NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of Recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU
Protocol number	C4591010
Protocol version identifier	4.0
Date	07 January 2022
EU Post-Authorization Study (PAS) register number	EUPAS41302
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 Authorization Holder(s) (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	The research questions addressed by this study are a) What are the incidence rates of medically attended safety events of interest (based on the list of adverse events of special interest [AESI]) and other clinically significant events among persons vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine and b) Are these rates elevated relative to estimated expected rates?

	Primary study objectives: • Estimate the real-world incidence of medically attended safety events of interest and other clinically significant events among individuals vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine after authorization in the European Union (EU). *Secondary objectives* • Evaluate whether the vaccine recipients experience increased risk of medically attended safety events of interest post-vaccination, via comparison with expected background rates and, as feasible, by self-controlled risk interval (SCRI) analysis; • Estimate the incidence rates of medically attended safety events of interest among subcohorts of interest such as pregnant vaccine recipients, immunocompromised participants, and stratified by age.
Country(-ies) of study	The study will be conducted in Germany, Italy and Spain. Other countries may be included in addition to, or as a replacement, for one or more of these countries, as required.
Author	Rachel Reeves IQVIA Inc. 23 Forbury Road Reading RG1 3JH United Kingdom

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany
MAH contact person	Constanze Blume

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
AESI	adverse events of special interest
CEPI	Coalition for Epidemic Preparedness
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GBS	Guillain-Barré Syndrome
GPP	good pharmacoepidemiology practice
HCP	health care provider
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
IRR	incidence rate ratio
LMP	last menstrual period
MAH	marketing authorization holder

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
modRNA	modified ribonucleic acid
NIS	non-interventional study
OE	observed to expected
PAS	post-authorization study
PASS	post-authorization safety study
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SciSC	Scientific Steering Committee
SESI	safety events of special interest
SPEAC	Safety Platform for Emergency vACcines
SCRI	self-controlled risk interval
TFN	toll free number
VAED	vaccine-associated enhanced disease
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Rachel Reeves, PhD, MRes	Associate Epidemiology Director	IQVIA Inc.	23 Forbury Road, Reading, RG1 3JH, United Kingdom
Priscilla Velentgas, PhD	Senior Principal	IQVIA Inc.	201 Broadway, Cambridge, MA USA
Heather Rubino, PhD, MS	Safety Surveillance Research, Head	Pfizer Inc.	235 E 42nd St, New York, NY 10017
Cherise Wong, PhD, ScM	Safety Surveillance Research, Associate Director	Pfizer Inc.	235 E 42nd St, New York, NY 10017

4. ABSTRACT

Full Study Title: A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of Recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU

Protocol version 4.0 dated 07 January 2022

Main author: Rachel Reeves, IQVIA Inc., 23 Forbury Road, Reading, RG1 3JH United Kingdom

Rationale and Background:

The World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak and associated disease (Coronavirus disease 2019 [COVID-19]) a global pandemic in March 2020. Despite public health efforts, the incidence of COVID-19 has continued to rise. Given the rapid transmission of COVID-19 and incidence of disease in Europe, the rapid development of an effective vaccine is of utmost importance.

The Pfizer-BioNTech COVID-19 messenger ribonucleic acid (mRNA) vaccine has been granted conditional marketing authorization by the European Medicines Agency (EMA) for the prevention of SARS-CoV-2 infection. This study is part of a larger active surveillance plan to provide comprehensive information on real-world safety of the Pfizer-BioNTech COVID-19 mRNA vaccine within a 2-year period following vaccination of individuals within the European Union (EU).

This prospective cohort study is designed as a 30-month non-interventional post-authorization safety study (PASS) including participants vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine as an approved vaccine and followed for up to 24

months for the occurrence of selected safety outcomes. The medically attended safety events of interest in this study are based on the adverse events of special interest (AESI) defined by the Coalition for Epidemic Preparedness (CEPI)-funded Safety Platform for Emergency vACcines (SPEAC) working with the Brighton Collaboration. Additional AESIs may be identified as information emerges about events potentially related to vaccines.

As vaccine recommendations are updated over time, approaches to investigating vaccine safety must flexibly account for this. Heterologous primary vaccination (two different COVID-19 vaccines [different manufacturers] received for the first and second doses of a primary [initial] course) and heterologous boosting (a third dose of a different manufacturers COVID-19 vaccine as a booster 3 to 6 months after a primary vaccination course) have joined vaccine recommendations. In light of this, this study will enroll participants based on receipt of the Pfizer-BioNTech COVID-19 mRNA vaccine, with Version 4.0 of the protocol amended to account for heterologous vaccination courses prior to or during the study period in order to reflect the real-world context of the study.

This non-interventional study (NIS) is designated as a PASS and is a commitment to the EMA.

Research Question and Objectives:

The research questions addressed by this study are: a) What are the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine, and b) Are these rates elevated relative to estimated expected rates?

Primary study objective:

- Estimate the real-world incidence of medically attended safety events of interest and other clinically significant events among individuals vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine after authorization in the EU.

Secondary objectives:

- Evaluate whether the vaccine recipients experience increased risk of medically attended safety events of interest post-vaccination, via comparison with expected background rates and, as feasible, by self-controlled risk interval (SCRI) analysis;

- Estimate the incidence rates of medically attended safety events of interest among subcohorts of interest such as pregnant vaccine recipients, immunocompromised participants, and stratified by age.

Study Design:

This prospective, observational cohort study is a multi-center, non-interventional PASS conducted to evaluate safety of study participants receiving the Pfizer-BioNTech COVID-19 mRNA vaccine. This study will not provide or make recommendations on any vaccine use.

Participants will be invited to enroll and consented in the study after the decision has been made to administer the vaccine.

The study period is 30 months. Each participant will be followed from baseline (vaccination dose received at index date, where index date is defined as the date of Pfizer-BioNTech COVID-19 mRNA vaccine dose received within the 5 days prior to enrolment, regardless of dose number) until death, withdrawal of consent, loss to follow-up, 24 months or end of study period, whichever occurs first.

Data will be collected at baseline directly from the participants receiving the vaccine and/or their designee; this may include a health care provider (HCP) or study staff at the site administering the vaccine.

This study will collect information on all reported occurrences of the medically attended safety events of interest, which is based on the AESI lists specified by ACCESS and SPEAC/Brighton Collaboration, for which the participant sought medical care during the study period. Participants will choose their preferred method for submitting follow-up data:

- Completing questionnaires via a participant portal within the study website or mobile app, or
- Telephone interview via outbound calls from the IQVIA call center.

Data collection will be performed at baseline (vaccination dose received at index date), and at weeks 1, 2, 4, 6, 8, 12 and every three months thereafter, through 24 months following index date (or until the occurrence of death, withdrawal of consent, loss to follow-up, or end of study period, whichever occurs first). In addition, data will be collected on any subsequent vaccine doses received during the study period. If a participant receives a subsequent Pfizer-BioNTech COVID-19 mRNA vaccine dose during the study period, the data collection schedule will reset based on the reported date of subsequent vaccine dose, with data collected at weeks 1, 2, 4, 6, 8, 12 and every three months thereafter from the reported date of subsequent vaccine dose only. If a participant receives another COVID-19 vaccine (**not** the Pfizer-BioNTech COVID-19 mRNA vaccine) dose during the study period, the data collection schedule will not reset, but the participant will remain in the study and the follow-up schedule will continue based on the previous Pfizer-BioNTech COVID-19 mRNA vaccine date. The observation period will not be extended if subsequent COVID-19 vaccine doses (either Pfizer-BioNTech COVID-19 mRNA vaccine or another vaccine) are received; the observation period will remain at 24 months following baseline (vaccination dose received at index date), or until the occurrence of death, withdrawal of consent, loss to follow-up, or end of study period, whichever occurs first. Participants may also report medically attended safety events of interest at any time outside of regular survey follow-up, via the participant portal within the study website or mobile app, or to the IQVIA call center.

Participant reported medically attended safety events of interest will be confirmed by the treating HCPs or through medical record documentation if needed to validate or establish the

diagnosis associated with the event and validate the occurrence of a safety event of interest, or other clinically significant event.

Population:

This primary data collection study will aim for up to 10,000 vaccine recipients with 2 years of follow-up data from a total of approximately 20 centers. In order to reach this estimated sample size of vaccine recipients with complete data, 13,334 participants will be targeted for enrolment, assuming a 25% dropout rate over the 2-year follow-up period. The study will be conducted in Germany, Italy and Spain. Other countries may be included in addition to, or as a replacement, for one or more of these countries, as required to fulfill study objectives.

It is anticipated that participants will be enrolled from settings based upon the regional availability and distribution of the Pfizer-BioNTech COVID-19 mRNA vaccine, and may include physician offices, hospitals, pharmacies, and/or vaccination centers. Eligible and consenting individuals will be enrolled in the study at the time of presentation for vaccination. Limited inclusion/exclusion criteria will be applied in this study, to ensure comprehensive capture of individuals receiving the Pfizer-BioNTech COVID-19 mRNA vaccine in real-world settings.

Participants will be considered enrolled if they meet the inclusion/exclusion criteria below, have provided informed consent (as required per local regulations), and have reported the date of Pfizer-BioNTech COVID-19 mRNA vaccination at baseline.

Inclusion criteria

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

1. Participant's age is 18 years and above, and in accordance with the approved product label of the country where the study is conducted.

2. Enrolment within 5 days of receipt of any dose (i.e. first, second, or any subsequent booster dose) of the Pfizer-BioNTech COVID-19 mRNA vaccine.

   Note:

   Heterologous primary vaccination (two different COVID-19 vaccines [different manufacturers] received for the first and second doses of a primary [initial] course) and heterologous boosting (a third dose of a different manufacturers COVID-19 vaccine as a booster 3 to 6 months after a primary vaccination course) are now commonplace.

   Individuals receiving heterologous booster doses are allowed to enroll in this study, if the booster dose received is the Pfizer-BioNTech COVID-19 mRNA vaccine. However, if a participant is enrolling at second Pfizer-BioNTech COVID-19 mRNA vaccine dose, the first dose received must have also been the Pfizer-BioNTech

COVID-19 mRNA vaccine[1]. If a participant is enrolling at second or booster dose of Pfizer-BioNTech COVID-19 mRNA vaccine, the participant must be able to provide the date and manufacturer of all previous COVID-19 vaccine doses received in order to be eligible for inclusion.

3. Adult participants willing to provide informed consent according to local regulations and complete all study procedures in accordance with the protocol, including consent for the study team to contact the treating HCP or healthcare facility to obtain additional information related to safety events reported by the participant.

Exclusion criteria

Participants will be excluded from the study if they do not meet the inclusion criteria or have prior receipt of any investigational COVID-19 vaccination.

Variables:

The key vaccine exposure, baseline, and safety outcome variables are listed below.

Variable	Role	Data Source(s)[a]
Date of index date dose COVID-19 vaccination	Exposure	Participant and/or their designee
Location where index date dose COVID-19 vaccine was administered	Exposure	Participant and/or their designee
Vaccine lot number (index date dose)	Exposure	Participant and/or their designee
Anatomical site where index date dose COVID-19 vaccine was administered	Exposure	Participant and/or their designee
Date of all subsequent dose(s) COVID-19 vaccination(s)	Exposure	Participant and/or their designee

[1] Including participants receiving the Pfizer-BioNTech COVID-19 mRNA vaccine as their second dose, who *have not* received the Pfizer-BioNTech COVID-19 mRNA vaccine as their first dose, would result in any vaccine effects being difficult to distinguish between manufacturers. No such restrictions are placed upon participants enrolling at booster doses, as the time window between doses is anticipated to be longer, with reduced likelihood of overlapping risk intervals.

Variable	Role	Data Source(s)[a]
Location where all subsequent dose(s) COVID-19 vaccine was/were administered	Exposure	Participant and/or their designee
Vaccine lot number (all subsequent doses)	Exposure	Participant and/or their designee
Anatomical site where all subsequent dose(s) COVID-19 vaccine(s) was/were administered	Exposure	Participant and/or their designee
Demographics	Baseline characteristics	Participant and/or their designee
Medical History	Baseline characteristics	Participant and/or their designee
Employment characteristics	Baseline characteristics	Participant
Concomitant medications and other vaccines	Baseline characteristics	Participant and/or their designee
Participant reported safety event of interest	Outcome	Participant and/or their designee
Validated safety event of interest	Outcome	Health care provider questionnaire or medical record review
Participant reported hospitalization (date and length of admission)	Outcome	Participant and/or their designee
Validated hospitalization (date and length of admission)	Outcome	Health care provider questionnaire or medical record review
Participant's designee reported death (date)	Outcome	Participant's designee

Variable	Role	Data Source(s)[a]
Validated death (date)	Outcome	Health care provider questionnaire or medical record review
Pregnancy status and last menstrual period (LMP) (if applicable)	Baseline characteristics	Participant, their designee, or medical record review
Pregnancy outcomes (if applicable)	Outcome (live birth, preterm birth or still birth)[b]	Participant, their designee, or medical record review

a. Designee may include HCP or study staff administering the vaccine.
b. Pregnancy outcomes will be collected during study follow-up period.

Data on vaccine information, changes in medical history, concomitant medication use (if vaccine received is the Pfizer-BioNTech COVID-19 mRNA vaccine), and pregnancy status (female participants of childbearing age only) will also be collected at all subsequent vaccine doses for all enrolled participants.

The following data will be collected directly from participants at pre-specified follow-up points outlined in the data collection schedule:

1. Pregnancy status (female participants of childbearing age only), and pregnancy outcomes (as applicable).

2. Details on occurrence of medically attended safety events of interest since the last follow-up.

3. Any changes in contact information.

4. Changes in preferred follow-up method – telephone interview or web/app-based questionnaire.

Data Sources:

Baseline data will be collected via an electronic Case Report Form (eCRF) directly from the persons receiving the vaccine and/or their designee; this may include HCP or study staff administering the vaccine. Follow-up assessments will be collected directly from participants or their designees through standard questionnaires at the specified follow-up points through 24 months following index date.

If the participant fails to submit follow-up data and is non-responsive to follow-up reminders or telephone calls, follow-up with a secondary contact and the participant's primary care provider will be attempted.

Outcome Data Collection and Review

Outcomes to be collected in this study will include medically attended safety events of interest that are based on:

- Participant self-report during the specified follow-up schedule, or
- Spontaneous participant self-report outside of the specified follow-up schedule.

All medically attended safety events of interest will be captured on the appropriate eCRFs as designated by Pfizer.

Participant reported events of interest will be actively followed up for validation through direct follow-up with the treating HCP or healthcare facility and/or review of medical record documentation.

Scientific Steering Committee

IQVIA will assemble a team of independent external advisors for a Scientific Steering Committee (SciSC) and will develop the charter for the SciSC with input from Pfizer. Global experts will be included with an estimated 3-5 members, who will participate in regular teleconferences over the study period, with additional conferences to be convened as required. The role of the SciSC is to provide guidance on study design issues, ensure safeguards of the interests of the participants, and evaluate the results of interim and final analyses.

Study Size:

This study will aim for up to 10,000 Pfizer-BioNTech COVID-19 mRNA vaccine recipients with 2 years of follow-up data to give adequate precision of the estimated incidence rate, using a 95% confidence level to estimate the incidence of medically attended safety events of interest and other clinically significant events. In order to reach this estimated sample size of vaccine recipients with complete data, 13,334 participants will be targeted for enrolment, assuming a 25% dropout rate over the 2-year follow-up period.

Data Analysis:

The study population of Pfizer-BioNTech COVID-19 mRNA vaccine recipients will be described in terms of demographic and health history characteristics, along with vaccination characteristics such as number of doses received and interval between doses. The incidence rates of medically attended safety events of interest will be estimated in the primary safety dataset of participants who enroll within 2 days of vaccination. Rates will also be estimated for the overall study population and within subcohorts of interest such as pregnant vaccine recipients, immunocompromised participants, and within age-categories. The final analysis will also be conducted for the following additional subcohorts of interest: Pfizer-BioNTech vaccine only; Heterologous vaccination (Pfizer-BioNTech booster[s] only; Heterologous primary course; Other combination heterologous vaccine course/booster). For events with a

sufficient number of cases, the observed rate will be compared with expected rates where available from historical or concurrent rates as reported in the scientific literature or other sources including those reported by the EMA-funded COVID-19 vaccine monitoring ACCESS program. For selected endpoints, such as those with acute onset and a definable risk window, a SCRI analysis will be implemented if case counts are sufficient. All statistical analyses will be described in a statistical analysis plan (SAP).

Milestones:

Data collection is planned to start 31 August 2021. Twice yearly interim reports are planned until 01 March 2024, with the final study report planned for 30 September 2024.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	09 August 2021	Milestones, Inclusion criteria, Recruitment and retention, Participant consent, Participant withdrawal	Changed start of data collection and report dates; clarified inclusion criteria relating to age; updated participant reminders; deleted "or his or her legally acceptable representative, or parent(s) or legal guardian if a minor" from Participant consent section; added paragraph in the Participant withdrawal section regarding participants who cannot be contacted following implementation of the reminder schedule	Delayed study launch
2	07 January 2022	Section 3 Responsible Parties	Updated Pfizer principal investigator	New principal investigator added to the study
2	07 January 2022	General	Minor administrative and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol
2	07 January 2022	Section 9.1 Study Design Section 9.3 Variables Section 9.4 Data Sources Section 18 (Annex 3)	Data collection schedule to be centered around the receipt of Pfizer-BioNTech COVID-19 mRNA vaccine doses; updated data collection on subsequent COVID-19 vaccine doses; and added Figure 1 to illustrate data collection schedule over time	The updates to the data collection schedule and data collected reflect the inclusion criteria change, with additional information required on prior and subsequent COVID-19 vaccination doses received
2	07 January 2022	Section 9.2.1 Inclusion criteria	Updated inclusion criteria to allow participants to be enrolled upon receipt of their second or booster doses of Pfizer-BioNTech COVID-19 mRNA vaccine	To broaden the eligible target population by including participants at their second dose or booster dose. This change is required in order to meet the target study size, as most of the general population have now received multiple COVID-19 vaccine doses (reducing the available target population if participants can only be enrolled at first dose, and introducing biases in the population eligible to enroll), and in light of new national vaccination strategy in Spain to administer Pfizer-

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
				BioNTech COVID-19 mRNA vaccine as a booster dose only
2	07 January 2022	Section 9.5 Study Size	Updated Table 4 to provide a range of estimates for study population size and varying attrition rates	To illustrate the change in precision of incidence rates that correspond to different scenarios of recruitment and retention
2	07 January 2022	Section 9.7 Data Analysis	Addition of subcohorts of interest for data analysis, based on COVID-19 vaccine manufacturer (Pfizer-BioNTech COVID-19 mRNA vaccines only, or heterologous vaccination)	Given the updated inclusion criteria, and given the potential for mixed exposure, the final analysis should also be conducted by subcohorts of interest based on whether participants received Pfizer-BioNTech COVID-19 mRNA vaccine, heterologous primary, or heterologous booster vaccination course
2	07 January 2022	Section 9.9 Limitations of research methods	Added an additional paragraph on attributing outcome to relevant exposure period	Participants may receive multiple vaccine doses underscoring the importance of subcohort updates to the Data Analysis approach in Section 9.7 and expanded data collection on COVID-19 vaccines, as methods to mitigate this
2	07 January 2022	Section 18 (Annex 3)	Inclusion of data collection on pregnancy outcomes during study follow-up period	Data on pregnancy outcomes is to be collected in this study, rather than in a sub-registry as previously stated

6. MILESTONES

Milestone	Planned date
Start of data collection	31 August 2021
Registration in the EU PAS register	08 June 2021
Progress report	01 September 2021
Interim Reports	01 March 2022 01 September 2022 01 March 2023 01 September 2023 01 March 2024
End of data collection	31 October 2023
Final study report	30 September 2024

7. RATIONALE AND BACKGROUND

7.1. Background

In December 2019, a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was first identified by public health officials in China. The World Health Organization (WHO) declared the SARS-CoV-2 outbreak and associated disease (Coronavirus disease 2019 [COVID-19]) a global pandemic in March 2020 (1). Despite public health efforts, the incidence of COVID-19 has continued to rise, largely affecting middle-aged persons with worsening clinical sequelae linked to increasing age and comorbid conditions (e.g. cardiovascular disease, diabetes, and chronic lung disease) (2).

Given the rapid transmission of COVID-19 and incidence of disease in Europe, the rapid development of an effective vaccine is of utmost importance. Pfizer's and BioNTech's BNT162b2 vaccine candidate safety and efficacy are being tested worldwide in a diverse sample of subjects; however, individuals who are pregnant or immunocompromised are not included in the pivotal study, which has incorporated inclusion of subjects between 12 and 15 years of age (3). The Pfizer-BioNTech COVID-19 messenger ribonucleic acid (mRNA) vaccine has been granted conditional marketing authorization by the European Medicines Agency (EMA) for the prevention of SARS-CoV-2 infection. This study is part of a larger active surveillance plan to provide comprehensive information on real-world safety of the Pfizer-BioNTech COVID-19 mRNA vaccine within a 2-year period following vaccination of individuals within the European Union (EU).

7.2. Rationale

This prospective cohort study is designed as a 30-month non-interventional post-authorization safety study (PASS) including participants vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine as an approved vaccine and followed for up to 24 months for the occurrence of selected safety outcomes. The medically attended safety events of interest in this study are based on the adverse events of special interest (AESI) defined by the Coalition for Epidemic Preparedness (CEPI)-funded Safety Platform for

Emergency vACcines (SPEAC) working with the Brighton Collaboration as well as the list of AESI from ACCESS. This group has identified a number of AESIs as a priority for PASS of COVID-19 vaccines. These AESIs include adverse events (AEs) previously identified with immunization in general (e.g. anaphylaxis, Guillain-Barré Syndrome [GBS]), with vaccine platforms (such as mRNA) relevant to COVID-19 vaccine development (such as vaccine-associated enhanced disease [VAED]), or with theoretical concerns based on immunopathogenesis (4, 5). Additional AESIs may be identified as information emerges about events potentially related to vaccines.

As vaccine recommendations are updated over time, approaches to investigating vaccine safety must flexibly account for this. Heterologous primary vaccination (two different COVID-19 vaccines [different manufacturers] received for the first and second doses of a primary [initial] course) and heterologous boosting (a third dose of a different manufacturers COVID-19 vaccine as a booster 3 to 6 months after a primary vaccination course) have joined vaccine recommendations In light of this, this study will enroll participants based on receipt of the Pfizer-BioNTech COVID-19 mRNA vaccine, with Version 4.0 of the protocol amended to account for heterologous vaccination courses prior to or during the study period in order to reflect the real-world context of the study.

This non-interventional study (NIS) is designated as a PASS and is a commitment to the EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The research questions addressed by this study are: a) What are the incidence rates of medically attended safety events of interest (based on the list of AESI) and other clinically significant events among persons vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine, and b) Are these rates elevated relative to estimated expected rates?

Primary study objective:

- Estimate the real-world incidence of medically attended safety events of interest and other clinically significant events among individuals vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine after authorization in the EU.

Secondary objectives:

- Evaluate whether the vaccine recipients experience increased risk of medically attended safety events of interest post-vaccination, via comparison with expected background rates and, as feasible, by self-controlled risk interval (SCRI) analysis;

- Estimate the incidence rates of medically attended safety events of interest among subcohorts of interest such as pregnant vaccine recipients, immunocompromised participants, and stratified by age.

9. RESEARCH METHODS

9.1. Study design

This is a prospective, observational, multi-center, non-interventional PASS conducted to evaluate safety of study participants receiving the Pfizer-BioNTech COVID-19 mRNA vaccine using a combination of primary data collection and secondary data analysis. This study will not provide or make recommendations on any vaccine use. Participants will be invited to enroll and consented in the study after the decision has been made to administer the vaccine, and participation in this study will not change or influence a participant's standard of care in any way. There are no protocol-mandated visits or procedures associated with the study. The study period is 30 months. Each participant will be followed from baseline (vaccination dose received at index date, where index date is defined as the date of Pfizer-BioNTech COVID-19 mRNA vaccine dose received within the 5 days prior to enrolment, regardless of dose number) until death, withdrawal of consent, loss to follow-up, 24 months or end of study period, whichever occurs first.

Data will be collected at baseline directly from the participants receiving the vaccine and/or their designee; this may include a health care provider (HCP) or study staff at the site administering the vaccine. Follow-up data on medically attended safety events of interest will be collected directly from persons receiving the vaccine.

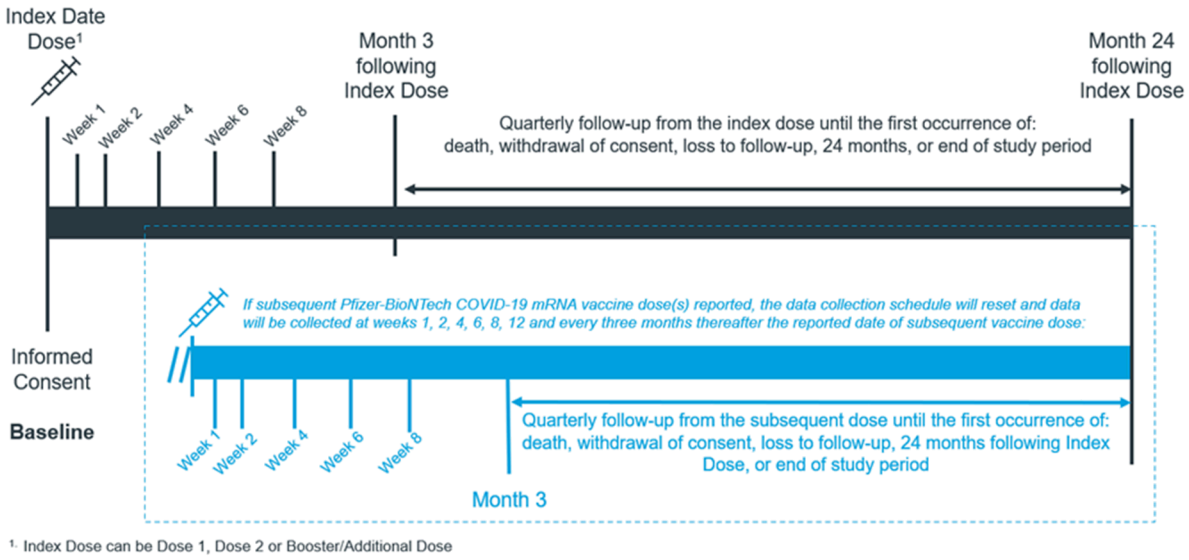
This study will collect information on all reported occurrences of the medically attended safety events of interest, which is based on the AESI lists specified by ACCESSS and SPEAC/Brighton Collaboration, for which the participant sought medical care during the study period. Participants will choose their preferred method for submitting follow-up data:

- Completing questionnaires via a participant portal within the study website or mobile app, or
- Telephone interview via outbound calls from the IQVIA call center.

Data collection will be performed at baseline (Pfizer-BioNTech COVID-19 mRNA vaccine dose received at index date), and at weeks 1, 2, 4, 6, 8, 12 and every three months thereafter, through 24 months following index date (or until the occurrence of death, withdrawal of consent, loss to follow-up, or end of study period, whichever occurs first). In addition, data will be collected on any subsequent vaccine doses received during the study period. If a participant receives a subsequent Pfizer-BioNTech COVID-19 mRNA vaccine dose during the study period, the data collection schedule will reset based on the reported date of subsequent vaccine dose, with data collected at weeks 1, 2, 4, 6, 8, 12 and every three months thereafter from the reported date of subsequent vaccine dose only. If a participant receives another COVID-19 vaccine (**not** the Pfizer-BioNTech COVID-19 mRNA vaccine) dose during the study period, the data collection schedule will not reset, but the participant will remain in the study and the follow-up schedule will continue based on the previous Pfizer-BioNTech COVID-19 mRNA vaccine date. The observation period will not be extended if subsequent doses are received; the observation period will remain at 24 months following baseline (vaccination dose received at index date), or until the occurrence of death, withdrawal of consent, loss to follow-up, or end of study period, whichever occurs first.

An overview of the data collection schedule is shown in Figure 1.

Figure 1. Data Collection Schedule



[1] Index Dose can be Dose 1, Dose 2 or Booster/Additional Dose

Participants may also report medically attended safety events of interest at any time outside of regular survey follow-up, via the participant portal within the study website or mobile app, or to the IQVIA call center.

Participant reported medically attended safety events of interest will be confirmed by the treating HCPs or through medical record documentation if needed to validate or establish the diagnosis associated with the event and validate the occurrence of a safety event of interest, or other clinically significant events. This process is further detailed in Section 10.

9.2. Setting

This primary data collection study will aim for up to 10,000 vaccine recipients with 2 years of follow-up data. In order to reach this estimated sample size of vaccine recipients with complete data, 13,334 participants will be targeted for enrolment, assuming a 25% dropout rate over the 2-year follow-up period. The study will be conducted in Germany, Italy and Spain in a total of approximately 20 centers. Other countries may be included in addition to, or as a replacement, for one or more of these countries, as required to fulfill study objectives.

It is anticipated that participants will be enrolled from settings based upon the regional availability and distribution of vaccine according to national or regional COVID-19 preparedness plans and may include physician offices, hospitals, pharmacies, and/or vaccination centers. Site selection criteria will include the projected availability of eligible participants in the enrolment period and the availability of physician (and other site staff) time to complete brief baseline case report forms (CRFs) where required. Selection criteria and basic site information (e.g. site size, site type) will be collected via a site qualification survey.

Limited inclusion/exclusion criteria will be applied in this study, to ensure comprehensive capture of individuals receiving the Pfizer-BioNTech COVID-19 mRNA vaccine in real-world settings.

Participants will be considered enrolled if they meet the inclusion/exclusion criteria below, have provided informed consent (as required per local regulations), and have reported the date of Pfizer-BioNTech COVID-19 mRNA vaccination at baseline.

9.2.1. Inclusion criteria

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

1. Participant's age is 18 years and above, and in accordance with the approved product label of the country where the study is conducted.

2. Enrolment within 5 days of receipt of any dose (i.e. first, second, or any subsequent booster dose) of the Pfizer-BioNTech COVID-19 mRNA vaccine.

   Note:

   Heterologous primary vaccination (two different COVID-19 vaccines [different manufacturers] received for the first and second doses of a primary [initial] course) and heterologous boosting (a third dose of a different manufacturers COVID-19 vaccine as a booster 3 to 6 months after a primary vaccination course) are now commonplace.

   Individuals receiving heterologous booster doses are allowed to enroll in this study, if the booster dose received is the Pfizer-BioNTech COVID-19 mRNA vaccine However, if a participant is enrolling at second Pfizer-BioNTech COVID-19 mRNA vaccine dose, the first dose received must have also been the Pfizer-BioNTech COVID-19 mRNA vaccine[2]. If a participant is enrolling at second or booster dose of Pfizer-BioNTech COVID-19 mRNA vaccine, the participant must be able to provide the date and manufacturer of all previous COVID-19 vaccine doses received in order to be eligible for inclusion.

3. Adult participants willing to provide informed consent according to local regulations and complete all study procedures in accordance with the protocol, including consent for the study team to contact the treating HCP or healthcare facility to obtain additional information related to safety events reported by the participant.

[2] Including patients receiving the Pfizer-BioNTech COVID-19 mRNA vaccine as their second dose, who *have not* received the Pfizer-BioNTech COVID-19 mRNA vaccine as their first dose, would result in any vaccine effects being difficult to distinguish between manufacturers. No such restrictions are placed upon participants enrolling at booster doses, as the time window between doses is anticipated to be longer, with reduced likelihood of overlapping risk intervals.

9.2.2. Exclusion criteria

Participants will be excluded from the study if they do not meet the inclusion criteria or have prior receipt of any investigational COVID-19 vaccination.

9.2.3. Recruitment and retention

After vaccination, all eligible individuals will be invited to participate in the study within 5 days of vaccination, and will be fully informed about the nature and objectives of the study, as well as the sharing of data relating to the study. The study recruitment strategy will encourage enrolment within 2 days of vaccination. Individuals will be provided adequate time to have questions answered prior to consenting to participate. Further details of the consent process are detailed in Section 9.2. All participants will be able to withdraw consent at any time via the app, or at any follow-up point via telephone.

Participants will be followed up at pre-specified, regular intervals. As described in Section 9.1, participants will have the opportunity to choose their preferred method of follow-up. Reminders will be sent if a participant fails to submit follow-up data via the app, and follow-up calls will be attempted if a participant fails to submit follow-up data via telephone. If the participant is non-responsive to follow-up reminders or telephone calls, follow-up with a secondary contact and the participant's primary care will be attempted, in order to determine whether non-response is due to a safety event of interest.

For participants who request to participate via the app, the following reminder schedule will be implemented:

For the weekly and bi-weekly questionnaires completed as needed after each dose:

- Two digital reminders,
- If digital reminders are ignored by the participant, the IQVIA call center will call to remind the participant to complete the questionnaire, as well as offer a Toll Free Number (TFN) if the participant would prefer to complete the questionnaire over the phone by talking to an agent,
- If no response to the call center or call-in to TFN, the named secondary contact provided by the participant will be contacted,

For the quarterly questionnaires after each dose:

- Three digital reminders,
- If digital reminders are ignored by the participant, the IQVIA call center will call to remind the patient to complete the questionnaire, as well as offer a TFN if the participant would prefer to complete the questionnaire over the phone by talking to an agent,
- If no response to the call center or call-in to TFN, the named secondary contact provided by the participant will be contacted,

For participants who indicate a phone call as their preferred method of follow-up, the reminder schedule will be similar to the approach described above, but rather than the initial digital reminders, the first follow-up attempts will be via the call center. If these are ignored, the call center will phone the named secondary contact.

9.3. Variables

The key vaccine exposure, baseline, and safety outcome variables are listed in Table 1 Detailed definitions are provided in Section 9.3.1.

Table 1. Key vaccine exposure, baseline, and safety outcome variables to be collected in this study

Variable	Role	Data Source(s)[a]
Date of index date dose COVID-19 vaccination	Exposure	Participant and/or their designee
Location where index date dose COVID-19 vaccine was administered	Exposure	Participant and/or their designee
Vaccine lot number (index date dose)	Exposure	Participant and/or their designee
Anatomical site where index date dose COVID-19 vaccine was administered	Exposure	Participant and/or their designee
Date of all subsequent dose(s) COVID-19 vaccination(s)	Exposure	Participant and/or their designee
Location where all subsequent COVID-19 vaccine dose(s) was/were administered	Exposure	Participant and/or their designee
Vaccine lot number (all subsequent doses)	Exposure	Participant and/or their designee

Table 1. Key vaccine exposure, baseline, and safety outcome variables to be collected in this study

Variable	Role	Data Source(s)[a]
Anatomical site where all subsequent COVID-19 vaccine(s) was/were administered	Exposure	Participant and/or their designee
Demographics	Baseline characteristics	Participant and/or their designee
Medical History	Baseline characteristics	Participant and/or their designee
Employment characteristics	Baseline characteristics	Participant
Concomitant medications and other vaccines	Baseline characteristics	Participant and/or their designee
Participant reported safety event of interest (described in Section 9.3.1)	Outcome	Participant and/or their designee
Validated safety event of interest	Outcome	Health care provider (HCP) questionnaire or medical record review
Participant reported hospitalization (date and length of admission)	Outcome	Participant and/or their designee
Validated hospitalization (date and length of admission)	Outcome	Health care provider questionnaire or medical record review
Participant's designee reported death (date)	Outcome	Participant's designee
Validated death (date)	Outcome	Health care provider questionnaire or medical record review
Pregnancy status and last menstrual period (LMP) (if applicable)	Baseline characteristics	Participant, their designee, or medical record review

Table 1. Key vaccine exposure, baseline, and safety outcome variables to be collected in this study

Variable	Role	Data Source(s)[a]
Pregnancy outcomes (if applicable)	Outcome (live birth, preterm birth or still birth)[b]	Participant, their designee, or medical record review

a. Designee may include HCP or study staff administering the vaccine.
b. Pregnancy outcomes will be collected during study follow-up period.

9.3.1. Safety Outcome Definitions

Data on medically attended safety events of interest will be collected from the time of participants' enrolment into the study until death, withdrawal of consent, loss to follow-up or end of study period, whichever occurs first.

Medically attended safety events of interest in this study are listed in Table 2. These events are based on the AESI lists developed by ACCESS and SPEAC/Brighton Collaboration, which consists of events previously identified with immunization in general (e.g. anaphylaxis, GBS), with vaccine platforms relevant to COVID-19 vaccine development, or with theoretical concerns based on immunopathogenesis or viral replication during wild type disease (4, 5).

Participant reported medically attended safety events of interest will be followed up with the treating HCPs or through medical record documentation if needed to validate or establish the diagnosis associated with the event and validate the occurrence of a safety event of interest, or other clinically significant event. Additional safety events may be added as endpoints based on emerging findings from clinical studies, spontaneous reports, literature or updates in guidance.

Table 2. Medically attended safety events of interest[a]

Body System	Safety Event
Neurologic	Generalized convulsion/ seizure
	Guillain-Barré Syndrome (GBS)
	Aseptic meningitis
	Encephalitis / Encephalomyelitis
	Other acute demyelinating diseases
	Transverse myelitis
	Multiple sclerosis
	Optic neuritis

Table 2. Medically attended safety events of interest[a]

Body System	Safety Event
	Bell's palsy
	Acute disseminated encephalomyelitis
Immunologic	Anaphylaxis
	Vasculitides*
	Arthritis and arthralgia
	Multisystem inflammatory syndrome in adults (MIS-A)
	Kawasaki disease
	Fibromyalgia
	Autoimmune thyroiditis
COVID-19	Severe COVID-19 disease * **
	Acute respiratory distress syndrome
	Microangiopathy*
	Heart failure and cardiogenic shock*
	Stress cardiomyopathy*
	Coronary artery disease*
	Arrythmia*
	Deep vein thrombosis
	Pulmonary embolus
	Cerebrovascular stroke
	Limb ischemia*
	Hemorrhagic disease*
	Acute kidney injury*
	Acute liver injury
	Chilblain-like lesions
	Single organ cutaneous vasculitis*
	Erythema multiforme*
	Anosmia, Ageusia
	Acute pancreatitis

Table 2. Medically attended safety events of interest[a]

Body System	Safety Event
	Rhabdomyolysis
	Subacute thyroiditis
Cardiac	Myocarditis
	Pericarditis
	Acute myocardial infarction
	Microangiopathy
	Heart failure
	Stress cardiomyopathy
	Coronary artery disease arrhythmia
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation
	Coagulation disorder (includes thrombotic disorders, bleeding disorders)
Other	Death
	Narcolepsy and cataplexy
	Non-anaphylactic allergic reactions
	Reactogenicity • Injection site reaction (redness, warmth, pain, itch, hematoma, swelling, induration) • Fever/feverishness • Shivering/chills • Headache • Vomiting and Diarrhoea • Myalgia/muscle pain • Arthralgia/joint pain • Malaise • Fatigue

a. The medically attended safety events of interest in this study are based on the adverse events of special interest (AESI) defined by ACCESS as well as the Coalition for Epidemic Preparedness (CEPI)-funded Safety Platform for Emergency vACcines (SPEAC) working with the Brighton Collaboration. Additional medically attended safety events of interest may be identified as information emerges about events potentially related to vaccines. Details on risk windows for events will be detailed in the SAP.

Table 2. Medically attended safety events of interest[a]

Body System	Safety Event

* Hospitalized manifestations only.
** All hospitalized COVID-19 disease will be assessed for vaccine-associated enhanced disease.

9.4. Data sources

Scheduled assessments for the study are presented in the Data Collection Schedule provided in Table 3 below. Participant informed consent must be obtained before any data are collected.

Baseline data will be collected via an electronic Case Report Form (eCRF). At baseline, data listed in Section 9.4.1 will be collected directly from the persons receiving the vaccine and/or their designee; this may include HCP or study staff administering the vaccine. Data describing vaccine administration on that date will also be collected.

For follow-up data, standard questionnaires will be completed by participants or their designees online or via the mobile app. The data listed in Section 9.4.2 will be collected. Telephone interviews will use a standard script for interviews. Both data collection methods will include information that reported medically attended safety events of interest and laboratory confirmed COVID-19 infections may trigger additional follow-up to obtain further information.

Participant reported medically attended safety events of interest will be reviewed and additional safety data will be collected from HCPs if needed to validate or establish the diagnosis associated with the event and validate the occurrence of the reported safety event or other clinically significant events. A standard questionnaire will be used for this follow-up.

Participants will be asked to report any subsequent COVID-19 vaccine received during the follow-up period. The data to be collected is listed in Section 9.4.3.

If the participant fails to submit follow-up data / is non-responsive to follow-up reminders or telephone calls, follow-up with a secondary contact will be conducted (as per Section 9.2.3) in order to determine whether non-response is due to a safety event of interest.

Table 3. Data Collection Schedule.

	Baseline	Each subsequent vaccine dose	Follow-up at weeks 1, 2, 4, 6, 8 and 12 following each Pfizer-BioNTech COVID-19 mRNA vaccine dose	Quarterly follow-up until 24 months following index date, or end of study, whichever occurs first
Informed consent	X			
Demographics	X			
Medical history	X	X		
Concomitant medication and other vaccines	X	X		
Pfizer-BioNTech COVID-19 mRNA vaccine information	X	X		
Pregnancy status (if applicable)	X	X	X	X
Occurrence of medically attended safety events of interest			X	X
Pregnancy outcomes (if applicable)			X	X
Contact information and preferred follow-up method	X	X	X	X
Reason for discontinuation from study (if applicable)			X	X

9.4.1. Baseline Assessment (vaccine dose received at index date)

The following data will be collected at baseline for all enrolled participants (further details in Annex 3):

1. Informed consent.
2. Unique identifier.
3. Demographics (age, gender, ethnicity, occupation).

4. Medical history, if available, including:
    - Allergies to medication,
    - Pre-existing co-morbidities, including (but not limited to) chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders,
    - Indicators of frailty[3],
    - Whether the participant is immunocompromised for any reason,
    - Presence of potential active viral disease within previous 3 days (fever, symptoms of cold, flu, or other inflammatory/infectious process),
    - Information of any prior laboratory confirmed diagnosis of COVID-19,
    - COVID-19 vaccination history prior to index date dose, including date(s) of previous immunization(s), dose(s), and manufacturer,
    - Pregnancy status (female participants of childbearing potential only).
5. Any concomitant medication taken within the 7 days prior to vaccination, if available, including prescription and non-prescription medication (e.g. herbal or homeopathic medication) as well as medication with long half-life or long-term effect (e.g. immunoglobulins, blood transfusions, immunosuppressants), and any other vaccines received.
6. Vaccination information (of index date Pfizer-BioNTech COVID-19 mRNA vaccine dose), including date of immunization, dose, lot number, anatomical site of injection.
7. Contact information (which may include telephone number and/or email address) for:
    - The participant,
    - A secondary contact for the participant [for follow-up purposes only],
    - Primary care physician [for follow-up purposes only].
8. Preferred participant follow-up method – telephone interview or web/app-based questionnaire.

[3] Indicators of frailty will be collected via two means: (1) directly from participants, during completion of the baseline questionnaire, and (2) from the treating health care provider during follow-up of safety events of interest reported by the participant. To collect indicators of frailty directly from participants, the PRISMA 7 questionnaire will be used for participants aged 65 years and over, and all participants will be asked a question on Self-Reported Health. See Annex 3 for further questionnaire details.

9.4.2. Weekly, monthly, and long-term follow-up, through 24 months following the index date vaccine dose

The following data will be collected directly from participants at pre-specified follow-up points outlined in the data collection schedule (further details in Annex 3).:

1. Pregnancy status (female participants of childbearing potential only), and pregnancy outcomes (as applicable).
2. Details of medically attended safety events of interest, including laboratory confirmed diagnosis of COVID-19, since the last follow-up.
3. Any changes in contact information.
4. Changes in preferred follow-up method – telephone interview or web/app-based questionnaire.
5. Discontinuation data will be collected for all enrolled participants at the time of discontinuation:
    - Date of discontinuation.
    - Number of vaccine doses received at the time of discontinuation.
    - Reason for discontinuation.

Data on reactogenicity will be collected only during week 1 following each Pfizer-BioNTech vaccine dose.

9.4.3. Each subsequent COVID-19 vaccine dose during the follow-up period

Participants will be asked to report any subsequent COVID-19 dose received during the follow-up period (further details in Annex 3).

The following information will be collected at all subsequent COVID-19 vaccine doses (irrespective of whether the vaccine received was the Pfizer-BioNTech COVID-19 mRNA vaccine or another COVID-19 vaccine):

1. Vaccine manufacturer.
2. Date of immunization.
3. Pregnancy status (female participants of childbearing potential only).
4. Any changes in contact information.
5. Changes in preferred follow-up method – telephone interview or web/app-based questionnaire.

If the vaccine received was the Pfizer-BioNTech COVID-19 mRNA vaccine, the following information will also be collected:

6. Additional vaccination information, including dose, lot number, anatomical site of injection.
7. Changes in prior submitted medical history, including any other vaccines received, and concomitant medication use within the 7 days prior to vaccination, if available.

9.5. Study size

The primary objective of this study is to quantify the incidence of medically attended safety events of interest by estimating their incidence rates per 10,000 person-years, calculated as the number of participants experiencing the event after receiving a dose of the Pfizer-BioNTech COVID-19 mRNA vaccine during the person-time at risk (numerator) divided by the total person-time at risk (denominator).

The target for enrolment will be approximately 13,334 participants (vaccine recipients). Table 4 provides illustrative examples of expected margin of error ([width of confidence interval/2]) for different incidence rates per 10,000 person-years. The margin of error was calculated for a range of attrition rates (25%, 40%, and 55%) for illustrative purposes.

Table 4. Margin Of Error Scenarios For Targeted Sample Size And Different Incidence Rates Over A 24-Month Follow-Up Period

Target n	Attrition rate assumption	Expected n who complete 24 months follow-up	Incidence rate (per 10,000 person-years)	95% Confidence intervals (exact) according to different incidence scenarios	Margin of error
13,334	25%	10,000	1	[0, 3]	1.5
			5	[3, 9]	3.0
			10	[6, 15]	4.5
			50	[41, 60]	9.5
			250	[230, 271]	20.5
			500	[472, 530]	29.0
			2500	[2436, 2565]	64.5
			5000	[4910, 5092]	91.0
	40%	8,000	1	[0, 4]	2.0
			5	[2, 10]	4.0

Table 4. Margin Of Error Scenarios For Targeted Sample Size And Different Incidence Rates Over A 24-Month Follow-Up Period

Target n	Attrition rate assumption	Expected n who complete 24 months follow-up	Incidence rate (per 10,000 person-years)	95% Confidence intervals (exact) according to different incidence scenarios	Margin of error
			10	[5, 17]	6.0
			50	[39, 64]	12.5
			250	[223, 279]	28.0
			500	[462, 540]	39.0
			2500	[2414, 2588]	87.0
			5000	[4878, 5124]	123.0
	55%	6,000	1	[0, 6]	3.0
			5	[1, 12]	5.5
			10	[5, 20]	7.5
			50	[37, 68]	15.5
			250	[218, 286]	34.0
			500	[454, 549]	47.5
			2500	[2396, 2607]	105.5
			5000	[4853, 5151]	149.0

The 95% confidence intervals are derived using the (exact) Clopper and Pearson method.

Calculations were done in R Version 4.0.2.

Further analyses described in Section 9.7 for secondary endpoints will be exploratory in nature and will not involve formal hypothesis testing. The statistical analysis plan (SAP) will expand the statistical methods mentioned in Section 9.7 of this protocol.

9.6. Data management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the electronic data capture (EDC) system and followed up for resolution. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when locked for analysis.

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

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 completed CRF is required for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. IQVIA shall ensure that the CRFs are securely stored at the IQVIA data warehouse in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

IQVIA has ultimate responsibility for the collection and reporting of all data entered on the CRFs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRF serves as the source document. Any corrections to entries made in the CRFs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, IQVIA agrees to keep all study-related records. The records should be retained by IQVIA according to local regulations or as specified in the vendor contract, research agreement, whichever is longer. IQVIA must ensure that the records continue to be stored securely for so long as they are retained.

If IQVIA becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. 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 IQVIA and Pfizer have expressly agreed to a different period of retention

via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

9.7. Data analysis

The study population of Pfizer-BioNTech COVID-19 mRNA vaccine recipients will be described in terms of demographic characteristics (age, gender, ethnicity, occupation) and medical history characteristics outlined in Section 9.4.1. Vaccination characteristics, including number of doses received and interval between doses, will also be described.

The incidence rates of medically attended safety events of interest and corresponding 95% Poisson exact confidence intervals (95% CI) will be estimated in the primary safety dataset of participants who enroll within 2 days of vaccination. Rates will also be estimated for the overall study population and within subcohorts of interest such as pregnant vaccine recipients, immunocompromised participants, and within age-categories.

A final analysis will also be conducted for the following subcohorts of interest, given the potential for mixed exposure:

1. **Pfizer-BioNTech vaccine only**: all participants who only receive Pfizer-BioNTech COVID-19 mRNA vaccine(s), and no other COVID-19 vaccine(s), prior to index date and during their follow-up period.

2. **Heterologous vaccination:**

    a) **Pfizer-BioNTech booster(s) only:** all participants who received only Pfizer-BioNTech COVID-19 mRNA vaccine dose(s) as booster dose(s) during the study period, but where the primary vaccine course (prior to index date) was non-Pfizer-BioNTech.

    b) **Heterologous primary course:** all participants who received Pfizer-BioNTech COVID-19 mRNA vaccine as a first dose at index date, and then received a non-Pfizer-BioNTech second dose during their follow-up period. No booster doses were received.

    c) **Other combination heterologous vaccine course/booster**: all participants with a heterologous primary course and/or heterologous booster dose(s), who do not fit the criteria for inclusion in subcohorts 2(a)-(b) above.

It is anticipated that rates will be reported for the following intervals, overall and for each of the subcohorts of interest:

- Follow-up at weeks 1, 2, 4, 6 and 8 following a Pfizer-BioNTech COVID-19 mRNA vaccine dose,
- Quarterly follow-up following a Pfizer-BioNTech COVID-19 mRNA vaccine dose (until 24 months following index date vaccine dose, or end of study, whichever occurs first).

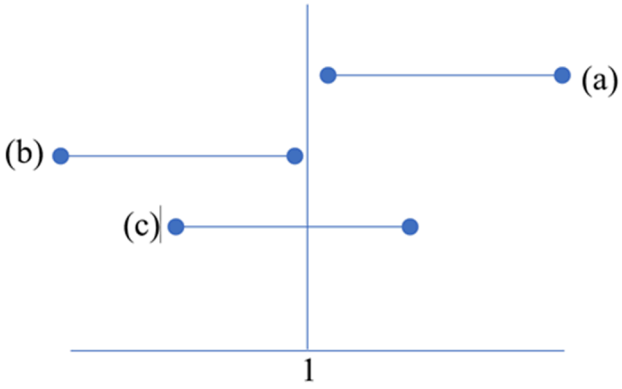
Time at risk will be assessed from the Pfizer-BioNTech COVID-19 mRNA vaccine dose until the subsequent follow-up time point or until the next Pfizer-BioNTech COVID-19 mRNA vaccine dose received, death, withdrawal of consent, loss to follow-up, 24 months or end of study period, whichever occurs first. Sensitivity analysis may be conducted with censoring at any COVID-19 vaccine dose received.

All cases of reported laboratory confirmed COVID-19 in the study population will be described by the Brighton Collaboration "Vaccine-associated Enhanced Disease" Working Group case definitions for COVID-19 VAED.

Counts of newly reported medically attended safety events of interest and counts of vaccinated participants will be summarized as per the intervals above. Counts will be summarized by whether medical validation of the event was possible, or not.

To answer the first secondary objective, the observed rate of events will be compared with expected rates using the Observed to Expected (OE) analysis approach (6). The core principle of OE analysis is to estimate the expected number of coincidental cases of medically attended safety events of interest, under the assumption of no association with the vaccine. Expected numbers are then compared with the number of cases actually reported in vaccine recipients. The expected background incidence rate of a particular safety event of interest is the number of new cases occurring naturally in the population, expressed in person-time. The comparison of OE number of medically attended safety events of interest will be expressed as the ratio of the observed over the expected: an OE ratio equal to 1 means that the observed number of cases equals the expected number of cases, whereas an OE ratio greater than 1 signals an excess of risk in the vaccinated population. The statistical uncertainty of the OE analysis will often be driven by the observed number of cases, which are often rare events. To deal with this statistical uncertainty, a 95% Poisson exact confidence interval (95% CI) will be calculated (7). If the lower limit of the 95% CI of the OE ratio is greater than 1, the observed value is considered significantly higher than expected (Figure 2, case [a]). If the upper limit of the 95% CI of the OE ratio is lower than one, the observed value is considered significantly lower than expected (Figure 2, case [b]). If the 95% CI contains 1, then the observed and the expected numbers will not be considered significantly different (Figure 2, case [c]).

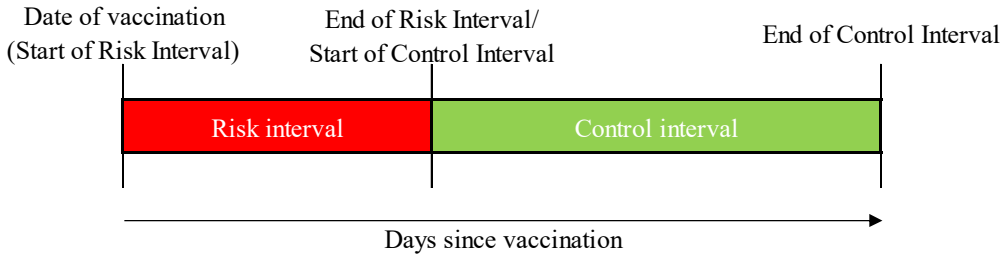
Figure 2. Observed to Expected (OE) Ratios and 95% Confidence Intervals (CIs)



Expected background rates of safety event of interest will be obtained from the EMA-funded COVID-19 vaccine monitoring ACCESS program (8). The ACCESS program is generating background incidence rates of AESI for COVID-19 vaccines over the period 2017 to 2020 from 10 healthcare databases in 7 European countries (8). The analysis in this study will include age-categories in line with the published incidence rates from ACCESS (18-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80+). For safety event of interest which are not expected to be investigated through the ACCESS program, expected rates will be obtained from historical or concurrent rates reported in the literature, including from reports or data available through health authorities or large databases where possible (9, 10). This OE analysis has been favorably compared with other methods for active surveillance of vaccine safety (10).

For selected endpoints, such as those with acute onset and a defined risk window (listed in Annex 4), a SCRI analysis will be implemented if case counts are sufficient. SCRI analysis, described by Farrington (11, 12, 13), compares incidence rates between "risk" and "control" time periods (intervals) among vaccinated individuals, under the assumption that the risk of onset of a safety event of interest on a day during the risk period is the same as that on a day during the control period. The risk interval is a biologically plausible window of time following a vaccine when a safety event of interest could be caused by the vaccine (Figure 3).

Figure 3. Self-Controlled Risk Interval (SCRI) analysis: defining risk and control intervals



Medically attended safety events of interest caused by the vaccine would be expected to cluster shortly after vaccination, and therefore medically attended safety events of interest caused by the vaccine would be expected to have higher incidence rates in the risk interval than in the control interval for an individual. If medically attended safety events of interest are found to cluster in the pre-defined risk window shortly after vaccination, this would suggest – though not confirm – a causal association. The comparison of the risk to the control windows can be expressed as the ratio of the safety event of interest incidence rate on the risk interval over the 1 on control interval: an incidence rate ratio (IRR) of 1 means that the incidence rate is the same in both intervals, whereas an IRR greater than 1 signals an excess of risk in the risk interval (shortly after vaccination). If the lower limit of the 95% CI of the IRR is greater than 1, the incidence rate in the risk interval is considered significantly higher than that in the control interval; if the upper limit of the 95%CI of the IRR is lower than 1, the incidence rate in the risk interval is considered significantly lower than that in the control interval; if the 95%CI contains 1, the incidence rates are not considered significantly different between the 2 intervals. This methodology has been widely used in vaccine safety studies and has been shown to be a powerful and practical method of assessing vaccine safety, with the self-controlled design implicitly controlling for fixed (non time-varying) confounding factors (e.g. sex, ethnicity) (13, 14).

The SCRI analysis will be carried out as part of the final analysis following database lock. Risk intervals for each safety event of interest will be sourced from published literature. The IRR of medically attended safety events of interest occurring in the risk interval versus the control period will be estimated by fitting a conditional Poisson regression model (15). For each safety event of interest, analyses will be restricted to individuals who experience that safety event of interest either during the risk or the control interval.
Sensitivity analysis may be conducted considering different assumptions of the risk and control window lengths.

Table 5 depicts the planned analyses related to each study objective.

Table 5. Planned analysis by study objective

Objective	Outcome of interest	Planned analysis
Primary study objective: Estimate the real-world incidence of medically attended safety events of interest and other clinically significant events among individuals vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine after approval in the EU.	Medically attended safety events of interest, and other clinically significant events	Incidence rates per 10,000 person-years and corresponding 95% Poisson exact CI. Incidence rates precision estimates as provided in Section 9.5.
Secondary objective: Evaluate whether the vaccine recipients experience increased risk of medically attended safety events of interest post-vaccination, via comparison with expected background rates and, as feasible, by self-controlled risk interval (SCRI) analysis.	Medically attended safety events of interest	OE analysis: Safety event of interest (observed) incidence rates in cohort of study participants compared to background (expected) incidence rates, obtained from the EMA-funded COVID-19 vaccine monitoring ACCESS program or, if unavailable, from historical or concurrent rates reported in the literature. SCRI analysis: Incidence rate ratio (IRR) of medically attended safety events of interest occurring in the risk interval versus the control period, estimated by conditional Poisson regression models. Sensitivity analysis for SCRI: considering different lengths of the risk and control intervals.

Table 5. Planned analysis by study objective

Objective	Outcome of interest	Planned analysis
Secondary objective: Estimate the incidence rates of medically attended safety events of interest among sub-cohorts of interest such as pregnant vaccine recipients, immunocompromised participants, and stratified by age.	Medically attended safety events of interest	Incidence rates per 10,000 person-years and corresponding exact Poisson 95%CI*: • Among sub-cohort of pregnant vaccine recipients, • Among sub-cohort of immunocompromised participants, • Stratified by age: 18-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80 and above.

European Union (EU); 95% Poisson exact confidence intervals (95% CI); self-controlled risk interval (SCRI); incidence rate ratio (IRR).

*analysis presented by subcohorts of Pfizer-BNT COVID-19 mRNA vaccine, or heterologous vaccination courses, in the final report.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP will include the pre-defined expected background rates of medically attended safety events of interest for the OE analysis, including those published by the ACCESS program, and the risk intervals for medically attended safety events of interest anticipated to be included in the SCRI analysis if case counts are sufficient. Sensitivity analyses will also be detailed in the SAP.

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. Handling of missing data

It is optimal to prevent missing data, to the extent possible, through strategies set forth in the design and conduct of a study. For the current study, we will aim to minimize missing information by:

- Following the larger active surveillance plan, aiming to actively engage participants to provide information on safety events.
- Ensuring that primary variables of interest are those that are routinely collected as part of real-world clinical care and are available via medical charts, physician and/or participant reporting, as appropriate.
- Collecting only critical data elements (i.e. variables aligned with the study objectives) to minimize site/participant burden.

- Including "not applicable", "not done" on CRFs to differentiate these from values that are truly unknown.
- Training of sites and data abstractors regarding data collection; setting reporting windows around a target timepoint.
- Planning for random missingness, loss to follow-up, and attrition in the sample size calculations.

Should missing data occur, the data will be analyzed as they are recorded in the study eCRFs. Counts of missing data will be reported for demographic and medical history variables, as outlined in Section 9.4.1 . Missing safety data will not be imputed. Handling of missing data, including partial/completely missing dates, will be described in the SAP.

9.8. Quality control

A study monitoring plan that is appropriate for the study design will be developed and implemented. IQVIA will provide training on the conduct of the study to all relevant staff involved in the study. Representatives of Pfizer's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.9. Limitations of the research methods

This is a non-interventional, multinational, multi-center PASS to further document the safety profile of participants vaccinated with the Pfizer-BioNTech COVID-19 mRNA vaccine. Participants will be followed for up to 24 months after their vaccine dose.

The time frame of 24 months post-vaccination will allow evaluation of the long-term safety profile of the Pfizer-BioNTech COVID-19 mRNA vaccine in a real-world population. To reduce the likelihood of sampling bias, broad inclusion criteria and consecutive participant selection will be applied.

Recruiting participants soon after vaccination is important to prevent over-representation of participants who elect to enroll only after experiencing an event. The study recruitment strategy will encourage enrolment within 2 days of vaccination, but in consideration of the enrolment goal of up to 10,000 participants, diverse and changing local vaccine roll-out strategies, and to provide potential participants enough time to inform themselves fully before consenting, only enrollment within 5 days of vaccination will be eligible.

There is potential for loss to follow-up prior to study completion. To reduce the likelihood of loss to follow-up, active monitoring of participants will be employed. For participants who discontinue the study prematurely, the reason(s) for discontinuation will be recorded. The sponsor will aim to minimize missing information by the measures outlined in Section 9.7.1.

There is also the potential for recall bias where participants may not remember or report events that occurred in between the questionnaire intervals. This is likely to be minimized by focusing on serious events and hospitalizations.

As participants may receive multiple vaccine doses during the study period, and may receive different types of COVID-19 vaccine, attributing outcomes to the relevant exposure period may be challenging. However, this will be mitigated through the collection of data on other vaccines (including date and manufacturer), including those received prior to the index date dose (e.g. to facilitate exclusion of participants who received the Pfizer-BioNTech COVID-19 mRNA vaccine as their second dose, who *did not* receive the same vaccine as their first dose), as well as through sensitivity analysis.

9.10. Other aspects

9.10.1. Study management

This study will be performed by IQVIA, with guidance, input, review and approval of Pfizer, including development of materials, recruitment, training and management of sites, EDC and data management and analysis.

9.10.2. Scientific Steering Committee

IQVIA will assemble a team of independent external advisors for a Scientific Steering Committee (SciSC) and will develop the charter for the SciSC with input from Pfizer. Global experts will be included with an estimated 3-5 members, who will participate in regular teleconferences over the study period, with additional conferences to be convened as required. The role of the SciSC is to provide guidance on study design issues, ensure safeguards of the interests of the participants, and evaluate the results of interim and final analyses.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Participant information

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

Participant personal data will be stored at IQVIA in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. IQVIA will implement 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, IQVIA shall be responsible for determining whether a personal data breach has in fact occurred and, if so, 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 authorized parties, any participant names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, participant-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with the vendor contract and applicable privacy laws.

10.2. Participant consent

The informed consent materials and any participant recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent materials used during the informed consent process and any participant recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

IQVIA must ensure each study participant, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. IQVIA further must ensure that each study participant, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

10.3. Participant withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of IQVIA or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document participant outcome, if applicable. IQVIA would inquire about the reason for withdrawal and follow-up with the participant regarding any unresolved AEs.

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Participants who cannot be contacted following implementation of the reminder schedule (Section 9.1) are still considered to be in follow-up through the 24-month follow-up period if they are not considered withdrawn as described above.

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

It is the responsibility of IQVIA to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g. statement regarding agreement to participate), and other relevant documents, (e.g. recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by IQVIA. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements applicable to non-interventional studies, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for

Pharmacoepidemiology, Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), and the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

To address the safety surveillance objectives of this study, the management and reporting of AEs/adverse reactions are separated into three components. The first component entails primary data collection, in which Pfizer-BioNTech COVID-19 mRNA vaccine recipients opt to participate and complete a web-based data collection tool. The data collection tool completed by participants is designed to provide information on the occurrence of a potential safety event of interest or other clinically significant diagnosis.

The second component entails primary data collection, in which IQVIA Safety Review Team contacts the participant's HCP to request validation of participant reported safety events of special interest (SESIs) via review of the medical record as authorized by the participant. For the medical validation of such SESIs the IQVIA Safety Review Team will contact the healthcare provider by email to explain the reason for the contact, provide documentation of informed consent and solicit validation of the participant reported SESI and associated details via a pre-defined data collection instrument (a package including the participant's Informed Consent Form (ICF) and a targeted data collection tool will be sent via this email route to the named healthcare provider). The healthcare provider will provide response documentation via email to the IQVIA Safety Review Team who will review to validate events for the statistical analyses (Section 9.7). The IQVIA Safety Review Team, as reviewers of this primary data collection instrument, will be responsible for reporting any product safety information volunteered by the respondent.

The third component entails human review of unstructured secondary data, in which the IQVIA Safety Review Team may obtain the medical record directly and will review the medical records as part of the validation process designed to validate events for inclusion in the statistical analyses (Section 9.7). This would occur in lieu of healthcare provider medical validation via email.

The requirements to report to Pfizer Safety any product safety information volunteered by the participant or their healthcare provider during an interaction with the IQVIA Safety Review Team or IQVIA call center staff or discovered during medical record review are described in two separate sections below.

Product safety information volunteered by participants

This study does not involve data collection on individual patients by their treating healthcare professionals. The web-based participant questionnaires for this study will be completed online via a secure website, and do not provide a free text field where study participants could specify information that may constitute product safety information. However, it is possible that a study participant may volunteer product safety information to the IQVIA Call

Center staff (for example during completion of a survey assessment by phone) or that a participant's healthcare provider may volunteer product safety information when providing response documentation via email to the IQVIA Safety Review Team during event validation. This information will be provided as described below.

The following safety events must be reported on the NIS adverse event monitoring (AEM) Report Form: serious and non-serious AEs when associated with the use of the Pfizer products, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

In the event that a study participant volunteers product safety information, the IQVIA Call Center staff and IQVIA Safety Review Team must complete the NIS AEM Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form* is the study participant's or healthcare provider's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant. IQVIA Call Center staff who will serve to address any query from a study participant must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

**Non-Interventional Study Adverse Event Report Form for Protocols without Stipulated Active Collection of Adverse Events; this type of report is managed as spontaneous by Pfizer Safety.*

These trainings must be completed by IQVIA call center staff and IQVIA Safety Review Team 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. The IQVIA call center and IQVIA Safety Review Team will also provide copies of all signed training certificates to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

Medical record review abstraction

In this study protocol, the IQVIA Safety Review Team may perform 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 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 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.

***Non-Interventional Study Adverse Event Report Form For Protocols with Stipulated Active Collection of Adverse Events; this type of report is managed as solicited by Pfizer Safety.*

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:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by IQVIA Safety Review Team 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

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 IQVIA 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.

In addition, IQVIA will inform Pfizer immediately of any urgent safety measures taken by the investigator and/or IQVIA to protect the study participants against any immediate hazard, and of any serious breaches of this NIS protocol that the party becomes aware of.

Submission of the interim and final reports is planned per the schedule outlined in Section 6.

The PASS will be registered in the EU PAS register. The final study results will be published in the EU PAS registry when available, as well as in a relevant peer-reviewed journal.

13. REFERENCES

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2. CDC COVID-19 Response Team. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020 Mar 27;69(12):343-346. doi: 10.15585/mmwr.mm6912e2. PMID: 32214079.

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6. Mahaux O, Bauchau V and Holle LV. Pharmacoepidemiological considerations in observed to expected analyses for vaccines. Pharmocoepidemiology and Drug Safety. 2016;25:214-222.

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14. Chia-Hung L, Yi-Chun Y, Wan-Ting H, Wei-Chu Chie, Arnold CK. Assessment of pre-specified adverse events following varicella vaccine: A population-based self-controlled risk interval study. Vaccine. 2020;38(11):2495-2502.

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title: A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of Recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU

EU PAS Register® number: EUPAS41302

Section **1: Milestones**	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[4]	☒	☐	☐	6
1.1.2 End of data collection[5]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section **2: Research question**	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8

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

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

Section **2: Research question**	Yes	No	N/A	Section Number
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section **3: Study design**		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
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
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.1
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

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)	☒	☐	☐	9.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
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?	☐	☐	☒	

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
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.4
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)	☒	☐	☐	9.3, 9.4
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	18
	9.3.3 Covariates and other characteristics?	☒	☐	☐	18

Section 9: Data sources	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

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
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

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?	☒	☐	☐	9.10.2

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
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)?	☒	☐	☐	6, 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol:	Rachel Reeves	
Date: 07/January/2022		
Signature:	RmReeves	

18. ANNEX 3. ADDITIONAL INFORMATION

18.1. Core Data Collection

As described in protocol Section 9, questionnaires will be administered via the study website/mobile app, or via outbound calls from the IQVIA call center. Each follow-up method will ask the same questions to elicit the same information irrespective of whether the participant is submitting their data via the study website/mobile app or the IQVIA call center. A study identification number will be assigned to each participant, and for each questionnaire the date of completion will be stored.

Four different questionnaires will be administered to collect data from participants: Baseline (Index Date Dose), Subsequent Dose(s), and Follow-up. An additional questionnaire will be administered by email from the IQVIA Pharmacovigilance Team to confirm patient-reported medically attended safety events of interest with the treating health care provider (HCP). The data to be collected in these questionnaires are detailed below. Closed questions will be used, with limited free text fields used as indicated below. Medical Dictionary for Regulatory Activities (MedDRA) or Drugbank codes will be applied by MedDRA trained coders to any HCP-provided free text prior to analysis.

18.1.1. Baseline questionnaire (index date dose)

- Informed consent
- Age in years (autocalculated based on date of birth, where possible)
- Sex (male/female)
- Ethnicity/Race
- Occupation (sector, e.g. Health & Social Care)
- Medical history
    - Height/Weight
    - Current conditions *(select all that apply)*
        - Asthma
        - Chronic cardiac disease
        - Chronic hematological disease
        - Chronic kidney disease
        - Chronic neurological disorder
        - Chronic obstructive pulmonary disease (COPD)
        - Congestive heart failure
        - Dementia
        - Diabetes
        - HIV/AIDS
        - Immunocompromised (any cause)
        - Solid tumour (localized or metastatic)
        - Leukemia
        - Lymphoma
        - Liver disease
        - Rheumatological disorder
        - Other (specify) *(medDRA coded)*

  - How would you rate your health on a scale of 0-10?
  - Frailty (Prisma 7 Questions[6]) *(patients age 65+ years only)*
    - Are you more than 85 years? *(this question will be filled from previous responses)*
    - Male? *(this question will be filled from previous responses)*
    - In general, do you have any health problems that require you to limit your activities?
    - Do you need someone to help you on a regular basis?
    - In general, do you have any health problems that require you to stay at home?
    - In case of need can you count on someone close to you?
    - Do you regularly use a stick, walker or wheelchair to get about?
  - Any concomitant medication taken within 7 days prior to vaccination *(Drugbank coded)*
  - Any prior COVID-19 vaccinations
    - Date of vaccination
    - Dose number
    - Manufacturer
  - Any vaccinations (other than the COVID-19 vaccine) in the last 6 months
  - Allergies to medication
  - Prior infection with test-confirmed SARS-CoV-2 / COVID-19 disease
  - Presence of potential active viral disease within previous 3 days prior to vaccination (e.g. fever, symptoms of cold, flu, or other inflammatory/infectious process)
  - Pregnancy status (female participants of childbearing potential only)
- Vaccination information (of index dose):
  - Date of vaccination
  - Location (i.e. vaccination center)
  - Vaccine lot number
  - Anatomical site where vaccine was administered (i.e. which arm)
- Contact information for:
  - The participant
  - A secondary contact for the participant [for follow-up purposes only]
  - Primary care physician [for safety follow-up]
- Preferred participant follow-up method – telephone interview or web/app-based questionnaire

18.1.2. Each subsequent COVID-19 vaccine dose questionnaire

- Vaccination information:
  - Manufacturer
  - Date of vaccination
- Pregnancy status (female participants of childbearing potential only)

[6] https://www.bgs.org.uk/sites/default/files/content/resources/files/2018-05-23/fff_full.pdf

- Any changes in contact information
- Any changes in preferred participant follow-up method

The following additional fields completed if the vaccine received is the Pfizer-BioNTech COVID-19 mRNA vaccine:

- Additional vaccination information:
  - Location (i.e. vaccination center)
  - Vaccine lot number
  - Anatomical site where vaccine was administered
- Any changes in prior submitted medical history
  - Any concomitant medication taken within 7 days prior to vaccination *(Drugbank coded)*
  - Any other vaccinations (other than the COVID-19 vaccine, and other than any previously reported) in the last 6 months
  - Presence of potential active viral disease within previous 3 days prior to vaccination (e.g. fever, symptoms of cold, flu, or other inflammatory/infectious process)

18.1.3. Safety outcome follow-up questionnaire (weekly, monthly, and long-term follow-up, through 24 months following the index date vaccine dose)

In addition to discontinuation data being collected during follow up (discontinuation date, number of vaccine doses received by discontinuation, and discontinuation reason), outcome follow up will include:

- Pregnancy status (female participants of childbearing potential only)
- Have you received any non-routine (unplanned) medical care since your vaccination / last follow-up questionnaire? *(with the below options to be tailored for each country)*
  - Yes – primary care physician / general practitioner
  - Yes – emergency department
  - Yes – hospital (inpatient)
  - Yes – hospital (outpatient)
  - Yes – Intensive Care Unit or High Dependency Unit
  - No

If a participant selects yes to any of the above, they will be asked how many events they need to report, and asked to complete all of the following questions for each event:

- What was the main purpose of your non-routine (unplanned) medical care?
  - I have been diagnosed with this condition in the past, but my symptoms changed or got worse
  - I experienced new symptoms and was diagnosed with this condition for the first time
- Relevant details will be collected:
  - Date of visit
  - Date of end of visit (if applicable)

  - Details of HCP (as minimum: name, location, email)
- Were you diagnosed with any of the following *(closed question for medically attended safety events of interest as listed in protocol Section 9.3.1)*
- Were you seeking care for any of the following symptoms *(closed question for reactogenicity as listed as part of the medically attended safety events of interest in protocol Section 9.3.1 (note: reactogenicity questions will only be solicited at week 1 post each dose)*
- Did you receive any other diagnosis from your health care provider? *(medDRA coded)*
- For each event/diagnosis, select an outcome:
  - Recovered
  - Recovered with some lasting effects
  - Getting better
  - Condition/symptom continuing
  - Unknown
- Change in pregnancy status (female participants of childbearing potential only) since your vaccination / last follow-up questionnaire
- Any changes in contact information since your vaccination / last follow-up questionnaire
- Any changes in preferred participant follow-up method since your vaccination / last follow-up questionnaire

18.1.4. Pregnancy outcomes questionnaire (as applicable)

- Self-reported pregnancy outcome:
  - Spontaneous abortion (miscarriage) (≤20 gestational weeks)
  - Elective or therapeutic termination
  - Live birth
  - Stillbirth (>20 gestational weeks, prior to delivery)
  - Ectopic pregnancy (a pregnancy outside the uterus)
  - Molar pregnancy (a non-viable fertilized egg implants in the uterus)
- Date of pregnancy outcome
- Gestational age at pregnancy outcome (weeks)

18.1.5. Treating HCP questionnaire for medically attended safety events of interest

The treating HCP will be provided with details of the event as reported by the participant (type of event [e.g. general practitioner visit or hospital admission], reported dates, diagnosis, and outcome) and asked to confirm:

- Whether they were the treating physician for the patient at the reported practice/hospital (if not, details of treating physician to be provided if possible)
- Confirmation of relevant dates (e.g. date of visit/hospitalization, date of discharge)
- Confirmation of the diagnosis (i.e. whether the participant reported diagnosis was correct, or if a different diagnosis was given. If a different diagnosis, details to be provided by the HCP)

- Confirmation of outcome:
  - Recovered/resolved
  - Resolved with sequelae
  - Recovering/resolving
  - Not recovered/not resolved
  - Unknown
- Confirmation of any indication the patient should be considered to be 'frail'

In addition, if the participant has laboratory confirmed severe COVID-19 disease, the HCP will be asked to assess the possibility of vaccine-associated enhanced disease (VAED) according to published Brighton Collaboration criteria.

19. ANNEX 4. SAFETY EVENTS FOR WHICH A SELF-CONTROLLED RISK INTERVAL (SCRI) ANALYSIS WOULD BE A VALID APPROACH

The following table lists the medically attended safety events of interest for which the Self-Controlled Risk Interval (SCRI) analysis would be a valid approach based on a known risk interval of these events after vaccination. The specific risk windows for each safety event of interest to be included in the SCRI analysis will be detailed in the statistical analysis plan (SAP), and these will be aligned with risk windows informed by the Brighton Collaboration and other published literature as available.

Body System	**Safety Event**
Neurologic	Generalized convulsion/ seizure
	Guillain-Barré Syndrome (GBS)
	Aseptic meningitis
	Encephalitis / Encephalomyelitis
	Other acute demyelinating diseases
	Transverse myelitis
	Multiple sclerosis
	Optic neuritis
	Bell's palsy
	Acute disseminated encephalomyelitis
Immunologic	Anaphylaxis
	Arthritis and arthralgia
	Multisystem inflammatory syndrome in adults (MIS-A)
	Kawasaki disease
COVID-19	Severe COVID-19 disease
	Deep vein thrombosis
	Pulmonary embolus
	Cerebrovascular stroke
	Acute kidney injury
	Acute liver injury
	Rhabdomyolysis
Cardiac	Myocarditis
	Pericarditis
	Acute myocardial infarction
Hematologic	Thrombocytopenia
	Disseminated intravascular coagulation
Other	Death
	Narcolepsy and cataplexy
	Non-anaphylactic allergic reactions

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