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CBER Surveillance Program  
Office of Biostatistics and Epidemiology (OBE)  
Center for Biologics Evaluation and Research (CBER)

**Through:** Steven Anderson, PhD  
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FDA-CBER-2021-5683-1804703

1. **Objective:** Summary evaluation of 3 post-EUA (authorization) studies proposed for the COVID-19 vaccine by Pfizer in their Emergency Use Authorization (EUA) submission.
2. **Review of post-authorization active surveillance plan**  
Please see OBE/Division of Epidemiology (DE) pharmacovigilance plan (PVP) review memo for details of the pharmacovigilance plan. Pfizer's PVP included 3 proposed studies. The proposed active surveillance plan is reviewed here by the CBER Surveillance Program.

### **VA study, protocol number C4591012**

#### **The following are overarching questions about the study data source.**

Please confirm that Pfizer has signed agreements with the VA to conduct the proposed studies.

On page 17, the study plan indicates that the study period “will commence following Pfizer-BioNTech COVID-19 vaccine EUA” approval and will continue for 30 months. Please describe the anticipated number of doses that will be provided to VA patients and whether there will be eligibility criteria set up for patients receiving the vaccine.

Since page 23 states “The CDW does not include information on any care received outside of a VHA facility.” and page 31, “9.9 Strengths and Limitations of Research Methods” states the limitation of incomplete ascertainment of vaccine exposures (i.e., Pfizer-BioNTech COVID-19 vaccine and influenza vaccine), we know that veterans receive some of their health care services outside of the VA system. Additionally, a large portion of the veteran population who is  $\geq 65$  years old (at higher risk of developing COVID-19 and perhaps a sicker population) receives a large portion of health care through Medicare system and not VA system. Please explain how this study plans to deal with the incomplete health care data of the study population, how the incomplete data may impact the study results, and how you plan to address this issue.

#### **The following are specific questions about the study design.**

Page 13, “8. RESEARCH QUESTION AND OBJECTIVES”: primary objectives only include descriptive statistics and do not address association between the vaccine exposure and safety outcomes. To evaluate the association between the vaccine exposure and the outcomes, we recommend including “Evaluate whether the vaccine recipients experience increased risk of AESI and other clinically significant events post-vaccination” as one of the primary objectives, instead of a secondary objective in the current protocol.

Page 13, “8. RESEARCH QUESTION AND OBJECTIVES” and Page 17, “9.2.2. Subgroups”: The study plan outlines the subgroups of the study population that will be included in the analysis. We know that over 90% of the VA population is male, and the median age is 46 years old. In other words, the VA population is not representative of the general US population. Please explain why this population was chosen for this safety

surveillance study. How could the results of this study be generalized to inform the safety of the Pfizer-BioNTech COVID-19 vaccine in the general US population?

Page 17, “9.1.2. Current vs. Historical Cohort Design”, states the historical comparator is individuals who received the seasonal influenza vaccine in five prior seasons ranging from 2014/2015 to 2018/2019.

Please provide justification as to why such a comparator group is chosen.

We suggest that you consider inclusion of 2019/2020 flu season in addition to other seasons you have selected as another comparator period since the health care utilization in this season, during the pandemic, may be somewhat more reflective of the utilization after the vaccine is administered to the population.

Page 20, “9.3.3. Outcomes”: a list of proposed outcomes and potential factors to operationalize safety outcomes are presented, but none has been specified to be included in the study. Please specify the list of safety outcomes that will be included in each study design and as well as the risk interval for each outcome.

Please specify what control window (i.e., pre- and post-vaccination) will be used for each eligible outcome for the self-controlled risk interval (SCRI) design. Also, please explain how you would approach the overlapping risk and control windows for the two doses of the vaccine (pages 15-16). We recommend using both pre- and post-control windows as a complementary analysis.

Please specify the washout period for each safety outcome. Also, the current examples (6 or 12 months before vaccination) anchor on the vaccination date. Please clarify how outcomes will be ascertained if a pre-vaccination control window is used.

Page 18, “9.3.1.1. Pfizer-BioNTech COVID-19 Vaccine Groups of Interest”, presents 4 cohorts according to individuals’ status and timing of receiving a seasonal influenza vaccine. Page 26, “9.7.3. Signal Detection Analyses”, states “Analyses will be conducted among all individuals receiving the vaccine, individuals who received Pfizer-BioNTech COVID-19 vaccine without seasonal flu vaccine (Cohort A will be used for SCRI; Cohort A+B will be used for current vs. historical analyses), and individuals receiving Pfizer-BioNTech COVID-19 vaccine and seasonal flu vaccine on the same day (Cohort D), along with sub-cohorts receiving only one dose vs. two doses. It is unclear why Cohort C is not included in “9.7.3. Signal Detection Analyses” and how cohorts C and D will be analyzed. Please describe the purpose of these two cohorts and add a secondary or tertiary objective for the inclusion, if needed.

## **DoD study, protocol number C4591011**

### **The following are overarching questions about the study data source.**

Please confirm whether Pfizer has already signed agreements with the DoD to have access to their data and conduct the proposed studies.

Please confirm whether Pfizer currently has an agreement with DoD to distribute the vaccine such that it can be administered to the members receiving care in the DoD system. If so, what is the anticipated date of vaccine distribution and the number of doses that will be provided to DoD? Are there eligibility criteria set up for receiving the vaccine? These questions attempt to understand how fast DoD participants can be enrolled into this study and whether these participants will have certain demographic and clinical characteristics.

On page 16, it is stated that for the military personnel and their dependents about 40% of health care services is administered by the military health service (MHS) and about 60% of services is purchased and delivered by the private sector. Please address how your study will capture records for the 60% of health care services delivered outside the MHS. Please describe whether there is a direct individual-level linkage made between the two data sources (MHS and purchased care), and if so, whether your study will have access to the linked data.

### **The following are specific questions about the study design.**

To evaluate the association between vaccine exposure and outcomes of interest, an inferential study is needed. The proposed primary objective of “[e]stimate the real-world incidence of safety events of interest (AESI)” and “[c]haracterize the utilization patterns of vaccine” are descriptive analyses and do not evaluate association. Please reassign the proposed secondary objective of “[e]valuate whether the vaccine recipients experience increased risk of AESI post-vaccination” (Section 8, pp 12 of 26) as the primary objective. The proposed primary objective of “[e]stimate the real-world incidence of safety events of interest (AESI)” and “[c]haracterize the utilization patterns of vaccine” can be relegated to secondary objectives.

Please explain whether you plan to perform analysis per vaccine dose and overall in both cohort and self-controlled studies.

Please specify the list of outcomes that will be evaluated in each of cohort and self-controlled studies.

Verification of outcomes by reviewing medical charts is an important component of observational studies particularly for certain rare events or difficult to diagnose events. Please explain whether you plan to perform medical chart review to verify any of the adverse events or outcomes in these studies.

Please define the study parameters for self-controlled case series for each outcome including risk window and dose-specific and all-doses analysis.

Please determine the follow-up period for both short-term and long-term events in each study design (cohort and self-controlled).

Please explain whether mortality data is captured in the DoD database since it will be an outcome of interest to be evaluated.

On page 18-19 the cohort study design is listed as sensitivity analysis. Please explain why and modify the study to have this study design as one of the primary study designs since a cohort design is one of the strongest study designs amongst observational studies.

### **Health Care Workers study, protocol number C4591008**

#### **The following are overarching questions about the study data sources.**

Page 10 ‘Setting’: the study suggests using the health care workers registry as one source of study population. Use of such a registry may result in a large loss to follow-up after the vaccine is available to health care workers; and if participation is all based on self-report vs. active data collection by the study conductors, loss to follow-up and incomplete data reporting will be significant. Also, accuracy of many elements of reported data would have to be considered because there is recall bias and other issues associated with self-reporting. The other data source ‘health care systems utilizing Pfizer vaccine’ is not defined and is not determined when it will be defined. The enrollment from those sites is also entirely based on self-enrollment which would experience the same issues as described above. Moreover, there are uncertainties about when health care facilities will distribute the vaccine to their workers to be qualified to participate in such a study. When other COVID-19 vaccines are made available to the health care workers, those patients won’t be eligible to participate in Pfizer’s study. Please explain how you will address this challenge.

Page 10, health care facilities that participate in this study are not currently identified and it is not clear which facilities will provide the vaccine to their workers and what proportion of the workers would choose to receive the vaccine so the enrollment process may take a long time. Thus, the current plan for the study includes a lot of uncertainty about the start date of the study, the number of health care facilities that can be recruited and how long it might take, and the number of participants.

#### **The following are specific questions about the study design.**

Page 9 ‘Research Question and Objectives’: to evaluate the association between the vaccine and outcomes of interest requires an inferential study, but your current primary objectives only perform descriptive and not inferential analysis. Please select ‘evaluate whether the vaccine recipients experience increased risk of AESI and other clinically

significant events post-vaccination’ as a primary objective instead of a secondary objective.

Given the diversity of participants in the health care workers registry and health care systems geographically, it will be extremely difficult, time-consuming, and infeasible to get access to participants’ medical records so ascertainment of medical information other than what is self-reported by the participants is questionable particularly given the large size of the planned study population. Please explain how you will address this challenge.

Page 13 ‘Overall Study Design’ and page 14 ‘Study Variables’: all data collection seems to rely on electronic self-report by participants. This puts a lot of burden on participants without much of an incentive. Thus, missing data, lack of or incomplete reporting, and loss to follow-up will be major issues for the study. Please explain how you will address this issue.

Please explain how death and hospitalization data are collected given that a hospitalized patient may be unable to do all his/her electronic self-reporting and patient death may not be self-reported.

Page 15-16 ‘AESI’: you have listed a number of adverse events, but you don’t list the ones that will be evaluated in this study. Please list all the outcomes that will be evaluated in this study.

Page 17 ‘Schedule of Assessment’: some of the data that are expected to be reported by the patients may not be known by the patients. For example, vaccine lot number; patients may not even know the brand of the vaccine they would receive. Therefore, all data collection based on self-report and self-knowledge will lead to a lot of missing and inaccurate data. Please explain how you will address this issue.

Page 19 ‘Proxy Completion’: many participants may be reluctant to provide contact information for a ‘proxy’ for contact and data collection purposes. Please explain how you will address this issue.

Page 19 ‘Study Size’: expecting only 25% loss to follow-up in the study is unrealistic given that the responsibility for enrollment and data collection for a long time period falls entirely on the study participants. Please explain how you will address this issue.

Page 20 ‘Anticipated Attrition’: the anticipated rates described in this section seem to be too optimistic, and data or evidence to support the anticipated attrition is not presented. Given that the responsibility for enrollment and data collection for a long time period falls entirely on the study participants, the expectations listed here may not be realistic. Please justify the anticipated attrition rate and provide evidence to support it. If you agree that the anticipated attrition rate is too optimistic, please modify study plans to make the enrollment and data collection aspects of the study more active on the part of Pfizer and less reliant on the part of the participants.

Page 24 Data Analysis: there are contradictory statements in this section. One section states ‘While this study is not inferential in nature...’. Another section states ‘...a self-controlled case series analysis will be conducted...’. These two statements are contradictory because a self-controlled study is an inferential study design. In addition, on page 9 one secondary objective of the study is listed as ‘evaluate whether the vaccine recipients experience increased risk of AESI and other clinically significant events post-vaccination’. This objective implies an inferential study design and analytic method. The self-controlled design is mentioned which would imply that each person is used as his/her own control. However, no study design parameters and no analytic parameters are described in this document. Please plan on conducting an inferential study with the primary objective of evaluating the risk of specified adverse events in the vaccinated population and use the self-controlled study design for this purpose. Please provide all design and statistical analytic parameters of the study including the risk and control windows.

### 3. Conclusions

FDA will review study protocols upon submission and provide comments to the sponsor on the study design. Please note, that the EUA letter dated December 11, 2020, includes the following condition of use: *Pfizer Inc. will conduct post-authorization observational study(ies) to evaluate the association between Pfizer-BioNTech COVID-19 Vaccine and a pre-specified list of adverse events of special interest, along with deaths and hospitalizations, and severe COVID-19. The study population should include individuals administered the authorized Pfizer-BioNTech COVID-19 Vaccine under this EUA in the general U.S. population (16 years of age and older), populations of interest such as healthcare workers, pregnant women, immunocompromised individuals, subpopulations with specific comorbidities. The study(ies) should be conducted in large scale databases with an active comparator. Pfizer Inc. will provide protocols and status update reports to the IND 19736 with agreed-upon study designs and milestone dates.*