NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Assessment of risk factors for Myocarditis in the United States (US) using Electronic Health Records and Claims data
Protocol number	C4591055
Protocol version identifier	2.0
Date	11 Jan 2025
EU Post Authorization Study (PAS) register number	EUPAS104403
Active substance	Pfizer-BioNTech coronavirus disease 2019 (COVID-19) Vaccine is single-stranded, 5'-capped messenger ribonucleic acid (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine
Research question and objectives	Research question: What are the risk factors for myocarditis among the following three cohorts? 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020). Primary objective: 1. To assess and compare demographic, medical history, and comorbidities that may be risk factors for myocarditis in each of three cohorts: 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020).

	Secondary objectives: 1. To examine the risk factors in each myocarditis cohort stratified by age group at diagnosis, sex, time period and follow-up time (years) 2. To assess and compare the validity of myocarditis diagnosis case definitions in administrative data for each cohort, via calculating the positive predictive value (PPV) using electronic medical record review
Country(ies) of study	United States
Author	Scott P. Kelly, PhD Pfizer Inc. 66 Hudson Blvd, New York, NY 10001

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
CCC	Complex chronic conditions
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CK-MB	Creatine kinase-myoglobin binding
cMR	Cardiovascular magnetic resonance
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus disease 2019
CPT	Current Procedure Terminology
CRP	C-reactive protein
ECG	Electrocardiogram
EHR	Electronic health records
EMA	European Medicines Agency
EMB	Endomyocardial biopsy
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HCUP CCS	Healthcare Cost and Utilization Project Clinical Classifications Software
HEOR	Health Economics and Outcomes Research
HIPAA	Health Information Insurance Portability and Accountability Act (HIPAA) Privacy
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICMJE	International Committee of Medical Journal Editors
IDN	Integrated delivery network
IEC	Independent Ethics Committee

Abbreviation	Definition
IRB	Institutional Review Board
mRNA	Messenger ribonucleic acid
NCHS	National Center for Health Statistics
NDC	National Drug Center
NI	Non-interventional
NLP	Natural language processing
OR	Odd ratio
PASS	Post-Authorization Safety Study
PPV	Positive predictive value
QC	Quality control
RAPID3	Routine assessment of patient index data 3
RWD	Real world data
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
TBD	To be determined
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Scott P. Kelly, PhD	Senior Director, Epidemiology, Global Medical Epidemiology, Worldwide Research & Development	Pfizer, Inc.	66 Hudson Blvd East, New York, NY 10001 United States
Claudia Ana Ianos, MD	Senior Director, MD, Safety Risk Lead Worldwide Research & Development	Pfizer Inc.	Schärenmoosstrasse 99, 8052 Zürich, Switzerland
Cynthia de Luise, PhD, MPH	Senior Director/Safety Surveillance Research	Pfizer, Inc	66 Hudson Blvd East, New York, NY 10001 United States
Stephen Schachterle, PhD, MPH	Director, Global Medical Epidemiology, Worldwide Research & Development	Pfizer, Inc. ·	66 Hudson Blvd East, New York, NY 10001 United States
Irene Margolin-Katz	Clinical Data Manager	Optum Inc.	1325 Boylston Street, Boston, MA 02135 United States
Cynthia Senerchia, RN, MS	Vice President Strategic Operations	Optum Inc.	1325 Boylston Street, Boston, MA 02135 United States
Jonathan C. Johnson	Director Health Economics and Outcomes Research	Optum Inc.	11000 Optum Circle, Eden Prairie, MN 55344 United States

4. ABSTRACT

Title: Assessment of risk factors for Myocarditis in the US using Electronic Health Records (EHR) and Claims data

Version 2.0, 11 Jan 2025

Scott P. Kelly, PhD, Pfizer, Inc.

Rationale and background: Myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria. During the COVID-19 era, diagnostic criteria for myocarditis have been based on those from the Centers for Disease Control and Prevention (CDC) and the Brighton Collaboration. Although the aetiology of myocarditis often remains undetermined, a large variety of infectious agents, systemic diseases, drugs, and toxins can cause the disease. To date, for myocarditis of any cause, only younger age, male gender, as well as engagement in competitive athletics were established as risk factors for myocarditis. Myocarditis has been reported after SARS-CoV-2 infection, as well as an adverse event (AE) following immunization with Coronavirus disease 2019 (COVID-19) mRNA vaccine, with higher rates after a second dose compared with first dose. Outside of these characteristics, an understanding of risk factors that predispose individuals or contribute to the development of myocarditis after exposure to infections or drugs/vaccines is limited.

Given limited information obtained to date, the objective of this study is to gain understanding of the risk factors for myocarditis in the US prior to and during the COVID-19 era. This study will examine the risk factors for myocarditis in general, as well as serve to advance the knowledge of myocarditis of various etiologies. Specifically, this study will use real world, statistically deidentified administrative EHR and claims data, in combination with deidentified medical note review by Optum to validate a sample of the myocarditis cases, with the objective to examine and compare demographic and clinical characteristics that may be associated with risk of myocarditis after any dose of mRNA COVID-19 vaccine, myocarditis after SARS-CoV-2 infection (2020-later), or acute/viral myocarditis prior to COVID-19 (pre-2020). A population-based view of patients' longitudinal journey that captures adequate medical history prior to myocarditis diagnosis may also help inform potential future clinical trial inclusion/exclusion criteria, as well as generate hypotheses for potential myocarditis mechanisms of action.

Research question and objectives: This study will address the following research question, **"**What are the risk factors for myocarditis among the following three cohorts? 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020)."

Primary objective:

1. To assess and compare demographic, medical history, and comorbidities that may be risk factors for myocarditis in each of three cohorts: 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020).

Secondary objectives:

1. To examine the risk factors in each myocarditis cohort stratified by age group at diagnosis, sex, time period and follow-up time (years).

2. To assess and compare the validity of myocarditis diagnosis case definitions in administrative data for each cohort, via calculating the PPV using electronic medical record review.

Study design: This is a NI, observational, retrospective cohort study utilizing a nested case-control design with secondary data collection.

Population:

This study will use the US-based Optum's Electronic Health Record (EHR) data, with supplemental linkage to Optum's Integrated Claims-Clinical adjudicated claims dataset for those patients in the EHR who also have claims data available. For a subset of patients in the EHR, patient electronic clinical notes exist which will allow manual clinician review at Optum to confirm myocarditis cases based on available data that align with the Brighton Collaboration criteria. The proposed study period is 01 January 2010 to most recent available at the time of start of data collection (31 March 2023)), to allow sufficient baseline time to examine risk factors for patients with myocarditis in each of the three cohorts, with index dates of 2016-later.

Among the overall Optum EHR study population of all ages, the following mutually exclusive cohorts and index dates will be defined to address the study objectives:

- Cohort 1 - Post-mRNA COVID-19 vaccination myocarditis cohort: first date of a myocarditis diagnosis code within 21 days after vaccination from 11 December 2020 to most recent data available, allowing for at least 30 days pre or post index for medical notes to confirm diagnosis through end of study period.

- Cohort 2 - Post-SARS-CoV-2 infection myocarditis: first date of a myocarditis diagnosis code within 8 weeks after a positive SARS-Cov-2 test from 01 January 2020 to most recent data available, allowing for at least 30 days pre or post index for medical notes to confirm diagnosis through end of study period.

- Cohort 3 - Pre-COVID myocarditis: most recent date of a myocarditis diagnosis from 01 January 2016 to 01 November 2019, allowing for at least 30 days pre or post index for medical notes to confirm diagnosis through end of study period.

- Controls - for the multivariable risk factor analysis, a random sample of matched patients without myocarditis will be selected, e.g. with an encounter date during the same month as the index date for the myocarditis case, and with a similar amount of follow-up time from entry into the cohort and activity in the database. Additional matching criteria may be

determined, and details of the matching methods and appropriate modeling considerations will be provided in the statistical analysis plan (SAP).

Variables: The outcome in this study is myocarditis, categorized into three cohorts: 1) myocarditis post mRNA COVID-19 vaccination, 2) myocarditis post-SARS-CoV-2 infection, or 3) acute/viral myocarditis pre-2020. Myocarditis will be identified with ICD-10-CM codes in EHR and claims data. In addition, Brighton Collaboration Criteria will be used as the basis during manual reviews of electronic medical notes by two clinicians at Optum to validate a subset of the cases. Exposure variables will include potential risk factors for myocarditis including demographic characteristics, diagnoses and procedures defined with ICD-10 codes, treatments (prescriptions) and laboratory tests identified in the EHR. Covariates include medical comorbidities and other treatments at index, as well as healthcare utilization before index, and may include other factors not considered as risk factors for myocarditis.

Data sources: Optum's statistically de-identified Electronic Health Record (EHR) and Integrated Claims-Clinical dataset, which combines adjudicated claims data (where available) with Optum's EHR data, are the data sources for this study. In addition, this study will use data available in the medical records for a subset of myocarditis patients that have clinical patient notes and other data that cannot be mapped into the larger structured database.

Study size: Optum's longitudinal EHR repository is derived from dozens of healthcare provider organizations in the US, that include more than 57 contributing sources and 111K sites of care: treating more than 106 million patients receiving care in the US. Based on initial feasibility assessment of the Optum EHR database, there were approximately 240 myocarditis cases within 21 days of mRNA vaccination, 1,730 myocarditis cases after SARS-CoV-2 infection, and 7,200 myocarditis cases prior to 01 November 2019. In addition, the large size of the database will allow for matching of each myocarditis case with controls for the risk factor analyses.

Data analysis:

Primary Objective:

In primary analyses, descriptive statistics will be presented to characterize myocarditis patients in terms of demographic and clinical characteristics (including clinical characteristics of the myocarditis episode, as well as clinical history of the patient) as of the index date (date of myocarditis diagnosis code for myocarditis cases, or matched month/year among the control group). Additionally, appropriate statistical models such as conditional logistic regression or generalized estimating equations (GEE) incorporating non-independence of observations will be described in greater detail in the SAP. Models will estimate odds ratios (ORs) and 95% CIs of associations between demographics, clinical characteristics, and empirical model identified risk factors (based on either a stepwise selection approaches or via statistical significance in univariate models) and myocarditis. These models will be run for the myocarditis cases and controls identified with ICD-10-CM codes in the administrative EHR and claims data, as well as for the cases that are validated by clinician reviews as myocarditis using available Brighton Collaboration Criteria and information in the medical record notes.

Secondary Objectives:

In secondary analyses, all analyses above will be performed in the following *a priori* specified subgroups: 1) myocarditis case definitions in each cohort; 2) age group at index date, to be determined based on the distribution of cases (e.g. less than 40 years of age versus 40+ years; <18 years versus 18-39 years versus 40+ years); 3) sex; and 4) available follow-up time (years). In additional secondary analyses, we will assess the PPV of myocarditis diagnosis definitions that were created using algorithms in the EHR compared with those cases that are validated based on the review at Optum of the electronic medical notes.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.1	31 January 2024	Administrative	Section 3. RESPONSIBLE PARTIES	Principal Investigator Change	Some Principal Investigator/s no long with Pfizer
1.1	31 January 2024	Administrative	Section 6 Milestones	Update end of data collection and final study report planned date	Most recent data available in the database at time of data collection updated to 31 March 2023
1.1	31 January 2024	Administrative	Section 9.1. Study Design Section 9.2.1. Inclusion criteria	Removal of requirement for minimum of 3 medical notes for Cohorts 2 and 3	Requirements for notes now consistent for all three Cohorts
1.1	31 January 2024	Administrative	Section 9.6. Data management	Addition of sections	Missing from previous version of the protocol to describe the data collection tools and record retention requirements
1.2	25 July 2024	Administrative	Section 6 Milestones	Update end of data collection and final study report planned date	Delays with the vendor for case adjudication and construction of the controls
2.0	11 January 2025	Substantial	Section 6 Milestones	Update end of data collection and final study report planned date	Updated study milestone needs and incorporated all former changes

6. MILESTONES

Milestone	Planned date
Registration in the EU PAS register	25 May 2023
Start of data collection	26 May 2023
End of data collection	30 May 2025
Final study report	30 November 2025

7. RATIONALE AND BACKGROUND

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria. Clinically, myocarditis can present in a variety of ways, ranging from mild symptoms of chest pain and palpitations associated with transient Electrocardiogram (ECG) changes to life-threatening cardiogenic shock and ventricular arrhythmia [1]. Myocarditis is a challenging diagnosis due to the heterogeneity of clinical presentations, and several classifications exist [2,8]. During the COVID-19 era, diagnostic criteria have been based on those from the CDC and the Brighton Collaboration.[3,4] The actual incidence of myocarditis is also difficult to determine as endomyocardial biopsy (EMB), the diagnostic gold standard, is used infrequently.[2] It is estimated that approximatively 1.5 million individuals experience myocarditis per year worldwide, with the incidence varying from 1 to 40 per 100,000 depending upon the population characteristics. [5,6,7]

Although the aetiology of myocarditis often remains undetermined, a large variety of infectious agents, systemic diseases, drugs, and toxins can cause the disease. Molecular techniques suggest that viral infections are the most important cause of myocarditis in North America and Europe with genomes of enterovirus, adenovirus, influenza viruses, human herpes virus-6 (HHV-6), Epstein-Barr-virus, cytomegalovirus, hepatitis C virus, and parvovirus B19 reported in the myocardium of patients with myocarditis.[8] In almost 50-80% of cases, no cause is ever found.[9]

Outcome and prognosis of myocarditis depends on aetiology, clinical presentation, and disease stage. The fatality rate for myocarditis varies according to the methodology, geographic region, or time of the study, and generally converge to a rate of 5% myocarditis resulting in death in the short-term, and much higher if the acute episode required admission in intensive care or use of mechanical circulatory support, or if the myocarditis diagnosis was confirmed on histology.[10,11,12,13,14,15]

To date, for myocarditis of any cause, only younger age, male gender, as well as engagement in competitive athletics were established as risk factors for myocarditis. [10,1316,17] Population studies show that incidence of myocarditis tends to peak around adolescence through 40 years of age. [10] During pre-COVID-19 timeframes, the female-to-male ratio was between 1:1.5 and 1:1.7 in series of patients with myocarditis.[18,19] Outside of these characteristics, an understanding of risk factors that predispose individuals or contribute to the development of myocarditis after exposure to infections or drugs/vaccines is limited.

Higher myocarditis risk has been reported after SARS-CoV-2 infection, ranging from 5.4 per 100,000 persons (54 per million) for girls 5-11 years to 57.2 per 100,000 persons (572/million) for males 30 years of age or older within a 7-day risk window of infection.[20] Heymans and Cooper

reviewed a variety of studies and concluded that SARS-CoV-2 infection caused 1000 to 4000 cases of myocarditis per 100,000 people, which was higher than most other reports.[21] In a large meta-analysis, Ling et al. reported SARS-CoV-2 infection caused 1100 cases of myocarditis per 100,000 people.[22] After the acute natural infection, from which most recover, long-term cardiovascular sequelae are possible. The risk and 1-year burden of cardiovascular disease in survivors of acute COVID-19 are substantial, with increased risk of cerebrovascular disorders (stroke, transient ischemic attack), dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease.[23]

Myocarditis has been reported as an AE following immunization with COVID-19 mRNA vaccine. In aggregate, epidemiology studies reported higher risk after Dose 2 compared to Dose 1 [24], shorter duration between Dose 1 and Dose 2 [25, 26], and among younger males compared to older males or females of any age post-vaccination, with the highest excess risk reported in young males being <1 case per 10,000 vaccine doses.[27] The clinical course of post-vaccination myocarditis and pericarditis tends to be mild, responds to standard of care treatments and requires a relatively short duration of hospitalisation (2-4 days).[28] Short-term data on mortality is reassuring, with some studies showing a lower mortality compared with myocarditis of other causes, and other studies finding statistically comparable rates.[29,30] The prognosis is comparable with myocarditis of other causes.[29] Apart from male gender, younger age, and second dose, no other risk factors were identified for post-vaccine myocarditis.

Given limited information obtained to date, the objective of this study is to gain understanding of the risk factors for myocarditis in the US prior to and during the COVID-19 era. This study will examine the risk factors for myocarditis in general, as well as serve to advance the knowledge of myocarditis of various etiologies. Specifically, this study will examine and compare demographic and clinical characteristics that may be associated with risk of myocarditis after any dose of mRNA COVID-19 vaccine, myocarditis after SARS-CoV-2 infection (2020-later), or acute/viral myocarditis prior to COVID-19 (pre-2020). This study aims to provide a broader context for myocarditis following SARS-CoV-2 mRNA vaccination using a data source that has sufficiently detailed demographic and clinical information on a large number of patients, with medical chart review to adjudicate myocarditis cases via Brighton Collaboration criteria. [31] Identifying potential new risk factors for acute/viral myocarditis prior to the COVID-19 era, myocarditis after SARS-CoV-2 mRNA vaccine, or myocarditis after SARS-CoV-2 infection is important to contextualize and mitigate safety events while providing public health insights. In addition, this large-scale population-based study using real-world data (RWD) via EHR may help to identify risk factors that may differ from tertiary/referral center studies. A population-based view of patients' longitudinal journey that captures adequate medical history may also help inform potential future clinical trial inclusion/exclusion criteria, as well as generate hypotheses for potential myocarditis mechanisms of action.

This NI study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to characterize risk factors for myocarditis in the following three cohorts: 1) myocarditis diagnosed post any type of mRNA COVID-19 vaccine, 2) myocarditis diagnosed post SARS-CoV-2 infection (2020-2022), or 3) myocarditis diagnosed prior to the COVID-19 era (pre-2020). To accomplish this objective, the study will characterize demographics, medical history, and comorbidities of patients with myocarditis prior to diagnosis during a baseline period and then examine risk factors for myocarditis using multivariable models. Myocarditis cases identified in the EHR or claims post-vaccine or post COVID-19 infection, as well as a sample of cases in the pre COVID era cohort, will be validated by clinicians using the Brighton Collaboration criteria [31] applied to review of medical records at Optum as the gold standard. Using those validated cases, the study will also assess and compare the PPV for the myocarditis definitions based on codes for the three cohorts in the Optum deidentified EHR data.

Among patients diagnosed with myocarditis in the deidentified Optum EHR data, the study specific objectives are detailed below.

Research question:

What are the risk factors for myocarditis among the following three cohorts? 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020).

Primary objective:

1. To assess and compare demographic, medical history, and comorbidities that may be risk factors for myocarditis in each of three cohorts: 1) Myocarditis after mRNA COVID-19 vaccine, 2) Myocarditis after SARS-CoV-2 infection (2020-2022), or 3) Acute/viral myocarditis prior to the COVID-19 era (pre-2020).

Secondary objectives:

1. To examine the risk factors in each myocarditis cohort stratified by age group at diagnosis, sex, time period and follow-up time (years).

2. To assess and compare the validity of myocarditis diagnosis case definitions in administrative data for each cohort, via calculating the PPV using electronic medical record review.

9. RESEARCH METHODS

9.1. Study design

This is a NI, observational, retrospective cohort study utilizing a nested case-control design with secondary data collection. The broader cohort for this study is the Optum EHR database during the proposed study period of 01 January 2010 to most recent available at the time of start of data

collection (31 March 2023). This study period has been chosen to reflect the most current and complete data in the Optum database, with sufficient baseline time to examine risk factors for patients with myocarditis in each of the cohorts with index dates of 2016-later.

Figure 1 summarizes the overall study design. Among the overall Optum EHR study population, the following mutually exclusive cohorts and index dates will be defined to address the study objectives:

- Cohort 1 - Post-mRNA COVID-19 vaccination myocarditis cohort: first date of a myocarditis diagnosis code within 21 days after vaccination from 11 December 2020 to most recent data available, allowing for at least 30 days pre or post index myocarditis diagnosis for medical notes to confirm diagnosis through end of study period.

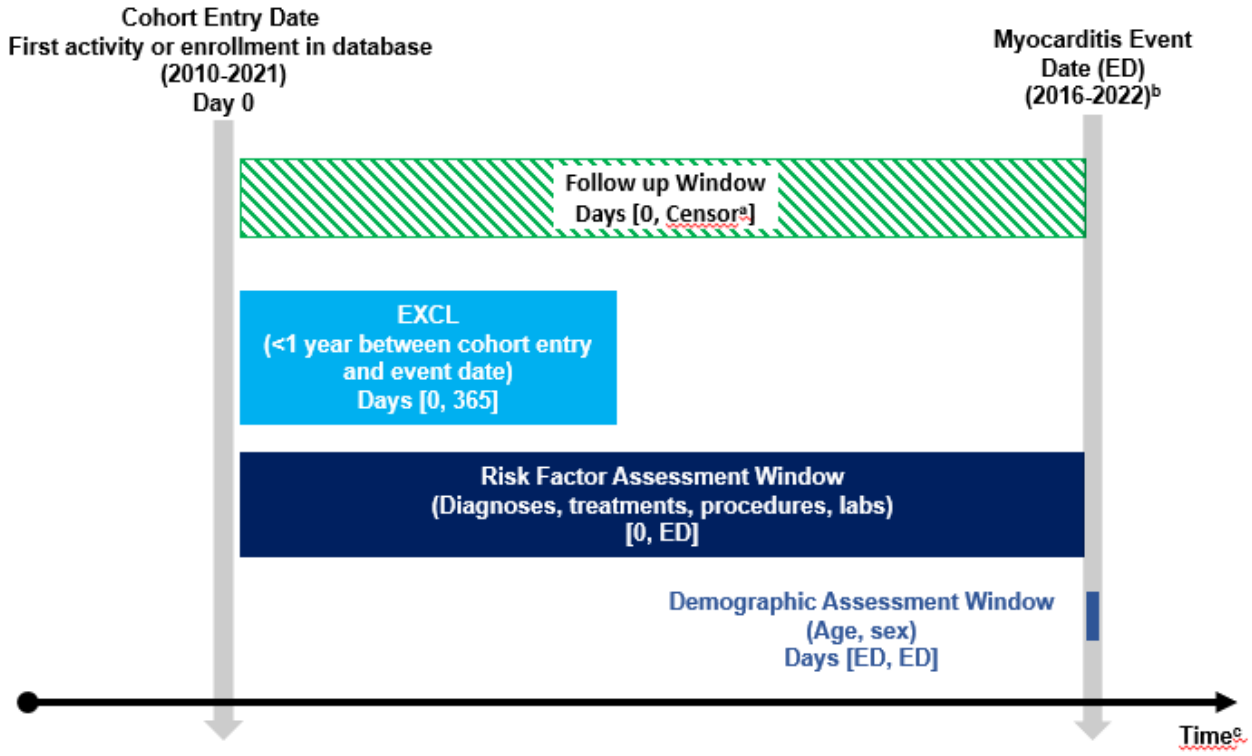
- Cohort 2 - Post-SARS-CoV-2 infection myocarditis: first date of a myocarditis diagnosis code within 8 weeks after a positive SARS-CoV-2 test from 01 January 2020 to most recent data available, allowing for at least 30 days pre or post index myocarditis diagnosis for medical notes to confirm diagnosis through end of study period.

- Cohort 3 - Pre-COVID myocarditis: most recent date of a myocarditis diagnosis from 01 January 2016 to 01 November 2019, allowing for at least 30 days pre or post index myocarditis diagnosis for medical notes to confirm diagnosis through end of study period.

- Controls - for the multivariable risk factor analysis, a random sample of matched patients without myocarditis will be selected, e.g. with an encounter date within the same month as the index date for the myocarditis case, and with a similar amount of follow-up time from entry into the cohort and activity in the database. Additional matching criteria may be determined, and details of the matching methods and appropriate modeling considerations will be provided in the SAP.

Additional details on index dates and episode definitions will be provided in the SAP.

Figure 1. Study Design



a. Censored at minimum of myocarditis diagnosis, death, disenrollment, or end of the study period
b. Controls risk-set matched on e.g. month/year of cohort entry, duration of follow up (from cohort entry), integrated delivery network (IDN). Matching criteria will be detailed in the SAP.
c. Timeframe for each myocarditis sub-cohort:
   1) Post-vaccination myocarditis: December 11, 2020 - November 01, 2022
   2) Post-SARS-CoV-2 myocarditis: January 01, 2020 - November 01, 2022
   3) Pre-COVID era myocarditis: January 01, 2016 – November 01, 2019

9.2. Setting

This study will use the US-based Optum's deidentified Electronic Health Record (EHR) data, with supplemental linkage to Optum's Integrated Claims-Clinical adjudicated claims dataset for those patients in the EHR who also have claims data available. For a subset of patients in the EHR, data exist including patient electronic clinical notes which will allow manual clinician review at Optum to confirm myocarditis cases based on available data that align with the Brighton Collaboration criteria.[31] Review of clinical notes will not be conducted for the random sample of patients without evidence of myocarditis that will serve as controls for the risk factor analysis. Optum's role, processes, and data is described in more detail in Section 9.4.

9.2.1. Inclusion criteria

Patients must meet all of the following criteria to be eligible for inclusion in the study:

1. All ages

Myocarditis cases:

2. Diagnosis of myocarditis identified using ICD codes in EHR and/or claims when available. (ICD codes will be provided in the SAP)

3. At least one myocarditis inpatient record or two myocarditis records of any type dated greater than or equal to 30 days apart

4. Myocarditis diagnosis date between 01 January 2016 – most recent EHR data available (31 March 2023)

5. At least 365 days of enrollment or activity in the EHR prior to the index myocarditis diagnosis.

Myocarditis cases meeting the above criteria will be divided into the following three cohorts with their own unique inclusion criteria:

a) Cohort 1 - Post- mRNA COVID-19 vaccine myocarditis cases:

   1. Myocarditis diagnosis date 11 December 2020 or later

   2. Record of mRNA vaccination within 21 days prior to the myocarditis diagnosis without a record of SARS-CoV-2 positive test within 8 weeks prior to myocarditis diagnosis

   3. Availability of medical notes to use for confirmation of myocarditis post-mRNA COVID-19 vaccination thirty days before or after the index event

b) Cohort 2 - Post- SARS-CoV-2 infection myocarditis cases:

   1. Myocarditis diagnosis date 01 January 2020 or later

   2. Record of SARS-CoV-2 positive test within 8 weeks prior to myocarditis diagnosis, with no record of mRNA COVID-19 vaccination during that time

   3. Availability of medical notes to use for confirmation of myocarditis post-SARS-CoV-2 infection thirty days before or after the index event

c) Cohort 3 - Pre-COVID-19-era acute/viral myocarditis cases:

   1. Most recent Myocarditis diagnosis date prior to 01 November 2019

   2. Availability of medical notes to use for confirmation of myocarditis within thirty days before or after the index event

Controls for risk factor analysis:

1. Medical encounter and during the same month as their matched myocarditis case (index date for control – select date closest to matched myocarditis case if ≥1 date/encounters are present)

2. At least 365 days of enrollment or activity in the EHR prior to index

3. No evidence of myocarditis prior to the index date

4. Details of matching criteria will be provided in the SAP

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Less than 365 days between the first recorded date a patient had activity of any kind recorded the Optum EHR database and a patients first recorded ICD code of myocarditis based on the cohort criteria above, or the index date for the controls.

Relevant codes/operational criteria for this study will be documented in an SAP, which will be dated, filed and maintained by the sponsor.

9.3. Variables

As described above, patients in the myocarditis cohorts will be identified via ICD codes in the EHR data, and a subset will be confirmed using Brighton Collaboration criteria [31] and medical record review. The main study variables of interest, including demographics, diagnostic, therapeutic and laboratory/examinations are listed in **Table 1: Variables and associated roles.** Operational definitions, codes, more detailed listings of comorbidities, procedures and treatments, as well as any additional variables will be provided in the SAP.

Table 1. Variables and Associated Roles (Detailed Operationalization to be Described in SAP)

Variable	Role
Year of birth	Demographic
Sex	Demographic
Race/Ethnicity	Demographic
Geographic region (census regions)	Demographic
Payer type	Demographic
Date of matched encounter (index date for controls)	Index
Date of qualifying myocarditis diagnosis (index date for cases)	Diagnosis and index
Age at time of diagnosis (e.g., index date, or if unavailable then age entered or calculated in database closest to myocarditis diagnosis)	Diagnosis

Variable	Role
Time to diagnosis (time from first Optum EHR record until first myocarditis diagnosis date)	Diagnosis
Time since diagnosis (time from first myocarditis diagnosis date until last date in the Optum EHR or date of death)	Diagnosis
Laboratory biomarkers *if feasible* (e.g. troponin, CRP, CK-MB, CPK, additional lab markers TBD)	Diagnosis
Imaging* (e.g. echocardiogram, Cardiac MRI, Cardiac Magnetic Resonance, cMR, ECG)	Diagnosis
Procedures* (Biopsy / cardiac biopsy)	Diagnosis
mRNA COVID-19 vaccination	Exposure
SARS-CoV-2 infection	Exposure
Medical comorbidities prior to diagnosis/index date** (e.g. Charlson categories, Feudtner Complex chronic conditions [CCC] for pediatric populations, Healthcare Cost and Utilization Project Clinical Classifications Software [HCUP CCS] groups, incl. cardiac, immune, inflammatory conditions)	Medical history
Treatments prior to diagnosis/index date* (e.g. prior cardiac or COVID-related treatments, frequency of other drug classes)	Medical history
Procedures prior to diagnosis/index date* (e.g. cardiac, HCUP CCS groups)	Medical history
Labs of interest prior to diagnosis/index date* (e.g. labs mentioned above, as well as other cardiac labs, basic metabolic panel, complete blood count, urinalysis, thyroid test, lipid panel, cultures)	Medical history
Prior HCU within the 6 months prior to diagnosis/index date (e.g. hospitalizations, emergency department, other outpatient visits)	Medical history

* Results of these tests will not be available, only whether the results supported the Brighton Criteria.

** Detailed variables within each and relevant codes/operational criteria for each will be documented in a SAP, which will be dated, filed and maintained by the sponsor.

9.4. Data sources

Optum's Electronic Health Record (EHR) and Integrated Claims-Clinical dataset, which combines adjudicated claims data (where available) with Optum's EHR data, are the data sources for this study. Optum integrates EHR data with claims, prescribing, dispensing, and practice management data by partnering directly with several multi-specialty medical groups, IDNs and hospital chains to extract data from their EHR and various information technology systems in the US. By normalizing, validating, and aggregating the de-identified data, Optum generates a longitudinal view of patient care.

Optum’s longitudinal EHR repository is derived from dozens of healthcare provider organizations in the US, that include more than 57 contributing sources and 111K sites of care: treating more than 106 million patients receiving care in the US. The data is certified as de-identified by an independent

statistical expert following HIPAA statistical de-identification rules and managed according to Optum® customer data use agreements[1],[2]. Clinical, claims and other medical administrative data is obtained from both Inpatient and Ambulatory EHRs, practice management systems and numerous other internal systems. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Optum® data elements include demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures. In addition, Optum® uses natural language processing (NLP) computing technology to transform critical facts from physician notes into usable datasets. The NLP data provides detailed information regarding signs and symptoms, family history, disease related scores (i.e. RAPID3 for RA, or CHADS2 for stroke risk), genetic testing, medication changes, and physician rationale behind prescribing decisions that might never be recorded in the EHR.

Diagnosis data, laboratory data, and surgical procedure data for the study period of interest will be first be obtained from structured data (via International Classification of Diseases, Ninth Revision/Tenth Revision, Clinical Modification [ICD-9-CM/ICD-10-CM], International Classification of Diseases, Ninth Revision/Tenth Revision, Procedure Classification System [ICD-9-PCS/ICD-10-PCS], or Current Procedure Terminology (CPT) codes where applicable. Drug treatment data may also be pulled from prescription written, medication administration, and procedure tables when appropriate (via ICD-9-CM/ICD-10-CM, National Drug Center [NDC], CPT, and Healthcare Common Procedure Coding System [HCPCS] codes where applicable). In addition, Optum will use data available in the medical records for a subset of myocarditis patients that have clinical patient notes and other data that cannot be mapped into the larger structured database. These data may contain verbatim medical data, including text-based descriptions of medical information, such as medical records, physician notes, neurological scans, X-rays, or narrative fields in a database. When possible/appropriate, for validation of myocarditis diagnoses and analyses of risk factors and background epidemiology, lab data will also be used to augment the structured electronic health data.

9.5. Study size

This is a NI study with no *a priori* hypotheses specified; therefore, sample size calculations are not applicable. Based on initial feasibility assessment of the Optum EHR database, there were approximately 240 myocarditis cases within 21 days of mRNA vaccination, 1,730 myocarditis cases after SARS-CoV-2 infection, and 7,200 myocarditis cases prior to 01 November 2019. In addition, the large size of the database will allow for matching of each myocarditis case with controls for the risk factor analyses.

[1] 45 CFR 164.514(b)(1).

[2] Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Information Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Dated as September 4, 2012, as first released on November 26, 2012).

9.6. Data management

Two major data sources for this study are described in greater detail in various sections throughout the protocol. Their collection, retrieval, preparation, and storage are summarized as follows:

1) Optum's EHR database: The EHR Database is a longitudinally linked structured data source. It has been formally de-identified by an independent statistical expert following HIPAA statistical de-identification rules and managed according to Optum® customer data use agreements[1],[2]. The EHR includes structured fields rendered by NLP technology, wherein Optum data experts mine provider notes and then normalize, validate, and integrate them into the electronic database.

   In addition to these structured data, Optum has clinical notes available from some EHR systems and is able to use technology to search the verbatim text for phrases of interest and extract a small portion of those notes for review and clinical assessment. All data elements from this source are stored on Optum's firewalled, password-protected database. These data can only be extracted by approved Optum study personnel using standard and commercially available software (e.g., SAS, SQL, Python).

2) Optum's Integrated Claims-Clinical database: The EHR will be supplementally linked to patients in Optum's Integrated Claims-Clinical adjudicated claims database. For a subset of these patients, electronic clinical notes will undergo manual clinician review to confirm myocarditis cases.

For the validation process using the electronic clinical notes (which will be converted to deidentified structured data for analyses), the Optum Natural Language Programming (NLP) team will determine if clinical notes are available for all qualifying patients with post-vaccine myocarditis, all qualifying post-SARS-CoV-2 infection myocarditis, as well as random samples of myocarditis diagnosed pre-2020. Optum will perform a series of "enhanced search" queries on the patient notes to determine key term content. Next, the Optum NLP team will use the key terms to extract note snippets into a file for review by the Optum Clinical team. These notes snippets will then be used to validate myocarditis cases per the Brighton Collaboration Criteria that were identified in the EHR using the inclusion and exclusion criteria specified in Section 9.2. After clinical review of the notes involving two clinicians from Optum, and categorization of the content for analysis, the resulting table of criteria will be created. The myocarditis cases will then be classified as validated or not validated, and relevant information entered into a spreadsheet that will serve as the data collection tool. Finally, the Optum clinical review team will provide these results of the case validation to the Optum Health Economics and Outcomes Research (HEOR) analytics team, whose members will identify matched controls for each case and conduct the multivariable analyses to assess risk factors for myocarditis

[1] 45 CFR 164.514(b)(1).

[2] Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Information Insurance Portability and Accountability Act (HIPAA) Privacy Rule (Dated as 04 September 2012, as first released on 26 November 2012).

using the structured data. This information will also be used to calculate the PPV of the algorithm used to initially identify the myocarditis cases in the structured EHR database.

Data will be transferred from the clinical review team to Optum's HEOR team via standard Data Transfer API (application programming interface). Extraction, merging, and cleaning of EHR and NLP-rendered data will be performed and adjudicated by at least two HEOR programmers and two HEOR analysts/directors. All data steps and code locations are formally documented in a data dictionary and are reviewed by the directing analyst and researcher before commencement of programming.

The Optum database is regularly updated. The date and version of the database will be specified in the report of the cohort, and any intermediate datasets will be archived as necessary for these results that will be submitted to a regulatory agency or published.

All analyses for this study will be conducted in SAS (version 9.4 or higher, SAS Institute, Cary, NC, US).

9.6.1. Data collection tools (DCTs)

As used in this protocol, the term DCT 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 DCT is required and should be completed for each included patient for whom outcomes are being adjudicated via ~~medical record review~~ **electronic health record note snippet review**. The completed original DCTs are maintained by Optum and should not be made available in any form to third parties, except for appropriate regulatory authorities, without written permission from Pfizer. Optum shall ensure that the DCTs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Optum has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the DCTs are true. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are ~~the hospital or the physician's chart~~ **note snippets from the electronic health record**. In these cases, data collected on the DCTs must match those ~~charts~~ **notes.**

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Optum agrees to keep all study-related records, including sufficient information to link records, (e.g., DCTs and ~~hospital records~~ **encrypted note snippets**), electronic copies of all DCTs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by Optum according to local

regulations or as specified in the Optum contract, whichever is longer. Optum must ensure that the records continue to be stored securely for so long as they are retained.

If Optum becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified, and study records should be retained under an arrangement acceptable to Pfizer that protects the confidentiality of the records (e.g., secure off-site storage). Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Optum and Pfizer have expressly agreed to a different period of retention via a separate written agreement.

If Pfizer would like the Study Records kept longer than the 15-year retention period, Pfizer will notify Optum prior to the end of the 15-year retention period.

9.7. Data analysis

Primary objective

In primary analyses, descriptive statistics will be presented to characterize myocarditis patients in terms of demographic and clinical characteristics (including clinical characteristics of the myocarditis episode, as well as clinical history of the patient) as of the index date (date of myocarditis diagnosis code for myocarditis cases, or matched month/year among the control group). Specific demographics and clinical characteristics of interest are described in Section 9.3. Descriptive statistics will include counts and percentages for categorical data. For continuous variables, we will provide statistics such as mean, median, standard deviation, and range.

Additionally, appropriate statistical models such as conditional logistic regression or generalized estimating equations (GEE) incorporating non-independence of observations will be described in greater detail in the SAP. These models will estimate odds ratios (ORs) and 95% CIs of associations between demographics, clinical characteristics, and empirical model identified risk factors (based on either a stepwise selection approaches or via statistical significance in univariate models) and myocarditis. Models may incorporate laboratory based prognostic indices, severity status, clinical risk factors noted in Section 9.3 along with potential empirical model identified risk factors. These models will be run for the myocarditis cases and controls identified with ICD-10-CM codes in the EHR, and according to the inclusion and exclusion criteria as provided in Section 9.2, as well as for the cases that are validated by clinician reviews as myocarditis using the available Brighton Collaboration Criteria and information in medical record notes, as specified in Section 9.6 . Model parameters will be detailed in the SAP.

Secondary objectives

In secondary analyses, all analyses above will be performed in the following *a priori* specified subgroups: 1) myocarditis case definition (based on criteria outlined in Section 9.2.1 – Inclusion Criteria); 2) age group at index date, to be determined based on the distribution of cases (e.g. less than 40 years of age versus 40+ years; <18 years versus 18-39 years versus 40+ years); 3) sex; and 4) available follow-up time (years).

In additional secondary analyses, we will assess the PPV of myocarditis diagnosis definitions that were created using algorithms in the EHR compared with those cases that are validated based on the review of the electronic medical notes as specified in Section 9.6.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP, which 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.

9.8. Quality control

All codes and/or code algorithms will be reviewed by the Safety Risk Lead in the Safety Surveillance and Risk Management group for the Pfizer COVID-19 vaccine program, as well as the protocol authors. The ICD-9-CM and ICD-10-CM codes used in the study will be reviewed against relevant codes used in the Food and Drug Administration (FDA) Sentinel program whenever applicable; if there are any discrepancies, the Sentinel codes will be used unless there is a strong rationale to use internally developed ICD codes and/or ICD algorithms instead. Additional validation of the code lists will be performed if warranted. All efforts will be made to ensure quality and safe storing of data and reports. Quality control (QC) checks will be performed on all SAS programming, data tables, and reports generated in the course of this research. QC findings and documentation of remedial action will be maintained. Storage of programming, data, and reports will be carried out per standard procedures, and as specified in Section 9.6.

In the validation study, after the Optum NLP team creates key term tags for use in the snippet review for the two Optum clinicians who will review patient notes with these key terms mentioned, the two clinicians will record their findings from the notes regarding whether the notes support a myocarditis diagnosis based on the Brighton Criteria. These results will be provided to the HEOR team for review and any clarifications or questions will be managed between the two groups until resolved.

9.9. Limitations of the research methods

This study has several strengths. First, it is a population-based study in a real-world population, increasing generalizability and external validity. Second, the Optum EHR database has both inpatient and outpatient data, in addition to laboratory data and microbiology results for a subset of patients that could be leveraged. In addition, the large sample size will enable the capture of a range of pre-specified health outcomes and clinical conditions, while the longitudinal nature of the data will allow us the ability to track risk factors, clinical manifestations, and changes in prognostic laboratory values over time.

However, the study also has several limitations. As is the case in any study based on secondary data sources, outcome misclassification is a possibility, as delayed and misdiagnosis of myocarditis is potentially high. However, the validation sub-study, which is being conducted concurrently, will allow us to evaluate potential misclassification of myocarditis, as well as key risk factors of interest. Diagnostic codes may also be incorrect or may be included as part of the diagnostic rule-out process or a record of a historical myocarditis event rather than an indication of a recent myocarditis, however by incorporating a multi-tier treatment and diagnostic algorithm to identify myocarditis, it will allow us to evaluate the robustness and accuracy of cases identified based on diagnosed criteria alone versus criteria that requires additional data such as medication or procedures for verification of

myocarditis. Laboratory results and vital signs/other biometric measures may be incomplete and therefore only available for a subset of the patients. Another limitation inherent to EHR databases is that information on prescriptions recorded for outpatients in this database does not necessarily indicate that the medication was consumed or taken as prescribed; similarly, medications filled over the counter or provided as samples by the physician may not be recorded in the database. Vaccine administrations or SARS-CoV-2 infections may not be recorded in the EHR, and so myocarditis after vaccination or COVID-19 infection may be missed. Similarly, due to the nature of EHR data, conditions not requiring treatment or office visits tend to be systematically under-recorded; therefore, it is possible that this study may only capture severe conditions that are considered in the risk factor models. Patients may have received health care outside of the network of providers and healthcare organizations that contribute to the Optum databases, or prior to having the index diagnosis and we may not be able to exclude the possibility that a patient was diagnosed with myocarditis, as well as other risk factors, prior to entry into a healthcare system where Optum has EHR access. Furthermore, if observed results using ICD-9 codes significantly differ from observed results using ICD-10 codes as a result of Centers for Medicare & Medicaid Services (CMS) and the National Center for Health Statistics (NCHS) ICD-9 to ICD-10 transition, we may modify our definitions as necessary.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational 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 Optum in encrypted electronic and will be password protected to ensure that only authorized study staff have access. Optum has implemented appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, Optum shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

10.2. Patient consent

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

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

IEC/IRB review was not required for this secondary data analysis study.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) [32], European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [33], FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data [34], and Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making [35].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

This study involves data that exist as structured data by the time of study start. In these 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 AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Unstructured Data Analysis

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions 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 non-interventional study (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 exposure during pregnancy in studies of pregnant women, data on the exposure to “PF-07302048 during pregnancy, are not reportable unless associated with serious or non-serious AEs.

- 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 one 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 a valid one 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) with Supplemental Topics."

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Statement" (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 statements must be provided to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study endpoints will be disseminated to the Pfizer Risk Management Committee. One or more abstracts may be developed and submitted to relevant scientific conference(s) and one or more manuscripts may be developed and submitted to relevant peer-reviewed medical journals. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed.

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 party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

[1] Al-Akchar M, Shams P, Kiel J. Acute Myocarditis. [Updated 2023 Feb 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441847/

[2] Heymans S, Dawson D, Fuster V, et al. Myocarditis following SARS-CoV2 mRNA vaccination against COVID-19: facts and open questions. J Am Coll Cardiol. 2022;80(14):1363-65.

[3] Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977-82.

[4] Sexson Tejtel SK, Munoz FM, Al-Ammouri I, et al. Myocarditis and pericarditis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2022;40:1499-511

[5] Golpour A, Patriki D, Hanson PJ, et al. Epidemiological Impact of Myocarditis. J Clin Med. 2021;10(4):603.

[6] Heymans S, Dawson D, Fuster V, et al. Myocarditis following SARS-CoV2 mRNA vaccination against COVID-19: facts and open questions. J Am Coll Cardiol. 2022;80(14):1363-65.

[7] Lasrado N, Yalaka B, Reddy J. Triggers of Inflammatory Heart Disease. Front Cell Dev Biol. 2020 Mar 24;8:192. doi: 10.3389/fcell.2020.00192. PMID: 32266270; PMCID: PMC7105865.

[8] Caforio AL, Pankuweit S, Arbustini E, et al; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013 Sep;34(33):2636-48, 2648a-2648d. doi: 10.1093/eurheartj/eht210. Epub 2013 Jul 3. PMID: 23824828.

[9] Kang M, Chippa V, An J. Viral Myocarditis. [Updated 2022 Sep 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459259/

[10] Kim MJ, Jung HO, Kim H, et al. 10-year survival outcome after clinically suspected acute myocarditis in adults: A nationwide study in the pre-COVID-19 era. PLoS One. 2023;18(1):e0281296.

[11] Chang JJ, Lin MS, Chen TH, et al. Heart failure and mortality of adult survivors from acute myocarditis requiring intensive care treatment - a nationwide cohort study. Int J Med Sci. 2017;14(12):1241-50.

[12] Lota AS, Halliday B, Tayal U, et al. Epidemiological trends and outcomes of acute myocarditis in the National Health Service of England. Circulation. 2019;140(Suppl_1):A11463.

[13] Kragholm KH, Lindgren FL, Zaremba T, et al. Mortality and ventricular arrhythmia after acute myocarditis: a nationwide registry-based follow-up study. Open Heart. 2021;8(2):e001806.

[14] Ammirati E, Cipriani M, Moro C, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: Multicenter Lombardy Registry. Circulation. 2018;138(11):1088-99.

[15] Pahuja M, Adegbala O, Mishra T, et al. Trends in the incidence of in-hospital mortality, cardiogenic shock, and utilization of mechanical circulatory support devices in myocarditis (analysis of national inpatient sample data, 2005-2014). J Card Fail. 2019;25(6):457-67.

[16] Pandey S, Rajasurya V. Nonviral Myocarditis. Stat Pearls; NCBI Bookshelf; last update Jun 3, 2020

[17] Vio R, Zorzi A, Corrado D. Myocarditis in the athlete: arrhythmogenic substrates, clinical manifestations, management and eligibility decisions. J CV Translational Research 2020; 13:284-95.

[18] Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, Moon TE. A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis treatment trial investigators. N Engl J Med 1995; 333: 269–275.

[19] Castrichini M, Porcari A, Baggio C, Gagno G, Maione D, Barbati G, Medo K, Mestroni L, Merlo M, Sinagra G. Sex differences in natural history of cardiovascular magnetic resonance- and biopsy-proven lymphocytic myocarditis. ESC Heart Fail. 2022 Aug 24. doi: 10.1002/ehf2.14102. Epub ahead of print. PMID: 36000547.

[20] Block JP, Boehmer TK, Forrest CB, et al. Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination — PCORnet, United States, January 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:517-523. DOI: http://dx.doi.org/10.15585/mmwr.mm7114e1.

[21] Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat Rev Cardiol. 2022 Feb;19(2):75-77. doi: 10.1038/s41569-021-00662-w. PMID: 34887571; PMCID: PMC8656440.

[22] Ling RR, Ramanathan K, Tan FL, Tai BC, Somani J, Fisher D, MacLaren G. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med. 2022 Jul;10(7):679-688. doi: 10.1016/S2213-2600(22)00059-5. Epub 2022 Apr 11. Erratum in: Lancet Respir Med. 2022 May 10;: PMID: 35421376; PMCID: PMC9000914.

[23] Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28:583-90.

[24] Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA. 2022;327(4):331-40.

[25] Moulia D. ACIP. Myocarditis and COVID-19 Vaccine Intervals: International Data and Policies. February 4, 2022 – CDC https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/11-COVID-Moulia-508.pdf

[26] Buchan SA, Seo CY, Johnson C, et al. Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval Among Adolescents and Adults in Ontario, Canada. JAMA Netw Open. 2022;5(6):e2218505. doi:10.1001/jamanetworkopen.2022.18505

[27] Mevorach D, Anis E, Cedar N, Hasin T, Bromberg M, Goldberg L, Levi N, Perzon O, Magadle N, Barhoum B, Parnassa E, Dichtiar R, Hershkovitz Y, Green MS, Ash N, Keinan-Boker L, Alroy-Preis S. Myocarditis After BNT162b2 COVID-19 Third Booster Vaccine in Israel. Circulation. 2022 Sep 6;146(10):802-804. doi: 10.1161/CIRCULATIONAHA.122.060961. Epub 2022 Sep 6. PMID: 36067275; PMCID: PMC9439627

[28] European Medicines Agency. Comirnaty https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty#product-information-section. Accessed March 10, 2023

[29] Husby A, Gulseth HL, Hovi P, et alClinical outcomes of myocarditis after SARS-CoV-2 mRNA vaccination in four Nordic countries: population based cohort studyBMJ Medicine 2023;2:e000373. doi: 10.1136/bmjmed-2022-000373

[30] Patel T, Kelleman M, West Z, Peter A, Dove M, Butto A, Oster ME. Comparison of Multisystem Inflammatory Syndrome in Children-Related Myocarditis, Classic Viral Myocarditis, and COVID-19 Vaccine-Related Myocarditis in Children. J Am Heart Assoc. 2022 May 3;11(9):e024393. doi: 10.1161/JAHA.121.024393. Epub 2022 Apr 27. PMID: 35475362; PMCID: PMC9238597.

[31] Brighton Collaboration. Myocarditis/Pericarditis Case Definition. https://brightoncollaboration.us/myocarditis-case-definition-update/ Accessed March 10, 2023.

[32] Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891

[33] European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

[34] FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf

[35] Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/

14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.