NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	HERO-Together Boost: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine
Protocol number	C4591049
Protocol version identifier	Version 3.0
Date	25 Apr 2025
HMA-EMA Catalogues of RWD Studies registration number	EUPAS105791
Active substance	N/A
Medicinal product	Pfizer-BioNTech COVID-19 Vaccine
Research question and objectives	The research question addressed by this study is: what are the incidence rates of safety events of interest among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a US cohort? *Primary study objectives:* • Estimate the real-world incidence of safety events of interest among recipients of the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization. *Secondary objectives* • Estimate the incidence rates of safety events of among subcohorts of interest, including individuals who are pregnant, individuals who are immunocompromised, and stratified by age.

Author	Emily O'Brien, PhD Duke Clinical Research Institute 200 Morris Street Durham, NC 27701

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
AESI	Adverse Event of Special Interest
BNT	BioNTech
CBER	Center for Biologics Evaluation and Research
CEA	Clinical Events Ascertainment
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CTMS	Clinical Trials Management System
DCT	Data Collection Tool
DIC	Disseminated Intravascular Coagulation
DCRI	Duke Clinical Research Institute
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHR	Electronic Health Record
EMA	European Medicines Agency
EUA	Emergency Use Authorization
EU-PAS	European Post Authorization Study
FDA	Food and Drug Administration
HERO	Healthcare Worker Exposure Response and Outcomes

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
HMA	Heads of Medicines Agencies
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KD	Kawasaki Disease
MS	Multiple Sclerosis
NI	Non-Interventional
NIS	Non-Interventional Study
ON	Optic Neuritis
PASS	Post-Authorization Safety Study
RNA	Ribonucleic Acid
RWD	Real World Data
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SPEAC	Safety Platform for Emergency vACcines
US	United States
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Emily O'Brien, PhD	Epidemiologist	Duke Clinical Research Institute	200 Morris Street Durham, NC 27701
Adrian Hernandez, MD, MHS	Executive Director	Duke Clinical Research Institute	200 Morris Street Durham, NC 27701
Cherise Wong, PhD	Epidemiologist	Pfizer Inc.	66 Hudson Boulevard E, New York, NY 10001

4. ABSTRACT

Title: HERO-Together Boost: A post-Emergency Use Authorization (EUA) observational cohort study to evaluate the safety of the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) vaccine.

Rationale and Background:

In January 2020, an outbreak of acute respiratory illness (COVID-19) was confirmed to be caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In November 2022, SARS-CoV-2 subvariants were the dominant strains causing COVID-19 in the United States (US). On 31 August 2022, the FDA authorized use of a COVID-19 vaccine for use as a single booster to provide a broadly protective immune response against COVID-19 caused by novel variants. The Healthcare Worker Exposure Response and Outcomes (HERO)-Together Boost study is designed to provide real-world safety information on a cohort of people receiving the Pfizer/BioNTech COVID-19 vaccine.

Research question and objectives:

The research question addressed by this study is: what are the incidence rates of safety events of interest among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a US cohort?

Primary study objectives:

- Estimate the real-world incidence of safety events of interest among recipients of the Pfizer-BioNTech COVID-19 vaccine following EUA.

Secondary objectives

- Estimate the incidence rates of safety events of interest among subcohorts of interest, including individuals who are pregnant, individuals who are immunocompromised, and stratified by age.

Study design:

This is a prospective observational cohort study of US residents, in which data are collected from participant self-report at regular intervals following vaccination, primarily using a secure web portal. Safety event occurrence will be confirmed by medical record review and/or linked claims/electronic health record (EHR) data. The study period will be 18 months.

Population: HERO-Together Boost is open to anyone aged 18 or older living in the US.

The study population must meet the following inclusion criteria:

- Age ≥18 years
- Able to speak and read/write English or Spanish
- Receipt of the first dose of a Pfizer- BioNTech COVID-19 vaccine for prevention of SARS-CoV-2 infection within the past 90 days
- Ability to provide date and manufacturer of all previous COVID-19 vaccine doses
- Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study

Variables:

Key variables include participant characteristics, vaccine exposure, and safety events of interest as outcomes. The compiled Adverse Events of Special Interests (AESIs) are guided by a combination of: the Priority List of AESI from the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project updated in October 2022, AESI per the Food and Drug Administration (FDA)-Center for Biologics Evaluation and Research (CBER) Best Initiative, spontaneous reporting, and framework from a preceding study (C4591008). The AESIs in this study include:

- Multisystem inflammatory syndrome (adults)
- Autoimmune thyroiditis
- Myocarditis
- Pericarditis
- Arrhythmia
- Heart failure
- Coronary artery disease
- Myocardial infarction
- Stress cardiomyopathy
- Thrombosis and Thromboembolism
- Hemorrhagic disease
- Disseminated intravascular coagulation (DIC)
- Chilblain-like lesions

- Erythema multiforme
- Single Organ Cutaneous Vasculitis
- Acute kidney injury
- Acute liver injury
- Anaphylaxis
- Thrombocytopenia
- Generalized convulsion
- Guillain Barré Syndrome
- Acute aseptic arthritis
- Aseptic meningitis
- Encephalitis / Encephalomyelitis
- Bell's Palsy
- Vaccine-associated enhanced disease (respiratory disease)
- Tinnitus
- Severe COVID-19 disease
- Death
- Stroke
- Fibromyalgia
- Kawasaki Disease (KD)
- Limb ischemia
- Microangiopathy
- Multiple Sclerosis (MS)
- Non-anaphylactic allergic reactions

- Narcolepsy/cataplexy
- Optic neuritis (ON)
- Other acute demyelinating diseases
- Transverse myelitis
- Pregnancy outcomes
- Acute disseminated encephalomyelitis
- Deep vein thrombosis
- Extensive limb swelling
- Pulmonary embolism
- Cerebral venous sinus thrombosis
- Vasculitides

Data sources: Data will be captured through several mechanisms. First, all participants will enter baseline data through a secure portal upon enrollment, and event capture for AESIs (hospitalized or non-hospitalized manifestations) will be entered into the portal. For a subset of events which are self-reported and hospitalized, a workflow to confirm event occurrence will proceed by two methods:

- centrally adjudicated, following automated medical record retrieval, and supplemented by manual medical record retrieval from the Call Center.
- additionally, third party data will be linked to participant reported data, through the use of novel linkage approaches (e.g. tokenization).

At a pre-defined checkpoint, concordance between participant-reported hospitalized data, medical record confirmation, and third-party linked outcome data will be evaluated to explore the operational feasibility of confirming event occurrence by using linked third-party data for hospitalized events. However, throughout study conduct, the study will continue with the participant-report of hospitalized AESI as the trigger for medical record request and retrieval, which will proceed via an automated third-party process where possible, with Call Center follow-up for remaining participants.

Participants will be followed from date of enrollment for up to 18-months following vaccine dose, until end of the study period, death, loss-to-follow up (no response after a notable interval of attempted Call Center contacts), or discontinuation from study. Following enrollment, all participants will be prompted to enter data into a secure participant facing web portal at 1 week, 4 weeks, 12 weeks, and 6, 12 and 18 months following receipt of the

booster dose of the vaccine. Additional dose/booster information will be solicited during follow up. Participants will be queried regarding their general health and events requiring medical attention. Participants who do not complete data entry within a notable period of time by the expected completion date for a given time point will be contacted by the Call Center for confirmation of health status.

Study Size: As the primary objective is descriptive, a large sample size target will facilitate adequate precision for a plausible range of AESIs rates in the population of vaccine recipients. Given prior experience with enrollment in a similar study, the precision (95% CIs) for a population of up to 20,000 participants was estimated for reference. However, enrollment outlook is uncertain, and precision calculations were repeated in this study for more conservative sample sizes such as 500 and 1,000. Overall, precision is high for observed event rates ranging from 0.01% to 20.0%.

Data analysis:

Vaccination and baseline characteristics will be summarized using descriptive statistics, including measures of central tendency and dispersion (means, medians, standard deviations) for continuous variables and percentages for categorical variables. The primary analysis for each objective will be restricted to participants who enrolled within 10 days of vaccination to mitigate the risk of selective enrollment and disproportionate representation of higher risk participants. The number and incidence rate for each safety event of interest will be calculated overall, and within subgroups of interest, including pregnant women, immunocompromised individuals, and within age groups. Rates will also be stratified by other baseline characteristics, such as race/ethnicity, work setting, prior COVID-19, and geographic region, data permitting. Detailed methodology for the statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP).

Milestones: Interim reports will be provided within 6 months after start of data collection and annually thereafter. The final study report will be provided 12 months within the end of data collection.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
2	25 Apr 2025	Section 6	Milestones were revised to provide actual dates and update the planned final report date	To reflect a communication to the FDA (14 Dec 2023)
		Abstract, Section 9.4, 9.7.1	Phase 1 event ascertainment will apply to the duration of the study; Phase 2 will not proceed. Analytic findings from cross comparing between self-report, adjudicated records, and linked records, will be completed and submitted by the time of final report submission.	Operational delays in privacy certification and tokenization process
		Section 12, Study Information Cover Page	EU Post Authorization Study (EU PAS) Register was updated to be EMA-HMA RWD Catalogues, and the registration number was added, respectively	HMA-EMA RWD Catalogue of studies replaced the European Union electronic register of post-authorization studies (EU PAS Register®) in 2024.
		Section 9.2.3	Removed statements pertaining to recruitment mechanisms.	Emails were not sent to HERO Together participants given success of pharmacy email campaign, and information on how participants learned about the study were not collected.
		Section 9.3 (Table 2)	COVID-19 vaccinations during follow-up which were non-Pfizer-BNT were re-categorized as a covariate	Follow up vaccination of non-Pfizer BNT formulation is not a primary exposure of interest.
1	08 March 2023	Section 9.7.2	A statement has been revised to: “Event rates will also be calculated overall and within subgroups of interest, including pregnant women, immunocompromised individuals, those with different vaccination histories (heterologous vs. homologous; *total number of vaccine doses*) and within age groups”.	By FDA request, to specify how additional COVID-19 vaccine doses received will be analyzed.

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 9.7.2	A statement has been added to the analytics methods: "Event frequencies, person-time at risk, and median time with interquartile ranges from vaccine receipt to event onset will be presented for each event of interest."	By FDA request, to comment on whether the analytic methods will include a description of time to onset for any adverse events of special interest.
		Section 9.3	Revisions to Table 2 include: • clarified that additional COVID-19 doses captured during follow-up will include non-Pfizer-BioNTech manufacturers. • added a row, "date(s) of additional prior COVID-19 vaccination"	By FDA request, to specify data elements that will capture additional COVID-19 vaccine doses.
		Sections 9.2.5, 9.3 (Table 2), 9.4.1	The term "index dose" has been added and defined.	To define that person time at-risk commences at the qualifying dose for study enrollment.
		Section 6	Start of data collection has been revised to "30 Jun 2023" instead of "30 Apr 2023"	To account for operational constraints.
		Multiple throughout protocol	The term "Pfizer-BioNTech COVID-19 vaccine" has replaced "Pfizer-BioNTech bivalent COVID-19 vaccine".	For consistency with the medicinal product name and what is on the market under Emergency Use Authorization.

6. MILESTONES

Milestone	Planned date	Actual date
Start of data collection	Estimated to be 30 June 2023	24 Aug 2023
End of data collection	18 months after start of data collection	27 Feb 2025
Interim reports	Within 6 months after start of data collection and annually thereafter	Interim report 1: 29 Feb 2024 Interim report 2: 28 Feb 2025
Registration in the European Union (EU) PAS register	Pending (prior to the start of data collection)	08 Aug 2023
Final study report	28 Feb 2026	

7. RATIONALE AND BACKGROUND

In December 2019, a viral pneumonia outbreak of unknown origin was identified in Wuhan, China.[1] By January 2020, the outbreak was confirmed to be caused by a novel coronavirus named SARS-CoV-2.[2] The outbreak quickly reached pandemic levels, spreading to 213 countries and territories worldwide. In February 2020, the World Health Organization (WHO) formally named the disease caused by SARS-CoV-2 the coronavirus disease 2019 (COVID-19).[3] As of 02 October 2020, a total of 34.6 million confirmed cases and over 1 million deaths related to COVID-19 have been reported.[4] Given the public health emergency caused by the virus, Pfizer-BioNTech was granted authorization of emergency use of their COVID-19 vaccine by the FDA on 11 December 2020, prior to full approval of the biologic license application for the prevention of COVID-19 for individuals 16 years of age and older. As of 08 July 2022, BNT162b (the monovalent COVID-19 messenger ribonucleic acid (mRNA) vaccine encoding the original SARS-CoV-2 S protein) has been fully licensed for use in individuals ≥12 years of age in the US.

In November 2022, SARS-CoV-2 subvariants were the dominant strains causing COVID-19 in the US. In response to the evolution of the pandemic, Pfizer-BioNTech developed updated versions of their mRNA-based COVID-19 vaccine, which include mRNA instructions for both the original SARS-CoV-2 and the Omicron subvariants B.A.4/5, and the original SARS-Cov-2 and Omicron subvariant B.A.1. On 31 August 2022, the US FDA granted EUA of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) 30 µg for use as a single booster dose to provide a broadly protective immune response against COVID-19, and administered at least 2 months after either the completion of primary vaccination or receipt of the most recent booster dose with a monovalent COVID-19 vaccine in individuals ≥12 years of age. Henceforth in this study protocol this Bivalent Original and Omicron BA.4/BA.5 booster vaccine will be referred to as the Pfizer-BioNTech COVID-19 vaccine.

The HERO-Together Boost study is designed to provide real-world safety information on a cohort of people receiving the Pfizer-BioNTech COVID-19 vaccine. This non-interventional study (NIS) is designated as a PASS, and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The research question addressed by this study is: what are the incidence rates of safety events of interest among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a US cohort?

Primary study objective:

- Estimate the real-world incidence of safety events of interest among recipients of the Pfizer-BioNTech COVID-19 vaccine following EUA.

Secondary study objective:

- Estimate the incidence rates of safety events of interest among subcohorts of interest, including individuals who are pregnant, individuals who are immunocompromised, and stratified by age.

9. RESEARCH METHODS

9.1. Study design

HERO-Together Boost is a prospective, observational, voluntary safety study designed to evaluate the incidence rates of safety events of interest in people 18 years of age and older who receive the Pfizer-BioNTech COVID-19 vaccine. The decision to be vaccinated is made at the discretion of the recipient, however receipt of the vaccine is required for inclusion in the study. This study will aim to enroll eligible recipients of the Pfizer-BioNTech vaccine and follow them during an 18-month study period. The study is a primary data collection study with a multi-layer approach to outcomes capture (Section 9.4.2), where safety event occurrence will be confirmed by medical record review and/or linked claims/EHR data. Information on hospitalization and diagnosis of safety events of interest will be collected from participant self-report at regular intervals following vaccination through a secure, participant-facing web portal. In this manner, digitally-driven methods of prospective enrollment and data collection will facilitate rapid enrollment and monitoring of safety events of interest. To address the primary objective, summary measures of incidence rates of safety events will be estimated.

9.2. Setting

The source population will be adults living in the US, whereby after enrollment study participants are followed for up to 18 months. Given the broad source population, the study will apply multiple recruitment strategies to ensure enrollment of a diverse sample to support generalizability of results. The primary study recruitment strategy (pharmacy email

invitations) may leverage oversampling of traditionally underrepresented populations to ensure adequate representation in the final analytic population.

9.2.1. Inclusion criteria

HERO-Together Boost is open to anyone aged 18 or older living in the US.

The study population must also meet the following inclusion criteria:

- Age ≥18 years
- Able to speak and read/write English or Spanish
- Receipt of the first dose of a Pfizer-BioNTech COVID-19 vaccine for prevention of SARS-CoV-2 infection within the past 90 days
- Ability to provide date and manufacturer of all previous COVID-19 vaccine doses
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study

9.2.2. Exclusion criteria

There are no exclusion criteria for this study.

9.2.3. Recruitment

A potential participant may learn about the opportunity to enroll in the study through a variety of mechanisms. The primary recruitment mechanism will be email outreach from commercial pharmacy partners.

In addition to email-based recruitment, recruitment efforts may leverage public communication, social media and other advertising, and printed enrollment materials with information about the study at vaccination sites. Additional efforts may include:

1. Digital recruitment through online advertising
2. Grand rounds/educational presentations to institutional audiences provided by HERO-Together Boost investigators;
3. Social media influencer partnerships; and
4. Participant-driven outreach including tag-a-friend campaigns and “Why I joined” videos on the study website

Given that the primary analysis will include recipients of the Pfizer-BioNTech COVID-19 vaccine, digital recruitment efforts will target the geographic regions represented in current Pfizer-BioNTech COVID-19 vaccine distribution plans. Participant enrollment through all channels will actively be tracked and recruitment plans will be revised to reflect the highest-yield strategies. While this study will use a convenience sampling strategy, specific attention will be devoted to enhancing diversity of the sample through (for example) targeted email outreach to historically underrepresented groups by a commercial pharmacy partner.

Diversity-Focused Recruitment

A diverse study population is critical to ensuring results from this study are generalizable. The study team will plan to implement up to 3 strategies focused on enhancing diversity in this study. These include 1) an extended recruitment plan with broad strategies to reach populations outside of traditional clinical research sites (for example, through social media and paid media partnerships) 2) culturally sensitive electronic and printed recruitment materials to ensure that imagery reflects a diverse population with respect to race/ethnicity and professional role; and 3) a targeted email campaign from a commercial pharmacy partner that prioritizes outreach to populations historically underrepresented in clinical research. The demographic and professional role distribution of enrolled participants will be continually monitored and diversity-focused recruitment strategies will be refined accordingly. All methods for recruitment and retention will be detailed in a separate recruitment and retention plan. Recognizing the limitations of an entirely participant-driven study, there are several safeguards in place to minimize missing and inaccurate data, and loss to follow-up (call center rescue, email reminders, ongoing communications from the study team, data entry checks). The Recruitment and Engagement plan is expected to be a living document, with refinements over time responding to enrollment trends, follow-up completion rates, and stakeholder feedback.

9.2.4. Enrollment

Potential participants recruited via the commercial pharmacy-supported email campaign will be directed to complete the screening questionnaire and informed consent form (ICF). Existing participants of the HERO-Together study will be instructed to complete a screening questionnaire and an ICF, at which point they will be enrolled in the study. In addition, proxy contact information will be collected at enrollment to support data capture in the event that the participant cannot be reached (e.g., participant is hospitalized).

Enrollment metrics will be monitored throughout the enrollment period and will be specified in the recruitment plan. Potential metrics of interest include time since vaccination, and demographic characteristics, to ensure a sufficient number meeting inclusion criteria for the primary analysis and sufficient numbers for subgroup analyses. Additional metrics may be included in the recruitment plan.

9.2.5. Participant Follow-up and Schedule of Assessments

Participants will be followed from date of enrollment until the end of the 18-month period following index vaccine dose, end of the study period, death, loss-to-follow up (no response after a notable interval of attempted Call Center contacts), or discontinuation from study. “Index dose” refers to the qualifying dose (receipt of the first dose of a Pfizer-BioNTech COVID-19 vaccine for prevention of SARS-CoV-2 infection within the past 90 days) for study enrollment. Following enrollment, all participants will be prompted to enter data into a secure participant facing web portal at 1 week, 4 weeks, 12 weeks, and 6, 12 and 18 months following receipt of the booster dose of the vaccine (see Table 1).

Table 1. Schedule of Assessments

	Enrollment Data Collection	***Follow-up Data Collection***			
	Baseline	After booster dose			
		1 week	4 weeks	12 weeks	6, 12, 18 months
E-consent	X				
Eligibility criteria confirmed	X				
Previous COVID-19 vaccine information	X				
Index Dose information Date Site	X				
Additional Dose information Date					X***
Medical record release	X**	X**	X**	X**	X**
Demographics form	X				
Medical history Medical history form	X				
Concomitant medications All current medications reported at baseline Changes to medications reported at follow-up	X				X*
COVID-19 Information Positive COVID-19 test with date COVID-19 diagnosis (presumptive)	X	X	X	X	X
Health questionnaire Potential safety events of interest Pregnancy status	X	X	X	X	X*

* Collected only at 6, 12, and 18 month intervals.
** Medical record release collected at the time of reporting a health event of interest.
*** Optional form.

9.2.6. Participant Retention

The Duke Clinical Research Institute (DCRI) Call Center will function as a "rescue" mechanism to reduce loss-to-follow up among study participants. If a participant does not complete an assessment after a notable period of time, the DCRI Call Center will be alerted to contact the participant and/or proxy using participant contact information transferred from the web portal into the communications system used by the Call Center. For additional details, please see Section 10.3.1 ("Strategies for Retention").

9.3. Variables

The key vaccine exposure, baseline, and safety outcome variables are listed in Table 2. Detailed definitions are provided in Section 9.3.1.

Table 2. Variables Used in Analyses

Variable	Role	Data Source(s)
Date of 1st dose COVID-19 vaccination	Covariate	Participant
Date of 2nd dose COVID-19 vaccination	Covariate	Participant
Date(s) of additional prior COVID-19 vaccination	Covariate	Participant
Date of index* COVID-19 vaccination ("booster")	Exposure	Participant
Date(s) of additional COVID-19 vaccination during follow-up**	Exposure	Participant
Vaccination details	Exposure variable	Participant
Pregnancy Information (pregnancy status and estimated due date)	Outcome (descriptive analyses) and covariate (safety analyses)	Participant
Demographics	Outcome (descriptive analyses) and covariate (safety analyses)	Participant
Medical History	Outcome (descriptive analyses) and covariate (safety analyses)	Participant
Non-COVID-19 vaccination details	Outcome (descriptive analyses) and covariate (safety analyses)	Participant
Concomitant medications	Outcome (descriptive analyses) and covariate (safety analyses)	Participant
Non-hospitalized safety events of interest	Outcome	Participant
Hospitalized safety events of interest		Participant, proxy, de-identified linked data, or medical record review
COVID-19 Diagnosis	Outcome	Participant
All-cause hospitalization	Outcome	Participant, proxy, de-identified linked data, or medical record review
Death	Outcome	Proxy, de-identified linked data, or medical record review

*Index dose refers to the qualifying dose for study enrollment

** non-Pfizer BioNTech vaccination during follow-up is a covariate.

9.3.1. Safety Event Definitions

The safety events of interest in this study are guided by a combination of: the Priority List of Adverse Events of Special Interest from the Brighton Collaboration's SPEAC Project updated in October 2022,[5] AESI per the FDA-CBER Best Initiative,[6] spontaneous reporting, and the framework from a preceding study (C4591008). The AESIs in this study include:

- Multisystem inflammatory syndrome (adults)
- Autoimmune thyroiditis

- Myocarditis
- Pericarditis
- Arrhythmia
- Heart failure
- Coronary artery disease
- Myocardial infarction
- Stress cardiomyopathy
- Thrombosis and Thromboembolism
- Hemorrhagic disease
- DIC
- Chilblain-like lesions
- Erythema multiforme
- Single Organ Cutaneous Vasculitis
- Acute kidney injury
- Acute liver injury
- Anaphylaxis
- Thrombocytopenia
- Generalized convulsion
- Guillain Barré Syndrome
- Acute aseptic arthritis
- Aseptic meningitis
- Encephalitis / Encephalomyelitis
- Bell's Palsy

- Vaccine-associated enhanced disease (respiratory disease)
- Tinnitus
- Severe COVID-19 disease
- Death
- Stroke
- Fibromyalgia
- KD
- Limb ischemia
- Microangiopathy
- MS
- Non-anaphylactic allergic reactions
- Narcolepsy/cataplexy
- ON
- Other acute demyelinating diseases
- Transverse myelitis
- Pregnancy outcomes
- Acute disseminated encephalomyelitis
- Deep vein thrombosis
- Extensive limb swelling
- Pulmonary embolism
- Cerebral venous sinus thrombosis
- Vasculitides

9.4. Data sources

Data on vaccine exposure, outcomes, and covariates will be captured through several mechanisms, described below. All participants will enter baseline data through a secure portal upon enrollment, and event capture for adverse events of special interest (hospitalized or non-hospitalized manifestations) will be entered into the portal (Section 9.4). For events which are self-reported and hospitalized, a workflow to confirm event occurrence will proceed by two methods (as described in Section 9.4.2.1 and 9.4.2.2). All AESIs of interest will be defined in a separate charter that will include standardized definitions from the published literature and/or developed in partnership with informatics and clinical specialists at the DCRI. Algorithms will be circulated for review prior to implementation.

All data collected in the context of this study will be stored and evaluated per applicable regulatory requirements and guidance for electronic records. Data will be stored and evaluated in a manner that protects participant confidentiality in accordance with the legal stipulations applying to confidentiality of data.

9.4.1. Call Center Data Collection

The DCRI Call Center will serve two main functions in this study:

a) To serve as a "rescue" mechanism to minimize incomplete data from non-response and loss to follow-up, and
b) To request medical records for confirmation of the occurrence of safety events of interest for records that cannot be requested through automated processes

The DCRI Call Center will function as a "rescue" mechanism for participants for whom automated medical record retrieval processes cannot be used. If a participant does not complete an assessment after a notable period of time, the DCRI Call Center will be alerted to contact the participant and/or proxy using participant contact information transferred from the web portal into the communications system used by the Call Center. This communications system manages call queues, scheduling, and call processing information. The study data obtained by the Call Center will be entered directly into the study portal. For a given survey assessment, if the participant is not reached after a notable interval of call attempts, the participant data will be considered missing.

9.4.2. Safety Event Ascertainment

Interim reports/results will contain non-hospitalized participant-reported outcomes, as well as hospitalized participant-reported outcomes. Throughout the study, attempts will be made to obtain medical records and adjudicate all participant self-reported events which lead to hospitalization. Participant-report of hospitalized AESI will trigger a medical record request, which will proceed via an automated third-party process where possible, with Call Center

follow-up for remaining participants. In addition, a subset of hospitalized participant-reported outcomes will be ascertained in 3 data streams:

1. Participant self-report through the online portal (Section 9.4.2.1)
2. Medical records, acquired via automated third-party retrieval (where available) or manual Call Center processes, and adjudicated (described Section 9.4.2.2)
3. De-identified third-party data sources, linked and acquired through privacy protecting strategies (e.g. tokenization in Section 9.4.2.3)

The goal is to understand the feasibility of using these data for event surveillance in a direct-to-participant safety study. Each data source has unique advantages in addition to potential drawbacks. While participant report through an online portal is low burden and allows for data capture from any eligible person regardless of proximity to a clinical site, prior work suggests it is often subject to information and recall bias, which can lead to event misclassification if used in isolation. Medical records with accompanying clinical event adjudication are highly valid but require substantial effort to access and analyze and are sometimes inaccessible due to participant/site refusal or time delays. In the automated third-party process, proof of participant authorization and required demographic details are shared with the third-party to enable retrieval through their provider network, and the resulting matched medical records are returned. While de-identified third-party data linked and acquired through privacy protecting strategies is a demonstrated pathway for data access and validated algorithms for event classification, it only covers a subset of the population and presents a time lag from event occurrence to availability of data within the 3rd party source.[6,7] Findings regarding operational feasibility and the degree of event concordance between ascertainment methods will be provided by the final report.

9.4.2.1. Participant Self-Report

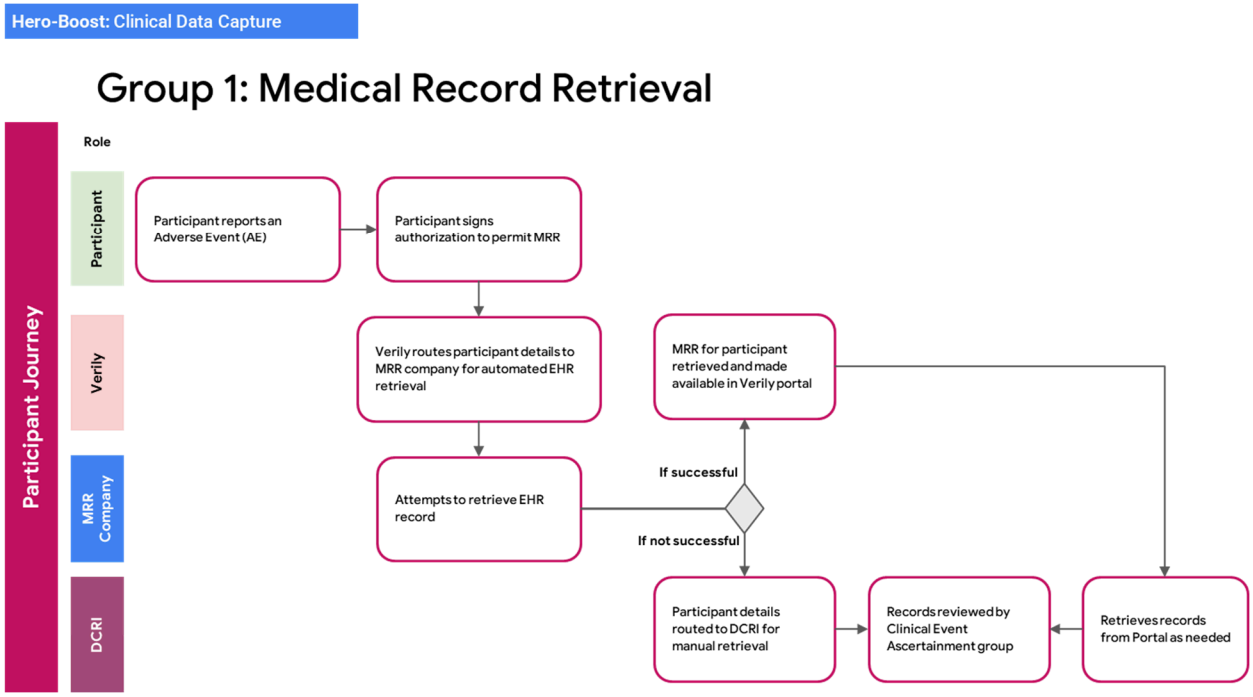
Participants will be followed from date of enrollment through the earliest of time point of 18 months following the index vaccine dose, end of the study period, death, loss-to-follow up (no response after a notable interval of attempted Call Center contacts), or discontinuation from study. Following enrollment, all participants will be prompted to enter data into a secure participant facing web portal at 1 week, 4 weeks, 12 weeks, and 6, 12 and 18 months following receipt of the index dose of the vaccine. Additional dose/booster information will be solicited during follow up. Participants will be queried regarding their general health and events requiring medical attention. Participants who do not complete data entry within a notable period of time of the expected completion date for a given time point will be contacted by the Call Center for confirmation of health status.

At enrollment, participants will provide contact information for a proxy to complete assessments in the situation where the participant is non-responsive to survey prompts. If a proxy cannot be reached, the Call Center will continue to contact the participant for a defined period of time, after which the data for that assessment will be marked as “missing”. Future assessments will be targeted for completion according to the planned schedule.

9.4.2.2. Medical Record Retrieval

For participants who report hospitalization for a potential AESI and provide a signed Medical Record Release form, medical records will be acquired via automated third-party retrieval processes (where coverage is available) or manual DCRI Call Center processes where necessary (Figure 1). Once medical records are obtained, hospitalized events will proceed through review by the Clinical Event Ascertainment group for confirmation of the occurrence of a safety event of interest (see "Clinical Event Adjudication" below in Section 9.4.2.2.1).

Figure 1. Event capture and classification



9.4.2.2.1. Clinical Event Adjudication

Medical records may be requested through an automated process supported by a third-party vendor or by the Call Center. The following components of medical records will be sought as appropriate:

- Emergency room notes
- Discharge summary/death summary
- Admission history and physical exam
- Progress/clinic/urgent care notes
- Diagnostic tests
- Lab reports
- Medication records

Upon completion of the CEA Charter and CEA adjudication platform system, these events will be adjudicated by CEA physician reviewers trained on the HERO-Together Boost study protocol and CEA charter. Safety event definitions will be specified a priori in the CEA charter as appropriate. The CEA group is responsible for ongoing analysis of potential safety events of interest and of their adjudication as study endpoints. The CEA group includes specialists relevant to the safety events of interest, including cardiologists, immunologists, neurologists, and other specialists. Additional details about review procedures will be provided in an adjudication charter.

9.4.2.3. De-identified Data Linkage

Feasibility of hospitalized event ascertainment via de-identified data linked through third-party sources, leveraging privacy sparing practices (e.g., tokenization) will also be explored. Because the extent of third-party linked data coverage varies with the study population and is unknown prior to the start of a prospective study, the study will evaluate overall coverage for the enrolled study population in different de-identified data sources at a pre-defined checkpoint. Overall coverage will be used to inform selection of specific de-identified data sources for linking with participant-reported study data; closed medical claims will be the primary type of data evaluated and the study may select a single de-identified data source or multiple data sources for linking. Linking algorithms use proprietary models to match tokenized data at specific accuracy thresholds. Following accrual of participant self-reported AESIs and prior to the end of data collection, the study will initiate the evaluation of agreement comparing events in the selected de-identified data sources to those reported by participants. In addition, the study will evaluate operational aspects of linking third-party data, including data capture and integration, data latency, time required for quality control and harmonization, and privacy certification. Results from these assessments will inform the feasibility of event ascertainment facilitated by tokenization.

Algorithms to map third-party linked data to events defined in the Clinical Events Ascertainment (CEA) charter will be informed by general and therapeutic area-specific data standards, including the standards efforts of professional societies. Published algorithms developed and validated using EHR data will be used whenever possible. EHR-based algorithms typically rely on diagnosis codes (ICD-9-CM and ICD-10-CM) and procedure codes (ICD-9-CM and ICD-10-PCS). Definitions will be updated as necessary to account for coding changes since protocol approval. If no published definition is available, mapping of diagnosis codes from ICD-9-CM to ICD-10-CM and mapping of procedure codes from ICD-9-CM to ICD-10-PCS will be done as appropriate using the general equivalence mappings provided by Centers for Medicare & Medicaid Services (CMS):

- Diagnosis code crosswalk: http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-CM-and-GEMs.html

- Procedure code crosswalk: http://www.cms.gov/Medicare/Coding/ICD10/2014-ICD-10-PCS.html

9.5. Study size

As the primary objective is descriptive, a large sample size target will facilitate adequate precision for a plausible range of AESI rates in the population of vaccine recipients. However, enrollment is uncertain and exact sample sizes for the study depend on numerous factors, including, but not limited to 1) vaccine hesitancy, which may impact initial recruitment; 2) coverage of participants within available data sources accessible via third-party linkage; 3) attrition during the consent/assent process due to privacy concerns about potential data linkage; 4) general participant attrition which is higher in direct-to-participant studies than site-supported studies; 5) timing of study launch, and 6) potential future changes in vaccine cost coverage. While several mechanisms are planned to help address these barriers (consent, targeted outreach from a commercial pharmacy partner, user experience-centered platform design and communications, and participation incentives), the study team will monitor both recruitment and attrition at each phase of study participation and revise our approaches as needed.

For the above reasons, precision calculations were obtained for sample sizes of 500, 1,000, 5,000 and 10,000, and as a reference to enrollment in a similar study, 20,000. Table 3 displays anticipated precision (95% confidence interval widths) generated using the Clopper-Pearson exact method for a range of safety event rates in a sample of 500, 1,000, 5,000, 10,000, and 20,000 participants (potential subgroups based on event data source and allowing for some exclusions due to attrition). As shown below, precision is high for observed event rates ranging from 0.01% to 20.0%.

Table 3. Estimated Precision of Observed Event Risks

Observed Risk	Exact 95% Confidence Interval (n=500)	Exact 95% Confidence Interval (n=1,000)	Exact 95% Confidence Interval (n=5,000)	Exact 95% Confidence Interval (n=10,000)	Exact 95% Confidence Interval (n=20,000)
0.01%	0.00, 0.76	0.00, 0.39	0.00, 0.09	0.00, 0.06	0.00, 0.04
0.05%	0.00, 0.84	0.00, 0.47	0.01, 0.16	0.02, 0.12	0.02, 0.09
0.1%	0.00, 0.93	0.00, 0.56	0.03, 0.23	0.04, 0.18	0.06, 0.15
0.5%	0.08, 1.59	0.16, 1.16	0.32, 0.74	0.37, 0.66	0.41, 0.61
1%	0.33, 2.32	0.48, 1.83	0.74, 1.32	0.81, 1.21	0.87, 1.15
2%	0.96, 3.65	1.23, 3.07	1.63, 2.43	1.73, 2.29	1.81, 2.20
5%	3.26, 7.29	3.73, 6.54	4.41, 5.64	4.58, 5.45	4.70, 5.31
10%	7.51, 12.97	8.21, 12.03	9.18, 10.87	9.42, 10.60	9.59, 10.42
20%	16.58, 23.78	17.56, 22.62	18.90, 21.14	19.22, 20.80	19.45, 20.56

9.6. Data management

The DCRI utilizes a “Fit for Purpose” approach to selecting and utilizing information systems, particularly as it pertains to electronic data capture (EDC), clinical trial management system (CTMS), analysis and reporting.

All solutions utilized by the DCRI are fully vetted by IT personnel, and representatives from core teams such as Clinical Data Management and Safety Surveillance to ensure solutions support primary business requirements and meet all applicable regulatory requirements (e.g., 21 CFR Part 11). Externally hosted solutions are audited to ensure compliance with appropriate security and data privacy requirements, and that robust data backup/recovery and business continuity solutions are in place.

The data management platform for this study is primarily focused on a single web-based portal that will support all data collection and interactions with participants and the DCRI Call Center. Related operational systems supporting the Call Center activities will be embedded within each of those organizations and interfaced via a routine set of data transfers or application interfaces. Study participants accessing the system directly and the emphasis on self-reported data does require primary identifiers to be maintained within a limited number of systems. These data will be secured such that it is only maintained in the minimum required systems and accessible to the minimum number of people to perform the study procedures described in this protocol. The primary method of identifying a participant will be with a unique participant identification number.

Participants will use a study portal developed by Verily Life Sciences (https://verily.com/; ("Verily") for the ICF, medical release form and data reporting. The Verily system leverages the Google infrastructure, including hosting, security, user account management and the study-specific data system. Leveraging this infrastructure ensures very high levels of system security and support are embedded in the portal. Although leveraging Google infrastructure, this is a stand-alone portal and no data are shared from other sources with the study, and no study data will be shared with any other Google systems.

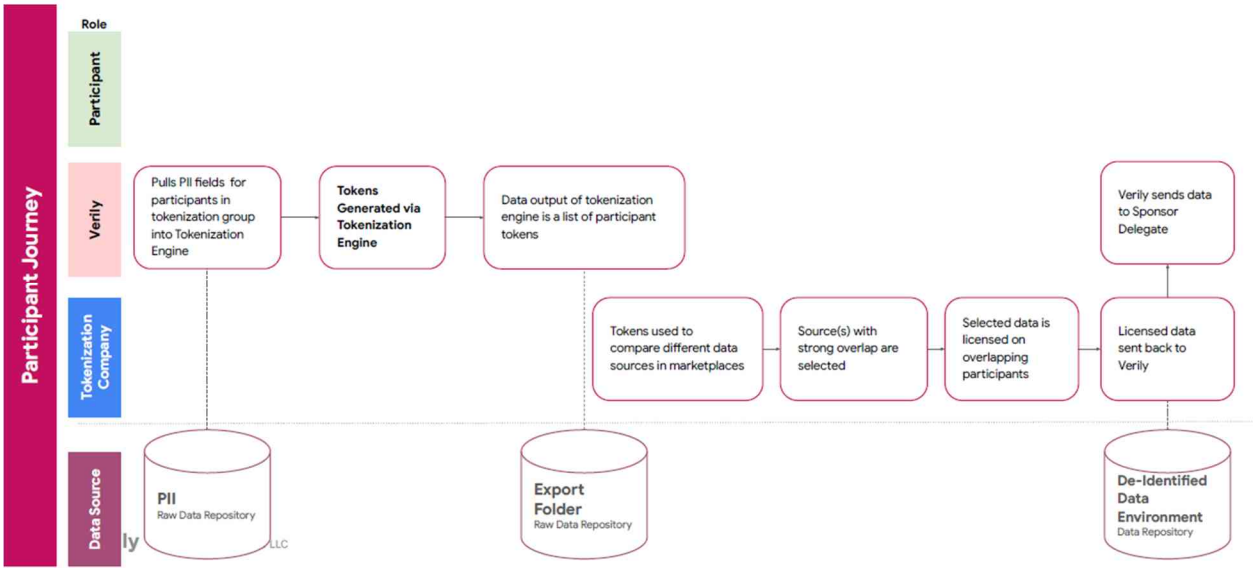
The Call Center staff will contact study participants directly, as described in the study consent form, to obtain follow-up information should a participant not respond directly within the portal. The participant contact information will be transferred from the portal into the communications system used by the Call Center for these contacts. This system manages call queues, scheduling, and call processing information. The study data obtained by the call center will be entered directly into the study portal. The study data is managed using a set of tools including Oracle (relational database management system), Informatica (data exchange/extract-transform-load procedures), Cognos (operational reporting), Microsoft SQL Server, and SAS Visual Analytics (statistics).

Data quality is managed at each stage of its lifecycle. Data collected in the portal conforms at inception to highly structured data elements and protocol-specific rules, subsequent data transfers are checked to conform to format and semantic specifications and all data is assessed for referential integrity across sources through a set of reconciliation practices upon integration then followed by a variety of logical checks within a participant and in aggregate.

Tokens to enable data linking are generated through a controlled and automated process, and the identified fields used to generate tokens are stored separately from the tokens themselves (Figure 2). For the de-identified data acquired and linked via third-party providers, data are stored in a separate de-identified data store to maintain de-identification and comply with

data use agreements and privacy certifications. This system has additional access controls to prevent any individual from accessing both identified and de-identified data. Additional restrictions and policies are placed on the de-identified data, including a restriction on attempting to re-identify participants. Study data can only be linked with de-identified data once a new privacy certificate has been obtained, and the linked data must remain de-identified.

Figure 2. Tokenization Data Flow



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

As used in this protocol, the term electronic CRF (eCRF) should be understood to refer to an electronic data record.

A completed eCRF is required for each included participant. The completed original eCRF 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. Verily shall ensure that the eCRF are securely stored at Verily in electronic form and will be password protected to prevent access by unauthorized third parties.

Verily has ultimate responsibility for the collection and reporting of all data entered on the eCRF as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRF serves as the source document. Any corrections to entries made in the eCRF 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, Verily agrees to keep all study-related records. The records should be retained by Verily according to local regulations or as specified in the Verily contract, whichever is longer. Verily must ensure that the records continue to be stored securely for so long as they are retained. If Verily 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 Verily and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

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

9.7. Data analysis

This study will aim to enroll all eligible participants (up to 20,000) who have received a Pfizer-BioNTech COVID-19 vaccine. A large study size, if feasibly enrolled, will help ensure a diverse population of participants with respect to geography and demographics, and as numbers allow, stratification by important subgroups of age, homologous/heterologous vaccine receipt, and region.

9.7.1. Considerations for Concordance Analysis

Data permitting, there will be calculation of concordance between hospitalized events in linked data (via tokenization) and participant-reported events for each AESI in the dataset, in addition to aggregate concordance for any AESI (yes or no). In these analyses, each type of event will be evaluated at the participant level; hence, where applicable, multiple events of a given type within a subject will be considered as a single first occurrence of that event for that participant. Concordance will be estimated individually for all AESIs represented in the initial sample of participant-reported events.

For categorical variables, estimated concordance metrics are based on the 2x2 cross-tabulation of values in the participant-reported and EHR-based data. For this analysis, agreement will be defined as the proportion of all positives that are identified as positives in the EHR data.

9.7.2. Analytic Methods

Vaccination and baseline characteristics will be summarized using descriptive statistics, including measures of central tendency and dispersion (means, medians, standard deviations) for continuous variables and percentages for categorical variables.

Interim and final reports will include descriptive statistics for both self-reported events overall and self-reported events that were hospitalized. The primary analysis for each objective will be restricted to participants who enrolled within 10 days of vaccination to mitigate the risk of selective enrollment and disproportionate representation of higher risk participants. The number and incidence rate for each safety event of interest will be calculated for participants enrolled within 10 days of vaccination and for participants enrolled at any time relative to vaccination. Event frequencies, person-time at risk, and median time with interquartile ranges from vaccine receipt to event onset will be presented for each event of interest. Event rates will also be calculated overall, and within subgroups of interest, including pregnant women, immunocompromised individuals, those with different vaccination histories (heterologous vs. homologous; total number of vaccine doses) and within age groups. Rates will also be stratified by other baseline characteristics, such as geographic region, data permitting. Multiple imputation-based methods will be used for missing data where feasible and appropriate and will be described in the SAP.

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 may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality control

Data will be transferred from the Verily platform to the DCRI data management team. Data will be reviewed for completeness and to identify any needed queries of the Verily platform or to transfer to the DCRI Call Center for follow-up with the participant.

Data captured by the DCRI Call Center will be input directly into the Verily platform for quality control.

Data reconciliation consists of resolving the primary participant identifiers and all queries generated by the EDC system. Both automatic and manual queries can be generated in the EDC system. Auto queries generate immediately upon data submission and manual queries are generated as a result of data review. Data quality strategies and data surveillance may also include data status reports and other data status reports as defined by the needs of the study.

Linked data licensed from external, third-party sources will be assessed for data quality, and the data quality report generated by Verily will be shared with DCRI.

9.9. Limitations of the research methods

There are several possible limitations to the proposed design worth noting:

Selection Bias

- Potential for imbalance in the number of subjects analyzed in the total study population vs. the primary safety population, if many participants enroll beyond the 10-day window since vaccination

Information Bias

- Underreporting of safety events by participants
- Misclassification of important exposure, outcome, and covariate data due to erroneous participant self-report
- Outcome misclassification in EHR and medical record data due to suboptimal linkage across data sources, duplicate events, missing data, lack of medical record availability

Generalizability

- Voluntary enrollment will be driven by study launch timing, vaccine willingness, among other factors.
- Enrollment that is lower than anticipated will reduce the ability to assess events, particularly uncommon events, with sufficient precision
- Enrollment of a homogenous study population with respect to demographics could limit generalizability

Event Precision

- Event rates will be estimated based on the assumption of observed person-time for all participants in the absence of death or censoring events (e.g., complete follow up). Because missed surveys may artificially inflate event rate denominators, the study will only include person-time accrued through the most recent check-in date or Call Center contact
- De-identified linked data with less than complete coverage (without matching EHR data) will reduce precision in study estimates.

Lastly, the ability to examine concordance between adjudicated events and participant-reported information is limited to calculating agreement, as only positively reported events are adjudicated.

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. Novel technologically enabled strategies (e.g. hashing and generating tokens in place of identifiers) will be used when possible to limit sharing of individually identifiable health data, and for the purpose of linking de-identified data

Participant personal data will be stored at Verily in encrypted electronic form and will be password protected through a multi-authenticated system to ensure that only authorized study staff have access. Verily 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, Verily 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. Study data that is based on de-identified data will also have a single, specific numerical code as the identifier, but this will be a different code than the one used in the primary study dataset. Verily will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with the research agreement and applicable privacy laws.

10.2. Patient consent

Participants will be consented using an electronic consent form. All consent forms will be IRB-approved before they are provided to the potential participant. Consent will be provided in both English and Spanish. At enrollment, participants who are existing members of HERO Together study will be instructed to log in to their existing profile, complete an ICF and enroll. Eligible individuals not yet enrolled in HERO-Together (e.g., those recruited via commercial pharmacy partner email campaigns) will be directed to complete the study-specific ICF form, and enroll. Electronic consent will be obtained by Verily's Baseline Platform, which currently supports both HERO-Together and the Project Baseline Community Study.

The Baseline Platform is compliant with all applicable regulatory standards, as follows:

a. FDA 21 CFR Part 11: The Baseline Platform supports electronic records and electronic signatures, maintaining rigorous access controls, audit trail, and identity

verification. Password management. Verily leverages Google's password policy designed to enhance system security by encouraging users to employ strong passwords and use them properly.

Authentication	Verily uses a user ID management system (Gaia) to authenticate users via Single Sign On (SSO).
Access Management	Verily restricts access to the Baseline Platform and its data to only authorized users or processes, based on the principle of strict need-to-know and least privilege.
Password Management	Verily leverages Google's password policy designed to enhance system security by encouraging users to employ strong passwords and use them properly.

b. HIPAA: The Baseline platform's ISO 27001 controls map to the HIPAA Security Rule (for more, please see HIPAA Security Rule Crosswalk to NIST Cybersecurity Framework).

10.3. Patient withdrawal

10.3.1. Strategies for Retention

Over the course of the study, a diverse set of approaches for participant engagement and retention may be employed, which may include, but are not limited to:

- Payment incentives for survey completion
- Newsletters with opportunities to be featured or contribute content
- Videos of study participants explaining their reasons for joining
- Links to expert content on COVID-19
- Feedback surveys so participants can voice their opinions
- Study-related goals and progress tracking
- Return of results on social media, through blogs, manuscripts, Facebook live events, and others

Additionally, there is an automated system built into the Verily platform that notifies the DCRI Call Center when a participant has not completed a survey. The DCRI Call Center, with their staff of bilingual interviewers (Spanish and English), operates 7 days a week, offers toll-free lines for participant use, and includes time zone accommodations.

Interviewers undergo extensive orientation, ethics training, training for pediatric interviews and are taught standardized interviewing techniques. The DCRI Call Center provides follow-up support to participants who do not complete their digital surveys - this process is known

as “rescue”. In addition, the Call Center is available to answer questions about the study prior to and during enrollment.

Participants are offered preferred times to call and a toll-free line to use at their convenience. Final engagement strategies will be detailed in the Recruitment and Engagement Plan, which will be developed in partnership with project stakeholders. This plan is expected to be a living document, with refinements over time in response to enrollment trends, follow-up completion rates, and stakeholder feedback.

10.3.2. Discontinuation of Participants

All study surveys are optional; participants may opt to complete some or all of the study assessments while enrolled. In the event a participant wants to stop his/her involvement in the study, the participant may immediately stop all activities. Participants will be asked to submit withdrawal requests via the contact information provided in the consent form. Until a formal withdrawal request is made, participants will continue to receive notifications about available study assessments, regardless of whether or not they have completed previous assessments.

Participants will be followed until participant closeout, withdrawal of consent, or death. A participant may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the principal investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Those who withdraw from the study will be asked to continue on study follow-up with limited participation through study closeout. Limited participation may include a call at 12 months and 18 months or collection of medical records to ascertain possible safety events. Descriptive analyses comparing baseline characteristics by participants who withdraw vs. continue will be conducted.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. No requests for third-party data will be made following the withdrawal date for participants who withdraw.

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

It is the responsibility of the DCRI to have prospective approval of the study protocol, protocol amendments, materials describing the consent process, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the DCRI. Copies of IRB/IEC approvals should be forwarded to Pfizer. All study procedures and materials will be reviewed and approved by a central IRB (WCG IRB).

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

To address the safety surveillance objectives of this study, the management and reporting of adverse events/adverse reactions are separated into two components. The first component entails primary data collection, in which Pfizer-BioNTech COVID-19 vaccine recipients in HERO-Together or in the Project Baseline Community Study opt to participate in HERO-Together-Boost and complete a web-based data collection tool. The data collection tool completed by the HERO-Together Boost participants is designed to provide preliminary information on the occurrence of a potential safety event of interest.

The second component entails secondary data collection, in which the HERO-Together Boost participant self-reported events are examined via review of the participant's medical record and/or linked EHR data. Regarding the review of participants' medical records, the DCRI Call Center will request medical records for any participants who reported in the data collection tool a potential safety event of interest. The CEA group will review the medical records as part of the adjudication process designed to confirm events for inclusion in the statistical analyses (Section 9.7). Regarding the examination of linked EHR data, linkage to health records (eg, EHR or claims), to confirm safety event of interest occurrence for inclusion in structured secondary data analysis, uses "tokens" as unique identifiers to link information for individuals who appear across more than one source of real-world data.

The requirements to report to Pfizer Safety any product safety information volunteered by a participant during an interaction with the DCRI Call Center, or discovered during medical record review, or in the context of tokenization as a linkage approach for secondary data analysis, are described in three separate sections below.

Product safety information volunteered by participants

This study does not involve data collection on individual patients by their treating healthcare professionals and the web-based questionnaires used in this study does not intend to identify product safety information. The web-based 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. Further, routine communication with study participants via email or phone with the DCRI is not expected during the conduct of the study. However, it is possible that a study participant may volunteer product safety information to DCRI Call Center staff during completion of a survey assessment by phone (a "rescue" assessment when the participant is non-responsive to online prompts), or for any other reason (e.g., seeking information about the purpose of the study); this information must be reported as described below.

The following safety events must be reported on the NIS AEM Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, 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.

For exposure during pregnancy in studies of pregnant women, data on the exposure to the Pfizer-BioNTech COVID-19 vaccine during pregnancy, are not reportable unless associated with serious or non-serious AEs.

In the event that a study participant volunteers product safety information, DCRI Call Center staff 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 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. DCRI Call Center staff who will serve to address any query from a study participant must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors* ".

**NIS Adverse Event (AE) Report Form for Protocols without Stipulated Active Collection of AEs; this type of report is managed as spontaneous by Pfizer Safety.*

These trainings must be completed by DCRI Call Center staff 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. DCRI Call Center will also provide copies of all signed training certificates to Pfizer. Re-training must be completed on an annual basis using the most current YRR training materials.

Medical record review abstraction

In this study protocol, the DCRI Clinical Event Ascertainment (CEA) group will 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 exposure during pregnancy in studies of pregnant women, data on the exposure to Pfizer-BioNTech COVID-19 vaccine during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

- 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.

***NIS AE Report Form For Protocols with Stipulated Active Collection of AEs; 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 (MM/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*".

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

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

Structured secondary data analysis of tokenization-linked records

Tokenization is a method through which linkage to real world data sources occurs. For this study, these data sources may include structured secondary databases such as closed claims data or EMR data which do not require human review of unstructured data.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim study reports will be completed according to a pre-defined milestone schedule. The final study results will be posted in the EMA-HMA RWD Catalogues Register. Results may be further disseminated through a variety of mechanisms, including presentation at national or international meetings and publication in peer-reviewed journals.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator at DCRI or Verily 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, the investigator will inform Pfizer immediately of any urgent safety measures taken by the DCRI or Verily to protect the study participants against any immediate hazard, and of any serious breaches of this NI (observational) study protocol that the DCRI or Verily becomes aware of.

13. REFERENCES

1. WHO Novel coronavirus – China. Jan 12, 2020. http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/.

2. Jiang S, Xia S, Ying T, Lu L. A novel coronavirus (2019-nCoV) causing pneumonia-associated respiratory syndrome. *Cell Mol Immunol.* 2020;17(5):554.

3. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Accessed October 2, 2020. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

4. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). https://coronavirus.jhu.edu/map.html.

5. Brighton Collaboration Priority List of Adverse Events of Special Interest: COVID-19. Accessed November 11, 2022. Available: https://brightoncollaboration.us/covid-19-aesi-list-5th-update-october-2022/.

6. Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring. CBER Surveillance Program. Accessed 18 January 2023. Available: https://bestinitiative.org/wp-content/uploads/2022/01/C19-Vax-Safety-AESI-Bkgd-Rate-Protocol-FINAL-2020.pdf

7. Kiernan D, Carton T, Sengwee T, et al. Establishing a framework for privacy-preserving record linkage among electronic health record and administrative claims databases within PCORnet, the National Patient-Centered Clinical Research Network. BMC Research Notes 2022; 15:337.

14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	C4591049_PROTOCOL AMENDMENT 2 V3_25APR2025
Document Title:	C4591049_PROTOCOL AMENDMENT 2 V3_25APR2025

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	01-May-2025 19:00:33	Final Approval
Asomaning, Kofi	01-May-2025 19:40:00	Final Approval