



NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers
Protocol number	C4591008
Protocol version identifier	Version 2.0
Date	27 January 2021
EU Post Authorization Study (PAS) register number	EUPAS38671
Active substance	N/A
Medicinal product	COVID-19 Vaccine BNT162b2
Research question and objectives	<p>The research questions addressed by this study are a) what are the incidence rates of safety events of interest and other clinically significant events among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a cohort of US healthcare workers and b) How do those rates compare to expected rates of those events?</p> <p><i>Primary study objectives:</i></p> <ul style="list-style-type: none">• Estimate the real-world incidence of safety events of interest and other clinically significant events among US healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization.

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	<p><i>Secondary objectives</i></p> <ul style="list-style-type: none">• Evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post-vaccination.• Estimate the incidence rates of safety events of interest and other clinically significant events among subcohorts of interest such as 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

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2. LIST OF ABBREVIATIONS

To be updated when protocol finalized.

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
AESI	Adverse Event of Special Interest
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DCRI	Duke Clinical Research Institute
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCW	Healthcare Worker
HERO	Healthcare Worker Exposure Response and Outcomes
ICF	Informed Consent Form
IRB	Institutional Review Board
MAAE	Medically Attended Adverse Event
NI	Non-Interventional
NIS	Non-Interventional Study
NISL	Non-Interventional Study Lead
PASS	Post-Authorization Safety Study
PCORI	Patient-Centered Outcomes Research Institute
RCT	Randomized Clinical Trial
RMP	Risk Management Plan
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
WHO	World Health Organization

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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
Heather Rubino, PhD, MS	Global Medical Epidemiology, Director	Pfizer Inc.	235 E 42 nd St, New York, NY 10017
Ann Madsen, PhD	Global Medical Epidemiology, Sr. Director	Pfizer Inc.	235 E 42 nd St, New York, NY 10017

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4. ABSTRACT

Title: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers

Rationale and background: Pfizer-BioNTech COVID-19 vaccine was approved for emergency use authorization (EUA) to prevent Coronavirus Disease 2019 (COVID-19) for individuals 16 years of age and older. Detailed distribution plans for the COVID-19 vaccine within the US are determined by local jurisdictions based on federal recommendations to prioritize vaccination of healthcare workers and people living in long term care facilities under an EUA. This study is designed to provide early real-world safety information on a cohort of vaccinated health workers for two years after vaccination. This non-interventional study is designated as a PASS and is included in the US pharmacovigilance plan.

Research question and objectives: The research questions addressed by this study are a) what are the incidence rates of adverse safety events of interest and other clinically significant events among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a cohort of US healthcare workers, and b) How do those rates compare to expected rates of those events?

Primary study objectives:

- Estimate the real-world incidence of safety events of interest and other clinically significant events among US healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization.

Secondary objectives

- Evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post-vaccination.
- Estimate the incidence rates of safety events of interest and other clinically significant events among subcohorts of interest such as individuals who are pregnant, individuals who are immunocompromised, and stratified by age.

Study design: This is a prospective observational cohort study of US healthcare workers, in which data are collected from participant self-report at regular intervals following vaccination, primarily using a secure web portal, as well as medical records for confirming the occurrence of safety events. The study period will be 30 months.

Population: Study participants will be recruited from two sources:

- An existing registry study, the Healthcare Worker Exposure Response and Outcomes (HERO) Registry Study, which was launched in April 2020 to characterize

COVID-19 risk factors and outcomes among US healthcare workers by the Duke Clinical Research Institute (DCRI)

- Major health systems distributing Pfizer-BioNTech COVID-19 vaccine to its employees, as determined by local jurisdictional EUA rollout plans. Once receiving systems are identified, study navigators will be identified for vaccination sites within systems and activated to ensure broad geographic diversity in the surveillance study.

To be eligible for enrollment, individuals must meet all of the following criteria:

- Individual currently works in a setting where individuals receive healthcare in the US (“healthcare worker”; including emergency medical services).
- Age ≥ 18 years.
- Able to speak and read English or Spanish.
- Receipt of COVID-19 vaccine for prevention of SARS-CoV-2 infection within the past 60 days.
- Evidence of informed consent indicating that the participant (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
- Medical release providing for release of all pertinent medical information for assessment of vaccine safety during the one-year period prior to vaccination and during the follow-up period.

Variables: Key variables include vaccination exposure characteristics (eg, number of disease received, length of interval between doses) and safety events of interest, which are based on the Priority List of Adverse Events of Special Interest (AESI) from the Brighton Collaboration’s Safety Platform for Emergency vACcines (SPEAC) Project (<https://brightoncollaboration.us/priority-list-aesi-covid/>) accessed 12/13/2020 The safety events of interest in this study include:

Neurologic:

- Generalized convulsion/seizures
- Guillain-Barre Syndrome
- Aseptic meningitis
- Encephalitis/encephalomyelitis
- Other acute demyelinating diseases

- Transverse myelitis
- Multiple sclerosis
- Optic neuritis
- Bell's palsy

Immunologic:

- Anaphylaxis
- Vasculitides*
- Arthritis/arthralgia
- Multisystem inflammatory syndrome (in adults)
- Kawasaki disease
- Fibromyalgia
- Autoimmune thyroiditis

COVID-19:

- Severe COVID-19 disease*
- Microangiopathy*
- Heart failure and cardiogenic shock*
- Stress cardiomyopathy*
- Coronary artery disease*
- Arrhythmia*
- Deep vein thrombosis
- Pulmonary embolus
- Cerebrovascular stroke
- Limb ischemia*
- Hemorrhagic disease*

- Acute kidney injury*
- Liver injury
- Chillblain-like lesions
- Single organ cutaneous vasculitis*
- Erythema multiforme*

Cardiac:

- Myocarditis
- Pericarditis
- Acute myocardial infarction

Hematologic:

- Thrombocytopenia
- Disseminated intravascular coagulation

Other:

- Pregnancy outcomes
- Death
- Narcolepsy and cataplexy;
- Non-anaphylactic allergic reactions

*Hospitalized manifestations only

Data sources: Data will be collected via participant self-report and medical record review. Following enrollment, the participant will enter vaccination and other baseline data into a secure participant facing web-portal. During follow-up, participants will be prompted to provide information on hospitalizations and diagnoses of safety events of interest at the following time points following receipt of the first vaccine dose: 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and then at 6, 9, 12, 18, and 24 months. Individuals with longer than a 2-day interval between vaccination and enrollment will be administered a retrospective

assessment to capture self-reported safety information occurring within this interval. The DCRI Call Center will follow-up on non-responsive participants and request medical records for participants reporting hospitalization or diagnosis of a safety event. The DCRI Clinical Event Ascertainment (CEA) group will adjudicate medical records for event confirmation.

Study size: The study aims to enroll at least 20,000 healthcare workers who have received a COVID-19 vaccine. As the primary objective is descriptive, this sample size target is designed to ensure adequate precision for a plausible range of safety event rates in the population of vaccinated healthcare workers.

To address the secondary objective regarding assessment of increased risk, a self-matched comparative analysis will be undertaken for feasible safety events (eg, events with a known risk interval). Statistical power to detect various effect sizes assuming a range of background incidence rates in a self-matched comparative analysis will be described in the statistical analysis plan.

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 work setting and geographic region, data permitting.

To evaluate whether vaccinated persons experience increased risk, we will use qualitative and quantitative comparison approaches. Qualitative comparisons will be made using hospitalization rates among non-vaccinated healthcare workers available from the parent HERO registry and external sources of background event rates. A self-matched comparative analysis will then be conducted for events that appear to be associated with vaccination and are amenable to self-matched analysis, such as those with an adequate case count and known risk interval.

Detailed methodology for the statistical analyses of data collected in this study, including the analytic methods to be used for self-matched comparative analyses, will be documented in a statistical analysis plan.

Milestones: Data collection is anticipated to start 17 December 2020, with interim reports completed per the following schedule:

- 30 June 2021
- 31 December 2021
- 30 June 2022

- 31 December 2022

The final study report will be submitted by 31 December 2023.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	22 January 2021	<ul style="list-style-type: none"> Title page Abstract Milestones Rationale and Background 	<ul style="list-style-type: none"> Added field for EU PAS registration number on title page. Removed interim report on 31 March 2021. Removed designation as Category 3 post-authorization safety study in EU risk management plan (RMP) and noted study is included in the US PVP. 	<ul style="list-style-type: none"> EU PAS registration number was inadvertently left out. Data from the first quarter of 2021 are limited. US vaccinations program not fully deployed until January Study was not included in final RMP

6. MILESTONES

Milestone	Planned date
Start of data collection	17 December 2020
Registration in the EU PAS register	Prior to start of data collection, December 2020
Interim Reports	30 June 2021 31 December 2021 30 June 2022 31 December 2022
End of data collection	30 June 2023
Final study report	31 December 2023

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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).² The outbreak quickly reached pandemic levels, spreading to 213 countries and territories worldwide. In February 2020, the World Health Organization formally named the disease caused by SARS-CoV-2 the coronavirus disease 2019 (COVID-19).³ As of October 2, 2020, a total of 34.6 million confirmed cases and over 1 million deaths related to COVID-19 have been reported.⁴ Healthcare workers have been disproportionately affected by the pandemic, with an infection risk 11 times that of the general population.⁵ Due to this increased risk, the National Academies of Science, Engineering, and Medicine has prioritized healthcare workers for early receipt of vaccines to prevent SARS-CoV-2 infection.⁶

Given the public health emergency caused by the virus, Pfizer-BioNTech was granted authorization of emergency use of their COVID-19 vaccine by the Food and Drug Administration on 11 December 2020, prior to full approval of the biologic license application (BLA) for the prevention of Coronavirus Disease 2019 (COVID-19) for individuals 16 years of age and older. Detailed distribution plans for the COVID-19 vaccine

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within the US are determined by local jurisdictions based on federal recommendations to prioritize vaccination of healthcare workers and people living in long term care facilities under an EUA. This study is designed to provide early real-world safety information on a cohort of vaccinated health workers for two years after vaccination.

This non-interventional study is designated as a PASS and is included in the US pharmacovigilance plan.

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8. RESEARCH QUESTION AND OBJECTIVES

The research questions addressed by this study are a) what are the incidence rates of safety events of interest and other clinically significant events among persons vaccinated with the Pfizer-BioNTech COVID-19 vaccine in a cohort of US healthcare workers and b) How do those rates compare to expected rates of those events?

Primary study objective:

- Estimate the real-world incidence of safety events of interest and other clinically significant events among US healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine following Emergency Use Authorization.

Secondary objectives

- Evaluate whether the vaccine recipients experience increased risk of safety events of interest and other clinically significant events post-vaccination.
- Estimate the incidence rates of safety events of interest and other clinically significant events among subcohorts of interest such as individuals who are pregnant, individuals who are immunocompromised, and stratified by age.

9. RESEARCH METHODS

9.1. Study Design

This study is a prospective observational study designed to evaluate the incidence rates of safety events of interest and other clinically significant events within a cohort of healthcare workers who receive the Pfizer-BioNTech COVID-19 vaccine under the EUA program in the United States. The study is a primary data collection study with review of medical records. Receipt of the vaccine is required for inclusion in the study, but the decision to be vaccinated is made at the discretion of the recipient.

This study will aim to enroll and follow 20,000 vaccinated healthcare workers during a 30-month study period. Information on hospitalization and diagnosis of safety events of interest will be collected from participant self-report at regular intervals following vaccination, primarily using a secure web portal. Participant reports of safety events of interest and/or hospitalization trigger a request for and review of participant medical record information for adjudication of the event (see [Figure 2](#) for additional details). To address the primary objective, incidence rates of safety events will be estimated based on cases confirmed by adjudication. To address the secondary objective regarding assessment of increased risk, a self-matched comparative analysis will be undertaken for feasible safety events (eg, events with a known risk interval and sufficient case counts). Additional context for the rates observed in vaccinated individuals will be sought from population background rates and unvaccinated person years in the HERO registry.

9.2. Setting

Healthcare worker participants, including individuals with and without medical training, will be recruited from two sources. The first is the Healthcare Worker Exposure Response and Outcomes (HERO) Registry Study, launched in April 2020 to characterize COVID-19 risk factors and outcomes among healthcare workers (HCWs) in the United States by the Duke Clinical Research Institute (DCRI). The overall goal of the HERO Registry is to create and engage a community of HCWs, who may be eligible for participation in future research studies, including studies of COVID-19 prophylaxis and treatment. Participants complete periodic questionnaires that capture data on demographics, medical history, employment characteristics, COVID testing/diagnosis, quality of life, and personal protective equipment (PPE) availability via an online portal. The registry currently comprises approximately 17,000 participants in all 50 states and is recruiting new HCWs for inclusion in the registry on an ongoing basis. Due to the broad definition of healthcare worker and limited inclusion/exclusion criteria, the registry supports enrollment of a diverse population and greater generalizability of results.

Table 1 provides a current description of registry members, demonstrating the diversity of healthcare workers who self-enrolled into the registry. The current demographic composition of the Registry is shown in [Table 2](#).

Table 1. HERO Registry Participants (Preliminary Data)

HERO Registry Participants (n=15,629)	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Physician	3265	20.89	3265	20.89
Nurse (RN/LPN)	5202	33.28	8467	54.17
Paramedic/Emergency Medical Technician	463	2.96	8930	57.14
Other (free text)	2442	15.62	11372	72.76
Physician's assistant/Nurse practitioner (PA/NP)	1226	7.84	12598	80.61
Other Health Diagnosing and Treating Practitioners	1321	8.45	13919	89.06
Health technologists, technicians, and clinical support staff	343	2.19	14262	91.25
Healthcare support, administrative, and research staff	1367	8.75	15629	100.00
Frequency Missing = 220				

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Table 2. Current Demographic Composition of the Registry (Preliminary Data)

		Gender			Total
		Male	Female	Other ^a	
Race	White	2,973 (18.56%)	10,507 (65.59%)	41 (0.26%)	13,521 (84.41%)
	Black or African American	123 (0.77%)	487 (3.04%)	2 (0.01%)	612 (3.82%)
	American Indian or Alaska Native	7 (0.04%)	33 (0.21%)	1 (0.01%)	41 (0.26%)
	Asian	364 (2.27%)	588 (3.67%)	2 (0.01%)	954 (5.96%)
	Native Hawaiian or Other Pacific Islander	4 (0.02%)	16 (0.10%)	0 (0.00%)	20 (0.12%)
	Other	81 (0.51%)	180 (1.12%)	0 (0.00%)	261 (1.63%)
	Multi-race	72 (0.45%)	237 (1.48%)	2 (0.01%)	311 (1.94%)
	Not Available (Prefer not to answer)	94 (0.59%)	184 (1.15%)	21 (0.13%)	299 (1.87%)
	Ethnicity	Yes, Hispanic (Latino/Latina)	303 (1.89%)	961 (6.00%)	4 (0.02%)
No, not of Hispanic, Latino, or Spanish origin		3,347 (20.89%)	11,137 (69.52%)	46 (0.29%)	14,530 (90.70%)
Not Available (Prefer not to answer)		68 (0.42%)	134 (0.84%)	19 (0.12%)	221 (1.38%)
Total		3,718 (23.21%)	12,232 (76.36%)	69 (0.43%)	16,019 (100.00%)

a. Gender = Other include MTF, FTM, gender expansive/variant, gender not listed, and prefer not to answer

Existing HERO members will be sent notifications of the opportunity to participate in a study of long-term outcomes after vaccination as part of the HERO study infrastructure.

The second source will be major health systems distributing Pfizer-BioNTech COVID-19 vaccine to its employees, as determined by local jurisdictional EUA rollout plans. Healthcare systems will be prioritized for involvement based on the ordered number of Pfizer COVID-19 vaccine doses, feasibility of recruitment and geographic diversity. Once receiving systems are identified, study navigators will be identified for assignment to vaccination sites within these systems to facilitate enrollment of vaccine recipients.

In this study, there will not be treating-healthcare providers as investigators overseeing the recruitment, enrollment, and data collection for study participants. Rather, individuals will self-enroll via a secure participant-facing web portal, either at the vaccination site or remotely. The web portal is developed and supported by a technology company called Verily.

9.2.1. Inclusion Criteria

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

- Individual currently works in a setting where individuals receive healthcare in the US (“healthcare worker”; including emergency medical services).
- Age \geq 18 years.
- Able to speak and read English or Spanish.
- Receipt of COVID-19 vaccine for prevention of SARS-CoV-2 infection within the past 60 days.
- Evidence of informed consent indicating that the participant (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
- Medical release providing for release of all pertinent medical information for assessment of vaccine safety during the one-year period prior to vaccination and during the follow-up period.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study. All participants meeting inclusion criteria will be eligible for analysis.

9.2.3. Recruitment

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 ensure that recruitment goals are met, while minimizing missing and inaccurate data, and loss to follow-up.

A healthcare worker may learn about the opportunity to receive the vaccine either through his/her employer or by email sent to existing HERO Registry members. Recruitment materials may also be present in the vaccine administration area.

All recruitment materials will focus on enrollment into a research study on vaccine safety and will avoid language promoting the Pfizer-BioNTech COVID-19 vaccine itself. Existing HERO members will receive instructions as to how they can express interest in joining the study and enroll. If a HERO member expresses interest but, after a notable period of time, has yet to enroll in the study, additional follow-up will be conducted to remind them of the opportunity and help them navigate the enrollment process.

Recruitment of HCWs not participating in the HERO registry will occur via public communication, social media and other advertising, printed enrollment materials with information about the study at vaccination sites.

9.2.4. Enrollment

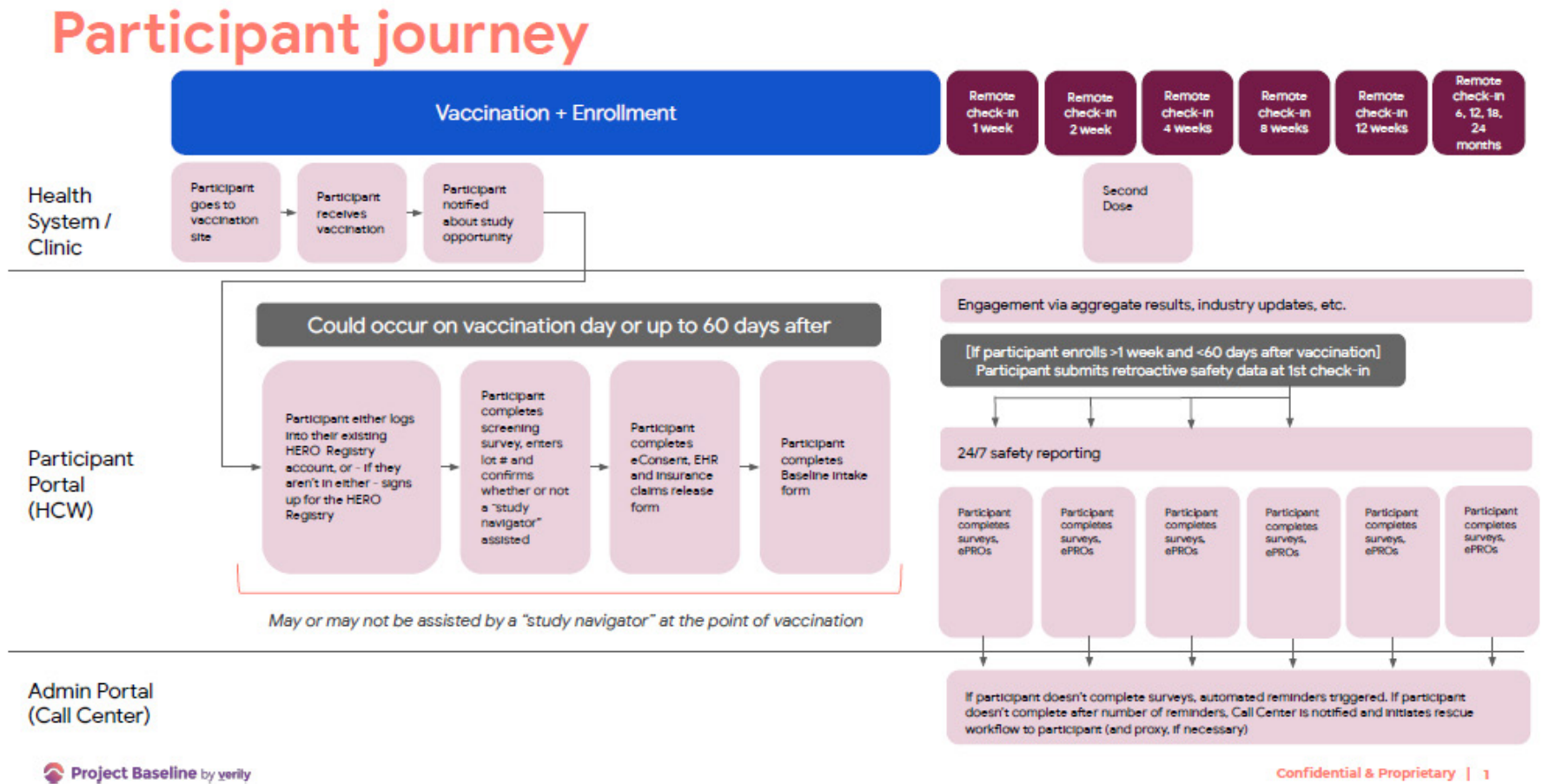
Healthcare workers may enroll at the vaccination site or may self-enroll remotely. At select vaccination sites, study navigators will be available to assist with recruitment and enrollment after individuals are vaccinated. Virtual study navigators may also assist with enrollment via phone and/or text. Study navigators will assist with entry of vaccine-related information (date, manufacturer, lot #) in the online platform to ensure accuracy. Based on conversations with many institutions affiliated with the parent HERO Registry study, optimal navigator workflow will be determined depending on institutional plans for vaccination. For example, at some institutions, the navigator will interact with the potential participant shortly before receiving the vaccine (eg, at the time of registration, or at check-in to the vaccine administration area), while others may interact with potential participants in the recovery area where healthcare workers will spend time after the vaccine.

Existing members of the HERO Registry will be instructed to complete a screening questionnaire, an informed consent form (ICF), and a medical release form, at which point they will be enrolled in the study. Non-members will be enrolled in the HERO Registry and then directed to complete the screening questionnaire, informed consent and medical release form. In addition, proxy contact information will be collected at enrollment to support data capture in the event that the participant cannot be reached (eg, 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 proportion of total participants receiving each available vaccine, to ensure a sufficient number of Pfizer-BioNTech vaccine recipients for inclusion in the primary analysis. Additional metrics may be included in the recruitment plan.

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Figure 1. Overall Study Design



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The HERO Registry is ‘siteless’ and enrollment has primarily been driven through word of mouth, coupled with some promotional materials provided to 40 healthcare institutions affiliated with PCORnet and the HERO-Hydroxychloroquine trial. From April to October 2020, only 164 Registry participants (<1%) have withdrawn from the Registry.

Deviations from enrollment projections will be identified rapidly; efforts to increase awareness of the study will be undertaken accordingly.

9.2.5. Retention

One strategy for retaining participants in the study relies on engagement through the HERO Registry parent study within which this COVID-19 vaccine study will be conducted. As part of the HERO registry, participant engagement is sought by a series of community building activities and modules that are informed by the participant’s “voice.” HERO registry members have demonstrated high responsiveness. Approximately 78% of HERO Registry members filled out an additional survey after enrollment, and nearly 60% returned to complete two or more surveys. As described below, “rescue” strategies to prompt survey completion have resulted in substantially improved completion.

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, 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.

The role of the DCRI Call Center will be to rescue surveys that are not completed, or are missing key components, by contacting participants, using contact information provided by the participant at baseline. Participants are offered preferred times to call and a toll-free line to use at their convenience.

In the HERO-Hydroxychloroquine randomized controlled trial, which was conducted within the HERO registry and required participant self-report of data, the Call Center successfully rescued 81% of surveys administered at 2, 4, and 8 weeks that were not completed on time.

Other recent projects involving DCRI Call Center services have observed similarly high rates of rescue. These include the ARTEMIS trial of coronary artery disease and anticoagulants, which enrolled 11,000 participants and achieved an 88% rescue rate for surveys administered at 3 and 12 months; and PROVIDE-HF, a heart failure trial that enrolled 400 participants and achieved a 79% rescue rate for those who did not return to the online portal at baseline, 2, 4, 8, and 12 weeks.

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9.2.6. Participant Follow-up and Data Collection

Participants will be followed from date of enrollment until the end of the 24-month period following first 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 enter data into a secure participant facing web-portal at 1 week, 2 weeks, 4 weeks, 8 weeks, 12 weeks, and 6-, 9-, 12- 18-, and 24-months following receipt of the first dose of the vaccine. Second dose 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. For participants who report clinically important medical event (eg, non-routine visit to medical provider or hospitalization) medical records will be obtained for review by the Clinical Event Ascertainment group for confirmation of the occurrence of a safety event of interest. For any participant who reports a potential safety event, medical records during the year prior to vaccination may also be reviewed to support a self-matched comparative analysis (See [Section 9.3.1](#) for additional details).

9.3. Variables

Table 3 lists variables of interest for this study; detailed operational definitions of all variables will be provided in the statistical analysis plan.

Table 3. Study Variables

Variable	Role	Data Source(s)
Date of 1 st dose COVID-19 vaccination	Exposure	Participant
Site where 1 st dose COVID-19 vaccine was administered	Exposure	Participant
COVID-19 vaccine lot number (1 st dose)	Exposure	Participant
Date of 2 nd dose COVID-19 vaccination	Exposure	Participant
Site where 2 nd dose COVID-19 vaccine was administered	Exposure	Participant
COVID-19 vaccine lot number (2 nd dose)	Exposure	Participant
Pregnancy Information (pregnancy status and estimated due date)	Outcome (utilization analyses) and covariate (safety analyses)	Participant

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Table 3. Study Variables

Variable	Role	Data Source(s)
Demographics	Outcome (utilization analyses) and covariate (safety analyses)	Participant
Medical History	Outcome (utilization analyses) and covariate (safety analyses)	Participant
Employment characteristics	Outcome (utilization analyses) and covariate (safety analyses)	Participant
Vaccination details	Exposure variable	Participant
Concomitant medications	Outcome (utilization analyses) and covariate (safety analyses)	Participant
Participant-reported outcomes	Outcome	Participant
Safety events of interest (Section 9.3.1)	Outcome	Participant, proxy, or medical record/insurance claims review
COVID-19 Diagnosis	Outcome	Participant, proxy, or medical record/insurance claims review
Hospitalizations	Outcome	Participant, proxy, or medical record/insurance claims review
Death	Outcome	Proxy, or medical record/insurance claims review

9.3.1. Safety events of interest

The safety events of interest in this study are based on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration’s Safety Platform for Emergency vACcines (SPEAC) Project (<https://brightoncollaboration.us/priority-list-aesi-covid/>) accessed 12/13/2020) and CDC enhanced safety monitoring recommendations (<https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-09/COVID-03-Shimabukuro.pdf>, accessed 12/13/2020). Safety event definitions will be specified a priori in the clinical events ascertainment (CEA) charter as appropriate. The safety events of interest in this study include:

Neurologic:

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- Generalized convulsion/seizures
- Guillain-Barre Syndrome
- Aseptic meningitis
- Encephalitis/encephalomyelitis
- Other acute demyelinating diseases
- Transverse myelitis
- Multiple sclerosis
- Optic neuritis
- Bell's palsy

Immunologic:

- Anaphylaxis
- Vasculitides*
- Arthritis/arthralgia
- Multisystem inflammatory syndrome (in adults)
- Kawasaki disease
- Fibromyalgia
- Autoimmune thyroiditis

COVID-19:

- Severe COVID-19 disease*
- Microangiopathy*
- Heart failure and cardiogenic shock*
- Stress cardiomyopathy*
- Coronary artery disease*
- Arrhythmia*

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- Deep vein thrombosis
- Pulmonary embolus
- Cerebrovascular stroke
- Limb ischemia*
- Hemorrhagic disease*
- Acute kidney injury*
- Liver injury
- Chillblain-like lesions
- Single organ cutaneous vasculitis*
- Erythema multiforme*

Cardiac:

- Myocarditis
- Pericarditis
- Acute myocardial infarction

Hematologic:

- Thrombocytopenia
- Disseminated intravascular coagulation

Other:

- Pregnancy outcomes
- Death
- Narcolepsy and cataplexy;
- Non-anaphylactic allergic reactions

*Hospitalized manifestations only

9.4. Data Sources

Data will be captured through several mechanisms, described below. 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. Participant Self-report

Participants will provide information on COVID-19 vaccination, baseline characteristics, seeking of non-routine medical care (including hospitalization) and potential occurrence of safety events of interest. Following enrollment, the participant will enter data into a secure participant facing web-portal (“Digital Platform”). Data entry will occur according to the schedule of assessments described in Table 4. Participants who miss assessments during follow-up, and individuals with a longer than a 2-day interval between vaccination and enrollment will be administered a retrospective assessment to capture self-reported safety information occurring within this interval. If an assessment is incomplete after a notable period of time, the participant will be contacted by the Call Center for completion of missed assessments.

Table 4. Schedule of Assessments

	<i>Enrollment Data Collection</i>	<i>Follow-up Data Collection</i>					
		After 1 st dose					
	Baseline	1 week	2 weeks	4 weeks	8 weeks	12 weeks	6, 9, 12, 18, 24 months
E-consent	X						
Eligibility criteria confirmed	X						
Vaccine Dose 1 information <ul style="list-style-type: none"> • Date • Lot number • Site 	X						
Vaccine Dose 2 information <ul style="list-style-type: none"> • Date • Lot number • Site 				X (and subsequent visits if second dose not reported as received)			
Medical release	X						
Demographics <ul style="list-style-type: none"> • Demographics form 	X						
Medical history <ul style="list-style-type: none"> • Medical history form 	X						
Employment Information <ul style="list-style-type: none"> • Employment information form 	X						

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Concomitant medications <ul style="list-style-type: none"> All current medications reported at baseline Changes to medications reported at follow-up 	X						X*
PROs <ul style="list-style-type: none"> Fatigue severity scale PROMIS Global 10 CDC Impact Scale 	X	X	X	X	X	X	X*
COVID-19 Information <ul style="list-style-type: none"> Positive COVID-19 test with date COVID-19 diagnosis (presumptive) 	X	X	X	X	X	X	X
Health questionnaire <ul style="list-style-type: none"> Potential safety events of interest or clinically significant events Pregnancy status 	X	X	X	X	X	X	X

* PROs and medication information collected only at 6, 12, 18, and 24 month intervals.

9.4.2. Call Center Data Collection

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

1. To serve as a “rescue” mechanism to minimize incomplete data from non-response and loss to follow-up, and
2. To request medical records for confirmation of the occurrence of safety events of interest.

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 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.

9.4.3. Clinical Events Ascertainment (CEA)

The Call Center will request medical records for all participants reporting a hospitalization or potential safety event of interest at any point during follow-up. The following components of medical records will be sought as appropriate:

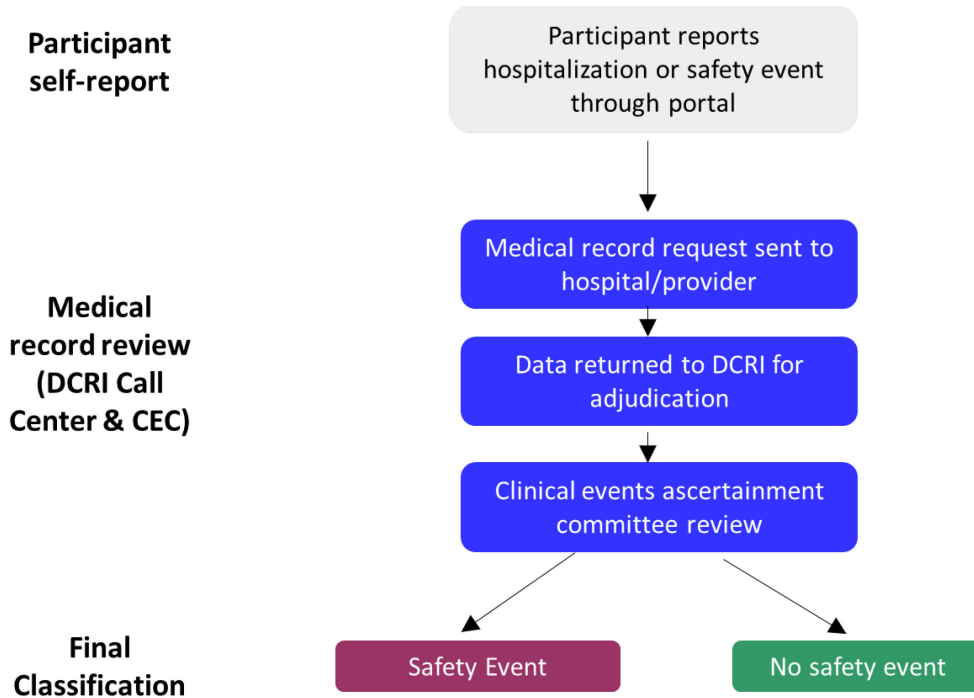
- Emergency room notes
- Discharge summary/death summary
- Admission history and physical exam
- Progress/clinic/urgent care notes
- Diagnostic tests
- Lab reports
- Medication records

For each participant-reported event, the DCRI Clinical Event Ascertainment (CEA) group will review the medical records and confirm the occurrence of an event as part of an adjudication process. Safety event definitions will be specified a priori in the clinical events ascertainment (CEA) charter as appropriate. Refer to Figure 2 for a summary of this process.

The CEA group is responsible for ongoing analysis of potential safety events of interest or other clinically significant diagnoses 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.

Figure 2. Confirmation of Safety Events of Interest During Follow-up



9.4.4. Proxy Completion

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. If more than 2 consecutive assessments are missed and no proxy can be reached, medical records will be requested for further investigation about the reason for loss to follow-up (for example, the participant has died).

9.5. Study Size

This study will aim to enroll at least 20,000 healthcare workers who have received the Pfizer-BioNTech COVID-19 vaccine for prevention of COVID-19. This study size will help ensure a diverse population of healthcare workers with respect to geography, primary work setting, and demographics, and stratification by important subgroups of professional role, age, and region. It is anticipated that there will be at least 15,000 participants who received the Pfizer-BioNTech COVID-19 vaccine with complete assessments throughout the follow-up period.

As the primary objective is descriptive, this sample size target is designed to ensure adequate precision for a plausible range of AE and SAE rates in the population of vaccinated

healthcare workers. Table 5 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 20,000 participants (overall) and samples of 5,000 and 10,000 participants (potential subgroups and allowing for some exclusions due to attrition). As shown below, precision is high for observed event rates ranging from 0.1% to 20.0%.

Table 5. Estimated Precision of Observed Event Rates

Observed Rate	Exact 95% Confidence Interval (n=5,000)	Exact 95% Confidence Interval (n=10,000)	Exact 95% Confidence Interval (n=20,000)
0.1%	0.0, 0.23	0.0, 0.18	0.0, 0.15
0.5%	0.32, 0.74	0.37, 0.66	0.41, 0.61
1%	0.74, 1.32	0.81, 1.21	0.87, 1.15
2%	1.63, 2.43	1.73, 2.29	1.81, 2.20
5%	4.41, 5.64	4.58, 5.45	4.70, 5.31
10%	9.18, 10.87	9.42, 10.60	9.59, 10.42
20%	18.90, 21.14	19.22, 20.80	19.45, 20.56

Based on experience to date with the HERO registry, in this study we forecast a 2% withdrawal rate, a 75% survey completion rate and enrollment of n=200 participants (1%) who would be excluded from primary analyses due to receipt of non- Pfizer-BioNTech vaccine. This would result in withdrawal of n=400 people, exclusion of n=200 participants due to receiving a non-Pfizer-BioNTech vaccine and no or partial questionnaire data for ~4,900 participants. Therefore, we anticipate that enrollment of approximately 20,000 participants will result in comprehensive questionnaire data for approximately 14,500 participants.

To address the second objective regarding assessment of increased risk of safety events in vaccinated individuals, informal comparisons will be made with hospitalization rates among non-vaccinated healthcare workers available from the parent HERO registry. To formally evaluate whether vaccinated persons experience increased risk, a self-matched comparative analysis will be conducted for feasible events, such as those with an adequate case count and known risk interval. Statistical power to detect various effect sizes assuming a range of background incidence rates in a self-matched comparative analysis will be described in the statistical analysis plan.

9.6. Data Management

The DCRI utilizes a “Fit for Purpose” approach to selecting and utilizing information systems, particularly as it pertains to EDC, 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 (eg,

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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. The figure below (Figure 3) illustrates the systems and interactions required to enable a well-coordinated study delivery plan. 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.

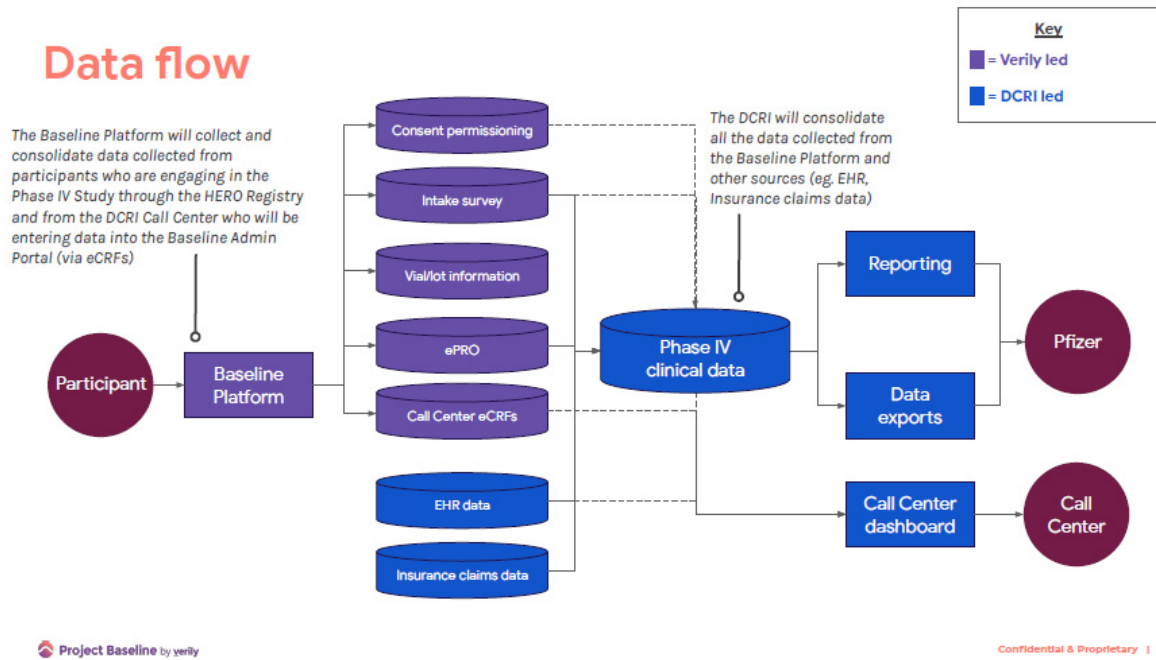
Participants will use a study portal developed by Verily for the informed consent form, medical release form and data reporting. The Verily system leverages the Google infrastructure, including hosting, security, user account management and the study-specific data system. Leveraging this infrastructure 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), MS SQL, SAS, 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.

Figure 3. Data Flow Diagram

NO



NOTE: Pfizer will not receive individual level data only aggregate reports

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term eCRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A completed 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 the 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.

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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. Record 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

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.

Only those safety events that were adjudicated as confirmed cases will be included in the primary analysis. 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 work setting and geographic region, data permitting. Multiple imputation methods will be used for missing data as appropriate and will be described in the statistical analysis plan.

To evaluate whether vaccinated persons experience increased risk, we will use qualitative and quantitative comparison approaches. Qualitative comparisons will be made using hospitalization rates among non-vaccinated healthcare workers available from the parent HERO registry and external sources of background event rates. A self-matched comparative analysis will then be conducted for events that appear to be associated with vaccination are amenable to self-matched analysis, such as those with an adequate case count and known risk interval.

Detailed methodology for summary and statistical analyses of data collected in this study, including the analytic methods to be used for self-matched comparative analyses, will be documented in a statistical analysis plan (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 nightly. 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 and CEA group will be input directly into the Verily platform for quality control.

Data reconciliation consists of reconciling the primary participant identifiers and all queries generated by the EDC system are resolved online. 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.

9.9. Limitations of the Research Methods

This study is intended to provide comprehensive real-world safety information about the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers, who will be among the first individuals to be vaccinated as part of an EUA. A key strength of this study is the capture of data on vaccination during a pandemic when vaccines will be administered outside of usual settings of doctor's offices and pharmacies. Additional strengths include the utilization of an existing cohort of healthcare workers, the HERO Registry, who are already engaged in COVID-related research and the minimal burden on participants for safety data collection via a web portal.

To help maximize enrollment of vaccinated healthcare workers, there is flexibility in participant enrollment location (on-site or remote) and timing (up to 60 days following the first vaccination dose). However, for individuals enrolling several days or weeks following vaccination, there is the potential for preferential self-enrollment of individuals experiencing a safety event (or early symptoms of a safety event). To help mitigate this, individuals with a more than a 2-day interval between vaccination and enrollment will be administered an assessment to capture self-reported safety information occurring within this interval, and the primary analysis will be restricted to individuals enrolling within 10 days of first vaccination dose

Because participants enroll voluntarily, the generalizability of study results will depend on the diversity of the enrolled sample. Sample diversity will be enhanced through several key design features, including the large study size, the broad definition of healthcare workers, and placement of study navigators in geographically diverse vaccination sites. Additionally, the study team will regularly review aggregate participant characteristics for representativeness and will tailor engagement strategies address any areas of underrepresentation. The observational nature of this study also has the potential to introduce bias due to measured and

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unmeasured confounders. Bias reduction strategies include capture of clinical covariates/ employment characteristics, robust follow-up data ascertainment through a central call center to reduce missing data, and self-matched comparative analyses.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Participant Information

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

Participant personal data will be stored at 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. 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. Participant Consent

At enrollment, HCWs who are existing members of the Healthcare Worker Exposure Response and Outcomes (HERO) Registry will be instructed to log in to their existing profile, complete an informed consent form (ICF) and medical release form, and enroll. Eligible individuals not yet enrolled in HERO but wanting to participate in this vaccine study will be enrolled in the HERO Registry and then directed to complete the study-specific ICF and medical release form, and enroll. Electronic consent will be obtained by Verily's Baseline Platform, which currently supports the HERO registry.

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. Participant Withdrawal

Participants will be followed until participant closeout, withdrawal of consent, or death. A participant may withdraw from the study at any time at his/her 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 24 months or collection of medical records to ascertain possible safety events.

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.

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, (eg, 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 (Western 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 (GPP) issued by the

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International Society for Pharmacoepidemiology, and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

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 the HERO Registry opt to participate and complete a web-based data collection tool. The data collection tool completed by the HERO Registry participants is designed to provide preliminary information on the occurrence of a potential safety event of interest or other clinically significant diagnosis.

The second component entails secondary data collection, in which the HERO Registry participant self-reported events are examined via review of the participant's medical record. The DCRI Call Center will request medical records for any participants who reported in the data collection tool a potential safety event of interest or other clinically significant diagnosis. 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](#)).

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 are described in two separate sections below.

Product safety information volunteered by participants

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

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:

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

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

These trainings must be completed by 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 Your Reporting Responsibilities 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 adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS AEM Report Form** to Pfizer Safety are as follows:

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

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

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

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

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

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

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

These trainings must be completed by 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 Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim study reports will be completed according to the milestone schedule in [Section 4](#). The final study results will be posted in the European Union (EU) Post-Authorization Study (PAS) Register. Results will be further disseminated through a variety of mechanisms, including presentation at national meetings and publication in peer-reviewed journals.

In the event of any prohibition or restriction imposed (eg, 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.

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13. REFERENCES

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

To be added when protocol finalized.

ANNEX 2. ADDITIONAL INFORMATION

N/A.

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