

NON-INTERVENTIONAL (NI) STUDY PROTOCOL SYNOPSIS

Title	Postapproval safety of SARS-CoV-2 mRNA-1273 vaccine: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity
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Medicinal product	mRNA-1273 vaccine
Product reference	
Procedure number	N/A
Marketing authorisation holder(s)	ModernaTX Inc.
Joint PASS	TBD
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Research question and objectives	<p>This study aims to monitor, refine and, where warranted, evaluate potential safety signals associated with the introduction of SARS-CoV-2 mRNA-1273 vaccine.</p> <p>The objectives of this study are to:</p> <ol style="list-style-type: none"> 1. Estimate crude incidence rates and incidence rate ratios at key time periods and among key populations <ol style="list-style-type: none"> a. Estimate rates of pre-defined AESIs in unvaccinated individuals during pre-COVID 19, active COVID-19, and post-EUA period b. Estimate incidence parameters for pre-defined AESIs among mRNA-1273-vaccinated individuals in post-EUA period. compare observed IR to background rates estimated in Objective 1(a) c. Estimate background rates and incidence parameters for additionally-identified AESIs 2. Estimate age/sex adjusted incidence rate ratio for specific AESIs meeting pre-specified evaluation threshold (completed as needed) 3. Estimate relative risk for specific AESIs continuing to

	meet pre-specified evaluation threshold (completed as needed)
Country(-ies) of study	U.S.
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2. List of abbreviations

List of abbreviations will be completed upon protocol finalization.

Abbreviations	Definition
ACCESS	vACcine Covid-19 monitoring readinESS
ACIP	Advisory Committee On Immunization Practices
AE	Adverse Event
AEP	Action Evidence Platform
AESI	Adverse Events of Special Interest
EUA	Emergency Use Authorization
CI	Confidence Interval
CCI	Charlson Comorbidity Index
CMS	Center for Medicare & Medicaid Services
CPT	Current Procedural Terminology
DME	Durable Medical Equipment
EMA	European Medicine Agency
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GPP	Good Pharmacoepidemiological Practice

HIPAA	Health Insurance Portability and Accountability Act
ICD	International Classification of Disease
ICMJE	International Committee of Medical Journal Editors
IR	Incidence Rate
O/E	Observed to Expected
OTC	Over-the-counter
NMPA	China National Medical Products Administration
PHI	Protected health information
PII	Personal identifying information
PMDA	Pharmaceuticals and Medical Devices Agency
RI	Relative Incidence
SAP	Statistical Analysis Plan
SCRI	Self-controlled risk interval
SNF	Skilled Nursing Facility
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
US	United States
VAC4EU	Vaccine monitoring Collaboration for Europe
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink

3. Responsible parties *<To be reviewed by Moderna>*

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4. Abstract *<To be completed with full protocol>*

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5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
n/a	n/a	n/a	n/a	n/a

6. Milestones <To be completed with full protocol>

Milestone	Planned date

7. Rationale and background

In the context of pandemic COVID-19 disease, Moderna has rapidly developed SARS-CoV-2 mRNA-1273 vaccine. Phase 1 (NCT04283461) efficacy results were positive, notably in the elderly population (65 years old and above), with only mild to moderate safety events reported.^{1,2} A dose-confirmation phase 2a trial (NCT04405076) was then conducted followed by a phase 3 trial (NCT04470427) which has shown a very high vaccine efficacy rate of 94.1% in adults.¹ Given the extremely quick development of SARS-CoV-2 mRNA-1273 vaccine, additional safety surveillance is needed in the post-marketing setting given that safety concerns have been raised in the past following mass vaccination campaigns either with existing or new vaccines.

The present study aims to estimate background rates of Adverse Events of Special Interest (AESIs) for the pre-emergency use authorization (EUA) of SARS-CoV-2 mRNA-1273 vaccine and then after EUA in an adult US population. This will help contextualize potential safety signals and inform on the need for further investigations, notably using observed-to-expected (O/E) analyses where a safety concern has been raised from literature or medical reviews, disproportionate reporting or unexpected temporal relationship. In the event that O/E analysis results show observed values higher than expected, self-controlled risk interval (SCRI) analyses will be conducted to further investigate the safety signal.

8. Research question and objectives

This study aims to monitor, refine and, where warranted, evaluate potential safety signals associated with the introduction of SARS-CoV-2 mRNA-1273 vaccine.

The objectives of this study are to:

1. Estimate crude incidence rates and incidence rate ratios
 - a. Estimate background rates of pre-defined AESIs:
 - i. Estimate background rates in the era that is immediately preceding the emergence of COVID-19 ("Time Period 1")
 - ii. Estimate background rates in the era following the emergence of COVID-19 but before widespread availability of vaccines ("Time Period 2")
 - iii. Estimate rates among unvaccinated individuals in the era of vaccine availability ("Time Period 3")
 - b. Estimate incidence parameters for pre-defined AESIs among mRNA-1273-vaccinated individuals:
 - i. Estimate observed incidence rate in Time Period 3
 - ii. Compare observed incidence rate to background rates for Time Periods 1 and 2 estimated in Objective 1a(i-ii)
 - c. Estimate background rates and incidence parameters for additionally-identified AESIs:

¹<https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study>

- i. Complete Objective 1a analyses for additionally-identified AESIs
 - ii. Complete Objective 1b analyses for additionally-identified AESIs
2. Estimate age/sex adjusted incidence rate ratio for specific AESIs meeting pre-specified evaluation threshold
3. Estimate relative risk for specific AESIs meeting pre-specified evaluation threshold

9. Research methods

9.1. Study design

The description of research methods below will reference several concepts:

- **Pre-defined AESIs:** a list of predefined AESIs is proposed in this protocol synopsis in Section 9.3.2
- **Time Periods:** For consistency, we reference three time periods of interest. The specific dates of each time period are noted in Section 9.2.
 - **Time Period 1** is defined as the era that is immediately preceding the emergence of COVID-19.
 - **Time Period 2** is defined as the era following the emergence of COVID-19 but before widespread availability of vaccines.
 - **Time Period 3** is defined as the era of vaccine availability.

All objectives will be completed as soon as feasible, based on timing of data availability.

Objective 1. In Objective 1, crude IRs and IRRs are estimated. All rates and ratios will be estimated in the overall populations, and in subgroups defined by age group, sex, and calendar period. Additional subgroups can be considered as warranted. All analyses are defined in full in the statistical analysis plan (SAP).

In Objective 1a, IRs for pre-defined AESIs are estimated in (i) Time Period 1; (ii) Time Period 2; and (iii) among presumed unvaccinated patients in Time Period 3. IRs for a particular AESI will be estimated by dividing the number of observed cases (unique per patient) by the cumulative person-time.

In Objective 1b, observed IRs for pre-defined AESIs are estimated in Time Period 3 among mRNA-1273-vaccinated individuals. Further, crude IRRs will be estimated to compare IRs for mRNA-1273-vaccinated individuals in Time Period 3 to the IRs estimated in Time Periods 1 and 2 as part of Objective 1a above. These analyses will occur at the earlier of 4 months after an EUA for mRNA-1273 or when a sufficient number of individuals have been vaccinated, and may be repeated periodically as needed. Vaccine uptake will be monitored on a bi-weekly basis.

As incidence rate ratios are estimated in Objectives 1a and 1b, they will be evaluated to determine whether further study is warranted. Objective 2 will be triggered for a given AESI if any of the following criteria are met:

- The overall crude IRR reaches a threshold of ≥ 2 (a threshold drawn from prior experience).
- The crude IRR in any subgroup reaches a threshold of ≥ 2
- The sponsor determines that this analysis will assist with safety signal validation and/or assessment

Objective 2. In Objective 2, observed versus expected IRRs are estimated for those specific AESIs identified in Objective 1. The number of observed cases of specific AESIs will be estimated among the mRNA-1273 vaccinated population in Time Period 3, with estimates from Objective 1b. Estimates of the expected number of cases will be computed using the background rates for Time Periods 1 and 2, as assessed in Objectives 1a, and the total person-time at risk during the risk periods. Estimates will be stratified by age, sex, geographic region, and calendar period as observed in the vaccinated population.

The observed and estimated expected numbers of AESI events among mRNA-1273 vaccinated adults in Time Period 3 will be compared and the O/E (observed to expected) ratio measure will be calculated and a confidence interval (CI) estimated. CIs will also be estimated around the number of events observed in the risk period.

Objective 3 analyses will be triggered if any of the following criteria are met:

- The lower bound of the 95% CI of the observed number of cases is higher than the estimated number of expected cases as measured in Objective 1b (Time Period 3)
- The lower bound of the 95% CI of the O/E ratio is greater than 1
- The sponsor determines that this analysis will assist with safety signal validation and/or assessment

Objective 3. Objective 3 estimates the relative risk for AESIs identified for further study. The potential risk associated with mRNA-1273 vaccine and specific AESIs will be estimated using a self-controlled risk interval (SCRI) analysis of mRNA-1273 exposed cases identified in Time Period 3. The SCRI design has been widely used for post-licensure vaccine safety monitoring to detect potential elevated risks of adverse events following vaccination. The main advantage of this design is that it adjusts implicitly for fixed non-time-varying covariates as only exposed cases are being used. However, adjustment needs to be made for time-varying covariates. Compared to cohort designs that use large amounts of historical or concurrent data on unexposed individuals, or self-control case series methods, the SCRI design has less statistical power.^{4,5} In the SCRI design, the length of the risk and control periods are fixed, but may be unequal. Each AESI will be assigned specific risk and control periods based on biologically plausible mechanisms.

9.2. Setting

The study population will be selected from HealthVerity's aggregated medical and pharmacy claims database that represents healthcare utilization for over 140 million patients between 1 Dec 2018 and the end of the study period (see Section 9.4). Objectives 1 and 2 will utilize historical medical and pharmacy claims data to support estimation of background rates. Upon vaccine launch and administration, a biweekly refresh of medical and pharmacy claims for specific patient cohorts will accumulate throughout the study period to support Objectives 1, 2, and 3.

The historical medical and pharmacy claims data will include up to 45 million patients. Patient data is included from the larger database if the following inclusion criteria are met: have both medical and pharmacy benefit coverage, at least 28 days of continuous medical enrollment, date of birth before 2008, and non-missing values for both gender and age. From the remaining patients, a stratified random sample will be generated by gender and age to mirror distributions from 2019 Census Estimates. As subgroups of interest are identified throughout the course of study, additional medical and pharmacy claims that represent up to 9.9 million patients may be added.²

Upon market entry of the first US SARS-CoV-2 vaccine, adjudicated and pre-adjudicated medical and pharmacy claims from patients in the above dataset will be made available monthly by HealthVerity. In addition, adjudicated and pre-adjudicated medical and pharmacy claims data for all patients in the 137-million patient database with appropriate CPT codes indicating administration of any SARS-CoV-2 vaccination will be included. Manufacturer-specific vaccinations will be inferred from dose information, identified via CPT code modifiers.

To support the study objectives, three primary cohorts of interest will be formed:

Cohort 1: Entire cohort meeting eligibility in **Time Period 1:** Pre-COVID period from 1 Dec 2018 to 30 Nov 2019

Cohort 2: Entire cohort meeting eligibility in **Time Period 2:** Post-COVID, Pre-EUA period from 1 Dec 2019 to one day prior to first US SARS-CoV-2 vaccine EUA

Cohort 3: Entire cohort meeting eligibility in **Time Period 3:** Post-EUA period from date of first US SARS-CoV-2 vaccine EUA to 31 Dec 2022 comprised of mRNA-1273 vaccinated, otherwise vaccinated, and presumed unvaccinated sub-cohorts

The cohort entry date will be defined as the first date during the cohort time period that the patient has a health care claim for any service type (e.g., inpatient, outpatient, DME, SNF, medication, etc.).

² Data use and licensing for this data source allow for use of up to 40% of the total patient population for the background rate analyses. There will be no sampling of vaccinated patients; all vaccinated individuals will be included.

9.2.1. Study period

The study will include data from the HealthVerity database (see Section 9.4 for further details) from 1 Dec 2018 until 31 Dec 2022.

9.2.2. Study population

Cohorts 1 and 2 will be static adult cohorts representing time prior to mRNA-1273 vaccine EUA. They will serve to estimate background rates across pre-COVID-19 period (Time Period 1) and active COVID-19 period (Time Period 2) objective 1a(i-ii) and will be leveraged for objective 2 (where warranted).

Cohort 3 will be an adult cohort with vaccinated and presumed unvaccinated individuals from the time after mRNA-1273 vaccine EUA up to 31 Dec 2022. Cohort 3 data will be updated biweekly during the first 6 months following EUA and monthly thereafter; updates will both extend follow-up time for existing patients and may include new patients. Cohort 3 will serve to estimate IRs after mRNA-1273 vaccine EUA (Objectives 1a and 1b) and will be leveraged for Objectives 2 and 3 where warranted.

Subgroups will be defined based on age, sex, calendar period, and other clinical and non-clinical factors as needed.

9.2.3. Inclusion criteria

To be included in this study, participants must meet the following criteria:

- Included in a health plan covered by HealthVerity database (see Section 9.4)
- Covered by a health plan during at least one period of interest (pre-COVID-19, active COVID-19 and post-vaccine periods), but not necessarily the full period
- Aged 18 years old or above

9.2.4. Exclusion criteria

None.

9.3. Variables

9.3.1. Exposures

The mRNA-1273 vaccination schedule consists of two 100 µg doses within a one month period, with the second dose likely between 28 and 31 days of the first. Exposure to mRNA-1273 vaccine will be identified through specific CPT code 91301 and modifiers 011A (1st dose) and 012A (2nd dose). CPT codes and modifiers are expected to be fully reported as a result of insurance reimbursement requirements set by CMS and others.

9.3.2. Outcomes

AESIs will be identified in claims data and defined using ICD-10 codes. To the extent possible, existing validated algorithms will be used to define those outcomes. Algorithms may be adapted from other sources such as the VAC4EU initiative³ or created for this study. The operational definition for each outcome will be presented as an annex of the full study protocol.

The below table provides the list of predefined AESIs for which Objective 1 IRs will be calculated. Several sources have been considered to define this list: CDC/FDA's VAERS and VSD, and the ACCESS project endorsed by EMA. Additional AESIs may be added during this study in the event of a safety concern arising during the vaccination campaign or as indicated by Phase 3 clinical trial data.

List of Predefined AESIs
Diagnosed COVID-19 disease (vaccine-associated enhanced disease)
Pregnancy adverse outcomes (gestational diabetes, pre-eclampsia, preterm labor, spontaneous abortion, stillbirth)
Inpatient death
Acute disseminated encephalomyelitis (ADEM)
Acute myocardial infarction (AMI)
Acute respiratory distress syndrome (ARDS)
Anaphylaxis
Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
Bell's Palsy
Diabetes type 1
Disseminated intravascular coagulation (DIC)
Encephalitis / Encephalomyelitis
Encephalopathy
Guillain-Barré Syndrome (GBS)
Kawasaki disease
Meningitis
Meningoencephalitis

³ <https://vac4eu.org/covid-19-vaccine-monitoring/>

Multisystem Inflammatory Syndrome
Myelitis
Myocarditis, pericarditis
Narcolepsy / cataplexy
Seizures/convulsions
Stroke
Thrombocytopenia
Transverse myelitis
Venous thromboembolism (VTE)

9.3.3. Covariates

The following covariates will be considered for this study:

- age
- sex
- geographical location (US region or smaller)
- payer type (e.g., Medicare, Medicaid, commercial)
- high-risk conditions (e.g., immunocompromised patients, patients with cardiovascular disease, etc.)
- others to be defined in the full study protocol

The operational definition for each covariate will be presented as an annex of the full study protocol.

9.4. Data sources

This retrospective observational cohort study will use secondary, de-identified individual-level medical and pharmacy claims data provided by HealthVerity. The data represent more than 140 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems.

HealthVerity data contain near real-time medical claims and outpatient pharmacy transactions, including drugs, diagnoses, and procedures. These data are drawn from a variety of US sources which include Veradigm and over 70 other data partners. Data elements include provider-submitted claims, adjudicated insurance claims, and pharmacy billing manager claims submissions. They update in near real-time, with minimal lag between time of claim submission and time of inclusion in the database. 12+ months of historical data is available for many patients. Hospitalizations are included in the data at a summary level. Vaccinations will be

captured via manufacturer-specific CPT codes. Drugs dispensed by a pharmacy are generally very well captured, while OTC medications are not. Death information is generally available with minimal lag for patients who die in a hospital setting.

To create linkages across databases to ensure de-identified, longitudinal, de-duplicated patient data, all data partners use the HealthVerity technology within their system to create a unique, secure, encrypted, and non-identifiable patient token. This token is then employed as a consistent linkage key across datasets. The linkage of patients has high accuracy: 99.7% of linkage made are made correctly (0.3% false positives), and 96% of possible linkages are made (4% false negative) and is done according to HIPAA regulations. With real-time assembly of data requiring the use of multiple sources, this approach appropriately balances timeliness with fidelity of linkage.

All data include key factors such as patient age, gender, and 3-digit zip level. Race and ethnicity information is not available. Use of data and the precise granularity available is controlled by HIPAA requirements or application of public health exemption. No PHI (protected health information) or PII (personal identifying information) leaves the data owner's possession, and all research data were certified HIPAA compliant by expert determination.

9.5. Study size

The analysis population for background and post-vaccine rates will be formed by up to 54.9 million patients from the HealthVerity database. The population for vaccinated individuals will be formed from the entirety of available HealthVerity data from over 140 million patients.

AESI-specific sample size calculations will be performed when a particular AESI enters the third stage analysis. For illustration, the table below provides example sample size estimates for 3 AESIs (Guillain-Barré syndrome [GBS], anaphylaxis and encephalitis), and is based on the following simplifying assumptions and parameters:

- Administration of 2 doses of vaccine within a 31-day interval
- 1-year observation period
- No effect of age on risk of the AESI
- 0.80 power
- $\alpha=5\%$
- Total risk period = 2 x upper bound of the post-vaccination risk periods as follows ⁴⁻⁷:
 - 1–42 days for GBS (the risk period of the first dose ends when the second dose is administered)
 - 1–21 days for encephalitis
 - 0–2 days for anaphylaxis
- Minimal detectable risk ratio (RR) = 1.5, 2 or 3

Outcome	Estimated US incidence	Expected events in HealthVerity ^a	Total risk period (days) ^b	Cases required by minimal detectable RR		
				RR=1.5	RR=2	RR=3
GBS	1.2 - 3.0 cases per 100,000 inhabitants ⁶	492 - 1230	73	263	83	31
Encephalitis	7.3 hospitalized cases per 100,000 inhabitants ⁷	2,993	42	396	121	42
Anaphylaxis	42 cases per 100,000 person-years ⁸	17,220	4	3,514	1,018	319

^a Estimated US incidence x 41 million adult patients (with medical and pharmacy claims in HealthVerity)

^b assuming administration of 2 doses within a 31-day interval and a one-year observation period

Note: Sample size was calculated using R package for self-controlled case series studies ^{9,10}.

The simplifying assumptions and varied parameters above may be varied in the actual sample size calculations for a particular AESI entering the third stage analysis.

9.6. Data management

All data management and statistical analyses will be conducted using the Aetion Evidence Platform[□] which is a software developed by Aetion, Inc. (<http://www.aetion.com>) for real-world data analysis. The AEP is an analytic platform on which data can be used to generate evidence by executing analyses in a transparent and reproducible manner that has been validated for a range of studies. The AEP has been accepted for use in FDA context previously, i.e. for the RCT DUPLICATE project and in the COVID-19 Research Collaboration and COVID-19 Evidence Accelerator.

FDA reviewers can be provided access to AEP to review the results and access the underlying data, upon submission of the interim and final study reports. All of the components used for the study (e.g., cohorts, defined outcomes/covariates, results) will be available for review through the AEP.

9.7. Data analysis

Analyses will be performed using the Aetion Evidence Platform. A SAP will be finalized before study analysis begins.

For **Objective 1**, AESI IRs will be descriptively reported. Background IRs per 1,000 person-years will be computed with 95% CI (assuming a normal binomial distribution) for Time Period

1 pre-COVID-19 and Time Period 2 active COVID-19 periods (both prior to mRNA-1273 vaccine EUA) and Time Period 3 (after mRNA-1273 vaccine EUA). Background IRs in US adults will be stratified by age group, sex, and calendar period and estimated within subgroups of interest.

At pre-specified intervals, among both the vaccinated and presumed unvaccinated, observed IRs per 1,000 person-years will be computed with 95% CI in Time Period 3 after mRNA-1273 vaccine EUA. Observed IRs will be stratified as above.

Both background and observed IRs will be estimated from detection of new onset or first diagnosis of the AESI, as the count of exposed individuals allows. Sensitivity analyses will be considered, such as requiring that an AESI be observed at least twice in 30 days.

The incidence rate ratio (IRR) with 95% CI will be calculated to estimate the relative change in IRs pre/post mRNA-1273 vaccine EUA. This will be performed separately for Time Period 1 (pre-COVID-19 period) and Time Period 2 (active COVID-19 period). IRRs will be calculated overall and may be stratified as above.

For **Objective 2**, when the pre-specified criteria are met for a particular AESI, the observed vs expected event ratios (O/Es) and corresponding 95% CI will be calculated, as the ratio of the number of events among those vaccinated with mRNA-1273 to the number of events expected in this population from background rates.

The number of events among those vaccinated will be enumerated as the observed value. The expected value will be calculated as follows:

$$\text{Number Expected (NE)} = \sum_s [\text{Background incidence rate}]_s \times [\text{Exposed persons}]_s \times \text{time at risk calculated in Objective 1}$$

- where s is the age, sex, and calendar month stratum
- The time at risk is the cumulative sum of days for all persons exposed to the vaccine during which there is medical plausibility there is a vaccine-associated increased risk of experiencing an event. The time at risk will be calculated by summing the risk window days after a dose is administered. This considers the real-world implication that persons are not fully compliant and do not receive both doses of vaccine.

Subsequent analysis of the potential risk associated with mRNA-1273 vaccine will be triggered by the confidence interval of the observed AESI event crossing the threshold of the estimated expected events. Confidence intervals (CI) will be calculated around the number of events observed in the risk period.³ If the 95% lower bound of the 95% CI of the observed number of cases is higher than the estimated expected number of cases, the observed number is deemed

significantly higher than the expected and will trigger the SCRI analysis. Likewise, when the lower bound of the 95% CI of the O/E ratio is greater than 1, the observed number is deemed significantly higher than the expected and will trigger the SCRI analysis.

Therefore, if the observed number of cases (lower bound) is greater than the estimated expected number of cases, the observed is higher than the expected.

For **Objective 3**, when the pre-specified criteria are met for a particular AESI, the risk ratio (RR) of each AESI triggered in Objective 2 will be estimated using a self-controlled risk interval (SCRI) design, and fitting a conditional Poisson regression model. Adjustments for variables dependent on seasonality and other time-varying covariates will be performed. Sensitivity analyses by applying different risk and control periods may be performed.

9.8. Quality control

9.8.1. Data Quality Control

Data provided by HealthVerity will be examined for completeness and consistency, including identifying any issues with missing files or variations in data structure. Standard data quality checks include:

- Generating statistics for each variable including the number of records observed, the number of unique values observed, the number of null values observed and percent fill, and the most frequently occurring values
- Comparing the schema of data received with the expected schema per vendor documentation
- Creating event density distributions for new datasets and data updates in order to explore event data over time and identify possible gaps or missing files
- Checking for variables with high proportions of missing data
- Cross-checking imported record counts against original data counts
- Cross-checking patient event dates against enrollment files (where available)
- Parallel coding for final validation of data transformation before platform deployment

If any quality issues are identified, the data provider will replace any necessary files or data items, and the verification process will be repeated.

9.8.2. Analysis Results Quality Control

All results will be reviewed by the principal investigators to evaluate internal consistency of counts and totals. All calculated variables will be checked against the component variables (cross-tabs) to ensure accuracy. For example, categorical age would be compared with continuous age to confirm that each category of age contained only persons of the expected age ranges within that category.

9.9. Limitations of the research methods

Limitations will be described in more detail in the complete protocol, where mitigation techniques will also be discussed. A selection of limitations includes:

- General limitations inherent to database studies and other non-randomized research
- Potential for misclassification of key variables such as vaccination status, potential confounders and AESIs
- Potential for selection bias (e.g., from loss to follow-up) and residual confounding

9.10. Other Aspects

Not applicable.

10. Protection of human subjects

This study was designed and shall be implemented and reported in accordance with Good Pharmacoepidemiological Practice (GPP), with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. Given this is a retrospective database study using de-identified data, informed consent is not required.

11. Management and reporting of adverse events / adverse reactions

Individual cases of above specified safety outcomes possibly associated with mRNA-1273 vaccination during this study will not be reported as it is a retrospective database study. Data will be reported as per study design and milestones.

12. Plans for disseminating and communicating study results

The results of this study will be submitted for publication as scientific papers in peer-reviewed journals. The manuscripts will be prepared in accordance with the current guidelines including STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and ICMJE authorship guidelines.

13. References

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