data analysis, including planned tables, figures, and listings for inclusion in the final study report will be provided in the SAP. High-level analyses and presentations are provided below.

9.7.1 Descriptive analyses

Attrition diagrams demonstrating the application of the inclusion and exclusion criteria will be provided. For both the case-cohort and cohort study designs, demographic characteristics of the study population and baseline characteristics will be summarised from each data source, using standard descriptive statistics. Count and percentage will be presented for categorical variables. Mean, standard deviation, median and interquartile range will be presented for continuous variables, as feasible. The number of non-missing data will be added to the summary statistics. These summary statistics will be presented for each country separately, as well as overall. Differences in baseline risks will be investigated and addressed in the statistical models as appropriate.

Country-specific counts of persons with a record of Moderna vaccination targeting SARS-CoV-2 in the datasets will be tabulated. Vaccine recipients will be described in terms of sex, age (groups), previous infection with SARS-CoV-2 and a list of relevant covariables (e.g., health care utilization, comorbidities, medicine usage and lifestyle factors), to the extent feasible for each DAP.

9.7.2 Main analyses

Case-cohort analysis

For the case-cohort analysis, all cases of myocarditis and pericarditis and the full sampled control cohort will be described with respect to demographic characteristics, lifestyle factors, medical history and vaccination history. As the control cohort will be sampled 1,000 times, these variables will be described taking averages of the 1,000 samples.

Per DAP, a conditional logistic regression methodology will be applied to identify potential risk factors for development of myocarditis and pericarditis within the Moderna vaccination targeting SARS-CoV-2-exposed population (Primary objective 1). The analysis will be performed per DAP (i.e., models will be trained locally for each DAP), and results will be presented on DAP level. The parameter estimates, standard errors (SEs), and odds ratios (ORs) for each relevant model parameter will be presented together with a 95% confidence interval (CI).

Cohort analysis

To identify differences in clinical course (Primary objective 2) and differences in risk factors (Secondary objective 1) for vaccine associated myocarditis/pericarditis and vaccine unrelated myocarditis/pericarditis, cases in the cohort analysis will be compared based on vaccination status. Outcomes and identified follow-up care will also be characterized, where feasible. If sequelae or unusually severe cases are identified, cases with and without sequelae will be compared.

Standard descriptive statistics (see Section 9.7) will be used to characterise clinical course, outcomes, and long-term outcomes following the initial myocarditis/pericarditis episode. Cox regression analysis will be utilized to compare the presence of sequelae following myocarditis/pericarditis (e.g., death, subsequent cardiovascular events, cardiac hospitalizations) between recent Moderna vaccination targeting SARS-CoV-2-exposed and unexposed cases as feasible.

If myocarditis and pericarditis cases with severe presentation or long-term sequelae are identified, a similar modelling approach for the cohort design will be applied to explore applicable risk factors as feasible (Secondary objective 2). Candidate risk factors will be selected using a two-step variable selection method: starting with a univariate approach for the selection of relevant variables, and followed by a stepwise backward variable selection approach.

The analysis will be performed per DAP (i.e., models will be trained locally for each DAP), and results will be presented on DAP level. The parameter estimate, SE, and hazard ratio (HR) for each model parameter will be presented together with its 95% CI.

Further details on all analyses can be found in the SAP.

9.7.3 Subgroup analyses

Descriptive statistics will be presented for the subgroups as defined in Section 9.3.4. Statistical analyses on subgroups will be considered only if feasible based on available sample size.

9.7.4 Missing data

Because of the type of data, missing data are expected to occur due to e.g., the nature of the medical information collected/the source of the data, the amount of data collected and the heterogeneity of databases used.

It is not always possible to differentiate absence from missingness in routinely collected databases. However, the following steps are considered when missingness can be established.

Missingness will first be investigated by presenting an overview of the relevant variables and the frequency and percentage of missing data thereof.

In case the missingness is very limited (<5% for each DAP), a complete-case analysis will be performed.

In case of a larger missingness rate, using a complete-case analysis may introduce bias but also limit the number of cases for inclusion in the prediction model. Considering its informative role in health databases, missing data will be taken into account as a separate category.[15,16,17]This will be further specified in the SAP.

9.7.5 Sensitivity analyses

Sensitivity analysis will focus on the robustness of results regarding assumptions of the study design, outcome definitions, assumed period of risk, and availability of key data elements and may include the following (as feasible based on available sample size within the applicable subgroups):

- The exposure window for recent exposure to Moderna vaccination targeting SARS-CoV-2 prior to myocarditis/pericarditis events will be shortened from 30 days to 7 days and 14 days.

- The myocarditis/pericarditis case definition may be modified to include (1) validated cases classified as Definitive or Probable (Level 1-2) for a restricted sensitivity analysis, or classified as Definitive, Probable, Possible, or Insufficient Information (Levels 1-4) for an expanded sensitivity analysis, by adjudication criteria according to the Brighton Collaboration Case Definition, or (2) all cases (including validated and unvalidated cases) .

- If a large number of individuals with a history of myocarditis/pericarditis are identified, these individuals may be excluded in sensitivity analyses.

9.7.6 Other analyses

Separate analyses for different Moderna vaccine products targeting SARS-CoV-2, for example, elasomeran, elasomeran/imelasomeran, elasomeran/davesomeran, will be performed as feasible for those DAPs that have data on different products available. For each vaccine variant, descriptive analyses will be presented. Both the case-cohort as the cohort analyses will be performed separately for the vaccine variants if the sample size for both vaccines is sufficiently large.

9.8 Quality control

The source, electronic routinely collected data, proposed for use in this study will undergo standard curation and quality-check procedures and curation by the data custodians. Standard operating procedures or internal process guidance at each research centre will be adhered to for the conduct of the study. These procedures will include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, and standards for writing analysis plans. Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each partner should maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents.

This study will be conducted in accordance with the Guideline on good pharmacovigilance practices (GVP), including the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct.[18]

9.9 Limitations of the research methods

With the use of large secondary administrative databases in general, it remains difficult to ascertain the details of myocarditis and pericarditis events and other high-resolution data. In addition, while including administrative databases from different countries increases generalizability and size of the overall dataset, it also introduces heterogeneity in data collection methods, data quality, availability of variables and relations between variables. It is recognized that especially the availability and collection of lifestyle factors will be a limiting factor on the risk factor data inclusion in the proposed analyses for both the case-cohort and cohort studies. These concerns are tackled as best as possible by using all the implemented infrastructure of VAC4EU including the well-defined CDM and quality control procedures executed at various stages. In addition, a case validation is performed to verify that cases are true cases, based on criteria from the Brighton Collaboration. Furthermore, heterogeneity between DAPs will be investigated by performing specified analyses both at a local level and overall, as feasible.

Despite the large size of the underlying populations, the size of the Moderna vaccination targeting SARS-CoV-2- exposed cohort that develop myocarditis/pericarditis is relatively small, and validation of cases may further reduce the number of cases included in analyses. This could limit the amount of risk factors and prognostic factors that can be investigated in the case-cohort design

and might make some (subgroup) analyses challenging regarding achieving adequately powered statistical analyses. Data availability may also limit our ability to address primary and secondary study objectives related to the identification of lifestyle factors as risk factors for the development of myocarditis/pericarditis. While the merits of investigating lifestyle factors as potential risk factors may be questioned when the data availability cannot be assured, we believe it is central to the research question to consider and rule out potential confounders whenever possible. Namely, we want to be able to determine the risk of myocarditis or pericarditis following vaccinations targeting SARS-CoV-2 over and above other common factors (e.g., age, smoking status). To this end, we will investigate as many lifestyle factors as feasible across all DAPs. Where not feasible (i.e., certain DAPs are missing a given lifestyle factor), analyses will include a smaller subset of variables and/or will only be done for those DAPs that have the requisite data available.

The sampling of cases (i.e., myocarditis or pericarditis not following vaccination) to be validated could pose a limitation in the characterization of the clinical course of cases not following vaccination. As most myocarditis and pericarditis cases following vaccination are expected to occur in young adults, age-matched non-vaccine related myocarditis/pericarditis cases will also mainly comprise of young adults. This may lead to an underrepresentation of non-vaccination related cases in older individuals in the cohort analysis. However, the sensitivity analysis including all cases, regardless of being validated or not, will provide information regarding the clinical course of non-vaccine related cases in possible underrepresented age groups.

There are a few other potential validity issues in this study. Selection bias is not expected to pose a threat to validity, as the routinely collected data are sufficiently representative of the background population. That is, the registries have full population coverage in Denmark and Norway, while the regional databases in Spain are representative with respect to background rates and demographic distributions of the underlying populations. Similarly, the CPRD is broadly representative of the UK population (see Annex 3).[19]

Information bias may cause a threat in classification of the outcomes (myocarditis/pericarditis), in both the case-cohort and cohort studies. As became more well-known among the general public that myocardial side effects may occur after vaccinations targeting SARS-CoV-2 with young males most at risk, the chances of diagnosis among young males may have become higher compared to other groups. This could be due to young males' increased vigilance and a corresponding increase in their likelihood to report symptoms following vaccination. Alternatively or in conjunction, the well-documented nocebo effect[Error! Reference source not found.,Error! Reference source not found.,Error! Reference source not found.] suggests increased knowledge and negative expectations of a given side effect can render its occurrence more likely. While beyond the scope of the current studies to determine the rate of information bias in the case-cohort and cohort samples, it is worth noting its occurrence may contribute to variance in observed myocarditis/pericarditis among certain subsamples (namely young males). Our inability to disentangle the rate of nocebo vaccine-related myocarditis constitutes a limitation, recognized and seen as not insignificant by other COVID-19 researchers.[22,23]

Conducting retrospective analyses on observational data, we will attempt to adjust for potential confounders in both the case-cohort and cohort studies. Namely, we will perform multivariable analyses as feasible, examining the effect of predictors of interest over and above potential confounders. Moreover, we will attempt to control for the effects of lifestyle variables as much as statistically possible and feasible by including them as covariables into the multivariable model.

9.10 Other aspects

Not applicable.

10. Protection of human subjects

The proposed study is non-interventional, re-using routinely collected health and administrative data. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each data access provider should apply for an independent ethics committee or other review according to local regulations. Data protection and privacy regulations (GDPR) will be observed in collecting, forwarding, processing, and storing data from study participants. Whenever required by data protection regulations, implicit or explicit cell counts that potentially allow for identification of individuals (e.g., counts of 1-4 in most countries), appropriate masking methods will be applied. All participating investigators/data access providers will obtain all required governance approval for conducting this study. Security processes should be in place to ensure the safety of all systems and data. Every effort should be made to ensure that data are kept secure so that they cannot be accessed by anyone except the study team. Appropriate data storage and archiving procedures will be followed by each DAP and the coordinating centre, with periodic backups.

11. Management and reporting of adverse events/adverse reactions

Analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic health care records, systematic reviews or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarised in the study report, where applicable.[18,24] According to the GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products "All adverse events/reactions collected as part of [non-interventional post-authorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not

required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report." Module VIII – Post-Authorization Safety Studies, echoes this approach. The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.[5,9]

12. Plans for disseminating and communicating study results

Per GVP Module VIII: "For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication."[24]

The protocol and the final study report will be subject to mandatory publication in the EU PAS register and will comply with ENCePP or Code of Conduct, according to which study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[25], RECORD, and RECORD-PE[26,27] checklist will be followed, and recommendations on reproducible reporting of electronic health care data base studies should be followed.[28]

13. References

1. Statistics and Research. Coronavirus (COVID-19) Vaccinations. Published 2021. Accessed 14 June, 2021

2. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. *Nat Hum Behav* 2021 doi: 10.1038/s41562-021-01122-8 [published Online First: 2021/05/12]

3. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *N Engl J Med* 2020;383(25):2427-38. doi: 10.1056/NEJMoa2028436 [published Online First: 2020/09/30]

4. EMA. COVID-19 Vaccine Moderna Risk Management Plan

5. EMA. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 3-6 May 2021

6. EMA. Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis, 09 July 2021

7. Husby A, Hansen J, Fosbøl E, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *BMJ* 2021; Dec 16;375:e068665. doi: 10.1136/bmj-2021-068665

8. Oster ME, Shay DK, Su JR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. *JAMA* 2022; Jan 25;327(4):331-340. doi: 10.1001/jama.2021.24110

9. Manfredi R, Bianco F, Bucciarelli V, et al. Clinical Profiles and CMR Findings of Young Adults and Pediatrics with Acute Myocarditis Following mRNA COVID-19 Vaccination: A Case Series. Vaccines 2022 Jan 22;10(2):169. doi: 10.3390/vaccines10020169

10. Sexson Tejtel SK, Munoz FM, Al-Ammouri I, et al. Myocarditis and pericarditis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2022 Mar 1;40(10):1499-1511. doi: 10.1016/j.vaccine.2021.11.074. Epub 2022 Jan 31.

11. Gail M, Williams R, Byar DP, et al. How many controls? J Chronic Dis. 1976 Nov;29(11):723-31. doi: 10.1016/0021-9681(76)90073-4

12. Lane S, Yeomans A, Shakir S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK,

Europe and the USA and of the scientific literature. BMJ Open May 25;12(5):e059223. doi: 10.1136/bmjopen-2021-059223. Erratum in: BMJ Open. 2022 Jul 5;12(7):e059223corr1

13. Wong HL, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet. 2022 Jun 11;399(10342):2191-2199. doi: 10.1016/S0140-6736(22)00791-7

14. Dodd C, Gini R, Sturkenboom M, et al. Reposrt on existing common data models and proposals for ConcePTION.

15. Agniel D, Kohane IS, Weber GM. Biases in electronic health record data due to processes within the healthcare system: retrospective observational study. BMJ. 2018 Apr 30;361:k1479. doi: 10.1136/bmj.k1479. Erratum in: BMJ. 2018 Oct 18;363:k4416.

16. Madden JM, Lakoma MD, Rusinak D, et al. Missing clinical and behavioral health data in a large electronic health record (EHR) system. J Am Med Inform Assoc. 2016 Nov;23(6):1143-1149. doi: 10.1093/jamia/ocw021

17. Groenwold RHH. Informative missingness in electronic health record systems: the curse of knowing. Diagn Progn Res. 2020 Jul 2;4:8. doi: 10.1186/s41512-020-00077-0

18. EMA. Guideline on good pharmacovigilance practices (GVP)

19. Medicines & Healthcare products Regulatory Agency. Clinical Practice Research Datalink. https://cprd.com/

20. Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. Psychosom Med. 2011 Sep;73(7):598-603. doi: 10.1097/PSY.0b013e3182294a50.

21. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. Clin Pharmacol Ther. 1987 Sep;42(3):250-3. doi: 10.1038/clpt.1987.142

22. Geers AL, Clemens KS, Faasse K, Colagiuri B, Webster R, Vase L, Sieg M, Jason E, Colloca L. Psychosocial Factors Predict COVID-19 Vaccine Side Effects. Psychother Psychosom. 2022;91(2):136-138. doi: 10.1159/000519853

23. Amanzio M, Mitsikostas DD, Giovannelli F, et al. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. Lancet Reg Health Eur. 2022 Jan;12:100253. doi: 10.1016/j.lanepe.2021.100253

24. EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies

25. Von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*

2007;335(7624):806-8. doi: 10.1136/bmj.39335.541782.AD [published Online First: 2007/10/20]

26. Langan SM, Schmidt SA, Wing K, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ* 2018;363:k3532. doi: 10.1136/bmj.k3532 [published Online First: 2018/11/16]

27. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015;12(10):e1001885. doi: 10.1371/journal.pmed.1001885 [published Online First: 2015/10/07]

28. Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. *Pharmacoepidemiol Drug Saf* 2017;26(9):1018-32. doi: 10.1002/pds.4295 [published Online First: 2017/09/16]

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1			
2			
…			

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title: Clinical course, outcomes and risk factors of myocarditis and pericarditis following administration of Moderna vaccines targeting SARS-CoV-2.

Short title: Myocarditis after mRNA-1273

EU PAS Register® number: Protocol will be registered before start of the data collection
Study reference number (if applicable): N/A

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7 & 8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Hypotheses testing is not applicable: this study aims to assess clinical course, outcomes and risk factors for post-vaccine myocarditis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2 & 9.2.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4 & 9.7.5

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☐	☒	☐	9.3 & 9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	9.3 & 9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9.3 & 9.7 & 9.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.5
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☒	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☒	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.4

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: David Ong

Date: dd/Month/year

Signature: _____

Annex 3. Description of the participating data sources

Denmark: Danish population registries

Denmark has a tax-funded health care system ensuring universal access to health care, and with this system health contacts are recorded in administrative and health registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish resident, originally for taxation purposes. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers. All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information. For the purpose of the study we will obtain information from the following registries. The Danish National Prescription Registry includes data on all outpatient dispensing of medications and vaccines at Danish pharmacies from 1995 and onwards, including dispensing date, ATC code, product code and amount. The Danish National Health Service Register includes data on primary care services, including general practitioner contacts, examinations, procedures, pregnancy-related visits, vaccinations (other than COVID-19); psychologist or psychiatrist and other primary care provider visits; etc. From the Danish Civil Registration System, data on demographics (sex, date of birth) and censoring (migration, vital status). The Danish National Patient Registry contains diagnoses and procedures from all hospitalizations since 1977 and contacts to hospital outpatient clinics since 1995. The Danish databases were characterised in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment and could participate in near real-time monitoring. Use of the Danish Vaccination Registry will be involved to ascertain vaccinations outside GP offices and to ascertain vaccine brand. Danish health care and the flow of data into the registries have been described in a recent publication (https://www.ncbi.nlm.nih.gov/pubmed/31372058).

Norway: Norwegian population registries

The core data that University of Oslo (UIO) has access to is the health care administrative databases of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants. Norway has a universal public health care system, consisting of primary health care services and specialist health care services. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. The most commonly used registries are administrated by The Norwegian Institute of Public Health, The Norwegian Directorate of Health and Statistics Norway. The Norwegian national identity number was introduced in the 1960s. This identifier is assigned to every person at birth or upon immigration; it is 11 digits long and encodes date of birth and sex. The code is included in all national registries, allowing accurate linkage among them. Information about all Norwegian National Registries can be found here: www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/

Spain: SIDIAP

The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' - SIDIAP; www.sidiap.org) was created in 2010 by the Catalan Health Institute (CHI) and the IDIAPJGol Institute. It includes information collected since 01 January 2006 during routine visits at 278 primary care centres pertaining to the CHI in Catalonia (North-East Spain) with 3,414 participating GPs. SIDIAP has pseudo-anonymised records for 5.7 million people (80% of the Catalan population) being highly representative of the Catalan population. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs, pediatricians and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals and primary care laboratory test results. It can also be linked to other data sources, such as the hospital discharge database, on a project by project basis. Health professionals gather this information using ICD-10 codes, ATC codes and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. In relation to vaccines, SIDIAP includes all routine childhood and adult immunizations, including the antigen and the number of administered doses. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. The SIDIAP database is updated annually at each start of the year. With the COVID-19 pandemic, there is the possibility to have shorter term updates in order to monitor the evolution of the pandemic. Recent reports have shown the SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the ENCePP resources database www.encepp.eu/encepp/resourcesDatabase.jsp). The SIDIAP database was characterised in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment.

Spain: FISABIO

The Valencia Health System Integrated Database (VID) is a set of population-wide electronic databases covering residents of the Valencia region in Spain, representing approximately 5 million individuals (https://pubmed.ncbi.nlm.nih.gov/31977043/). All the information in the VID databases can be linked at the individual level through a single personal identification. The data sets in the VID are as follows:

- The Population Information System (SIP) is a database that provides basic information on health system coverage (e.g., dates and causes of Valencia health system entitlement or disentitlement, insurance modality, pharmaceutical co-payment status, assigned health care department) as well as some sociodemographic data (e.g., sex, date of birth, nationality, geographic location). Importantly, the SIP database includes the date of death captured from the Mortality Registry. The SIP database is paramount to the VID, as it is the source of the individual, exclusive, and permanent identifier number associated with each

individual (the SIP number), which is then used throughout the rest of the databases, thereby allowing data linkage across the multiple databases in the network.

- The Ambulatory Medical Record (ABUCASIS) is the electronic medical record for primary and specialised outpatient activity, with 96% population coverage since 2009. ABUCASIS is integrated by two main modules: the Ambulatory Information System (SIA) and the Pharmaceutical Module (GAIA), including paediatric and adult primary care, mental health care, prenatal care, and specialist outpatient services, as well as providing information about dates, visits, procedures, laboratory test results, diagnoses, and clinical and lifestyle information. It also includes information on several health programmes (e.g., healthy children, vaccines, pregnancy, notifiable diseases), the primary care nurse clinical record, and the health-related social assistance record. The SIA module uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for coding diagnoses (and, partially, the International Classification of Diseases, 10th Revision, Spanish Edition [ICD-10-ES] from 2019). The SIA also uses the Clinical Risk Groups system to stratify the morbidity of the entire population.

- The GAIA Pharmaceutical module stores data on all outpatient pharmaceutical prescriptions and dispensings, including both primary care and outpatient hospital departments, using the Anatomical Therapeutic Chemical (ATC) classification system and the National Pharmaceutical Catalogue, which allow the identification of the exact content of each dispensing. GAIA does not include in-hospital medication or medication administered in the Accident and Emergency Department (AED). GAIA provides detailed information on prescriptions issued by physicians, such as the duration of treatment and dosage.

- The Hospital Medical Record (ORION) provides comprehensive information covering all areas of specialised care, from admission, outpatient consultations, hospitalisation, emergencies, diagnostic services (e.g., laboratory tests, imaging, microbiology, pathology), pharmacy, surgical block including day surgery, critical care, prevention and safety, social work, at home hospitalisation, and day hospitalisation. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated and available for all hospitals, including the Minimum Basic Data Set at Hospital Discharge (MBDS) and the AED clinical record.

- The MBDS is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the Valencia health system hospitals, including public-private partnership hospitals (approximately 450,000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographic area and zone of residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode, and the diagnosis-related group(s) assigned at discharge. The MBDS used the ICD-

9-CM system for coding through December 2015 and ICD-10-ES afterward. The MBDS was extended in 2015 to include the "present on admission" diagnosis marker and information on tumour morphology.

- The AED clinical record was launched in 2008 and collects triage data, diagnoses, tests, and procedures performed in public emergency departments. As with the MBDS, the coding system used the ICD-9-CM until December 2015 and the ICD-10-ES thereafter. Diagnosis codification has been increasing from approximately 45% of all emergency department visits between 2008 and 2014 up to approximately 75% in 2017, largely due to the progressive incorporation of hospital coding.

- Data on vaccine exposure may be obtained from the Vaccine Information System (VIS), which includes information on vaccine type, manufacturer, batch number, number of doses, location and administration date, adverse reactions related to vaccines, and if applicable, risk groups. Information in the VIS is updated daily.

All databases included in the VID are updated frequently (every 1 to 3 months), except the MBDS database, which is updated every 6 months. Information on pregnancy and pregnancy outcomes is available in the VID database, although some end dates of pregnancy may be missing. However, the mother-baby linkage is not available.

United Kingdom: CPRD & HES

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerised medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care as necessary. Secondary care teams also feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. The majority of the data are coded in Read Codes. Validation of data with original records (specialist letters) is also available. The dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage when GOLD & Aurum versions are used. There are currently approximately 42 million patients (acceptable for research purposes) – of which 13 million are active (still alive and registered with the GP practice) – in approximately 1,700 practices (https://cprd.com/Data). Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summary (date and Read and SNOMED codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). For a

proportion of the CPRD panel practices (>80%), the GPs have agreed to permit CPRD to link at patient level to the Hospital Episode Statistics (HES) data. CPRD is listed under the ENCePP resources database, access will be provided by the DSRU. The CPRD was not yet characterised in the ADVANCE project, where the UK THIN and RCGP databases were used, but has been largely used in vaccine studies. The HES database contains details of all admissions to National Health System (NHS) hospitals in England; approximately 60% of GP practices in the CPRD are linked to the HES database. Not all patients in the CPRD have linked data (e.g. if they live outside England or if their GP has not agreed that their data should be used in this way). As with standard CPRD patients, HES data are limited to research-standard patients. CPRD records are linked to the HES using a combination of the patient's NHS number, gender and date of birth. The Drug Safety Research Unit (DSRU) is the leading UK centre for pharmacovigilance and pharmacoepidemiology which has led and coordinated many large studies across the UK. The Unit has ample experience of monitoring the post-authorisation safety of vaccines, notably active surveillance on the H1N1 swine flu vaccine and an active surveillance study and six enhanced passive surveillance studies on the children's seasonal influenza vaccine. The DSRU works with the UK's National Institute for Health Research (NIHR) Clinical Research Network, which facilitates research in the National Health Service (NHS) and provides access to a large network of research-ready health care professionals, including GPs. The DSRU also has experience of study designs based on patient reported outcomes.

Signature Page for VV-CLIN-016832 v1.0

2nd Approval	PPD PPD 26-Jan-2024 11:39:43 GMT+0000

2nd Approval	PPD PPD 26-Jan-2024 16:04:33 GMT+0000

Signature Page for VV-CLIN-016832 v1.0