

NON-INTERVENTIONAL STUDY INTERIM REPORT ABSTRACT

Title: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran’s Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine

Date: 22 June 2021

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Keywords: Pfizer-BioNTech COVID-19 vaccine, emergency use authorization (EUA), rapid cycle analysis, safety signal, Veterans Health Administration (VHA)

Rationale and background:

In March 2020, the World Health Organization (WHO) declared a global pandemic for the coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ On December 11, 2020, the United States (US) Food and Drug Administration (FDA) issued its first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19 disease in individuals 16 years of age and older.² This vaccine (Pfizer-BioNTech COVID-19 Vaccine) is one of the three COVID-19 vaccines that received EUA in the US.

On January 27, 2021, Pfizer, in collaboration with the US Veterans Health Administration (VHA) and Analysis Group, submitted a study protocol (protocol C4591012; Appendix 1) for post-EUA active safety surveillance of safety events of interest among individuals 16 years of age and older in the VHA system. Safety events of interest for the current study include 42 safety outcomes that were selected based primarily on the Priority List of Adverse Events of Special Interest from the Brighton Collaboration’s Safety Platform for Emergency vACcines (SPEAC) Project and from the preliminary list of safety events of interest presented at the September 22, 2020, meeting of Centers for Disease Control and Prevention’s (CDC’s) Advisory Committee on Immunization Practices (ACIP) on the enhanced safety monitoring of COVID-19 vaccines.^{3,4}

The study uses data from a large-scale electronic medical record (EMR) database from the VHA to identify and evaluate rapid-cycle, near real-time potential safety signals associated with Pfizer-BioNTech COVID-19 vaccine. Data included for analysis commences on December 11, 2020 and will continue through June 10, 2023 – i.e., 30 months following the issuance of the EUA for Pfizer-BioNTech COVID-19 vaccine. Four interim reports are planned on June 30, 2021; December 31, 2021; June 30, 2022; and December 31, 2022, with a final report to be issued on December 31, 2023.

In this first interim report, the data included for analysis spans from December 11, 2020 to March 12, 2021, and the data were locked on April 26, 2021. This first interim report

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describes the selection of two samples of individuals within the VHA: individuals who received Pfizer-BioNTech COVID-19 vaccine between December 11, 2020 (EUA approval date by the US FDA) and March 12, 2021 (data cutoff date), and recipients of seasonal influenza vaccine(s) during the five prior influenza seasons (2014/2015 through 2018/2019). The demographic and clinical characteristics and vaccine utilization patterns among the two samples of individuals are described pursuant to the secondary study objective. Due to the short time between the data lock date and the first interim report issuance date, this report does not include results from the safety signal analyses pursuant to the primary study objectives.

All references to the study protocol in this first interim report pertain to the study protocol Version 1.0 dated January 27, 2021 (see Appendix 1). Meanwhile, a protocol amendment is currently under development to address the FDA's comments on the study protocol Version 1.0, communicated electronically to Pfizer on May 12, 2021.

Research question and objectives:

Research question: what are the incidence rates of safety events of interest (based on adverse events of special interest [AESI]) among individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine within the US VHA system overall and in sub-cohorts of interest as compared to expected rates of those events?

Primary study objectives:

To assess whether individuals in the VHA system experience increased risk of safety events of interest following receipt of Pfizer-BioNTech COVID-19 vaccine; and

To assess whether sub-cohorts of interest (i.e., immunocompromised, elderly, with specific comorbidities, individuals receiving only one dose of Pfizer-BioNTech COVID-19 vaccine, and individuals with prior SARS-CoV-2 infection) in the VHA system experience increased risk of safety events of interest following receipt of Pfizer-BioNTech COVID-19 vaccine.

Secondary study objective:

To characterize utilization patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within the VHA including estimating the proportion of individuals receiving vaccine, two-dose vaccine completion rate, and distribution of time gaps between the first and second dose, demographics and health histories of recipients, overall and among the sub-cohorts of interest.

This first interim report pertains to the secondary study objective.

Study design:

This post-EUA active safety surveillance program will employ a rapid-cycle, longitudinal, observational cohort study design to provide early real-world safety information.

- The self-controlled risk interval (SCRI) design will be used to sequentially monitor the occurrence of safety events of interest while controlling for time-invariant confounders. The SCRI design uses data from cases (i.e., individuals who experience safety events of interest following vaccination) to compare the risk interval following Pfizer-BioNTech COVID-19 vaccination to pre- or post-vaccination non-risk intervals (“pre-vaccination control interval” and “post-vaccination control interval”, respectively) in the same individual.
- An active comparator design will be used to sequentially monitor the occurrence of safety events of interest among individuals that receive Pfizer-BioNTech COVID-19 vaccinations as compared to recipients of influenza vaccine in the VHA during 2014/2015 through 2018/2019 influenza seasons. Data in peri-COVID time periods from January 2020 to present are excluded because of pandemic-associated under-utilization of health resources and under-reporting of medical events.

Setting:

The study population consists of VHA enrollees, which largely include veterans, and is kept as broad as possible under inclusion and exclusion criteria to be representative of the real-world population at the VHA receiving Pfizer-BioNTech COVID-19 vaccine.

Subjects and study size:

A total of 750,999 individuals received at least one dose of Pfizer-BioNTech COVID-19 vaccine from December 11, 2020 to March 12, 2021 in the VHA database. The active comparator group includes a fixed cohort of 4,277,220 historical seasonal influenza vaccine recipients who received a total of 10,529,071 seasonal influenza vaccines across successive influenza seasons between 2014/2015 through 2018/2019.

Data source, variables, and statistical methods:

Data source: The VHA is the largest integrated health care system in the US, providing comprehensive healthcare services, including primary, specialty and inpatient care, rehabilitation, long-term and home care, and other services to over nine million veterans through 1,293 health care facilities, including 171 medical centers and 1,112 outpatient sites of varying care complexity.⁵ In addition to veterans, VHA enrollees may also include employees and certain categories of family members of the veterans, but these are a minority among all VHA enrollees. The study relies on secondary data from the Corporate Data Warehouse (CDW) in the National Veterans Affairs Health Care Network. The CDW data, which are updated daily, include standard EMR for all medical encounter information in the VHA system. The CDW consolidates data from the VHA’s EMR system and contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, immunizations, and lab results. Information is also available on date of death, COVID-19 infection status, and COVID-19 and seasonal influenza vaccination status.

Variables:

Outcomes: Outcomes include 42 safety events of interest (Table 14.2 in Section 14 of the interim report). The list of outcome safety events may be modified over time as new safety information about the COVID-19 vaccines emerges. No outcomes were analyzed as part of this first interim report.

Exposures: Administration of Pfizer-BioNTech COVID-19 vaccine post-EUA approval and date of immunization for each dose were identified in the CDW data based on the following codes:

- Current Procedural Terminology (CPT) code 91300 (Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) vaccine, mRNA/LNP, spike protein, preservative free, 30 mcg/0.3mL dosage, diluent reconstituted, for intramuscular use) and associated vaccine administration Healthcare Common procedure Coding System (HCPCS) codes corresponding to the first dose: 0001A (ADM SARS-CoV-2 30 mcg/0.3mL 1st), and the second dose: 0002A (ADM SARS-CoV-2 30 mcg/0.3mL 2nd);^{6,7} or
- 10 and 11-digit National Drug Codes (NDCs); 10-digit NDCs: 59267-1000-1, 59267-1000-2, 59267-1000-3), 11-digit NDCs: 59267-1000-01, 59267-1000-02, 59267-1000-03;⁸ or
- Immunization records that contain data on vaccine code descriptor, vaccine manufacturer (i.e., Pfizer), lot number, injection site, and date(s) of immunization.⁶

Administration of the seasonal influenza vaccine during 2014/2015 through 2018/2019 seasonal influenza seasons and date of immunization were identified in the CDW data based on CPT, HCPCS, and 10 and 11-digit NDCs codes (Table 14.3 in Section 14 of the interim report) as well as immunization records that contain data on vaccine code descriptor, vaccine manufacturer, lot number, injection site, and date(s) of immunization.

Key covariates: Baseline demographic (i.e., age, sex, race/ethnicity, and VHA service area) and clinical characteristics (i.e., smoking status, body mass index [BMI], history of anaphylaxis/allergic reactions, previous anaphylaxis of vaccine component, history of hospitalizations, Charlson Comorbidity Index [CCI], selected comorbidities, and immunization history) were assessed in the one-year baseline period before the date of vaccination with Pfizer-BioNTech COVID-19 vaccine for Pfizer-BioNTech COVID-19 vaccine recipients and prior to the date of seasonal influenza vaccination for active comparators (with the exception of BMI which was assessed based on a two-year baseline period to account for a reduction in the visits with BMI records available during the COVID-19 pandemic).

Statistical methods: Descriptive statistics (i.e., means, standard deviations (SD), medians, inter-quartile ranges [IQR], and proportions) were used to summarize baseline characteristics and patterns of vaccination with Pfizer-BioNTech COVID-19 vaccine (e.g., 2-dose completion rate, clinical setting where the vaccine was administered) among Pfizer-BioNTech COVID-19 vaccine recipients and baseline characteristics among historical active

comparators who received seasonal influenza vaccination. Standardized differences were used to compare baseline demographics and clinical characteristics between individuals vaccinated with Pfizer-BioNTech COVID-19 vaccine (at the time of the first Pfizer-BioNTech COVID-19 vaccine dose) and those vaccinated for seasonal influenza (at the time of the most recent seasonal influenza vaccine). Standardized differences below 10% were used to identify patient characteristics that were not well balanced between recipients of Pfizer-BioNTech COVID-19 vaccine and seasonal influenza vaccine.^{9,10} The count and proportion of individuals who received COVID-19 vaccine(s) from different manufacturer(s) in addition to Pfizer-BioNTech COVID-19 vaccine were also reported.

Statistical methods for the primary study objectives, which are not covered in this first interim report, include safety signal analyses for signal detection, signal evaluation, and signal verification, as described in Section 9.7.3 of the study protocol (Appendix 1).

Results:

Among 4,648,524 individuals with at least one healthcare encounter from December 11, 2020 to March 12, 2021, 17.1% (N = 793,264) received at least one Pfizer-BioNTech COVID-19 vaccine dose. Among the latter, 752,904 (94.9%) satisfied the one year of continuous enrollment in VHA healthcare benefits eligibility criteria, of whom most (N = 750,999; 99.7%) only received COVID-19 vaccine(s) from Pfizer-BioNTech and a minority (N = 1,905; 0.3%) received COVID-19 vaccine(s) from both Pfizer-BioNTech and another manufacturer (96.8% Moderna; 2.9% Johnson & Johnson; and 0.5% AstraZeneca). These 750,999 individuals form Pfizer-BioNTech vaccine cohort.

The seasonal influenza vaccine sample consisted of a total of 4,277,220 eligible individuals who received at least one seasonal influenza vaccine from the October 2014 - May 2015 influenza season to October 2018 - May 2019 influenza season. Individuals could receive one seasonal influenza vaccine per influenza season, for a maximum of five seasonal influenza vaccines from October 2014 to May 2019. Among the individuals in the seasonal influenza sample that satisfied the study eligibility criteria, an average of 2.46 seasonal influenza vaccines were observed per individual from October 2014 to May 2019.

The cohort of Pfizer-BioNTech COVID-19 vaccine recipients were on average 69.8 years of age (median: 72.0 years) and included 93.2% males and 64.2% White non-Hispanics, with the largest proportion of the vaccinees residing in the South (42.8%). While baseline demographic and clinical characteristics were generally similar between Pfizer-BioNTech COVID-19 vaccine recipients and the seasonal influenza vaccine recipients (standardized differences <10%, e.g., smoking status, BMI, comorbidities), one notable exception was the higher proportion of elderly individuals among Pfizer-BioNTech COVID-19 vaccine recipients compared to the seasonal influenza vaccine recipients (age 65 and 74 years: 41.2% vs. 33.8%, standardized difference 15.3%; age 75 years or older: 31.6% vs. 25.9%, standardized difference 12.5%).

Of the 750,999 individuals in Pfizer-BioNTech COVID-19 vaccine cohort, a total of 485,410 (64.6%) received both doses during the December 11, 2020 to March 12, 2021 study period.

Among the remaining 265,589 (35.4%) with only one dose observed, 94.1% had insufficient follow-up (<21 days) to receive a second dose administered per EUA recommended schedule. Among those who did have at least 21 days of follow-up between the first Pfizer-BioNTech COVID-19 dose and the data cut-off date, the proportion of Pfizer-BioNTech COVID-19 vaccine recipients who received both doses was high (95.3%). Of the 485,410 individuals who completed two Pfizer-BioNTech COVID-19 vaccine doses, 70.2% received the second dose exactly 21 days after the first dose, as recommended per the product label. The most common care setting where the first and second doses of Pfizer-BioNTech COVID-19 vaccine were received was in outpatient clinics (85.3% and 84.8%, respectively).

Discussion:

This interim report describes sample selection, baseline characteristics and vaccine utilization patterns among individuals who received Pfizer-BioNTech COVID-19 vaccine within the VHA system as compared to a historical sample of individuals who received seasonal influenza vaccine before the COVID-19 pandemic. Most baseline characteristics were well balanced between the study samples, suggesting that seasonal influenza vaccine from the five prior seasons is an appropriate active comparator for the safety surveillance of Pfizer-BioNTech COVID-19 vaccine.

Since CDC’s COVID-19 vaccine rollout recommendations gave priority to individuals 65 years and older in phases 1a through 1c, the higher proportion of older individuals with Pfizer-BioNTech COVID-19 vaccine was expected.¹¹ This distribution of age will likely change in subsequent interim reports as younger individuals become eligible to be vaccinated in the VHA. The higher proportion of men in this study was also expected, as the VHA population is predominantly male (approximately 90%).

The demographic and clinical characteristics of the Pfizer-BioNTech COVID-19 vaccine sample were consistent with existing data in the US population, which suggests that vaccine administration within the VHA system aligned with CDC’s vaccine rollout recommendations to prioritize the elderly population and individuals with underlying medical conditions.¹¹

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References:

- ¹ World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19 -11 March 2020 [Internet]. WHO; 2020 [cited 2020 Nov 11]. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020>
- ² U.S. Food and Drug Administration (FDA). Pfizer-BioNTech COVID-19 Vaccine [Internet]. FDA; 2021 [cited 2021 Apr 21]. Available from: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine>
- ³ Law B. SO2-D2.1.2 Priority List of COVID-19 Adverse Events of special interest: Quarterly update [Internet]. Brightoncollaboration.us; 2020 [cited 2021 Apr 23]. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf
- ⁴ Shimabukuro T. Enhanced safety monitoring for COVID-19 vaccines in early phase vaccination. National Center for Immunization & Respiratory Diseases; 2020. Available from: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-09/COVID-03-Shimabukuro.pdf>
- ⁵ U.S. Department of Veterans Affairs. Veterans Health Administration. Providing Health Care for Veterans [Internet]. U.S. Department of Veterans Affairs; 2020 [cited 2021 Apr 23]. Available from: <https://www.va.gov/health/>
- ⁶ American Medical Association (AMA). Appendix Q: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (coronavirus disease [COVID-19]) Vaccines [Internet]. AMA; 2021 [cited 2021 Jan 12]. Available from: <https://www.ama-assn.org/system/files/2020-11/covid-19-immunizations-appendix-q-table.pdf>
- ⁷ Centers for Medicare & Medicaid Services (CMS). COVID-19 Vaccines and Monoclonal Antibodies [Internet]. CMS; 2020 [cited 2021 Jan 14]. Available from: <https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-mono-clonal-antibodies>
- ⁸ Centers for Disease Control and Prevention (CDC). NDC11 to NDC10 Crosswalk Reference [Internet]. CDC; 2021 [cited April 30, 2021]. Available from: https://www2.cdc.gov/vaccines/iis/iisstandards/downloads/NDC/NDC_Reference_1110-tag508.pdf
- ⁹ Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat - Simul Comput.* 2009 Apr;38(6):1228-34.

¹⁰ Ahmed A, Perry GJ, Fleg JL, Love TE, Goff Jr DC, Kitzman DW. Outcomes in ambulatory chronic systolic and diastolic heart failure: a propensity score analysis. *American heart journal*. 2006 Nov 1;152(5):956-66.

¹¹ U.S. Department of Veterans Affairs. VA Caribbean Healthcare System [Internet]. 2021 [cited 2021 January 15]. Available from: https://www.caribbean.va.gov/pressreleases/COVID-19_Moderna_Vaccine.asp

Document Approval Record

Document Name:	C4591012 NI Study Interim Report Abstract
Document Title:	C4591012

Signed By:	Date(GMT)	Signing Capacity
Campbell, Ulka	23-Jun-2021 02:26:20	Final Approval
De Bernardi, Barbara	23-Jun-2021 09:48:35	EUQPPV Approval