NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Post-Authorisation Active Surveillance Study of Myocarditis and Pericarditis Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
Protocol number	C4591038
Protocol version identifier	5.0
Date	11 June 2025
EU Post-Authorisation Study (PAS) Register number	EUPAS47708
Active substance	BNT162b2
Medicinal product	COVID-19 messenger ribonucleic acid (mRNA) vaccine is a nucleoside-modified ribonucleic acid (modRNA) encoding the viral spike glycoprotein S of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Marketing Authorisation Holder(s) (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	The research question addressed by this study is: What is the clinical course of myocarditis and pericarditis cases after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine in European countries? Primary study objective: • To describe the clinical course (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis and pericarditis

	among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design Secondary study objective: • To examine and identify potential risk factors for myocarditis and pericarditis, such as age, sex, Pfizer-BioNTech COVID-19 vaccination status, vaccine doses received (e.g., first, second, third, and booster doses), and history of COVID-19, using a cohort study design
Country(-ies) of study	The Netherlands (NL), Italy (IT), Spain (ES), United Kingdom (UK), Norway (NO)
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Marketing Authorisation Holder(s)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACCESS	vACCine covid-19 monitoring readinESS
ACE	angiotensin-converting enzyme
AESI	adverse event of special interest
ARB	angiotensin-II receptor blocker
ARS Toscana	Agenzia Regionale di Sanità della Toscana (IT)
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control and Prevention
CDM	common data model
CI	confidence interval
cMR	cardiac magnetic resonance
COVID-19	coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
CRF	case report form
DEAP	data expert and access partner
DRE	Digital Research Environment
DSRU	Drug Safety Research Unit (UK)
DTP	diphtheria, tetanus, and pertussis
EHR	electronic health record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EpiChron	EpiChron Research Group on Chronic Diseases (ES)
ES	Spain
ETL	extraction, transformation, and loading
EU PAS Register	European Union electronic register of post-authorisation studies
EU	European Union
FAIR	findable, accessible, interoperable, and re-usable
GP	general practitioner

Abbreviation	Definition
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
HSD	Health Search Database (IT)
HZ	herpes zoster virus
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
ICPC	International Classification of Primary Care
IRB	institutional review board
IT	Italy
IR	Incidence rate
KUHR	Norway Control and Payment of Health Reimbursement
MAH	marketing authorisation holder
MBRN	Medical Birth Registry of Norway
mRNA	messenger RNA
MSIS	Norwegian Surveillance System for Communicable Diseases
NHR	Norwegian Health Registers (NO)
NHS	National Health Service (UK)
NI	non-informative
NIPH	Norwegian Institute of Public Health
NL	Netherlands
NO	Norway
NPR	National Patient Register
NSAID	non-steroidal anti-inflammatory drug
PASS	post-authorisation safety study
PHARMO	PHARMO Institute for Drug Outcomes Research (NL)
PHE	Public Health England
QC	quality control

Abbreviation	**Definition**
RR	risk ratio
RTI-HS	Research Triangle Institute Health Solutions
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIDIAP	Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [Information System for the Improvement of Research in Primary Care] (ES)
SQL	Structured Query Language
SSB	Statistics Norway
SYSVAK	Norwegian Immunisation Registry
UK	United Kingdom
UMCU	University Medical Center Utrecht
USA	United States of America
VAC4EU	Vaccine monitoring Collaboration for Europe
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Post-Authorisation Active Surveillance Study of Myocarditis and Pericarditis Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Version 5.0, 11 June 2025

Alejandro Arana, RTI Health Solutions, Barcelona, Spain

Rationale and background: The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. The Pfizer-BioNTech COVID-19 vaccine, Comirnaty® (tozinameran), a novel mRNA-based vaccine, has been authorised for use in the European Union (EU) for the prevention of COVID-19. Efficient and timely monitoring of the safety of the vaccine is needed in European countries. The safety of the Pfizer-BioNTech COVID-19 vaccine is being investigated in clinical and epidemiological studies conducted worldwide.

The Centers for Disease Control and Prevention (CDC) in the United States (US) issued a statement indicating a possible link between vaccination to prevent COVID-19 and myocarditis for both the Pfizer-BioNTech COVID-19 vaccine and the mRNA-1273 vaccine produced by Moderna. Several researchers have reported an increase in risk of myocarditis and/or pericarditis within 42 days of receiving the vaccination, compared with the risk among unexposed persons, particularly after the second dose and among young male recipients. European Medicines Agency (EMA)'s safety committee (Pharmacovigilance Risk Assessment Committee [PRAC]) has assessed recent data on the known risk of myocarditis and pericarditis following vaccination with COVID-19 vaccines Comirnaty and Spikevax (i.e., trade names for the Pfizer-BioNTech and Moderna COVID-19 vaccines, respectively). The outcome of the review confirms the risk of myocarditis and pericarditis, which is already reflected in the product information for these 2 vaccines.

To further examine the risk of myocarditis and pericarditis with the Pfizer-BioNTech COVID-19 vaccine, Pfizer and Vaccine monitoring Collaboration for Europe (VAC4EU) are conducting this study. This study is nested in the EUPAS41623 cohort study, titled *Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine*, which estimates the incidence rates of prespecified adverse events of special interest (AESIs) in 5 European countries among individuals who receive at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among unvaccinated individuals.

Research question and objectives: This study will address the following research question, "What is the clinical course of myocarditis and pericarditis cases after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine in European countries?"

Primary study objective

- To describe the clinical course (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis or pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.

Secondary study objective

- To examine and identify potential risk factors for myocarditis and pericarditis, such as age, sex, Pfizer-BioNTech COVID-19 vaccination status, vaccine doses received (e.g., first, second, third, and booster doses), and history of COVID-19, using a cohort study design

Study design: This cohort study is nested in the ongoing retrospective cohort study (EUPAS41623) titled *Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine*. The parent study includes individuals across 5 European countries who receive at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine, as well as individuals who did not receive a COVID-19 vaccine.

For the primary objective (natural history), the study will be conducted in the cohort of cases of myocarditis and of pericarditis identified in the full population of the parent study.

In the parent study component comparing risk of AESIs in vaccinated and unvaccinated individuals, the 2 groups are matched 1:1 on date of vaccination in the vaccinated group and date of study eligibility in the unvaccinated group. Individuals are also matched on age, sex, history of COVID-19, place of residence, history of influenza vaccination, pregnancy status, immunocompromised status, presence of pre-existing medical conditions, and socioeconomic status/education level. This matched population constitutes the cohort in which risk factors for myocarditis and pericarditis will be evaluated (secondary objective). The matching variables, vaccination status, and other baseline variables identified in a review of the medical literature will be considered as potential risk factors for the development of myocarditis and of pericarditis.

Population: The source population will comprise all individuals across 5 European countries (i.e., the Netherlands [NL], United Kingdom [UK], Italy [IT], Norway [NO], and Spain [ES]) who are registered in the health care database(s) used in the study and who are eligible to receive the Pfizer-BioNTech COVID-19 vaccine. The study period starts on the date of conditional approval of the Pfizer-BioNTech COVID-19 vaccine in each country: 01 December 2020 in UK and 21 December 2020 in NL, IT, ES, and NO. The study period will end on 31 March 2025, however, the end date may be earlier in some data sources depending on the latest date of data availability at that time. For start and end of data collection see Milestone Section at the end of the abstract and in Section 6.

Variables:

Exposure to vaccines will be assessed in each data source based on recorded prescription, dispensing, or administration of the Pfizer-BioNTech COVID-19 vaccine. Vaccine administration and date of vaccination will be obtained from all possible sources that capture COVID-19 vaccination.

Myocarditis/pericarditis: Standard algorithms for myocarditis and for pericarditis will be applied to participant data sources to identify potential cases. All potential cases of myocarditis or pericarditis in small databases and a sample of those in large populations will be validated against information available for each data source and classified based on the definitions of the Brighton Collaboration[1]. The validation process will be based on the review of the individuals' medical records by clinicians from the research team who will be blinded to COVID-19 vaccination status. Cardiac symptoms for myocarditis and pericarditis are acute chest pain or pressure; dyspnoea after exercise, at rest, or lying down; fatigue; diaphoresis; and sudden death. Other non-specific symptoms in adults are palpitations, abdominal pain, dizziness, syncope and cardiogenic shock, fatigue, oedema, and cough. In infants or young children, symptoms include irritability, vomiting, poor feeding, and sweating. The detection of these signs and symptoms during the validation process will be used to determine levels of certainty of the diagnosis.

Potential risk factors for myocarditis and pericarditis are demographics (such as male sex, young ages); status of Pfizer-BioNTech COVID-19 vaccination and non-COVID vaccinations; vaccine doses received (e.g., first, second, third, and booster doses); post-vaccination risk window of 1-14 days; history of COVID-19 and other infectious diseases; status of immunocompromising conditions and systemic immune-mediated diseases; and comedication use (prescriptions or dispensings only) during the year before time zero (defined as date of vaccination, or matched index date for comparator).

Treatments for myocarditis based on clinical presentation of mild symptoms include paracetamol and antivirals for viral myocarditis; immunosuppression treatment for autoimmune myocarditis; heart failure therapy (i.e., beta-blockers, diuretics, angiotensin-converting enzyme [ACE] inhibitors or angiotensin-II receptor blockers [ARBs], aldosterone antagonists, cardiac glycosides or calcium-channel blockers); and procedures (i.e., pacemaker, implantable cardiac defibrillator, mechanical circulatory support, and heart transplantation).

Treatments for pericarditis include antimicrobial treatment (for pericarditis of proven infectious origin); anti-inflammatory treatment (non-steroidal anti-inflammatory drugs [NSAIDs] and colchicine [for recurrent pericarditis]); and procedures (i.e., intrapericardial administration of steroids; pericardioscopy for direct instillation of treatments into the pericardial space; pericardial drainage; subdiaphragmatic laparoscopic technique, video-assisted thoracoscopic technique, and pericardioscopy for easy drainage of effusion; pericardiocentesis; cardiac catheterisation during pericardiocentesis; balloon pericardial window formation; instillation of sclerosing agents or fibrinolytic agents; and pericardiectomy).

Potential outcomes for myocarditis that will be evaluated are recovery, survival, hospitalisations, sudden cardiac death, heart failure, cardiogenic shock, fulminant myocarditis, inflammatory cardiomyopathy, heart transplant, and arrhythmia.

Potential outcomes for pericarditis that will be evaluated are recovery, survival, hospitalisations, and chronic, restrictive, and recurrent pericarditis.

Data sources: The study will be performed within the following selected data sources: Pedianet (IT), PHARMO Institute for Drug Outcomes Research (PHARMO) (NL), Norwegian Health Registers (NHR) (NO), EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron) (ES), and Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP) [Information System for the Improvement of Research in Primary Care] (ES), Clinical Practice Research Datalink (CPRD) (UK).

Study size: The study will be conducted in a source population of 38.9 million individuals captured across the electronic healthcare data sources. Based on the risk estimates and their 95% confidence intervals (CI) from Barda et al. [2], we expect to identify a range of approximately 400 to 1,100 cases of myocarditis for the primary objective.

Data analysis:

Natural history of myocarditis and pericarditis (primary objective): Individuals will be followed through recovery, death, or end of study period, whichever occurs first. The distributions of vaccination status and other baseline characteristics will be described. For continuous variables, means, standard deviations and quartiles will be estimated. For categorical variables, counts and proportions will be estimated. The missingness of variables will also be described. The occurrence of the different treatments and outcomes during follow-up will be described using counts and proportions. Continuous variables (e.g., length of stay) will be described using means, standard deviations and quartiles. When appropriate, the occurrence of time-to-event outcomes (e.g., death) will be described using the Kaplan-Meier estimator or curve.

Analysis will be performed overall by sex and age, COVID-19 history, vaccination status, and time since vaccination.

Risk factors for myocarditis and pericarditis (secondary objective): All individuals in the matched cohort of the parent study will be followed from the date of matching (i.e., the date of vaccination for those in the vaccinated group and a matched calendar date in the unvaccinated group) until the earliest occurrence of the following:

- Diagnosis of myocarditis or pericarditis
- Death
- Administrative end of follow-up

- Receipt of a non–Pfizer-BioNTech COVID-19 vaccine
- Unvaccinated member of the pair is vaccinated with the Pfizer-BioNTech COVID-19 (both the unvaccinated and vaccinated individuals of the pair will be censored).

All baseline variables, including vaccination status, will be treated as potential risk factors or effect modifiers for the development of myocarditis and/or pericarditis. A regression-based predictive analysis will be conducted to identify the variables that better predict the diagnoses. The strength of the association between the risk factors and a diagnosis of myocarditis or pericarditis will be estimated via risk ratios or hazard ratios, as appropriate.

To assess robustness, a sensitivity analysis will be conducted by repeating the analysis described above, including as cases of myocarditis or pericarditis only those meeting the Brighton Collaboration classification of "definitive"[2].

Milestones

- Protocol endorsement by EMA: 31 May 2022
- Registration in the EU PAS Register: 22 August 2022
- Start of data collection: 10 February 2023
- Interim report: 30 September 2023
- Planned End of data collection: 31 March 2025
- Planned Final study report: 30 June 2025

5. AMENDMENTS AND UPDATES

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
4	11 Jun 2025	Throughout	DAP (data access provider) changed to DEAP (data expert and access partner)	To reflect the change in VAC4EU name for partners
4	11 Jun 2025	3. Responsible Parties	Additions and removals of staff members at participating institutions	Personnel changes
4	11 Jun 2025	3. Responsible Parties	IDIAP removed from list of country coordinating investigators	To have only one country coordinating investigator per country. EpiChron serves as the coordinating institution for the study in Spain
4	11 Jun 2025	4. Abstract 6. Milestones 9.2.3 Study Period	Updated milestones and study period dates	Revision of milestone dates to reflect delay of end of data collection date and final study report date
4	11 Jun 2025	9.3.3.1 Identification and validation of myocarditis and pericarditis, by data source	Additional details on the validation process added	To provide further clarity
3	08 Aug 2024	General	Presentation of data sources was switched to alphabetical order throughout the document Minor administrative, formatting, and typographical changes have been made.	Updated to provide clarity and be consistent with remainder of protocol and other studies (C4591021 and C4591052)
3	08 Aug 2024	2. LIST OF ABBREVIATIONS	Removed abbreviations that only appear once or not at all in the text and added new ones	To conform with Pfizer style guide

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
3	08 Aug 2024	3.RESPONSIBLE PARTIES	Updated PIs list Updated country teams Updated degree(s) and added Other Responsible Parties Contributing to the Protocol	To list current team members
3	08 Aug 2024	4. ABSTRACT 6. MILESTONES	Updated milestones and study period dates	Revision of milestone dates to reflect delay of Study Completion date and Final Study Report date
3	08 Aug 2024	N/A	Justification for delay of final study report	The MAH requests an extension for delivery of the Final Study Report. The Final Study Report was initially planned for submission by 30 September 2024. This extension is needed to fully complete the validation of cases of myocarditis and pericarditis. Although the incidence of myocarditis and pericarditis continues to be extremely low, the size of the cohorts in the largest data sources (e.g. CPRD (UK), Norwegian health registers (NO), IDIAP (ES)) and the follow-up time of two years have yielded a large number of cases that require validation. Additional time is needed to complete this task. Since only a limited number of data sources have fit-for-purpose data, COVID-19 vaccine studies with VAC4EU have been mostly conducted in the same data sources which has led to capacity issues and queuing for scripts for the different PASS. This unexpected situation could not have been

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
				controlled by the MAH and given the unprecedented worldwide pandemic, could not have been reasonably anticipated when the timelines and milestones were initially planned in 2021. The MAH estimates that delivery of the Final Study Report is feasible by 30 June 2025. Estimated Study Completion date (same as End of Data Collection) will now be 31 December 2024 instead of the original date of 31 March 2024. These dates have been revised in 6: MILESTONES
3	08 Aug 2024	4. ABSTRACT 9.2 Setting	Re-ordered data sources. Removed Italian data sources: Agenzia Regionale di Sanità della Toscana (ARS) and Health Search Database (HSD) as they will not contribute to the study. Added Table 1 to summarise availability of data	To be consistent with other studies (C4591021 and C4591052). Data from ARS will not be extracted for the study due to national and regional re-assessment of regulations affecting their ability to provide public data for PASS studies. In the HSD data source (Italian GP databases) data on COVID-19 vaccination were missing for a high percentage of individuals and it was, therefore, not considered as fit for purpose and will not be extracted.
3	08 Aug 2024	4. ABSTRACT 9.3.3.1 Identification and validation of myocarditis and pericarditis, by data source	Added sampling strategy for validation.	In order to complete the validation of cases of myocarditis/pericarditis within a reasonable period of time, instead of validating all cases, a sampling strategy was implemented for those data access providers with a large number of cases

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
			In Pedianet, EpiChron and PHARMO all cases of myocarditis and pericarditis will be validated. In NHR, SIDIAP and CPRD the number of potential cases originally identified is large and there are insufficient resources (e.g. clinical reviewers) to validate all cases, therefore a sample of cases will be validated as follows: 1) All cases of myocarditis and pericarditis occurring within the first 21 days after T0 (for dose 1, dose 2, and dose 3) will be prioritized and selected for validation. 2) In NHR, SIDIAP and CPRD a random selection of additional cases of myocarditis and pericarditis events will be obtained and validated in order to reach a total of 300 of each diagnosis (myocarditis and pericarditis) in each of the three data sources which includes the already validated cases described in 1) above.	
			Updated description of the validation process for NHR	Revised outdated information
3	08 Aug 2024	9.2.3 Study period; Table 1	End of study period updated. Summary of vaccine launch and data availability dates added	The study period will end on 31 August 2023 (before 31 March 2023) to include the latest data availability from Pedianet and EpiChron.

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
				To further describe data availability dates in the various data sources
3	08 Aug 2024	9.3.4.1 Treatments for myocarditis	Replace aldosterone agonists by aldosterone antagonists	Correction of an error. Aldosterone agonists were erroneously mentioned as one of the myocarditis treatments,
3	08 Aug 2024	9.4. Data sources	Re-ordered and re-named data sources to be consistent with order in other studies (C4591021 and C4591052). ARS and HSD data sources removed	For consistency and to revise outdated information
		9.4.2 PHARMO (NL)	Update sources of data for PHARMO	Outpatient Pharmacy Database will not be used
		9.4.3 NHR (NO)	Updated number of active individuals	Outdated information
		9.4.5 SIDIAP (ES)	Updated number of active individuals	Outdated information
		9.4.6 CPRD (UK)	Updated sources of data for CPRD and numbers of active individuals. Disclaimer updated	Some COVID-19 specific databases linked to CPRD were identified as not being necessary in order to obtain study variables based on recent experience in the study
3	08 Aug 2024	9.6.1 Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record	Deleted sentence indicating that CRFs need to be signed	CRFs will not be collected and therefore it will not be possible to verify if they are signed as part of the QC process
3	08 Aug 2024	9.8 Quality control	Re-ordered and re-named data sources to be consistent with order in other studies (C4591021 and C4591052). ARS and HSD data sources removed	For consistency
3	08 Aug 2024	9.8.3 NHR (NO)	Added quality control information from NHR.	Previously missing
2	13 May 2022	4. ABSTRACT 6. MILESTONES	Added an interim report 9 months after the start of data collection	Request from EMA

Amendment number	**Date**	**Section of protocol changed**	**Summary of amendment/update**	**Reason**
2	13 May 2022	4. ABSTRACT 9.3.3.1 Identification and validation of myocarditis and pericarditis, by data source, 9.7.1.2 Natural history of myocarditis and pericarditis	Added a sensitivity analysis considering only cases of myocarditis or pericarditis that meet the Brighton Collaboration "definitive" classification	Request from EMA
2	13 May 2022	4. ABSTRACT 9.5. Study size	Refined the study size description and added precision estimates	Request from EMA
1	05 April 2022	8. RESEARCH QUESTION AND OBJECTIVES	Added stratification by vaccine dose received (e.g., first, second, third, and booster doses) to the secondary study objective	Request from CBER
1	05 April 2022	9.2.2.2. Risk factors for myocarditis and pericarditis (secondary objective)	Removed the exclusion criterion, "Have had a medical visit or a hospital visit in the 7 days before matching time zero (as an indicator of a health event not related to subsequent vaccination that could reduce the probability of receiving the vaccine)."	To align with request from EMA for the parent study (i.e., study C4591021)
1	05 April 2022	9.3.1. Exposure to vaccines, 9.7.2.1. Identification of risk factors for myocarditis and for pericarditis	Specified risk windows of 1-14 days after each vaccine dose for the risk factors analysis and 1-7 days and 1-21 days for sensitivity analyses	Request from CBER
1	05 April 2022	9.3.1. Exposure to vaccines, 9.7.1.1Characterisation of myocarditis and pericarditis cases,	Added analysis stratified by vaccine dose received (e.g., first, second, third, and booster doses) to the natural history and risk factors analyses	Request from CBER

Amendment number	**Date**	**Section of protocol changed**	**Summary of amendment/update**	**Reason**
		9.7.1.2Natural history of myocarditis and pericarditis, 9.7.2.1. Identification of risk factors for myocarditis and for pericarditis		
1	05 April 2022	9.3.2 COVID-19	Modified definition of history of COVID-19 to be more specific	Request from CBER
1	05 April 2022	9.3.4.3Outcomes for myocarditis or pericarditis	Added definition for recovery from myocarditis and pericarditis	Request from CBER
1	05 April 2022	9.3.5.1 Demographics	Modified age categories	To align with age groups as authorized and prioritized during vaccine rollout, and in anticipation of future indications of the vaccine in children younger than 16 years old
1	05 April 2022	General	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent throughout protocol

6. MILESTONES

Milestone	**Planned Date**	**Actual**
Protocol endorsement by EMA		31 May 2022
Registration in the EU PAS Register	To be registered before the start of data collection	22 August 2022
Start of data collection[1]	31 December 2022	10 February 2023
Interim report	30 September 2023	30 September 2023
End of data collection[2]	31 March 2025	31 March 2025
Final study report	30 June 2025	N/A

EMA = European Medicines Agency; EU PAS Register = European Union Electronic Register of Post-Authorisation Studies. N/A= Not Available

1 The start of data collection is defined as the planned date for starting data extraction for the purposes of the primary analysis.

2 The end of data collection is defined as the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

7. RATIONALE AND BACKGROUND

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), has resulted in a global pandemic. The Pfizer-BioNTech COVID-19 vaccine Comirnaty® (tozinameran), a novel mRNA-based vaccine, has been authorised for use in several countries, including those in the European Union (EU), for the prevention of COVID-19. Because of the relatively short prelicensure period and limited number of participants in clinical studies, efficient and timely monitoring of the safety of the vaccine will be needed in European countries.

The safety of the Pfizer-BioNTech COVID-19 vaccine has been investigated in clinical studies conducted in the United States (US), Europe, Turkey, South Africa, and South America and included over 43,000 patients aged 16 years or older. The overall safety profile of the vaccine was found to be favourable in the trial setting[2]. On 27 May 2021, the Centers for Disease Control and Prevention (CDC) in the US issued a statement indicating a possible link between vaccination to prevent COVID-19 and myocarditis for both the Pfizer-BioNTech COVID-19 vaccine and the mRNA-1273 vaccine produced by Moderna[3]. Researchers in Israel reported a 3-fold increased risk of myocarditis within 42 days of receiving the vaccination (hazard ratio, 3.24; 95% confidence interval [CI], 1.55 to 12.44), compared with the risk among unexposed persons. Myocarditis events were mostly concentrated among young male patients[2].

Among individuals in a large Israeli healthcare system who had received at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine, the estimated incidence of myocarditis within 42 days after receiving the first dose was 2.13 cases per 100,000 persons; the highest incidence was among males between the ages of 16 and 29 years, and most cases of myocarditis were mild or moderate in severity[4].

In another study conducted in Israel, the incidence of definite or probable cases of myocarditis (as defined by the Cochrane Collaboration), although low, increased after receipt of the Pfizer-BioNTech COVID-19 vaccine, particularly after the second dose, among young male recipients. The clinical presentation of myocarditis after vaccination was usually mild[5].

EMA's safety committee (Pharmacovigilance Risk Assessment Committee [PRAC]) has assessed recent data on the known risk of myocarditis and pericarditis following vaccination with COVID-19 vaccines Comirnaty and Spikevax (i.e., trade names for the Pfizer-BioNTech and Moderna COVID-19 vaccines, respectively). The outcome of the review confirms the risk of myocarditis and pericarditis, which is already reflected in the product information for these 2 vaccines[6].

To further examine the risk of myocarditis and pericarditis following the Pfizer-BioNTech COVID-19 vaccine, Pfizer and Vaccine monitoring Collaboration for Europe (VAC4EU) are conducting a study among individuals across 5 European countries. This study is nested in an ongoing active surveillance study (EUPAS41623) that estimates incidence rates of prespecified adverse events of special interest (AESIs), including myocarditis and pericarditis, among individuals who receive at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals who receive no COVID-19 vaccine.

This non-interventional study (NIS) is designated as a post-authorisation safety study (PASS) and is a commitment to the European Medicines Agency (EMA) and a post-marketing requirement by FDA.

8. RESEARCH QUESTION AND OBJECTIVES

The research question addressed by this study is, "What is the clinical course of myocarditis and of pericarditis cases after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine in European countries?"

Primary study objective:

- To describe the clinical course (treatment, survival, hospitalisations, long-term cardiac outcomes) of myocarditis or pericarditis among individuals diagnosed with myocarditis and/or pericarditis after receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine and among individuals diagnosed with myocarditis and/or pericarditis who had no prior COVID-19 vaccination, using a cohort study design.

Secondary study objective

- To examine and identify potential risk factors for myocarditis and pericarditis, such as age, sex, Pfizer-BioNTech COVID-19 vaccination status, vaccine doses received (e.g., first, second, third, and booster doses), and history of COVID-19, using a cohort study design

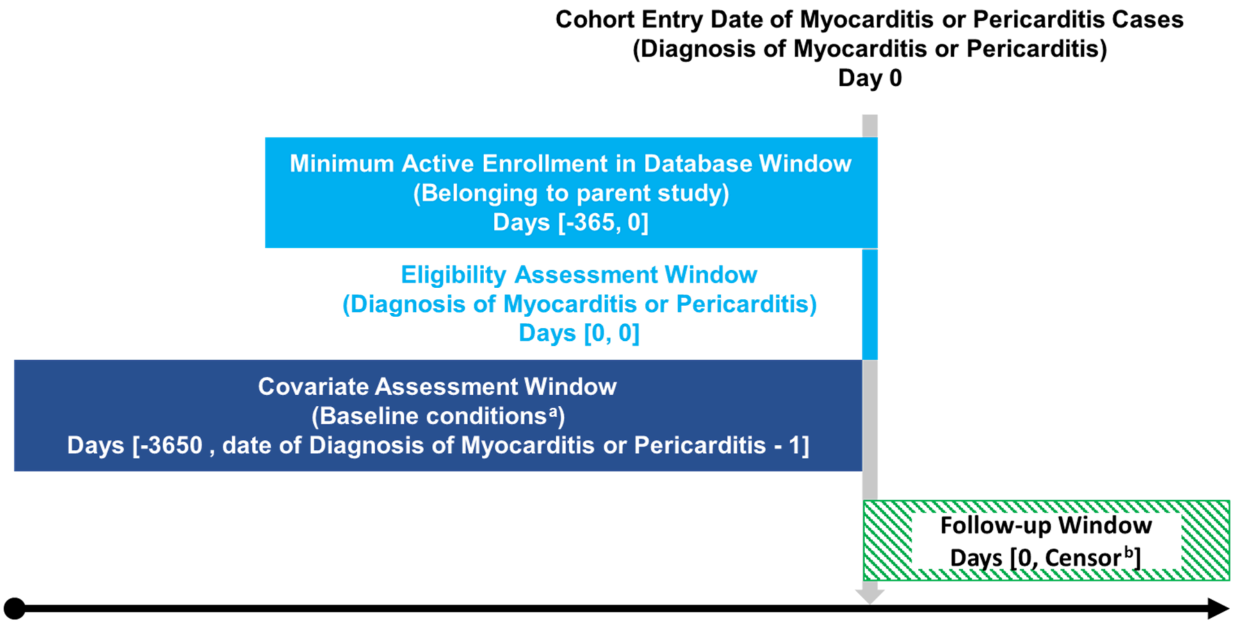
9. RESEARCH METHODS

9.1. Study design

This cohort study is nested in the ongoing retrospective cohort study (EUPAS41623) titled *Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine*. The parent study includes individuals across 5 European countries who receive at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine, as well as individuals who did not receive a COVID-19 vaccine.

For the **primary objective (natural history)**, the study will be conducted in the cohort of cases of myocarditis and of pericarditis identified in the full population of the parent study (Figure 1). The natural history of disease after such diagnoses will be described, both in individuals with prior Pfizer-BioNTech COVID19 vaccination and in individuals without any COVID-19 vaccination.

Figure 1. Assessment of covariates and follow-up windows for the primary objective (natural history)

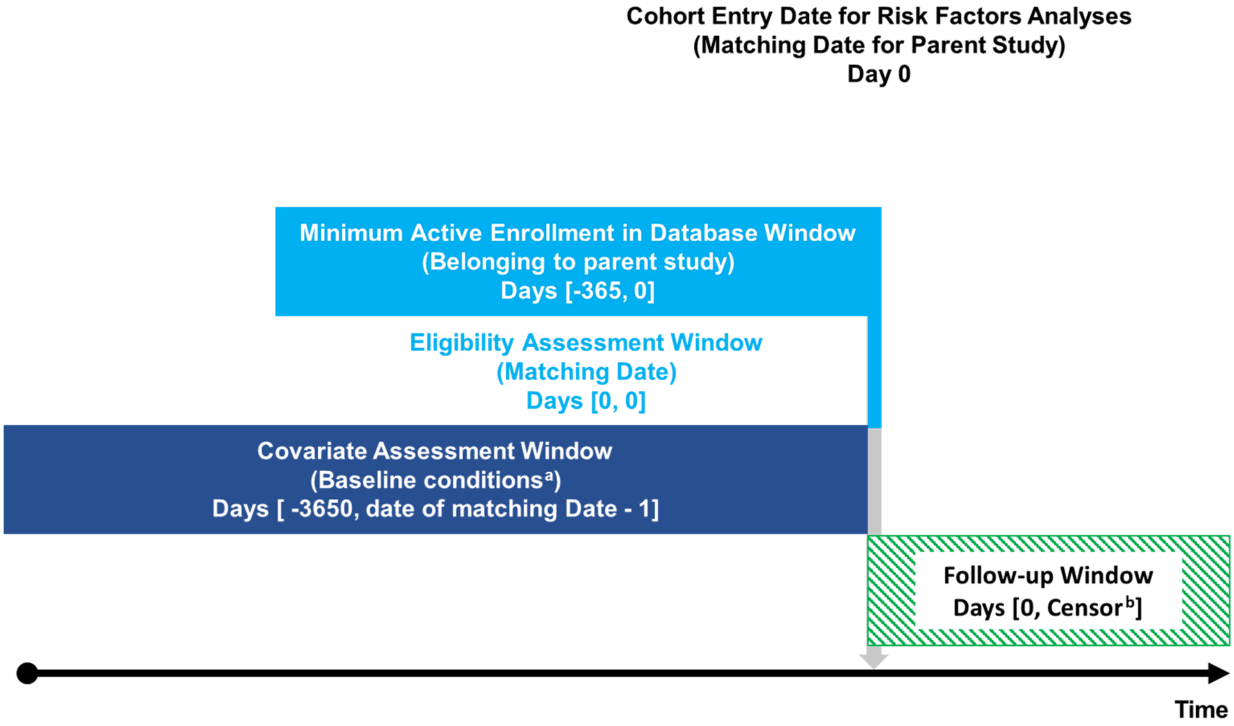


a. Baseline covariates will be assessed at the time of vaccination (or the corresponding matched date in unvaccinated individuals), or at the date of diagnosis of myocarditis/pericarditis if they are time varying or the myocarditis/pericarditis occurs in a non-matched individual.

b. Follow-up will be censored at the earliest of the following events: death, disenrollment from the data source, or end of the study period.

In the parent study component comparing risk of AESIs in individuals with Pfizer-BioNTech COVID-19 vaccination and in unvaccinated individuals, the 2 groups are matched 1:1 on date of vaccination in the vaccinated group and date of study eligibility in the unvaccinated group. Individuals are also matched on age, sex, history of COVID-19, place of residence, history of influenza vaccination, pregnancy status, immunocompromised status, presence of pre-existing medical conditions, and socioeconomic status/education level. This matched population constitutes the cohort in which **risk factors** for myocarditis and pericarditis will be evaluated (**secondary objective**) (Figure 2). The matching variables, vaccination status, and other baseline variables to be identified in a review of the medical literature will be considered as potential risk factors for the development of myocarditis and of pericarditis. For the secondary objective, the study cohort will include all individuals in the parent study matched comparative cohort.

Figure 2. Assessment of covariates and follow-up windows for the secondary objective (risk factors)



a. Baseline covariates are extracted at the date of matching in the parent study (i.e., the date of vaccination of the vaccinated component of the pair).

b. Follow-up will be censored at the earliest of the following events: death, disenrollment from the data source, end of the study period, receipt of a non–Pfizer-BioNTech COVID-19 vaccine or the unvaccinated member of the pair is vaccinated with the Pfizer-BioNTech COVID-19 (both the unvaccinated and vaccinated individuals of the pair will be censored).

9.2. Setting

For the implementation of this study, electronic healthcare databases in Europe will be used. The selected data sources and two-letter country codes are as follows:

- Pedianet (IT)
- PHARMO Institute for Drug Outcomes Research (PHARMO) (NL)
- The Norwegian Health Registers (NHR) (NO)
- EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron) (ES)
- Sistema d’Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP) [Information System for the Development of Primary Care Research] (ES)

- Clinical Practice Research Datalink (CPRD) (UK)

9.2.1. Inclusion criteria

9.2.1.1. Natural history of disease (primary objective)

Individuals must meet the following inclusion criteria to be eligible for inclusion in the cohort for the primary objective:

- Have a minimum of 12 months (or from birth if enrolled in the data source at birth) of active enrolment and history in one of the selected data sources to ensure adequate characterisation of medical history; this criterion may be met after the start of the study period.

- Have experienced an event of myocarditis or pericarditis. Cases will be classified as definitive, probable, or possible according to the case definition and classification of the Brighton Collaboration[1] and will be selected for cohort entry at the time of diagnosis.

9.2.1.2. Risk factors for myocarditis and pericarditis (secondary objective)

Individuals must meet the following inclusion criteria to be eligible for inclusion in the cohort for the secondary objective:

- Have a minimum of 12 months (or from birth if enrolled in the data source at birth) of active enrolment and history in one of the selected data sources to ensure adequate characterisation of medical history; this criterion may be met after the start of the study period.

- Have been included in the parent study matched comparative cohort. Individuals receiving at least 1 dose of the Pfizer-BioNTech COVID-19 vaccine (vaccinated group) and matched individuals not receiving any COVID-19 vaccine (unvaccinated group).

9.2.2. Exclusion criteria

9.2.2.1. Natural history of disease (primary objective)

Individuals meeting any of the following criteria will not be included in the cohort for the primary objective:

- History of vaccination with a non–Pfizer-BioNTech COVID-19 vaccine before time zero

9.2.2.2. Risk factors for myocarditis and pericarditis (secondary objective)

Individuals meeting any of the following criteria will not be included in the cohort for the secondary objective:

- History of vaccination with a non–Pfizer-BioNTech COVID-19 vaccine before time zero.

9.2.3. Study period

The study period starts on the date of conditional approval of the Pfizer-BioNTech COVID-19 vaccine in each country: 01 December 2020 in UK and 21 December 2020 in NL, IT, ES, and NO (see Table 1). The study period, i.e., the data collection period, will end on 31 March 2025.

Table 1. Summary of vaccine launch and data availability dates

Data source	Vaccine launch date	Data availability end date	
		Interim report 1	Final report
PEDIANET	31 May 2021 (for children aged 12-17)	31 August 2022	31 March 2025
PHARMO	05 January 2021	30 June 2022	31 March 2025
The Norwegian Health Registries (NHR)	27 December 2020	31 December 2021	31 March 2025
EpiChron	27 December 2020	31 July 2022	31 March 2025
SIDIAP	27 December 2020	30 June 2022	31 March 2025
CPRD	02 December 2020	21 March 2022	31 March 2025

9.2.4. Follow-up

9.2.4.1. Natural history of disease (primary objective)

Individuals will be followed from the diagnosis of myocarditis or pericarditis until the earliest occurrence of death, disenrollment from the data source, or end of the study period.

9.2.4.2. Risk factors for myocarditis and pericarditis (secondary objective)

Individuals in the matched cohort of the parent study will be followed from the date of matching (i.e., the date of vaccination for those in the vaccinated group and a matched calendar date in the unvaccinated group) until the earliest occurrence of the following:

- Diagnosis of myocarditis or pericarditis
- Death
- Administrative end of follow-up
- Receipt of a non–Pfizer-BioNTech COVID-19 vaccine
- Unvaccinated member of the pair is vaccinated with the Pfizer-BioNTech COVID-19 (both the unvaccinated and vaccinated individuals of the pair will be censored).

9.3. Variables

9.3.1. Exposure to vaccines

Exposure will be based on recorded prescription, dispensing, or administration of the Pfizer-BioNTech COVID-19 vaccine. Vaccine receipt and date of vaccination will be obtained from all possible sources that capture COVID-19 vaccination, such as pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Depending on the data source, vaccines may be identified via nationally used product codes—including batch numbers—where possible. Vaccination status will be used to define subgroups as well as potential risk factors.

Vaccination categories will be mutually exclusive. For the primary objective (clinical course description of myocarditis and pericarditis), individuals will be classified into vaccination categories at myocarditis/pericarditis diagnosis. For the secondary objective (identification of potential risk factors for myocarditis and pericarditis), person-time (not individuals) will be classified into the vaccination categories. The vaccination categories are as follows:

- Unvaccinated
- Received dose number *n* in the last 14 days
- Received dose number *n* 15 or more days ago

where *n* goes from 1 to the maximum number of Pfizer-BioNTech COVID-19 Vaccine approved doses for administration in the study population during the study period. For example, if *n*=3, the number of vaccination categories would be 7. The number of doses includes the initial primary dose series (e.g., 2 doses for the general population and 3 doses for immunocompromised individuals) as well as any booster doses.

In sensitivity analyses, the following alternative categories will be used:

- Sensitivity analysis 1:
  - Unvaccinated
  - Received dose number *n* in the last 7 days
  - Received dose number *n* 8 or more days ago
- Sensitivity analysis 2:
  - Unvaccinated
  - Received dose number *n* in the last 21 days
  - Received dose number *n* 22 or more days ago

Pedianet (IT): Information on COVID-19 vaccine will include date of immunisation, type of vaccine, vaccine batch, and dose. Information will be collected by the paediatrician at each contact with the patient.

PHARMO (NL): Data on vaccination will be included in PHARMO's General Practitioner database. Information on vaccines includes Anatomical Therapeutic Chemical (ATC) code, brand, batch, and date of application.**Norwegian health registers (NO)**: The national, electronic Norwegian Immunisation Registry (SYSVAK) was established in 1995 and records an individual's vaccination status and vaccination coverage in Norway. All vaccinations are subject to notification to SYSVAK and are registered without obtaining patient consent. This applies to all COVID-19 vaccines. In SYSVAK, the following data are registered: individual personal identifier, vaccine name and ATC code, vaccine batch number, date of vaccination, reason for vaccination as health care professional versus risk-group patient, and the centre where the vaccine was administered.

EpiChron – Aragon data sources (ES): The Aragon health system (Aragon, Spain) has implemented a specific vaccination register embedded in the EHR (electronic health record) system. The COVID-19 vaccine is being systematically registered in this register by healthcare professionals. This register can collect all the relevant information regarding the vaccination process, such as patient identifier; date of administration and due date for next dose, if applicable; centre of administration; part of the body where vaccine is administered; name of the vaccine; brand (laboratory); batch number; dose; and vaccination criterion (i.e., risk group to which the patient belongs). There is also a free-text section in which health professionals can include their observations (e.g., presence or absence of an allergic reaction).

SIDIAP (ES): For all 5.8 million individuals of the Catalan Institute of Health–Primary Care teams, SIDIAP will have available information on the administration of COVID-19 vaccines to individuals linked to a unique and anonymous identifier. The information will be originated from the EHR. For each patient, SIDIAP will have date and centre of administration, health professional administering the vaccine, dose, brand, reasons for vaccination (e.g., risk of group), and other information related to vaccination. As the Pfizer-BioNTech COVID-19 vaccine is indicated as a 2-dose vaccine series, multiple vaccinations per person will be identified.

CPRD (UK): The CPRD contains information recorded by National Health Service (NHS) primary care general practitioners (GPs); and information on the administration of COVID-19 vaccines to individuals will be available. This will include, alongside an encrypted unique patient identifier, the name of the vaccine; manufacturing company; dose; stage of the vaccine schedule; administration route; administration location (e.g., general practice); batch identifiers/numbers; date of administration; and medical observations, events, referrals, test results, and prescribed medications recorded by the GP prior to, on, or after the vaccination date. Free-text medical notes may also be available if recorded; however, this is dependent on patient anonymity being maintained. In addition, patient demographic, practice-level, and staff-level information is also available.

Furthermore, other CPRD-linked COVID-19 data sets that may provide further follow-up information on AESIs include the Public Health England (PHE) Second Generation Surveillance System (SGSS) COVID-19 positive virology test data, PHE COVID-19 Hospitalisation in England Surveillance System (CHESS), and the Intensive Care National Audit and Research Centre (ICNARC) data on COVID-19 intensive care admissions. Standard CPRD-linked data sets can also be obtained including Hospital Episode Statistics (HES) data sets covering hospital secondary care (Accident & Emergency, Admitted Patient Care, Inpatient and Outpatient), Office for National Statistics (ONS) data sets for Death Registry information, mother-baby link, and an algorithm-based Pregnancy Register.

9.3.2. COVID-19

- History of COVID-19 will be defined at any time prior to time zero as follows (will be used to define a subgroup of interest):
  - Previous diagnosis of COVID-19 (yes/no); OR
  - Positive test result for COVID-19 (yes/no) based on polymerase chain reaction (PCR) or antigen test as available in each data source.

9.3.3. Myocarditis and pericarditis

Myocarditis and pericarditis serve as eligibility criteria for the cohort to study the primary objective and as study outcomes for the cohort to examine the secondary objective. Myocarditis is inflammation of the heart muscle, and pericarditis is inflammation of the outer lining of the heart. In both cases, the body's immune system causes inflammation in response to an infection or some other trigger. These conditions can occur simultaneously or alone.

9.3.3.1. Identification and validation of myocarditis and pericarditis, by data source

Myocarditis and pericarditis will be identified based on patient profile review of EHRs by health care professionals. In addition, if considered necessary in a future evaluation of results, manual review of patient charts conducted by clinicians blinded to COVID-19 vaccine exposure will be performed when possible and will be based on data source structure.

Standard algorithms for myocarditis and for pericarditis to identify potential cases will be applied to the data sources based on the results of the vACCine covid-19 monitoring readinESS (ACCESS[7] project. ACCESS was a project funded by the EMA to prepare a European infrastructure to monitor COVID-19 vaccines. Algorithms will be tailored to each data source and will consider the nature of the records that have identified the outcome, e.g., primary care, access to hospital care, access to emergency care[8]. Multiple algorithms for the same outcome may be included in the analysis to assess the potential impact of differential misclassification.

In Pedianet, EpiChron and PHARMO, all cases of myocarditis and pericarditis will be validated.

In NHR, SIDIAP and CPRD the number of potential cases originally identified is large and there are insufficient resources (e.g. clinical reviewers) to validate all the cases, therefore a sample will be used for validation.

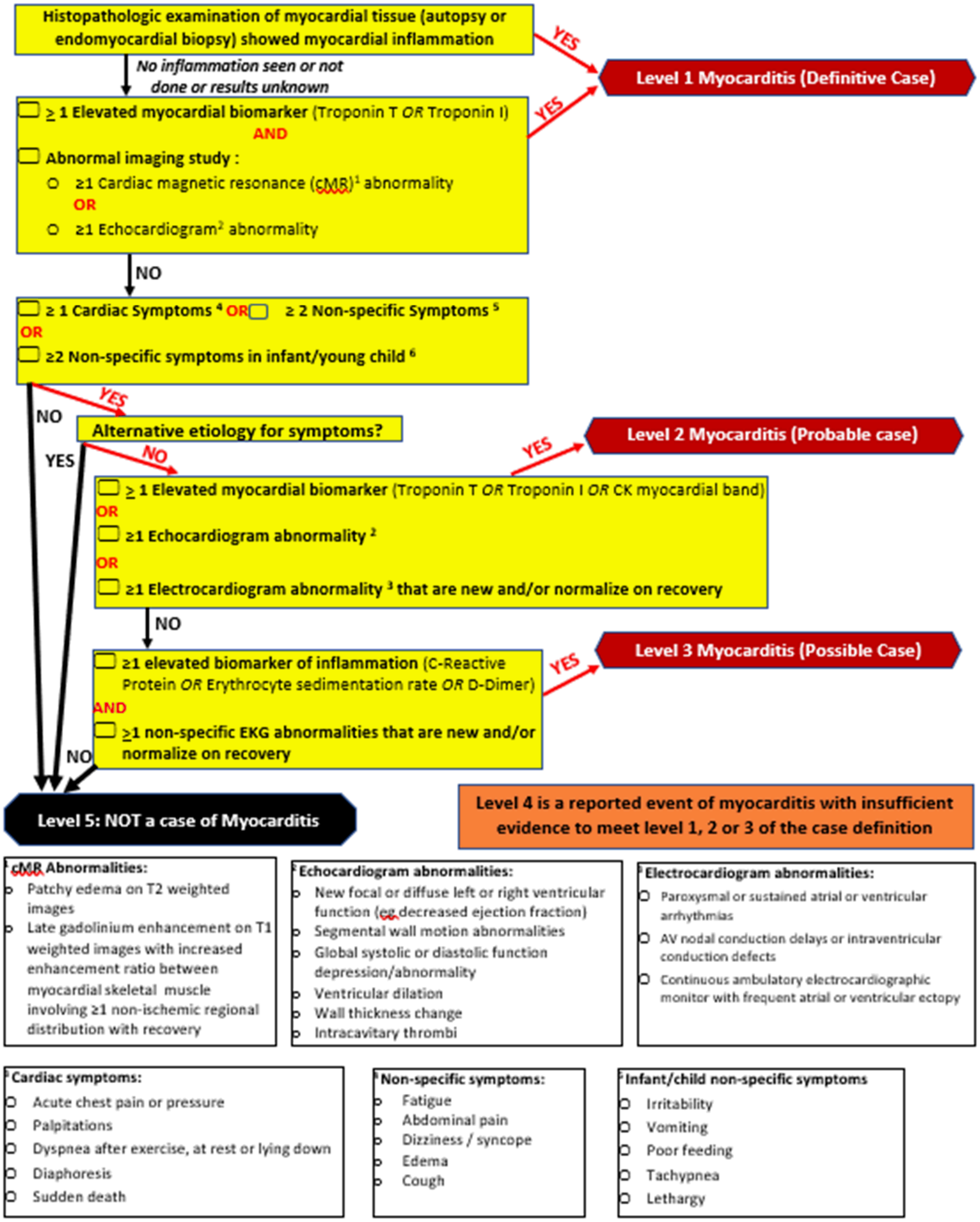
All cases of myocarditis and pericarditis events occurring within the first 21 days after T0 (for dose 1, dose 2, and dose 3) will be prioritized and selected for validation.

In NHR, SIDIAP and CPRD, a random selection of additional cases of myocarditis and pericarditis will be obtained and validated in order to reach a total of 300 cases of each diagnosis (myocarditis and pericarditis) in each data source, which includes the already validated cases described above.

For classification and validation of the cases, different procedures will be applied in different databases, as described below. The potential cases of myocarditis or pericarditis will be validated against information available for each data source. The validation process will be based on the review of the individuals' medical records by clinicians from the research team who will be blinded to COVID-19 vaccination status. The diagnostic criteria for myocarditis and for pericarditis to classify potential cases and the degree of certainty of diagnosis will be adapted from the case definition and classification of the Brighton Collaboration[1]. Cardiac symptoms for myocarditis and pericarditis are acute chest pain or pressure; dyspnoea after exercise, at rest, or lying down; fatigue; diaphoresis; and sudden death. Other non-specific symptoms in adults are palpitations, abdominal pain, dizziness, syncope and cardiogenic shock, fatigue, oedema, and cough. In infants or young children, symptoms include irritability, vomiting, poor feeding, and sweating. The detection of these signs and symptoms during the validation process will be used to determine levels of certainty of the diagnosis. Cases will be classified as definitive, probable, possible, having insufficient data, or having an alternative diagnosis. Cases of pericarditis with myocarditis will be included among these cases if they occurred alone or at the same time. For pictorial definitions to identify cases, see Figure 3 (myocarditis) and Figure 4 (pericarditis).

To assess robustness, the analyses for the secondary objective will be repeated in a sensitivity analysis considering as cases of myocarditis or pericarditis only those meeting the Brighton Collaboration classification of “definitive” [2] .

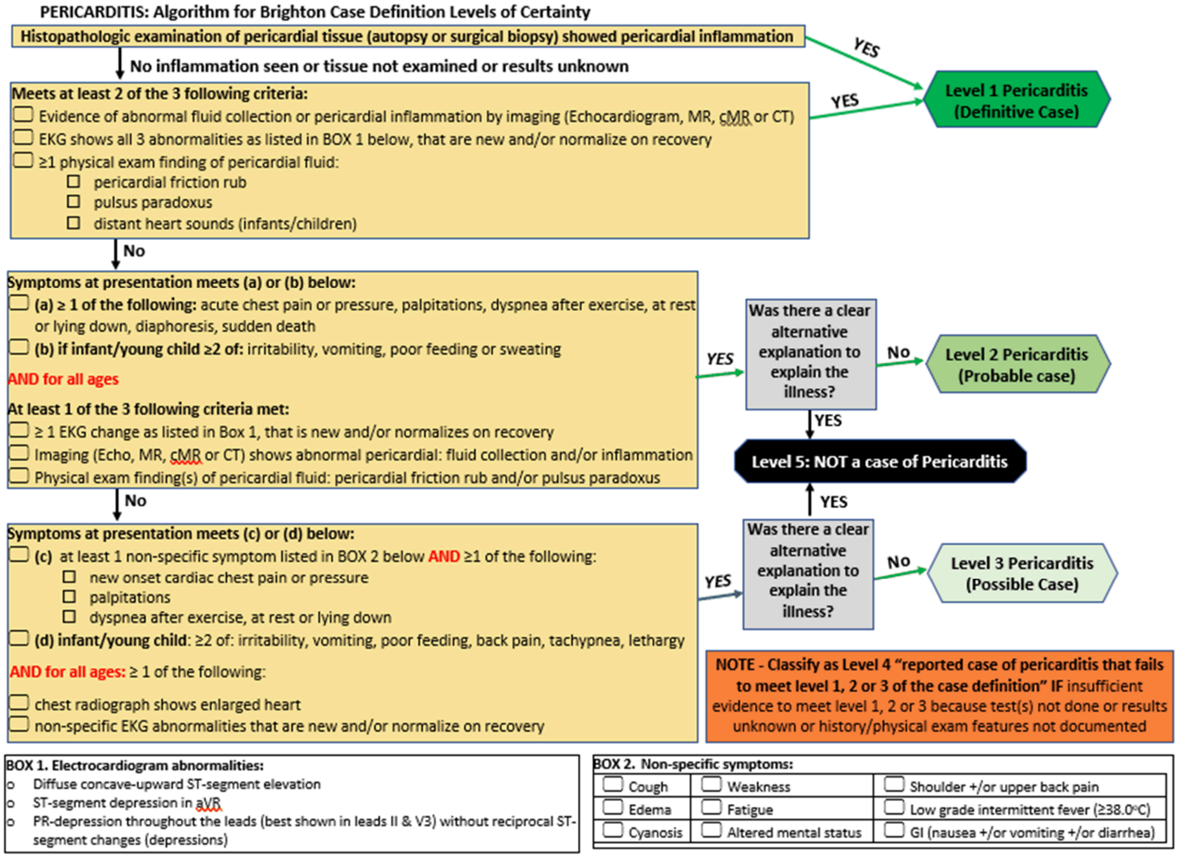
Figure 3. Identification of myocarditis



AV = atrioventricular; CK = creatine kinase; cMR = cardiac magnetic resonance [imaging]; EKG = electrocardiogram.

Note: The Brighton Case Definition for Myocarditis and Pericarditis was submitted to *Vaccine* on 19 November 2021.

Figure 4. Identification of pericarditis



PERICARDITIS: Algorithm for Brighton Case Definition Levels of Certainty

Histopathologic examination of pericardial tissue (autopsy or surgical biopsy) showed pericardial inflammation

No inflammation seen or tissue not examined or results unknown

Meets at least 2 of the 3 following criteria:
- ☐ Evidence of abnormal fluid collection or pericardial inflammation by imaging (Echocardiogram, MR, cMR or CT)
- ☐ EKG shows all 3 abnormalities as listed in BOX 1 below, that are new and/or normalize on recovery
- ☐ ≥1 physical exam finding of pericardial fluid:
  - ☐ pericardial friction rub
  - ☐ pulsus paradoxus
  - ☐ distant heart sounds (infants/children)

Level 1 Pericarditis (Definitive Case)

Symptoms at presentation meets (a) or (b) below:
- ☐ **(a) ≥ 1 of the following:** acute chest pain or pressure, palpitations, dyspnea after exercise, at rest or lying down, diaphoresis, sudden death
- ☐ **(b) if infant/young child ≥2 of:** irritability, vomiting, poor feeding or sweating

AND for all ages

At least 1 of the 3 following criteria met:
- ☐ ≥ 1 EKG change as listed in Box 1, that is new and/or normalizes on recovery
- ☐ Imaging (Echo, MR, cMR or CT) shows abnormal pericardial: fluid collection and/or inflammation
- ☐ Physical exam finding(s) of pericardial fluid: pericardial friction rub and/or pulsus paradoxus

Was there a clear alternative explanation to explain the illness?

Level 2 Pericarditis (Probable case)

Level 5: NOT a case of Pericarditis

Symptoms at presentation meets (c) or (d) below:
- ☐ **(c)** at least 1 non-specific symptom listed in BOX 2 below **AND** ≥1 of the following:
  - ☐ new onset cardiac chest pain or pressure
  - ☐ palpitations
  - ☐ dyspnea after exercise, at rest or lying down
- ☐ **(d) infant/young child**: ≥2 of: irritability, vomiting, poor feeding, back pain, tachypnea, lethargy

AND for all ages: ≥ 1 of the following:
- ☐ chest radiograph shows enlarged heart
- ☐ non-specific EKG abnormalities that are new and/or normalize on recovery

Was there a clear alternative explanation to explain the illness?

Level 3 Pericarditis (Possible Case)

NOTE - Classify as Level 4 "reported case of pericarditis that fails to meet level 1, 2 or 3 of the case definition" IF insufficient evidence to meet level 1, 2 or 3 because test(s) not done or results unknown or history/physical exam features not documented

BOX 1. Electrocardiogram abnormalities:
- Diffuse concave-upward ST-segment elevation
- ST-segment depression in aVR
- PR-depression throughout the leads (best shown in leads II & V3) without reciprocal ST-segment changes (depressions)

BOX 2. Non-specific symptoms:

☐ Cough	☐ Weakness	☐ Shoulder +/or upper back pain
☐ Edema	☐ Fatigue	☐ Low grade intermittent fever (≥38.0°C)
☐ Cyanosis	☐ Altered mental status	☐ GI (nausea +/or vomiting +/or diarrhea)

cMR = cardiac magnetic resonance [imaging]; CT = computed tomography; Echo = echocardiogram; EKG = electrocardiogram; GI = gastrointestinal; MR = magnetic resonance [imaging].

Note: The Brighton Case Definition for Myocarditis and Pericarditis was submitted to *Vaccine* on 19 November 2021.

Pedianet (IT): A validation mechanism including individual linkage with the electronic regional immunisation register will be in place. Furthermore, the validation process includes review by clinicians from the research team of the individual electronic medical records, which contain information from primary care reports. Clinicians are blinded to COVID-19 vaccination status.

PHARMO (NL): For the validation study, information on myocarditis and pericarditis will be derived from a patient profile of compiled, deidentified GP electronic health record data, and hospital diagnostic code data, blinded to COVID-19 vaccination status. Validation will be conducted by local medical professionals or PHARMO employees, provided approval by ethics committees and other local and/or national governing bodies.

NHR (NO): In Norway, the validation process will be based on the manual review of hospital charts by clinicians from the research team a subsample of individuals with the adverse event of interest, compared with registered diagnoses in the Patient Registry of

Norway. Clinicians are blinded to COVID-19 vaccination status. Results from validation studies are already available for selected health outcomes (e.g., intracranial haemorrhage, hip fractures, cancer). Depending on the AESI, validation will be possible by comparing the registered diagnoses in two separate registers (e.g., the Norwegian Patient Registry and the Norwegian Stroke Register).

EpiChron (ES): In Aragon (EpiChron) data sources, the proposed validation process is based on the review of the individuals' EHRs by clinicians from the research team who will be blinded to COVID-19 vaccination status. These records include information from primary care reports, hospital discharge reports (including hospital emergency rooms), and results of diagnostic tests and laboratory tests.

SIDIAP (ES): In SIDIAP, the validation process is part of data quality control (QC). Validation will be based on the review of the EHR information (ECAP) by clinicians from the research team who will be blinded to COVID-19 vaccination status.

CPRD (UK): In the United Kingdom (UK), validation will be conducted by review of EHR information for myocarditis and pericarditis by adjudicators who will be blinded to COVID-19 vaccination status.

9.3.4. Natural history of disease (primary objective)

Potential **outcomes for myocarditis** that will be evaluated are recovery, survival, hospitalisations, sudden cardiac death, heart failure, cardiogenic shock, fulminant myocarditis, inflammatory cardiomyopathy, heart transplant, and arrhythmia.

Potential **outcomes for pericarditis** that will be evaluated are recovery, survival, hospitalisations, and chronic, restrictive, and recurrent pericarditis.

The following variables will be assessed after the diagnosis of myocarditis/pericarditis.

9.3.4.1. Treatments for myocarditis

- Drugs for the condition (viral or autoimmune): paracetamol, antivirals, antibiotics, immunosuppressant agents
- Heart failure therapy (i.e., beta-blockers, diuretics, angiotensin-converting enzyme [ACE] inhibitors or angiotensin-II receptor blockers [ARBs], aldosterone antagonists, cardiac glycosides or calcium-channel blockers, anti-arrhythmics)
- Procedures (i.e., pacemaker, implantable cardiac defibrillator, mechanical circulatory support, and heart transplantation)

9.3.4.2. Treatments for pericarditis

- Antimicrobial treatment

- Anti-inflammatory treatment (non-steroidal anti-inflammatory drugs [NSAIDs] and colchicine [for recurrent pericarditis])
- Procedures (i.e., intrapericardial administration of steroids, pericardioscopy for direct instillation of treatments into the pericardial space, pericardial drainage; subdiaphragmatic laparoscopic technique, video-assisted thoracoscopic technique, and pericardioscopy for easy drainage of effusion; pericardiocentesis; cardiac catheterisation during pericardiocentesis; balloon pericardial window formation; instillation of sclerosing agents and fibrinolytic agents; and pericardiectomy)

9.3.4.3. Outcomes for myocarditis or pericarditis

- Hospitalisation
- Death
- Recovery: Recovery from myocarditis and pericarditis will be determined by a clinician after adjudication of the patient's medical records. Factors that will be considered in the determination include discharge from a hospital with a recovery outcome indicated in the discharge notes, resolution of signs/symptoms, discontinuation of therapy with anti-inflammatory medications, and normalised values of tests. Tests to be evaluated by the clinical adjudicator include the following: troponin normalised; cardiac magnetic resonance imaging; computed tomography; echocardiogram; and electrocardiogram. These measures will be further described and defined in the adjudication charter and/or the statistical analysis plan (SAP).
- Sudden cardiac death
- Heart failure
- Cardiogenic shock
- Fulminant myocarditis
- Chronic myocarditis
- Inflammatory cardiomyopathy
- Heart transplant
- Arrhythmia
- Chronic pericarditis
- Constrictive pericarditis

- Recurrent pericarditis

9.3.5. Baseline covariates

The following variables will be assessed at the time of vaccination (or the corresponding matched date in unvaccinated individuals). For the primary objective, time-varying variables will also be assessed at the time of myocarditis or pericarditis diagnosis. In the primary objective, baseline covariates will be used for the characterisation of the individuals with myocarditis or pericarditis, and to define subgroups of interest. In the secondary objective, baseline covariates will be treated as potential risk factors for myocarditis or pericarditis.

9.3.5.1. Demographics

- Age at time zero (will be used to define subgroups for analyses)
    - Age will be categorised as age categories in line with published background incidence rates from the ACCESS project (0-17, 18-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-79, 80+ years). This will allow for comparison of incidence rates in this study with background rates.
    - The age group 0-17 years will additionally be divided into the following age groups, where feasible: 0-1, 2-4, 5-11, 12-15, and 16-17 years.
- Sex (will be used to define subgroups for analyses)
- Pregnancy status and pregnancy trimester at time zero
- Race and/or ethnicity, as appropriate in each country
- Geographic region, as appropriate in each country
- Socioeconomic status, as available in each country (including housing, employment, and income, if available)
- Residency in a long-term care facility
- Healthcare worker or essential worker status, if available
- Date of vaccination (categorised as appropriate, e.g., by year or month)

9.3.5.2. Personal lifestyle characteristics

- Smoking status (if available)
- Body mass index (if available)

9.3.5.3. Comorbidities

- History of anaphylaxis
- History of allergies
- Diabetes mellitus (types 1 and 2)
- Hypertension
- Cardiovascular disease
- Cerebrovascular disease
- Chronic respiratory disease
- Chronic kidney disease
- Chronic liver disease
- Cancer
- Autoimmune disorders
- Influenza infection or other respiratory infections
- Charlson Comorbidity Index (may be included as the composite scale, or the scale components may be included as individual terms)

9.3.5.4. Immunocompromising conditions

- Immunodeficiencies
- Immunosuppressant medication use
- Human immunodeficiency virus and other immunosuppressing conditions

9.3.5.5. Comedication use in past year

Prescriptions or dispensings during the year before time zero, not including over-the-counter medication use:

- Analgesics
- Antibiotics
- Antiviral medications

- Corticosteroids
- NSAIDs
- Psychotropics
- Statins
- Novel oral anticoagulants
- Warfarin

9.3.5.6. Healthcare utilisation in recent past

Healthcare utilisation in the year before time zero and in the 2 weeks before time zero:

- Number of hospitalisations
- Number of emergency department visits
- Skilled nursing facility, nursing home, or extended care facility stay
- Primary care utilisation
- Cancer screening
- Other preventive health services, as appropriate
- COVID-19 tests

9.3.5.7. Other vaccinations

- Influenza
- Pneumococcus
- DTP (diphtheria, tetanus, and pertussis)
- TPV (poliovirus vaccine)
- MMR (measles, mumps and rubella)
- Hib (Haemophilus influenzae type b)
- HBV (hepatitis B virus)
- VZV (varicella zoster virus)

- HZ (herpes zoster virus)
- HPV (human papillomavirus)
- Meningococcus
- Rotavirus

9.3.5.8. Surrogates of frailty

- Wheelchair use
- Home hospital bed
- Paralysis
- Parkinson’s disease
- Skin ulcer
- Weakness
- Stroke/brain injury
- Ambulance transport
- Dementia
- Difficulty walking
- Home oxygen
- Rehabilitation care
- Psychiatric illness
- Sepsis
- Heart failure
- Podiatric care
- Bladder incontinence
- Diabetes complications
- Arthritis

- Coagulation deficiencies
- Vertigo
- Lipid abnormalities

9.4. Data sources

The study will use data from secondary EHR databases that are population based (see Section 9.2). All data sources will have the ability to provide data on COVID-19 vaccines (product types and dates), outcomes (diagnoses, procedures, and treatments), and important covariates. The extent to which COVID-19 vaccines, product types, and batch numbers will be captured in data sources is not currently known.

Data availability for each institution might be affected by third parties or external circumstances that are independent from the institution involved in the study, as described in Section 9.9.

9.4.1. Pedianet (IT)

Pedianet, a paediatric general practice research database, was established in 2000. It contains reason for accessing health care, health status (according to the Guidelines of Health Supervision of the American Academy of Pediatrics), demographic data, diagnosis and clinical details (free text or coded using the ICD-9-CM [International Classification of Diseases, Ninth Revision, Clinical Modification]), prescriptions (pharmaceutical prescriptions identified by the ATC code), specialist appointments, diagnostic procedures, hospital admissions, growth parameters, and outcome data of the children routinely seen by approximately 140 family paediatricians distributed throughout Italy.

Pedianet can link to other databases using unique patient identifiers. In the first database, information on routine childhood vaccination is captured, including vaccine brand and dose. In the second database, information on patient hospitalisation date, reason for hospitalisation, days of hospitalisations, and discharge diagnosis (up to 6 diagnoses) is captured. The family paediatrician's participation in the database is voluntary, and individuals and their parents provide consent for use of their data for research purposes. In Italy, each child is assigned to a family paediatrician, who is the referral for any health visit or any drug prescription; thus, the database contains a very detailed personal medical history. The data, generated during routine practice care using common software (JuniorBit®), are anonymised and sent monthly to a centralised database in Padua, Italy, for validation. The Pedianet database can be linked to regional vaccination data, which was successfully tested in several large European projects (e.g., ADVANCE, GRIP, EMIF, EU Alliance), where it was characterised and deemed fit for purpose to evaluate prescriptions including paediatric routine vaccines[11].

Children aged younger than 12 years will likely start receiving the Pfizer-BioNTech COVID-19 vaccine soon. This vaccine is expected to be the first COVID-19 vaccine rolled out among children, and most children in Italy are likely to receive it. Most of these individuals will be captured in Pedianet, as it is expected that approximately 10,000 vaccinated children aged 12 to 14 years will have data available in Pedianet.

Pedianet acknowledge that the data sources to which they have access include data on vaccine delivery and registration and agree to cooperate on addressing the study objectives by contributing to and providing reports based on such data

9.4.2. PHARMO (NL)

The PHARMO Database Network, which is maintained by the PHARMO Institute for Drug Outcomes Research, is a population-based network of EHR databases that combines anonymous data from different primary and secondary health care settings in the Netherlands for an active population of about 2 million. These different data sources—including data from general practices, in- and outpatient pharmacies, clinical laboratories, hospitals, the cancer register, the pathology register, and the perinatal register—are linked on a patient level through validated algorithms. To ensure data privacy in the PHARMO Database Network, the collection, processing, linkage, and anonymisation of the data are performed by STIZON, which is an independent, ISO/IEC 27001-certified foundation that acts as a trusted third party between the data sources and the PHARMO Institute. The longitudinal nature of the PHARMO Database Network enables the follow-up of more than 9 million individuals of a well-defined population in the Netherlands for an average of 12 years. Currently, the PHARMO Database Network covers over 6 million active individuals out of 17 million inhabitants of the Netherlands[9]. Data collection period, catchment area, and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. All EHRs in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. Other available information depends on the data source. A detailed description of the different data sources is given in subsequent sections. The PHARMO Institute is always seeking new opportunities to link with health care databases. Furthermore, it is possible to link additional data collections, such as data from chart reviews, patient-reported outcomes, or general practice trials.

The General Practitioner database comprises data from EHRs registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and health care product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity, and route of administration. Drug prescriptions are coded according to the World Health Organization (WHO) ATC classification system [www.whocc.no]. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org], which can be mapped to International Classification of Diseases (ICD) codes but can also be entered as free text. General practitioner data cover a catchment area representing 3.2 million residents (~20% of the Dutch population).The GP Database contains vaccinations administered by GPs and by the public health service, as GPs receive an automated notification when a patient has a positive coronavirus test or has been vaccinated via the public health service (provided that individuals have given their consent).

The Dutch government wanted everyone 18 years of age or older to have had at least 1 COVID-19 vaccination by the beginning of July 2021. This vaccination schedule depended on many factors (e.g., approval and effectiveness; delivery and distribution of vaccines to injection sites, such as hospitals and GPs; new developments; and advice from, for instance, the Health Council of the Netherlands, i.e., de Gezondheidsraad).

The Netherlands Perinatal Registry is maintained by Perined and comprises data on pregnancies, births, and neonatal outcomes of births in the Netherlands; data are voluntarily collected by perinatal caregivers mainly for benchmarking. For research purposes, the data are linked with the PHARMO Database Network, resulting in the PHARMO Perinatal Research Network[10]. Records include information on mothers (e.g., maternal age, obstetric history, parity), pregnancy (e.g., mode of conception, mode of delivery), and children (e.g., birth weight, gestational age, Apgar score). Diagnoses and symptoms are coded according to the Perinatal Registry code lists (www.perined.nl).

Permission to obtain these data on a by-project basis is needed from PHARMO as well as from Perined.

PHARMO acknowledges that the data sources to which they have access include data on vaccine delivery and registration and agrees to cooperate on addressing the study objectives by contributing to and providing reports based on such data.

9.4.3. NHR (NO)

The Norwegian data sources included in this project, accessed through a partnership with the University of Oslo, are several national health registers, i.e., the Medical Birth Registry of Norway (MBRN), the National Patient Register (NPR), Norway Control and Payment of Health Reimbursement (KUHR), the Norwegian Immunisation Registry (SYSVAK), the Norwegian Prescription Database (NorPD), and Statistics Norway (SSB) that cover a population of about 5.6 million.

The source population will be identified using the Norwegian Institute of Public Health (NIPH) copy of the Norwegian population data file from the National Registry. The NPR and KUHR (and the MBRN for the pregnant population) provide data on inpatient and outpatient diagnostic codes. Information on population background data is derived from SSB (e.g., education, occupation status, sex, age). Data on vaccination status are derived from SYSVAK and the NorPD. The latter register includes data on filled prescriptions for possible comedications and other prescription drug use.

9.4.3.1. Norwegian Immunisation Registry

The SYSVAK is the national electronic immunisation register that records an individual's vaccination status and vaccination coverage in Norway. It became nationwide in 1995 and includes information such as personal identity number, the vaccine code, disease vaccinated against, and vaccination date.

9.4.3.2. The Norwegian Patient Registry

The NPR is an administrative database of records reported by all government-owned hospitals and outpatient clinics and by all private health clinics that receive governmental reimbursement. The NPR contains information on admission to hospitals and specialist health care on an individual level from 2008. The data include date of admission and discharge, as well as primary and secondary diagnosis. The NPR has included Norwegian national identification numbers since 2008. Consequently, person-specific data from 2008 onwards are available. Diagnostic codes in the NPR follow the International Classification of Diseases, 10th Revision (ICD-10).

9.4.3.3. Norway Control and Payment of Health Reimbursement

The KUHR is an administrative database based on electronically submitted reimbursement claims from physicians to the Norwegian Health Economics Administration (HELFO). It contains information from primary health care, GP, and emergency services on morbidity, utilisation of health care services, and health care use. Person-specific data are available for the years 2010 through 2018. Diagnostic codes in the KUHR follow ICD-10, but the ICPC is more frequently used by GPs.

9.4.3.4. The Norwegian Prescription Database

Since January 2004, all pharmacies in Norway have been obliged to send data electronically to the NIPH regarding all prescribed drugs dispensed to individuals in ambulatory care (irrespective of reimbursement). Relevant variables for this project include detailed information on drugs dispensed and date of dispensing.

9.4.3.5. The Medical Birth Registry of Norway

The MBRN is a population-based register containing information on all births in Norway since 1967 (more than 2.3 million births). The MBRN is based on mandatory notification of all births or late abortions occurring at 12 weeks of gestation or later. The MBRN includes identification of the mother and father, including national identification numbers, parental demographic information, the mother's health before and during pregnancy, complications during pregnancy and delivery, and length of pregnancy, as well as information on the infant, including congenital malformations and other perinatal outcomes.

9.4.3.6. Statistics Norway

Statistics Norway provides microdata for research projects and includes information on population characteristics, housing conditions, education, income, and welfare benefits. These data are potential important confounders.

9.4.3.7. The National Registry

The National Registry (Folkeregisteret) holds information about all inhabitants in Norway. The NIPH holds a copy of the Norwegian population data file from the National Registry that will be used to identify the source population in Norway.

9.4.3.8. Norwegian Surveillance System for Communicable Diseases

Notification of infectious diseases to the Norwegian Surveillance System for Communicable Diseases (MSIS) is an important part in the surveillance of infectious diseases in Norway. Microbiological laboratories analysing specimens from humans, and all doctors in Norway, are required by law to send notification of certain diseases (71 in total, including SARS-CoV-2) to the MSIS central unit at the NIPH. The following variables are available since 1977: notifiable disease, month and year of diagnosis, age groups, county of residence, and place of diagnosis of the infection. Data on positive COVID-19 tests are updated continuously.

The University of Oslo acknowledges that the data sources to which they have access (described above) include data on vaccine delivery and registration and agrees to cooperate on addressing the study objectives by contributing to and providing reports based on such data.

9.4.4. EpiChron (ES)

The Spanish National Health System is organised at a regional level. Aragon is one of the regions, with approximately 1.3 million inhabitants. The following Aragon data sources will be used in this project, covering approximately 98% of the reference population:

- The user database (BDU) with sociodemographic information
- Individuals' EHRs from primary care (OMI-AP) and hospital care (Minimum Basic Data Set, CMBD, with data on hospital discharges and PCH database with data on visits to the emergency room)
- Individuals' pharmacotherapeutic history with prescriptions and dispensation of drugs in community pharmacies (Receta Electrónica database) and hospitals (for hospitalised patients and outpatients)

9.4.4.1. Aragon COVID-19 Registry

Furthermore, additional databases and registers at the local (i.e., hospital or primary care health care centre) and national (e.g., Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària [BIFAP] database and its CIAP dictionary; SINASP) levels, as well as new potential databases or registers that could be developed for the vaccination process during the project, will be explored and used if appropriate. All the information contained in these data sources is linked at the patient level through a pseudonymisation process and then anonymised for research purposes. The group's researchers have broad experience in the use of these databases for research on chronic diseases and COVID-19. From the Aragon Health Department, the following key persons will be directly involved in the project: Antonio Poncel-Falcó, Maria Isabel Cano del Pozo, Cristina Navarro Pemán, Ana Cristina Bandrés Liso, Mercedes Aza Pascual Salcedo, and Francisca González Rubio. The group developed the EpiChron Cohort Study[12] for the analysis of the clinical epidemiology of chronic diseases, multimorbidity, and polypharmacy using real-world data from some of the aforementioned databases during the period 2010-2020; more than 30 scientific publications have resulted from this study. The group has also developed the PRECOVID study[13], for the demographic and clinical characterisation of all COVID-19 patients in the Aragon region and for identifying variables associated with increased mortality risk. Diagnoses are coded initially according to the ICPC or ICD and are subsequently grouped into diagnostic clusters, if needed, using open software (i.e., Clinical Classifications Software). Drug prescriptions and dispensations are coded according to the WHO ATC classification system. Once the aforementioned data sources have been gathered and linked at the patient level, data undergo continuous QC checks that ensure their accuracy and reliability for research purposes.

Information on pregnancy, pregnancy outcomes, and mother-baby linkage from women who give birth in at least the 2 most relevant public hospitals in the Aragon region in which approximately 70% of births in the region occur is expected to be available in the EpiChron database. Mother-baby linkage is possible using Neosoft software at the hospital level, at which all information about the mother and baby is recorded. This information will be supplemented with information from the mother’s EHRs.

EpiChron acknowledges that the data sources to which they have access include data on vaccine delivery and registration and agrees to cooperate on addressing the study objectives by contributing to and providing reports based on such data.

9.4.5. SIDIAP (ES)

The Information System for the Improvement of Research in Primary Care (Sistema d’Informació per al Desenvolupament de la Investigació en Atenció Primària’ [SIDIAP]) was created in 2010 by the Catalan Health Institute and the IDIAPJGol Institute. It includes information collected since 01 January 2006 during routine visits at 278 primary care centres pertaining to the Catalan Health Institute in Catalonia (northeastern Spain) with 3,414 participating GPs. SIDIAP has pseudonymised records for 8 million people (80% of the Catalan population) and is highly representative of the Catalan population.

The SIDIAP data comprise the clinical and referral events registered by primary care health professionals (e.g., GPs, paediatricians, and nurses) and administrative staff in EHRs, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. The SIDIAP data can 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, and blood and urine test results.

Regarding vaccinations, SIDIAP includes all routine childhood and adult immunisations, 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 the start of each year.. Currently, with the COVID-19 pandemic, there is a possibility to have more frequent 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.[11] Information on pregnancy, pregnancy outcomes, and mother-baby linkage will be available in the SIDIAP database.

SIDIAP acknowledges that the data sources to which they have access include data on vaccine delivery and registration and agrees to cooperate on addressing the study objectives by contributing to and providing reports based on such data.

9.4.6. CPRD (UK)

The CPRD from the UK collates the computerised medical records of GPs in the UK who act as the gatekeepers of health care and maintain individuals' life-long EHRs. Accordingly, GPs are responsible for primary health care and specialist referrals; they also store information about specialist referrals and hospitalisations. General practitioners 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 provide 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. Most of the data are coded using Read or SNOMED codes. Data validation with original records (specialist letters) is also available.

The data set is generalisable to the UK population based on age, sex, socioeconomic class, and national geographic coverage when CPRD General Practitioner Online Database (GOLD) and/or CPRD Aurum versions are used.

Currently, data on approximately 41.2 million individuals are acceptable for research purposes, 13.3 million of whom are active (i.e., still alive and registered with the GP practice), in over 1345 primary care practices (https://cprd.com/Data). Data include demographics, all GP/health care professional consultations (e.g., phone calls, letters, emails, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments (including all prescriptions), all data referrals to other care providers, hospital discharge summary (date and Read/SNOMED codes), hospital clinic summary, preventive treatment and immunisations, and death (date and cause).

For a portion of the CPRD panel practices (> 80%), the GPs have agreed to permit the CPRD to link at the patient level to HES data. The CPRD is listed under the ENCePP resource database, and access will be provided by the Drug Safety Research Unit (DSRU). The CPRD was not yet characterised in the ADVANCE project, for which the UK THIN and RCGP databases were used but has been extensively used in vaccine studies.

The HES database contains details of all admissions to NHS hospitals in England (Accident & Emergency, Admitted Patient Care, Outpatients); approximately 38.4 million individuals 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, if their GP has not agreed that their data may be used in this way). As with standard CPRD patients, HES data are limited to patients with research standard data. CPRD records are linked to HES using a combination of the patient's NHS number, sex, and date of birth.[14] Additional CPRD-linked data sets include Death Registration data from the ONS, which includes information on the official date and causes of death (using ICD codes), mother-baby link, and an algorithm-based Pregnancy Register.

The CPRD Aurum Pregnancy Register, which uses a probabilistic algorithm, based on data in the primary care medical records, is a linked data set available with the CPRD Aurum database. For patients identified in the CPRD Aurum database, the mother-baby link will soon be available. However, information on pregnancy status and pregnancy outcomes will also be available in CPRD Aurum as events reported by the GP in the primary care medical records, although not all pregnancies are reported to the GP in the UK.

The DSRU acknowledges that the CPRD data sources they have access to include data on vaccine delivery and registration and undertakes to cooperate on addressing the study objectives by contributing to providing reports based on such data.

9.5. Study size

The study will be conducted in a source population of 38.9 million individuals captured across the electronic healthcare data sources. Based on the risk estimates and their 95% CIs from Barda et al.[2], we expect to identify a range of approximately 400 to 1,100 cases of myocarditis for the primary objective.

The secondary objective is to examine and identify potential risk factors for myocarditis and pericarditis. As part of this analysis, measures of association in the form of risk ratios will be provided. These measures of association will be complemented with 95% CIs, which will convey the precision with which the measure of association is estimated.
In Table 2 through Table 5, we present the expected precision[15], in the form of the width of the 95% CI, for different scenarios of strength of the association between the risk factor and the outcome (in the form of risk ratios, which will equal odds ratios because of the rarity of the outcome), patients at risk, and risk of the event among those not having the risk factor. Each scenario table contains estimations for risk factors with varying prevalence in the study population. The standard errors yielded by the precision calculations[15] were increased by 10% to account for the additional variance introduced in multivariable modelling.

Table 2. Scenario A: Estimated precision of the strength of the association between a risk factor and myocarditis/pericarditis when the prevalence of the risk factor is 50% (e.g., COVID-19 vaccine)

14-day risk of event among those without the risk factor	RR	1 Million	5 Million	10 Million
		95% CI	95% CI	95% CI
1/1,000,000	1.5	(0.03 - 76.84)	(0.26 - 8.72)	(0.43 - 5.21)
	2.5	(0.07 - 92.20)	(0.50 - 12.55)	(0.80 - 7.82)
	5.0	(0.18 - 141.10)	(1.12 - 22.27)	(1.74 - 14.38)
10/1,000,000	1.5	(0.43 - 5.21)	(0.86 - 2.62)	(1.01 - 2.22)
	2.5	(0.80 - 7.82)	(1.50 - 4.16)	(1.74 - 3.59)
	5.0	(1.74 - 14.38)	(3.12 - 8.02)	(3.58 - 6.98)
100/1,000,000	1.5	(1.01 - 2.22)	(1.26 - 1.79)	(1.32 - 1.70)
	2.5	(1.74 - 3.59)	(2.13 - 2.94)	(2.23 - 2.80)
	5.0	(3.58 - 6.98)	(4.31 - 5.81)	(4.50 - 5.56)

CI: confidence interval; RR: risk ratio.

Table 3. Scenario B: Estimated precision of the strength of the association between a risk factor and myocarditis/pericarditis when the prevalence of the risk factor is 25% (e.g., hypertension)

14-day risk of event among those without the risk factor	RR	1 Million	5 Million	10 Million
		95% CI	95% CI	95% CI
1/1,000,000	1.5	(0.02 - 111.88)	(0.22 - 10.32)	(0.38 - 5.87)
	2.5	(0.06 - 100.37)	(0.48 - 13.04)	(0.78 - 8.04)
	5.0	(0.21 - 116.57)	(1.22 - 20.44)	(1.85 - 13.53)
10/1,000,000	1.5	(0.38 - 5.87)	(0.82 - 2.76)	(0.97 - 2.31)
	2.5	(0.78 - 8.04)	(1.48 - 4.21)	(1.73 - 3.62)
	5.0	(1.85 - 13.53)	(3.20 - 7.81)	(3.65 - 6.85)
100/1,000,000	1.5	(0.97 - 2.31)	(1.24 - 1.82)	(1.31 - 1.72)
	2.5	(1.73 - 3.62)	(2.12 - 2.95)	(2.22 - 2.81)
	5.0	(3.65 - 6.85)	(4.34 - 5.76)	(4.53 - 5.52)

CI: confidence interval; RR: risk ratio.

Table 4. Scenario C: Estimated precision of the strength of the association between a risk factor and myocarditis/pericarditis when the prevalence of the risk factor is 10% (e.g., smoking)

14-day risk of event among those without the risk factor	RR	1 Million	5 Million	10 Million
		95% CI	95% CI	95% CI
1/1,000,000	1.5	NI	(0.10 - 22.08)	(0.22 - 10.04)
	2.5	(0.02 - 327.18)	(0.28 - 22.11)	(0.54 - 11.68)
	5.0	(0.11 - 224.14)	(0.91 - 27.39)	(1.50 - 16.64)
10/1,000,000	1.5	(0.22 - 10.04)	(0.64 - 3.51)	(0.82 - 2.74)
	2.5	(0.54 - 11.68)	(1.25 - 4.98)	(1.54 - 4.07)
	5.0	(1.50 - 16.64)	(2.92 - 8.56)	(3.42 - 7.31)
100/1,000,000	1.5	(0.82 - 2.74)	(1.15 - 1.96)	(1.24 - 1.81)
	2.5	(1.54 - 4.07)	(2.01 - 3.11)	(2.14 - 2.92)
	5.0	(3.42 - 7.31)	(4.22 - 5.93)	(4.43 - 5.64)

CI: confidence interval; NI: non-informative because range of values in CI extends from zero to >100; RR: risk ratio.

Table 5. Scenario D: The prevalence of the risk factor is 1% (e.g., immunocompromised)

14-day risk of event among those without the risk factor	RR	1 Million	5 Million	10 Million
		95% CI	95% CI	95% CI
1/1,000,000	1.5	NI	NI	NI
	2.5	NI	NI	NI
	5.0	NI	NI	NI
10/1,000,000	1.5	(0.01 - 409.20)	(0.12 - 18.43)	(0.25 - 8.84)
	2.5	(0.03 - 196.83)	(0.35 - 17.62)	(0.63 - 9.94)
	5.0	(0.22 - 113.80)	(1.24 - 20.23)	(1.86 - 13.43)
100/1,000,000	1.5	(0.25 - 8.84)	(0.68 - 3.32)	(0.86 - 2.63)
	2.5	(0.63 - 9.94)	(1.35 - 4.64)	(1.62 - 3.87)
	5.0	(1.86 - 13.43)	(3.21 - 7.78)	(3.66 - 6.83)

CI: confidence interval; NI: non-informative because range of values in CI extends from zero to >100; RR: risk ratio.

9.6. Data management

This study will be conducted in a distributed manner using a common protocol, common data model (CDM), and common analytic programs based on existing health data. The following steps will be implemented:

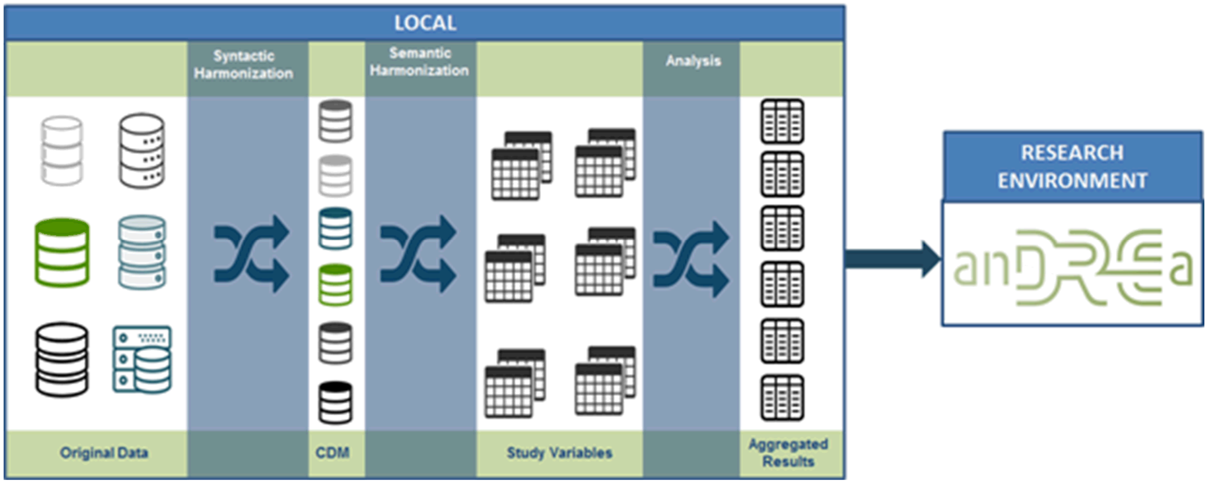
1. The extract, transform, and load (ETL) process will be used to convert data into a CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The CDM that will be used has been developed during the Innovative Medicines Initiative ConcePTION project[16]. In this

CDM, data are represented in a common structure, but the content of the data remain in their original format. The ETL design for each study is shared in a searchable findable, accessible, interoperable, and re-usable (FAIR) catalogue. FAIR is defined as findable, accessible, interoperable, and re-usable. The VAC4EU FAIR data catalogue is a metadata management tool designed to contain searchable metadata describing organisations that can provide access to specific data sources. Data quality checks will be conducted to measure the integrity of the ETL, as well as internal consistency within the context of the CDM (see Section 9.8).

2. Second, to reconcile differences across terminologies, a shared semantic foundation is built for the definition of events under study by collecting relevant concepts in a structured fashion using a standardised event definition template. The Codemapper tool was used to create diagnosis code lists based on completed event definition templates for each AESI and comorbid risk condition in the ACCESS project. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), 1 or more algorithms are constructed (typically 1 sensitive, or broad, algorithm and 1 specific, or narrow, algorithm) to operationalise the identification and measurement of each event. These algorithms may differ by database, as the components involved in the study variables may differ. Manual review of EHRs will be conducted for a sample of the events. Specifications for both ETL and semantic harmonisation will be shared in the catalogue.

3. Third, following conversion to harmonised study variable sets, R and SAS programs for the calculation of incidence and prevalence will be distributed to data access partners (DEAPs) for local deployment. The aggregated results produced by these scripts will then be uploaded to the Digital Research Environment (DRE) for pooled analysis and visualisation (see Figure 5). The DRE is made available through University Medical Center Utrecht (UMCU)/VAC4EU. The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate (https://www.andrea-consortium.org/azure-dre/).

Figure 5. Data management plan



CDM = common data model.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

This study will use secondary data collected in EHR databases. For the purpose of validating myocarditis and pericarditis, special forms will be developed and securely saved in environments assuring data protection and patient confidentiality according to the requirements of each country and DEAP.

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. A CRF is required and will be completed for each patient who is subject to an event/case verification/validation procedure. The completed original CRFs are the sole property of the DEAPs and will not be made available in any form to third parties, except for authorised representatives of Pfizer or appropriate regulatory authorities. The DEAPs will ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorised third parties.

The DEAPs have ultimate responsibility for the collection and reporting of all clinical and laboratory data entered on the CRFs for the purpose of event/case verification/validation and ensuring that data are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

The source documents are the hospital or physician charts. In these cases, data collected on the CRFs must match information in those charts.

9.6.2. Record retention

The final study aggregated results sets and statistical programmes will be archived and stored on the DRE and the VAC4EU SharePoint site. Validation of the QC of the statistical analysis will be documented. The final study protocol and possible amendments, the final statistical report, statistical programmes, and output files will be archived on a specific and secured central drive.

It is the responsibility of the principal investigator to inform the other investigators or institutions regarding when these documents no longer need to be retained. Study records or documents may also include the analyses files, syntaxes (usually stored at the site of the database), ETL specifications, and output of data quality checks.

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, DEAPs agree to keep all study-related records, including the identity of all participating individuals (sufficient information to link records, e.g., CRFs, hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by DEAPs according to local regulations or as specified in the vendor contract, whichever has a longer retention time. DEAPs must ensure that the records continue to be stored securely for as long as they are retained.

If UMCU becomes unable for any reason to continue retaining study records for the required period, Pfizer should be prospectively notified. In this case, the study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless UMCU and Penta and Pfizer have expressly agreed to a different retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

The investigators must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.3. Data extraction

Each DEAP will create ETL specifications using the standard ConcePTION ETL design template (accessible via this link: https://docs.google.com/document/d/1SWi31tnNJL7u5jJLbBHmoZa7AvfcVaqX7jiXgL9uAWg/edit). Following completion of this template and review by study statisticians, each DAEP will extract the relevant study data locally using their software (e.g., Stata, SAS, R, Oracle). These data will be loaded into the CDM structure in comma-separated values format. These data remain local (see Figure 5).

9.6.4. Data processing and transformation

Data processing and transformation will be conducted using R and SAS code against the syntactically harmonised CDM. The R and SAS scripts will first transform the data in the syntactically harmonised CDM to semantically harmonised study variables (see Figure 5). Following creation of study variables, the data will be characterised. This characterisation will include calculation of code counts and incidence rates, as well as benchmarking within the data source (over time), between data sources, and externally (against published estimates). Subsequently, R and SAS code to conduct analysis against semantically harmonised study variables will be distributed and run locally to produce aggregated results. The R and SAS scripts for these processing and analysis steps will be developed and tested centrally and sent to the DEAPs.

The R and SAS scripts are structured in modular form to ensure transparency. Functions to be used in the modules will be either standard R and SAS packages or packages specifically designed, developed, and tested for multi database studies. Scripts will be double-coded in SAS and R, and quality checks will be thoroughly documented.

The DEAPs will run the R and SAS code locally and send aggregated analysis results to the DRE using a secure file transfer protocol. In the DRE, results will be further plotted, inspected (for quality assessment), and pooled (if needed) for final reporting.

All final statistical computations will be performed on the DRE using R and/or SAS (SAS Institute; Cary, North Carolina). DEAPs will have access to the workspace for script verification.

Aggregated results, ETL specifications, and a repository of study scripts will be stored in the DRE.

9.6.5. Data access

Within the DRE, each project-specific area consists of a separate secure folder called a workspace. Each workspace is completely secure, and researchers are in full control of their data. Each workspace has its own list of users, which can be managed by its administrators.

The DRE architecture allows researchers to use a solution within the boundaries of data management rules and regulations. Although General Data Protection Regulation and Good (Clinical) Research Practice still apply to researchers, the DRE offers tools to more easily control and monitor which activities take place within projects.

All researchers who need access to the DRE are granted access to study-specific secure workspaces. Access to this workspace is possible only with double authentication using an identification code and password together with the user’s mobile phone for authentication.

Upload of files is possible for all researchers with access to the workspace within the DRE. Download of files is possible only after requesting and receiving permission from a workspace member with an “owner” role.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP that will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Natural history of myocarditis and pericarditis (primary objective)

9.7.1.1. Characterisation of myocarditis and pericarditis cases

The distributions of baseline characteristics will be described overall and by vaccination status, stratified by vaccine doses received (e.g., first, second, third, and booster doses) for the vaccinated group. For continuous variables, means, standard deviations, and quartiles will be estimated. For categorical variables, counts and proportions will be estimated. The missingness of variables will also be described.

9.7.1.2. Natural history of myocarditis and pericarditis

The occurrence of the different treatments and outcomes (Section 9.3.4) during follow-up will be described using counts and proportions; continuous variables (e.g., length of stay) will be described using standard statistics as in Section 9.7.1.1. When appropriate, the occurrence of time-to-event outcomes (e.g., death) will be described using the Kaplan-Meier estimator or curve.

Subgroup descriptive analysis will be performed by sex and age, COVID-19 history, vaccination status stratified by vaccine doses received (e.g., first, second, third, and booster doses), and time since vaccination.

9.7.2. Risk factors for myocarditis and pericarditis (secondary objective)

9.7.2.1. Identification of risk factors for myocarditis and for pericarditis

In addition to all baseline covariates (Section 9.3.5) and COVID-19 status (Section 9.3.2), vaccination status stratified by vaccine doses received (e.g., first, second, third, and booster doses) and a risk window of 1-14 days (Section 9.3.1) will be treated as potential risk factors or effect modifiers for the development of myocarditis and/or pericarditis. The risk windows of 1-7 days and 1-21 days will be examined in a sensitivity analysis. The distributions of baseline characteristics will be described overall and by vaccination status, including by vaccine doses received.

A regression-based predictive analysis will be conducted to identify the variables that better predict the diagnoses. The accuracy of the prediction will be estimated with standard estimators (e.g., positive predictive values, receiver operating characteristic [ROC] curves). The strength of the association between the risk factors and a diagnosis of myocarditis or pericarditis will be estimated via odds ratios or hazard ratios, as appropriate.

To assess robustness, a sensitivity analysis will be conducted by repeating the analysis described above, including as cases of myocarditis or pericarditis only those meeting the Brighton Collaboration classification of “definitive” [2] .

9.8. Quality control

Rigorous QC procedures will be applied to all deliverables. Data transformation into the CDM will be conducted by each subcontracted DEAP in its associated database, with processes as described in the following corresponding sections. Standard operating procedures or internal process guidance at each research centre will be used to guide the conduct of the study. These procedures include rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff.

At UMCU, as the scientific coordinating centre responsible for central data management and analysis, all documents undergo QC review and senior scientific review. Data management and statistical analysis follow standard operating procedures. All statistical analysis programmes will be double-coded by RTI.Health Solutions (RTI HS).

At RTI-HS, as the scientific coleader centre, all key study documents will undergo QC review, senior scientific review, and editorial review. Senior reviewers with expertise in the appropriate subject matter area will provide advice on the design of research study approaches and the conduct of the study and will review results, reports, and other key study documents.

9.8.1. Pedianet (IT)

Pedianet data processing includes, in addition to standardised procedures in SQL and Microsoft Access to extract data from database, QC steps aimed at verifying the correspondence between a diagnostic code and its open-text descriptor that are conducted through manual validation of clinical histories. QC checks of patient general data are conducted through the detection of outlier values and validation rules, grouping of diseases, and regular monitoring of aggregate clinical and drug data. All transformations in the data are logged in R scripts. To ensure code reliability, double programming in R and in Stata or Python is in place for all scripts.

9.8.2. PHARMO (NL)

PHARMO adheres to high standards throughout the research process based on robust methodologies, transparency, and scientific independence. PHARMO conducts studies in accordance with the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology*[17] and the *ENCePP Code of Conduct*[18]. PHARMO is ISO 9001:2015 certified. Standard operating procedures, work instructions, and checklists are used to guide the conduct of a study. These procedures and documents include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, rules and procedures for execution and QC of SAS programming, standards for writing protocols and reports, and requirements for senior scientific review of key study documents.

9.8.3. NHR (NO)

NHR at the University of Oslo will have centralised information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. All data will be stored and analysed within the 'Tjeneste for Sensitive Data' (TSD) platform, a service for sensitive data at the University of Oslo.[26,27] Only authorised researchers will have access, via a two-step authentication process, to manipulate the data within TSD. The study will be conducted according to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[28] and the *ENCePP Code of Conduct*.[25] Data quality is a high priority at the Norwegian Health Registries; updated data are released regularly for research purposes after centralised quality control. The University of Oslo has rules for secure and confidential data storage and analysis, as well as rules for data cleaning, linkage, and programming.

9.8.4. EpiChron (ES)

The data QC process in Aragon is conducted in 3 steps (i.e., data collection, data request and extraction, and data processing). Common data collection software and procedures guarantee standardised data input by all health care professionals. In the case of the hospital CMBD register and the drug dispensation database, their completion is systematic, uniform, and normative according to legal orders. Online specific training and chart documentation on the use of EHR software is regularly provided to physicians and nurses in Aragon. The data contained in each of the registers is routed to a specific service of the Department of Health, which performs a pseudonymisation of the data to encrypt individual-level identification codes, protecting individuals' privacy and complying with data protection laws. This new encrypted code is applied in all registers, enabling the linkage of data at the patient level. The resulting databases are stored on a central computer server, and access to the files is restricted to members of the research group by a double-entry password. The research group is a multidisciplinary qualified team including public health specialists, epidemiologists, clinicians, pharmacists, statisticians, and data managers; they are all trained in data management and patient data protection. Given that original databases are in different formats (e.g., Microsoft Access, Microsoft Excel, plain text), the SQL programming language is employed to extract the data. Stata statistical software (Release 12) is used for data processing, which includes a number of systematic steps aimed at improving the quality, accuracy, and reliability of the data for research purposes (e.g., QC of diagnoses to verify the correspondence between a diagnostic code and its open-text descriptor through manual validation of clinical histories and use of specific algorithms to search for specific key words or roots of words in open-text fields, QC of patient general data through the detection of outlier values and validation rules, grouping of diseases, and regular monitoring of aggregate clinical and drug data). The original databases also have their own QC processes. All changes conducted in the data are logged in Stata scripts, which are continuously revised and updated given the dynamic nature of the data processing.

9.8.5. SIDIAP (ES)

Data quality processes are implemented at each phase of the data flow cycle. QC checks are performed at the extraction and uploading steps. To assess data completeness, the elements presence are described by geographical area, registering physician, time, and the distribution function of values. Correctness is assessed by validity checks on outliers, out-of-range values, formatting errors, and logical dates incompatibilities. Completeness and correctness measures are used to inform decisions on the required transformations to improve data quality (e.g., harmonisation, normalisation, and clean-up) and the data fitness for the purpose of specific research projects.

9.8.6. CPRD (UK)

The DSRU has information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring that the premises provide suitable physical and environmental security, all equipment is secure and protected against malicious software, the network can be accessed only by authorised staff, telecommunication lines to the premises are protected from interception by being routed overhead or underground, and personnel receive training regarding security awareness. The study will be conducted according to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[19] and according to the *ENCePP Code of Conduct*.[18] Data quality is a high priority at the DSRU and is assured through a number of methods based on staff training, validated systems, error prevention, data monitoring, data cleaning, and documentation, including the following:

- Staff training on data processing standard operating procedures
- Data management plan for every research study outlining the legal basis for data collection, data flows, data access rights, data retention periods, etc.
- Routine data cleaning to screen for errors, missing values, and extreme values and diagnose their cause
- System process logs to document staff access, etc.

9.9. Limitations of the research methods

A data-related limitation of this study is the reliance on the accuracy of codes and algorithms to identify outcomes. Myocarditis and pericarditis diagnoses and their dates of occurrence will be validated, but the extent of validation may be limited because of the use of medical records. Because both myocarditis and pericarditis are rare events, the precision of the estimates may be poor due to a small number of cases.

The ability to identify specific COVID-19 vaccine products and dates of vaccination in these data sources is reflected in Section 9.3.1. The vaccination rates in the study countries are high.

Identification of baseline variables may be based on pharmacy dispensing records, general practice records, immunisation registers, medical records, or other secondary data sources. Baseline variables will be characterised at the time of vaccination in those individuals who receive a vaccine and at the corresponding matching date in those individuals who do not receive a vaccine. This date can be distant from the occurrence of myocarditis and thus, for the primary objective, where the start of follow-up to characterise the clinical course of individuals diagnosed with myocarditis or pericarditis is the date of diagnosis, patient characteristics that can change over time may be misclassified. Nevertheless, the role of baseline variables in the primary objective will be establishing subgroups, based on time-invariant variables like sex, age, and time since vaccination; therefore, such misclassification of time-varying variables should not be of relevance.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This is a NIS using secondary data collection and does not pose any risks for individuals. Each DEAP will apply for an independent ethics committee review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at DEAPs in encrypted electronic form and will be password protected to ensure that only authorised study staff have access.

DEAPs will implement appropriate technical and organisational measures to ensure that personal data can be recovered in the event of disaster. In the event of a potential personal data breach, DEAPs shall be responsible for determining whether a personal data breach has in fact occurred and, if so, for providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorised parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorised parties will be identified by this single, patient-specific code. In the case of data transfer, Pfizer will maintain high standards of confidentiality and protection of individuals' personal data consistent with the vendor contract and applicable privacy laws.

10.2. Patient consent

As this study does not involve data that are subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

Each DEAP will follow the local country and data custodian requirements to apply for access to the data. At the coordinating centre, RTI-HS will ask approval for exemption from review by the RTI International institutional review board. All correspondence with the institutional review board or independent ethics committee and applicable documentation will be retained as part of the study materials.

10.4. Ethical conduct of the study

This study will adhere to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[19] and has been designed in line with guidance from ENCePP, specifically, the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[17]. The *ENCePP Checklist for Study Protocols*[20] will be completed (see ANNEX 2).

The study is a post-authorisation study of vaccine safety and will comply with the definition of the non-interventional (observational) study referred to in the International Conference on Harmonisation tripartite guideline *Pharmacovigilance Planning E2E*[21] and provided in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*[22], and with the 2012 EU pharmacovigilance legislation, adopted 19 June 2012[23].

The study will be registered in the EU PAS Register[24] before data collection commences.

The research team and study sponsor should adhere to the general principles of transparency and independence in the *ENCePP Code of Conduct*[18] and the *ADVANCE Code of Conduct*[22].

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigour, and will follow generally accepted research practices described in the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* issued by the International Society for Pharmacoepidemiology[19]. An **independent scientific advisory committee** will be installed, comprising experts in vaccine safety studies.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves a combination of existing structured data and unstructured data, which will be converted to a structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In the study data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

For NIS designs that are based on secondary use of data, such as studies based on medical chart reviews or EHRs, systematic reviews, or meta-analyses, reporting of AEs/adverse drug reactions is not required. Reports of AEs/adverse drug reactions should only be summarised in the study report, where applicable.

According to the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*[25],

"All adverse events/reactions collected as part of [non-interventional post-authorisation 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-Authorisation Safety Studies[22] echoes this approach. Legislation in the EU further states that for certain study designs such as retrospective cohort studies, particularly those involving EHRs, it may not be feasible to make a causality assessment at the individual case level.

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the *data collection tool (e.g., chart abstraction form)* and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product, must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least 1 patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered valid in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement, "A 35-year-old female…" or "An elderly male…" Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness,” “Study Drug,” and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

“*Your Reporting Responsibilities (YRR) Training for Vendors*”

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a “Confirmation of Training Certificate” (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As per EMA GVP Module VIII, the study and its protocol will be registered in the EU PAS Register prior to the start of data collection, and the report or its summary will be registered after the regulatory review is completed. Results of analyses and interpretation will be delivered in report form, as a final report, at the end of the follow-up.

Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors[26]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed[27]. Independent publication rights will be granted to the research team in line with Section VIII.B.5., Publication of study results, of the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies*[28].

Upon study completion and finalisation of the study report, the results of this PASS will be submitted for publication, preferably in a relevant peer-reviewed journal, and posted in the EU PAS Register. Communication via other appropriate scientific venues will be considered.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator party responsible for collecting data from the participant is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Study title: Post-Authorisation Active Surveillance Study of Myocarditis and Pericarditis Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

EU PAS Register number:
Study reference number (if applicable):

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)	☐	☐	☒	
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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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
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)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

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

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, 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1
3.4	Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH])	☒	☐	☐	9.7.2.2
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?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.3
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.1.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation substudy)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) an appropriate comparator(s) identified?	☒	☐	☐	9.3.1.1, 9.3.1.2

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?	☒	☐	☐	9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.3.1, 9.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation substudy)	☒	☐	☐	9.3.3.1, 9.6.1, 9.9
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)	☒	☐	☐	9.1, 9.7.1.2, 9.7.2.1
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.1
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.3

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, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.2

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)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.3.1
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.5
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.3
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

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1.1, 9.7.1.2, 9.7.2.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.1.2,
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.1, 9.7.1.2, 9.7.2.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.2.2
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1.1
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	10.4

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 substudy, 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)	☒	☐	☐	9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

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:	Alejandro Arana	
Date:		
Signature:	To be signed upon PRAC endorsement	

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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