# Examining vaccine effectiveness (VE) of Flublok® Quadrivalent (Influenza Vaccine) relative to standard dose inactivated influenza vaccine among Kaiser Permanente Northern California members aged 18-64 years

Phase IV, multi-center, modified-cluster randomized study to assess the effectiveness of Flublok Quadrivalent vaccine compared to standard dose inactivated influenza vaccine in adults

## Study Protocol

| | |
|---|---|
| **Study Code:** | VAP00003 |
| **Development Phase:** | Phase IV |
| **Sponsor:** | Kaiser Permanente Northern California<br>Kaiser Permanente Vaccine Study Center<br>1 Kaiser Plaza, 16th Floor<br>Oakland, CA 94612 |
| **Product(s):** | Flublok Quadrivalent vaccine<br>*Standard-Dose Inactivated Influenza Vaccine (SD-IIV)**<br>* to be determined prior to influenza season |
| **Form / Route:** | Liquid/Intramuscular injection (0.5 mL) |
| **Indication For This Study:** | Comparative vaccine effectiveness of 2018-2019 and 2019-2020 formulations of Flublok Quadrivalent vaccine and SD-IIV in adults 18 through 64 years of age |
| **Manufacturer:** | Sanofi Pasteur Inc.<br>Discovery Drive, Swiftwater, PA 18370-0187, USA |
| **Principal Investigator:** | Nicola Klein, MD, PhD |
| **Contributing Investigators:** | Bruce Fireman, MA<br>Ned Lewis, MPH<br>Laurie Aukes, RN<br>John Hansen, MPH<br>Amber Hyman, MPH |
| **Project Manager and Study Leader** | Amber Hyman, MPH |
| **Version and Date of the Protocol:** | Version 2.0 dated 8 May 2020 |
| **ClinicalTrials.gov:** | NCT03694392 |

# History of Protocol Versions

## Table 1: Previous versions of the protocol

| Version* | Date | Comments |
|---|---|---|
| 0.1 | 18 July 2018 | Draft Protocol sent to Sanofi from KPVSC |
| 0.2 | 3 Aug 2018 | Revised draft protocol sent to Sanofi from KPVSC |
| 0.3 | 11 Sept 2018 | Revised draft protocol sent to Sanofi from KPVSC |
| **1.0** | **3 Oct 2018** | **Final protocol sent to Sanofi from KPVSC** |

* Versions in bold font have been approved by the Independent Ethics Committee(s) (IEC[s]) / Institutional Review Board(s) (IRB[s]) and used in the study.

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# Synopsis

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| **Company:** | *Sanofi Pasteur, Inc.* |
| **Products:** | *Flublok Quadrivalent (Influenza Vaccine)* |
| **Active Substances:** | • *45 μg hemagglutinin (HA) per virus strain per dose* |

| | |
|---|---|
| **Title of the Trial:** | *Examining vaccine effectiveness (VE) of Flublok® Quadrivalent (Influenza Vaccine) relative to standard dose inactivated influenza vaccine (SD-IIV) among Kaiser Permanente Northern California members aged 18-64 years* |
| **Development Phase:** | *Phase IV* |
| **Coordinating Investigator:** | *Nicola Klein, MD, PhD* |
| **Study Sites:** | *Kaiser Permanente Northern California* |
| **Planned Study Period:** | *August 2018 to May 2022* |
| **Study Design, Schedule of Study Procedures, and Methodology:** | *Multi-center, modified-cluster randomized study* |
| **Early Safety Data Review:** | *N/A* |
| **Interruption of the Study:** | *N/A* |
| **Observational Objectives:** | *To estimate the relative vaccine effectiveness of Flublok Quadrivalent vaccine versus SD-IIV in adults 18-64 years against select endpoints (specified below)* |
| **Observational Endpoints:** | *PCR-confirmed influenza, hospitalized influenza, hospitalized community-acquired pneumonia, and cardio-respiratory events* |
| **Planned Sample Size:** | *~2,400,000* |
| **Duration of Participation in the Study:** | *N/A; this is an observational, data-only study* |
| **Licensed Study Product 1:**<br>***Form:***<br>***Composition:***<br><br><br><br><br><br><br>***Route:*** | *Flublok Quadrivalent vaccine*<br>*Single 0.5 mL dose*<br>• *45 mcg HA of each of influenza types and subtypes A (H1N1), A (H3N2), and two B lineages (B/Yamagata and B/Victoria)*<br>• *sodium chloride (4.4 mg)*<br>• *monobasic sodium phosphate (0.195 mcg)*<br>• *dibasic sodium phosphate (1.3 mg), and polysorbate 20 (Tween®20) (27.5 mcg)*<br>• *may also contain residual amounts of baculovirus and Spodoptera frugiperda cell proteins (≤ 19 mcg), baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 mcg)*<br>*Liquid/Intramuscular injection (0.5 mL)* |
| **Licensed Study Product 2:**<br>***Form:***<br>***Composition:*** | *To be determined prior to each influenza season*<br>*Single 0.5 mL dose*<br>• *15 mcg HA of each of influenza types and subtypes A (H1N1), A (H3N2), and one or two B lineages (trivalent or quadrivalent, respectively, of B/Yamagata and/or B/Victoria)* |

| | |
|---|---|
| ***Route:*** | • *Additional composition details will vary, determined by national Kaiser Permanente vaccine procurement*<br>*Liquid/Intramuscular injection (0.5 mL)* |
| Inclusion Criteria: | *Adults 18-64 years who receive Flublok or standard dose inactivated influenza vaccine during the 2018-2019, 2019-2020, and 2020-2021 influenza seasons be determined prior to each influenza season* |
| Exclusion Criteria: | *Adults 18-64 years who do not receive Flublok or SD-IIV during the 2018-2019, 2019-2020, and/or 2020-2021 influenza seasons* |
| Statistical Methods: | • *The relative vaccine effectiveness will be calculated based on the formula rVE = 1 – relative Hazard Ratio (rHR), where rHR is estimated from a fully adjusted Cox Regression model (further described in Section 11.1).* |

# Table of Study Procedures

Not applicable.

# List of Abbreviations

| | |
|---|---|
| AESI | Adverse Event of Special Interest |
| CDC | Centers for Disease Control and Prevention |
| EMR | Electronic Medical Record |
| HR | Hazard Ratio |
| SD-IIV | Standard-Dose Inactivated Influenza Vaccine |
| SD-IIV4 | Standard-Dose Quadrivalent Inactivated Influenza Vaccine |
| ICD-10 | International Classification of Diseases, 10th Revision |
| ILI | Influenza-Like Illness |
| IRB | Institutional Review Board |
| KPNC | Kaiser Permanente Northern California |
| KPVSC | Kaiser Permanente Vaccine Study Center |
| PCR | Polymerase Chain Reaction |
| QIV | Quadrivalent Influenza Vaccine |
| RCT | Randomized Control Trial |
| RR | Relative Risk |
| rVE | Relative Vaccine Effectiveness |
| SAE | Serious Adverse Event |
| SUSAR | Suspected Unexpected Serious Adverse Event |
| VAERS | Vaccine Adverse Event Reporting System |
| VE | Vaccine Effectiveness |

# 1 Introduction

## 1.1 Background

Influenza viruses types A and B belong to the genus *Orthomyxoviridae* and are characterized as enveloped, negative-strand, segmented ribonucleic acid (RNA) viruses. The viral envelope contains 2 virus-coded glycoprotein spikes, the hemagglutinin (HA) and neuraminidase (NA) proteins, which are key antigens in the host response to influenza virus in both natural infection and vaccination. A third protein, M2, is a minor envelope component of the A-strain viruses.

Influenza is transmitted through inhalation of virus-containing droplets from infected individuals. The incubation period is usually 1 to 2 days. The virus multiplies in the ciliated columnar epithelium of the upper- and lower-respiratory tract, causing cellular necrosis and sloughing. Virus shedding typically begins just before illness onset (within 24 hours), rapidly peaks, and remains elevated for 1 to 2 days before rapidly declining to low levels. Usually, virus shedding lasts a total of 5 to 10 days.

There is considerable variation in the severity of illness in different individuals, partly due to age, general health, and immune status relative to previous influenza infections and vaccination. The classic symptoms include rapid onset (12 hours or less) of malaise, fever, myalgia, headache, and a non-productive cough or sore throat. Most symptoms last several days, but malaise and cough may last for a week or more. Complications of influenza include primary viral pneumonia, secondary bacterial pneumonia, and exacerbation of underlying medical conditions such as chronic obstructive pulmonary disease and congestive heart failure.

While influenza affects all age groups, seniors, children younger than 5 years of age, and persons with underlying health problems are at increased risk for complications. Members of high-risk groups who become ill with influenza are more likely than the general population to require hospitalization complications of the infection (e.g., pneumonia and cardiovascular events). Groups considered at higher risk for influenza-related complications include persons aged ≥65 years due to immunosenescence and adults 50–64 years of age and older because they are likely to have chronic medical conditions that put them at increased risk for severe influenza illness.

Antigenic variation is an important feature of the influenza virus. The viral HA and NA surface antigens are subject to continuous and sequential evolution within immune or partially immune populations. Antigenic drift results from mutation(s) affecting the RNA segment coding for either HA or NA, but more commonly HA. As a result, there is alteration in protein structure involving 1 or a few amino acids, resulting in minor changes in antigenicity. Antigenic variants within a subtype (e.g., H1 or H3) emerge and through natural selection gradually become the more predominant circulating virus strain, while the preceding antigenic variant is suppressed by specific immunity in the population. In contrast to antigenic drift, antigenic shift represents the emergence of completely new subtypes, typically through gene reassortment with other circulating strains and acquisition of antigenically different gene sequences. Antigenic shift occurs at irregular intervals and may lead to pandemics. While influenza B appears to be more genetically stable than influenza A, the dominant circulating B strain typically varies from season to season. For over a decade, both Yamagata and Victoria lineages have co-circulated during each

season with varying prevalence. The large antigenic divergence between the 2 influenza B lineages limits antigenic cross-reactivity, and immunity to 1 B lineage does not provide adequate protection against the other. Accordingly, switching from a trivalent vaccine to a quadrivalent vaccine is expected to prevent additional morbidity and mortality associated with mismatched influenza B strains that may occur with trivalent vaccines. With this in mind, Flublok Quadrivalent vaccine were developed.

Vaccination with influenza vaccine is the primary method for preventing influenza and its severe complications. It has been shown to be effective in reducing influenza-associated morbidity and mortality in groups at increased risk for influenza-related complications such as infants and young children and persons 50 years of age and older. Of note, immune responses to the vaccine are lower in seniors than those in young healthy adults. Strategies to improve immune responses to the vaccine in the elderly population could provide significant additional reductions in influenza-associated morbidity and mortality. One approach is to increase the dose of HA in vaccines. Previous studies evaluating the immune responses in terms of hemagglutination inhibition (HAI) antibodies with higher doses of HA per strain in different influenza vaccines support a dose-response effect.

Flublok Quadrivalent vaccine is a recombinant HA influenza vaccine indicated for active immunization against disease caused by influenza A subtype viruses and type B viruses contained in the vaccine for adults 18 years of age and older. Use of recombinant DNA techniques to produce vaccine antigen expressed in cell culture is a method that avoids growing the influenza viruses in embryonated hen's eggs. Recombinant technology also allows control over the sequence of the full-length HA produced. The recombinant proteins are highly purified and the vaccine contains no egg protein, preservatives, or antibiotics, any of which may produce hypersensitivity reaction in some individuals.

Flublok Quadrivalent vaccine contains 45 μg HA per virus strain per dose, 3 times the amount of HA compared to standard-dose inactivated quadrivalent influenza vaccine (SD-IIV4). The high purity of a recombinant antigen enables administration of a higher concentration of HA antigen without an increase in adverse effects in humans. This higher dose of antigen may be a particular advantage to older adults whose immune responses to influenza vaccines can be suboptimal.

During this study, Flublok Quadrivalent or SD-IIV will be administered according to the guidelines in the Prescribing Information materials and only to persons for whom it is indicated. The 2018–2019, 2019–2020, and 2020–2021 formulations of recombinant influenza vaccine (Flublok Quadrivalent vaccine) and SD-IIV will be evaluated as described below.

The overall objective of this study is to describe the effectiveness of Flublok Quadrivalent vaccine compared to SD-IIV in adults 18 through 64 years of age.

## 1.2 Background of the Product

### Previous Clinical Experience: Flublok Vaccine

Flublok vaccine (trivalent formulation) was first approved in the United States on 16 January 2013 for use in adults 18–49 years of age. Licensure was based on results of a randomized controlled efficacy trial of Flublok vs placebo in 2344 subjects. The age indication was expanded to include all adults 18 years of age and older in 2014 based on safety and immunogenicity data from 2 studies; the first was conducted among 869 adults 65 years of age and older and the second was conducted among 602 adults 50–64 years of age.

### *Flublok Quadrivalent Vaccine*

On 07 October 2016, the FDA licensed Flublok Quadrivalent vaccine for adults 18 years of age and older. This approval was based on 2 studies conducted during the 2014–2015 influenza season: (1) an immunogenicity and safety study of Flublok Quadrivalent vaccine versus SD-IIV4 in 1350 adults 18–49 years of age and (2) an efficacy, immunogenicity, and safety study of Flublok Quadrivalent vaccine versus SD-IIV4 in 9003 adults 50 years of age and older. In the former study (of adults 18–49 years of age), immunogenicity of Flublok Quadrivalent vaccine was non-inferior to that of the SD-IIV4 comparator for 3 of the 4 antigens; the response to the B Victoria lineage strain did not meet the non-inferiority criteria but the response was low in both vaccine groups, making comparisons uninterpretable. In the latter efficacy study of adults 50 years of age and older, Flublok Quadrivalent vaccine, compared to the SD-IIV4 comparator, demonstrated 30% to 43% greater efficacy in preventing laboratory-confirmed, protocol-defined influenza-like-illness caused by any viral type or subtype.

The most common local adverse reactions (ARs) to Flublok Quadrivalent vaccine include tenderness and pain at the injection site. The most common systemic reactions include headache, fatigue, myalgia, and arthralgia, with most events being mild to moderate in severity. Safety profiles of Flublok influenza vaccine and inactivated influenza vaccine (trivalent and quadrivalent comparisons) were demonstrated to be similar in clinical trials.

## 1.3 Potential Benefits and Risks

### 1.3.1 Potential Benefits to Subjects

Not applicable. This is not clinical trial. The present study is a prospective study using EMR data that are collected as part of routine clinical care.

### 1.3.2 Potential Risks to Subjects

Not applicable. This is not clinical trial. The present study is a prospective study using EMR data that are collected as part of routine clinical care.

### 1.4 Rationale for the Study

Interventions that prevent influenza have a positive impact on other consequences of influenza infection, including influenza-related hospitalizations, complications, and deaths. An improved vaccine for the prevention of influenza in older adults is expected to have significant impact on public health. In an efficacy, immunogenicity, and safety study of Flublok Quadrivalent vaccine versus SD-IIV4 among 9,003 adults 50 years of age and older, Flublok Quadrivalent vaccine, compared to SD-IIV4, demonstrated 30% to 43% greater efficacy in preventing laboratory-confirmed, protocol-defined influenza-like-illness caused by any viral type or subtype.

According to the Centers for Disease Control and Prevention, recombinant technology potentially offers additional flexibility over egg- and cell-propagated vaccines. Flublok Quadrivalent vaccine is specifically manufactured to achieve an exact genetic match to the HA of each influenza strain selected by the World Health Organization and the US Food and Drug Administration for inclusion in the annual seasonal influenza vaccine. In addition, recombinant-based influenza vaccines have the promising benefit to offer better protection by avoiding potential viral adaptation observed with egg- and cell-propagated influenza vaccines. The primary objective of the current study is to evaluate the relative vaccine effectiveness (rVE) of Flublok Quadrivalent vaccine compared to SD-IIV.

## 2 Study Objectives

### 2.1 Primary Objective

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against all PCR-confirmed influenza.

The endpoint for the primary objective is presented in Section 9.1.4.

### 2.2 Secondary Objectives

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against PCR-confirmed hospitalized influenza.
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against hospitalized community-acquired pneumonia.
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against hospitalized cardio-respiratory events combined (e.g., pneumonia, other lower respiratory infections, acute myocardial infarction, congestive heart failure, stroke).
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against PCR-confirmed influenza A.
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against PCR-confirmed influenza B.
- Sub-analyses of the above outcomes as feasible by the following pre-existing conditions:
    1. **Cardiovascular preexisting conditions composite, which may include:** myocardial infarction, cerebrovascular accident, atrial fibrillation, arrhythmias,

coronary artery disease, valvular heart disease/valvuloplasty, chronic/congestive heart failure and/or congenital heart defects, CABG, angioplasty/stents, cardioversion, pacemaker, implantable cardioverter defibrillator, LVAD, heart transplant, hypertensive disease

2. **Respiratory preexisting conditions composite, which may include:** COPD and/or pulmonary HTN
3. **Cardiorespiratory preexisting conditions composite:** combined pre-existing conditions (a) and (b) above
4. **Obesity:** based on available height/weight data for a calculated BMI ≥30 or an obesity diagnosis (e.g., ICD-10 E66.9)
5. **Diabetes:** based on a diagnosis of diabetes

The endpoint(s) for the secondary objective(s) are presented in Section 9.2.4.

## 2.3 Exploratory Objectives

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against exploratory outcomes such as:
    a. Diagnosed with influenza (includes [1] adults with a PCR-positive influenza and [2] adults clinically-diagnosed with influenza in any setting but not tested); this outcome will exclude those with a clinically-diagnosed influenza but are tested and PCR-negative)
    b. All-cause hospitalizations
    c. All-cause mortality

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in other age ranges of vaccinees — aged 18–64 years and aged 18–49 years — against outcomes such as (but not limited to):
    a. All PCR-confirmed influenza
    b. All PCR-confirmed influenza A and influenza B (separate rVE estimates)
    c. PCR-confirmed hospitalized pneumonia
    d. Hospitalized community-acquired pneumonia
    e. Hospitalized cardio-respiratory events combined
    f. All-cause hospitalization
    g. All-cause mortality

- Sub-analyses of the primary and secondary outcomes of sub-groups defined by pre-existing conditions (as described above in Section 2.2) will be conducted among adults 18–49 years as feasible

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV among adults aged 18–64 years for PCR-confirmed influenza A subtypes (A(H1N1)pdm09 and A(H3)) and lineage for type B influenza (B/Victoria, B/Yamagata) as feasible

The endpoint(s) for the observational objective(s) are presented in Section 9.3.4.

# 3 Investigators and Study Organization

This study will be conducted at Kaiser Permanente Northern California (KPNC), which is an integrated health care system with a membership population of approximately 4 million in 2018, including approximately 2.5 million adults between 18 to 64 years of age. The eligible population for this study includes all persons 18 to 64 years of age. KPNC members receive nearly all their care at KPNC facilities, which includes approximately 65 medical clinics and 27 hospitals. Diagnoses, laboratory tests, vaccines, and medications are all captured in KPNC's electronic medical record (EMR) and clinical databases.

# 4 Independent Ethics Committee / Institutional Review Board

Kaiser Permanente Vaccine Study Center (KPVSC) received IRB approval on April 3, 2018, to conduct the following prospective randomized observational study: "Examining vaccine effectiveness (VE) of Flublok Quadrivalent (Influenza Vaccine) relative to standard dose inactivated influenza vaccine among Kaiser Permanente Northern California members aged 18-64 years (Sanofi Pasteur)."

Because the present study is a prospective study using EMR data that are collected as part of routine clinical care, no informed consent will be required. Protected Health Information (PHI) will be used by the KPVSC team (i.e., Principal Investigator, Statistician, Data Manager, Data Analysts, Project Manager), but no PHI will be made available to anyone outside of KPVSC. All data reported to Sanofi Pasteur will be de-identified in accordance with Health Insurance Portability and Accountability Act of 1996 (HIPAA). Further, no individual-level data will be reported to Sanofi Pasteur.

# 5 Investigational Plan

## 5.1 Description of the Overall Study Design and Plan

### 5.1.1 Study Design

To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV against all PCR-confirmed influenza in vaccinees aged 18–64 years, this study will compare the incidence of PCR-confirmed influenza among Flublok Quadrivalent vaccinees versus SD-IIV vaccinees. Our primary comparison will be focused on adults aged 50–64 years at KPNC during the 2018–2019, 2019–2020, and 2020–2021 influenza seasons. We will also assess all adults aged 18–64 years for both influenza seasons.

### 5.1.2 Justification of the Study Design

Please refer to Section 11.1 for details.

### 5.1.3 Study Plan

This study will employ a design whereby KPVSC will ensure that all clinics in KPNC will receive alternating shipments of Flublok Quadrivalent vaccine or SD-IIV. All KPNC facilities will follow a schedule that alternates which vaccine is supplied to each influenza clinic throughout the 3-year study period.

We will block facilities and randomize within blocks (see **Section 5.1.4**), ensuring that roughly half the facilities within each block initially administer Flublok Quadrivalent vaccine and the other half administer a SD-IIV. After the initial supply, the half that started with Flublok Quadrivalent vaccine will be supplied with a SD-IIV, and the half that started with a SD-IIV will be supplied with Flublok Quadrivalent vaccine (see **Figure 1**). The supply of each clinic will then alternate between the two vaccines; that is, Flublok Quadrivalent vaccine alternating with a SD-IIV with each delivery of vaccine to the clinics.

**Figure 1:** Visual of block randomization influenza vaccine administration schedule

| | Week 1 | Week 2 | Week 3 |
|---|---|---|---|
| **Block A** | | | |
| Facility 1<br>Facility 3<br>Facility 5<br>Facility 7<br>Facility 9 | Flublok | Comparator IIV | Flublok |
| **Block B** | | | |
| Facility 2<br>Facility 4<br>Facility 6<br>Facility 8<br>Facility 10 | Comparator IIV | Flublok | Comparator IIV |

### Data Extraction

Pertinent data will be extracted from the KPNC databases to create study datasets in the required file format for analysis (e.g., Excel spreadsheets, SAS datasets). Databases from which data will be extracted include various encounters (inpatient, outpatient, hospitalizations, emergency department, etc.), laboratory tests, documentation of immunizations (e.g., influenza vaccination history), and clinical outcomes and diagnoses, as well as demographic and membership data.

The data analyst will perform validation of the study data throughout the data management process by utilizing the following types of checks as applicable:

- Internal consistency checks (e.g. data undergo range checks, including consistency of dates of birth with vaccination dates, checks for completeness and missing values, etc.)
- External data checks (e.g. data from one database may be compared with data from other databases)
- Error checks written for specific databases.

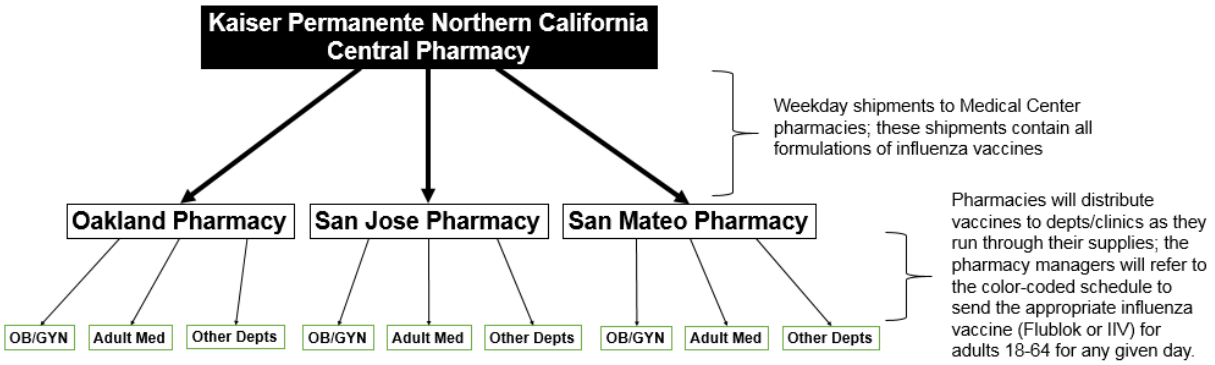
### 5.1.4 Vaccine Distribution Procedures

Based on prior annual influenza vaccine use, we anticipate that KPNC will administer influenza vaccines to approximately 800,000 individuals aged 18–64 years, including 350,000 persons aged 50–64 years each season.

Approximately 400,000 doses of Flublok Quadrivalent vaccine and 400,000 doses of comparator SD-IIV will be administered to adults aged 18–64 years in each of the influenza seasons 2018–2019, 2019–2020, and 2020–2021.

There are approximately 70 facilities that receive individual influenza vaccine shipments from the KPNC Central Pharmacy (the exact number varies slightly each year; see **Figure 2** for an example of the flow). KPNC Central Pharmacy begins "autoshipments" to the Medical Centers and their satellite facilities' main pharmacies in August in preparation for annual influenza vaccination clinics. For purposes of this study, medical center facilities include all associated satellite sites. KPNC Central Pharmacy determines the amount of vaccines to be shipped each day to the medical center facilities based upon vaccine use the previous year at each facility. For example, since Oakland Medical Center administered ~5% of all vaccines during the 2017–2018 influenza season, they would receive 5% of the daily shipment of vaccines during the subsequent 2018–2019 influenza season. Facilities may also request additional vaccine as needed.

**Figure 2.** Influenza Vaccine Distribution Flowchart Example




Once the facilities receive adequate influenza vaccines to distribute to all of their influenza vaccination clinics, they will prepare vaccine allotments for specific patient populations within each clinic (e.g., adult medicine, OB/GYN). We propose to randomize these facilities to distribute (and therefore administer) either Flublok Quadrivalent vaccine or a SD-IIV initially to all of their influenza vaccination clinics. Roughly half the facilities will first distribute Flublok Quadrivalent vaccine to be administered by their associated departments and clinics, while the other half will first distribute a SD-IIV for administration by their associated departments and clinics. The facilities will follow a weekly alternating schedule (with some variation due to usage) that indicates which vaccine is to be internally distributed to associated departments and clinics for the entire influenza season. Historically, >75% of vaccinations to adults aged 18–64 are administered prior to Thanksgiving.

Because the study design specifies that roughly equivalent amounts of Flublok Quadrivalent vaccine and SD-IIV will be administered at every KPNC facility throughout the influenza season, KPVSC will monitor on a weekly basis that Flublok Quadrivalent vaccine and SD-IIV are being distributed as much as possible in a balanced way (see Section 11.1 for further details).

In order to randomize which facilities will initially administer Flublok Quadrivalent vaccine and which will start with a SD-IIV, we will block facilities by size and service area. For example, there may be 4 facilities per block, and within the block, 2 facilities start with Flublok Quadrivalent vaccine and 2 facilities start with a SD-IIV.

**Staff Training: Pharmacy Staff, Influenza Clinic Injection Nurses, and Nurse Managers**

KPVSC will work closely with the KPNC Central Pharmacy, the KPNC influenza program manager, the pharmacy staff, and influenza coordinators at the ~70 facilities to ensure that staff are aware of the study and are trained to carry out the study protocol. Randomization will be controlled by KPVSC, and the individual pharmacies will then distribute the vaccine to the departments and clinics based on the schedule determined by KPVSC. We will conduct trainings with the pharmacy staff, influenza coordinators, and department managers so that all relevant staff are aware that Flublok Quadrivalent vaccine or a SD-IIV should be routinely administered to everyone 18–64 years of age without any preference for one vaccine over the other, and that vaccine use should be based only on what is available in the clinic at the time of vaccination.

In particular, we will emphasize that the injection nurse administering the vaccine should not preferentially choose one vaccine over the other, but instead use what is available in the refrigerator or portable cold storage box for the day. Based on routine influenza clinic operations, there is little potential for bias at the level of vaccine administration level (e.g., an injection nurse preferentially choosing one vaccine over the other), especially early in the season, when large numbers of influenza vaccine are administered on any given day; injection nurses are unlikely to spend time searching for a specific formulation based on preference. Further, by following the alternating vaccine supply schedule, we will reduce the likelihood that both Flublok Quadrivalent vaccine and SD-IIV are simultaneously available in the clinic. By having only one vaccine available for adults aged 18–64 years (Flublok Quadrivalent vaccine or SD-IIV), we hope to reduce the likelihood that an injection nurse is able to choose one vaccine over the other.

Because influenza vaccine is used at a very rapid pace once influenza clinics officially begin administering vaccine, the departments and clinics may request vaccine replenishment prior to the next distribution in order to ensure adequate supply. For this reason, it may be possible that a particular clinic will have both Flublok Quadrivalent vaccine and a SD-IIV available.

On a weekly basis, we will also monitor both the distribution of vaccine from KPNC Central Pharmacy to the facility pharmacies, as well as influenza vaccine administration. If we detect imbalances at either of these points, we will work closely with the affected facility(s) to attempt to correct the imbalance. Additional details may be found in Section 11.1.

### 5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ if there are manufacturing delays that affect Flublok Quadrivalent vaccine or SD-IIV vaccine(s).

Planned study period (total): August 2018 to May 2022

Anticipated first study member influenza vaccination date: September 16, 2018

Planned vaccination periods: August 2018 to April 2019, August 2019 to April 2020, August 2020 to April 2021

Planned date of draft study report: February 2022

Planned date of final study report: May 2022

## 5.2 Study Population

### 5.2.1 Recruitment Procedures

Eligible adults aged 18–64 years will receive either Flublok Quadrivalent vaccine or a SD-IIV in the course of routine influenza vaccination during each of the two influenza seasons of the study period.

### 5.2.2 Informed Consent Procedures

Not applicable. Because the present study is a prospective study using EMR data that are collected as part of routine clinical care, no informed consent will be required.

### 5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

### 5.2.4 Inclusion Criteria

An individual must fulfill all of the following criteria to be eligible for the study:

- Between the ages of ≥18 and <65 years at the time of influenza vaccination
- Receive either Flublok Quadrivalent vaccine or SD-IIV at a KPNC facility during the study period from August 2018 through April 2021

### 5.2.5 Exclusion Criteria

An individual fulfilling any of the following criteria is to be excluded from the study to the extent possible:

- Children <18 years old
- Adults ≥65 years old

### 5.2.6 Medical History

Prior to receiving an influenza vaccination (either Flublok Quadrivalent vaccine or SD-IIV), patients will be screened using an influenza vaccination screening form as part of a routine pre-vaccination assessment.

### 5.2.7 Contraindications for Subsequent Vaccinations

Severe hypersensitivity or adverse reaction to a previous dose of Flublok Quadrivalent vaccine or a SD-IIV.

### 5.2.8 Classification of Subjects Who Discontinue the Study

As this is not a clinical trial, there is not the possibility that a patient discontinues the study prior to completion. There is the possibility, however, that a patient is no longer a KPNC member at some point in the follow-up period following vaccination. Membership will be taken into account at the analysis stage to ensure that patients have adequate follow-up times.

### 5.2.9 Follow-up of Discontinuations

Not applicable.

### 5.2.10 Follow-up and Reporting of Pregnancies

We will include KPNC members who receive Flublok Quadrivalent vaccine or SD-IIV vaccine(s) while aged 18–64 years. Follow-up for outcomes based on PCR-confirmed influenza will include only the first positive PCR test (for influenza) per influenza season, and only if it is ≥14 days after vaccination, and follow-up will continue either through April 30 of each influenza season or until exit from KPNC, whichever occurs earlier. In the KPNC system, influenza PCR tests are used for clinical purposes, thus the "trigger" for an influenza PCR test is based on clinical presentation. The decision to test is up to each physician. KPNC also monitors the influenza season, which can affect the total amount of influenza testing at any point in the season.

Pregnancy is not an exclusion criterion for this study. Patients who are ≥18 years old and pregnant at the time of vaccination will be included in the analysis. Pregnant patients will be followed in the same way they normally would for routine influenza vaccination.

As described in Section 10.1, in the event that KPVSC reviews individual patient charts within the EMR and there is written notation in the medical record indicating that a health care provider attributed a serious or unexpected adverse event to Flublok Quadrivalent vaccine, KPVSC will report the adverse event possibly related to Flublok Quadrivalent vaccine.

## 5.3 Modification of the Study and Protocol

Any amendments to this study protocol must be discussed with and approved by Sanofi Pasteur. If agreement is reached concerning the need for an amendment, it will be approved in writing by Sanofi Pasteur, and the amended version of the protocol will replace the earlier version. Any substantial amendments (e.g., those that affect the conduct of the study, the safety of the subjects, or the analysis of the data) require KPNC IRB approval.

During the period for which KPNC IRB approval has already been given, KPVSC is responsible for ensuring that changes to an approved study are not initiated without KPNC IRB review and approval, except as needed to eliminate apparent immediate hazards to subjects.

## 5.4 Interruption of the Study

The study may be discontinued if data about Flublok Quadrivalent vaccine or comparator resulting from this or any other studies become available; or for administrative reasons; or on advice of Sanofi Pasteur, KPVSC, the KPNC IRB, or the governing regulatory authorities in the US where the study is taking place.

If the study is prematurely terminated or suspected, Sanofi Pasteur shall promptly inform KPVSC, the KPNC IRB, and the regulatory authorities of the reason for termination or suspension, as specified by the applicable regulatory requirements. If applicable, KPNC will follow internal protocols for notifying patients who may have received Flublok in the course of routine patient care.

# 6 Vaccines Administered

## 6.1 Identity of the Investigational Product(s)

### 6.1.1 Identity of Study Product(s)

Flublok Quadrivalent vaccine is indicated for active immunization against disease caused by influenza A subtype viruses and influenza type B viruses contained in the vaccine. Flublok Quadrivalent vaccine is a sterile solution supplied in prefilled, single-dose syringes, 0.5 mL.

#### 6.1.1.1 Composition

Flublok Quadrivalent vaccine is formulated to contain 180 mcg HA per 0.5 mL dose with 45 mcg HA of each of the following influenza types and subtypes: A (H1N1), A (H3N2), and two B lineages (B/Yamagata and B/Victoria).

A single 0.5 mL dose of Flublok Quadrivalent vaccine contains sodium chloride (4.4 mg), monobasic sodium phosphate (0.195 mcg), dibasic sodium phosphate (1.3 mg), and polysorbate 20 (Tween®20) (27.5 mcg). Each 0.5mL dose of Flublok Quadrivalent vaccine may also contain residual amounts of baculovirus and *Spodoptera frugiperda* cell proteins (≤ 19 mcg), baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 mcg).

Flublok Quadrivalent vaccine contains no egg proteins, antibiotics, or preservatives. The single-dose, pre-filled syringes contain no natural rubber latex.

#### 6.1.1.2 Preparation and Administration

Prior to administration, all Flublok Quadrivalent vaccine must be inspected visually for cracks, broken seals, correct label content, and extraneous particulate matter and/or discoloration, whenever solution and container permit. If any of these conditions exist, the vaccine must not be administered and another dose of Flublok Quadrivalent vaccine is to be used, and the event is to be reported to Sanofi Pasteur.

To administer the vaccine, invert the pre-filled syringe containing Flublok Quadrivalent vaccine gently prior to affixing the appropriate size needle for intramuscular administration. The preferred site for injection is the deltoid muscle. Flublok Quadrivalent vaccine should not be mixed in the same syringe with any other vaccine.

#### 6.1.1.3 Dose Selection and Timing

Not applicable.

### 6.1.2 Identity of Comparator SD-IIV Product(s)

SD-IIV is defined as all standard-dose quadrivalent inactivated egg-based influenza vaccines administered intramuscularly during the course of this study in KPNC facilities.

The comparator SD-IIV vaccine(s) that will be used each year is determined and ordered at the national KP level; thus KPVSC does not have influence over what comparator SD-IIV vaccine(s) are purchased. KPVSC will be notified of which comparator vaccine will be used within KPNC. The comparator influenza vaccine(s) will be acquired through national KP's usual procurement processes.

#### 6.1.2.1 Composition

Comparator SD-IIV influenza vaccine(s) will be used, as determined by national KP procurement.

SD-IIV vaccine(s) are formulated to contain 15 mcg HA or 60 mcg HA (trivalent or quadrivalent formulation, respectively) per 0.5 mL dose with 15 mcg HA of each of the following influenza types and subtypes: A (H1N1), A (H3N2), and one or two B lineages (trivalent or quadrivalent formulation, respectively; trivalent will contain either a B/Yamagata or B/Victoria strain as per FDA guidance). The specific final formulation will be dependent on comparator SD-IIV vaccine(s) that will be ordered and used each year as determined at the national KP level.

#### 6.1.2.2 Preparation and Administration

The procedures for preparing and administering the comparator SD-IIV influenza vaccine(s) will be prepared and administered as per the manufacturer's package insert.

#### 6.1.2.3 Dose Selection and Timing

Not applicable.

## 6.2 Identity of Other Product(s)

Not applicable.

## 6.3 Product Logistics

### 6.3.1 Labeling and Packaging

All vaccines will be supplied with their manufacturer's commercial labeling and packaging.

### 6.3.2 Product Shipment, Storage, and Accountability

#### 6.3.2.1 Product Shipment

Sanofi Pasteur will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (i.e., verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

#### 6.3.2.2 Product Storage

All temperature monitoring, including storage and shipment within KPNC sites, of Flublok Quadrivalent vaccine, will be per KPNC pharmacy's internal standard operating procedures. KPVSC itself will not directly monitor nor manage temperature excursions if they arise.

Any excursion of temperature during the initial shipment of Flublok Quadrivalent vaccine performed by Sanofi Pasteur shall require a full evaluation and shall be documented, reviewed, and approved by Sanofi Pasteur/Protein Sciences in accordance with its internal procedures. If there is a temperature excursion, KPNC must quarantine the clinical supply until the Sanofi Pasteur evaluation is complete.

Any excursion of temperature during storage or shipment performed by KPNC will require a full evaluation by KPNC, and shall be documented, reviewed, and approved by KPNC in accordance with its internal standard operating procedures. If KPNC requests additional evaluation needed for decision making from Sanofi Pasteur, Sanofi Pasteur will provide assistance in accordance with its internal procedures.

#### 6.3.2.3 Product Accountability

When patients receive Flublok Quadrivalent vaccine (or SD-IIV), the vaccine administrator will record the vaccination information into their medical record, including the formulation, dose, lot number, and date of vaccination.

### 6.3.3 Replacement Doses

If replacement doses are required, KPNC will contact Sanofi Pasteur to resolve as appropriate.

### 6.3.4 Disposal of Unused Products

Unused or wasted products will be destroyed in accordance with the instructions in the KPNC Operating Guidelines. Product accountability will be verified throughout the study period.

### 6.3.5 Recall of Products

Should Flublok Quadrivalent vaccine be recalled by a Health Authority or withdrawn from the market by Sanofi Pasteur, Sanofi Pasteur is responsible to immediately notify KPNC and KPNC shall cease to use Flublok Quadrivalent vaccine.

KPNC is responsible for the implementation of the recall or withdrawal of Flublok Quadrivalent vaccine and the destruction of the identified batches as per authorization from Sanofi Pasteur. KPNC shall be responsible to provide Sanofi Pasteur with all relevant documentation related to the recall operation.

Following a product recall, Sanofi Pasteur shall supply additional Flublok Quadrivalent vaccine for replacement for continuation of the conduct of the study.

## 6.4 Blinding and Code-breaking Procedures

Not applicable.

## 6.5 Randomization and Allocation Procedures

Subjects will not be individually randomized. A modified-cluster randomization scheme by facility will be deployed.

This study will employ a design whereby KPVSC will ensure that all clinics in KPNC will receive alternating distribution of Flublok Quadrivalent vaccine or SD-IIV. All KPNC facilities will follow a schedule that alternates which vaccine is supplied to each influenza clinic throughout the 3-year season period.

We will block facilities and randomize within blocks (see **Section 5.1.4**), ensuring that roughly half the facilities within each block initially administer Flublok Quadrivalent vaccine and the other half administer a SD-IIV. After the initial supply, the half that started with Flublok Quadrivalent vaccine will be supplied with the SD-IIV, and the half that started with SD-IIV will be supplied with Flublok Quadrivalent vaccine (see **Figure 1**). The supply of each clinic will then alternate between the two vaccines; that is, Flublok Quadrivalent vaccine alternating with SD-IIV with each delivery of vaccine to the clinics.

**Figure 1:** Visual of block randomization influenza vaccine administration schedule

| | Week 1 | Week 2 | Week 3 |
|---|---|---|---|
| **Block A** | | | |
| Facility 1<br>Facility 3<br>Facility 5<br>Facility 7<br>Facility 9 | Flublok | Comparator IIV | Flublok |
| **Block B** | | | |
| Facility 2<br>Facility 4<br>Facility 6<br>Facility 8<br>Facility 10 | Comparator IIV | Flublok | Comparator IIV |

### 6.6 Vaccine Administration Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified KPNC personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the study site as per KPNC standard operating procedures

### 6.7 Concomitant Medications and Other Therapies

Not applicable.

## 7 Management of Samples

Not applicable.

## 8 Endpoints and Assessment Methods

### 8.1 Primary Endpoints and Assessment Methods

#### 8.1.1 Relative Vaccine Effectiveness of Flublok Quadrivalent vaccine

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against all PCR-confirmed influenza.

The rVE will be calculated based on the following formula:

$$rVE = 1 - relative\ Hazard\ Ratio\ (rHR)$$

where rHR is estimated from the fully adjusted Cox Regression model (described in Section 11.1).

Diagnoses, laboratory tests, vaccines, and medications are all captured in the electronic medical record (EMR) and clinical databases. Member-reported race/ethnicity is available for approximately 85% of members, while the remaining are imputed using the RAND BISG algorithm.

All microbiological testing is conducted at KPNC laboratories that have used real-time PCR tests for influenza since 2006. PCR results are categorized as positive for influenza A; positive for influenza B; or negative for both. In the KPNC system, influenza PCR tests are used for clinical purposes, thus the "trigger" for an influenza PCR test is based on clinical presentation. The decision to test is up to each physician. KPNC monitors the influenza season which can affect the total amount of influenza testing in adults. Once the KPNC laboratories complete the PCR testing, the test result is updated in the patient's EMR.

The majority of KPNC's influenza cases are seen in the outpatient setting. Most of the remaining cases are treated in the ED with a very small portion admitted to hospital
Please refer to Section 5.1.1 for details pertaining to the assessment of rVE.

## 8.2 Secondary Endpoints and Assessment Methods

### 8.2.1 Relative Vaccine Effectiveness of Flublok

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against PCR-confirmed hospitalized influenza.
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against hospitalized community-acquired pneumonia.
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against hospitalized cardio-respiratory events combined (e.g., pneumonia, other lower respiratory infections, acute myocardial infarction, congestive heart failure, stroke).
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against PCR-confirmed influenza A.
- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against PCR-confirmed influenza B.
- Sub-analyses of the above outcomes as feasible by the following pre-existing conditions:
    6. **Cardiovascular preexisting conditions composite, which may include:** myocardial infarction, cerebrovascular accident, atrial fibrillation, arrhythmias, coronary artery disease, valvular heart disease/valvuloplasty, chronic/congestive heart failure and/or congenital heart defects, CABG, angioplasty/stents, cardioversion, pacemaker, implantable cardioverter defibrillator, LVAD, heart transplant, hypertensive disease
    7. **Respiratory preexisting conditions composite, which may include:** COPD and/or pulmonary HTN

8. **Cardiorespiratory preexisting conditions composite:** combined pre-existing conditions (a) and (b) above
9. **Obesity:** based on available height/weight data for a calculated BMI ≥30 or an obesity diagnosis (e.g., ICD-10 E66.9)
10. **Diabetes:** based on a diagnosis of diabetes

The rVE will be calculated based on the following formula:

$$rVE = 1 - relative\ Hazard\ Ratio\ (rHR)$$

where rHR is estimated from the fully adjusted Cox Regression model (described in Section 11.1).

Data on the secondary endpoints will be extracted from the KPNC databases that contain encounters on patient hospitalizations. ICD-10 codes will be extracted based on the discharge diagnoses recorded in the patients' EMR. The specific codes used to identify community-acquired pneumonia and cardio-respiratory events will be further specified in the SAP.

Please refer to Section 8.1.1 for details pertaining to PCR assessment, and Section 5.1.1 for details pertaining to the assessment of rVE.

## 8.3 Exploratory Endpoints and Assessment Methods

### 8.3.1 Relative Vaccine Effectiveness of Flublok

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in vaccinees aged 50–64 years against exploratory outcomes such as:
    a. Diagnosed with influenza (includes [1] adults with a PCR-positive influenza and [2] adults clinically-diagnosed with influenza in any setting but not tested); this outcome will exclude those with a clinically-diagnosed influenza but are tested and PCR-negative)
    b. All-cause hospitalizations
    c. All-cause mortality

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV in other age ranges of vaccinees — aged 18–64 years and aged 18–49 years — against outcomes such as (but not limited to):
    a. All PCR-confirmed influenza
    b. All PCR-confirmed influenza A and influenza B (separate rVE estimates)
    c. PCR-confirmed hospitalized pneumonia
    d. Hospitalized community-acquired pneumonia
    e. Hospitalized cardio-respiratory events combined
    f. All-cause hospitalization
    g. All-cause mortality

- Sub-analyses of the primary and secondary outcomes of sub-groups defined by pre-existing conditions (as described above in Section 2.2) will be conducted among adults 18–49 years as feasible

- To estimate the rVE of Flublok Quadrivalent vaccine versus SD-IIV among adults aged 18–64 years for PCR-confirmed influenza A subtypes (A(H1N1)pdm09 and A(H3)) and lineage for type B influenza (B/Victoria, B/Yamagata) as feasible

Data on the exploratory endpoints will be extracted from the KPNC databases that contain relevant encounters on patient hospitalizations and mortality. ICD-10 codes will be extracted based on the discharge diagnoses recorded in the patients' EMR. The specific codes used to identify diagnoses of interest will be further specified in the SAP.

Please refer to Section 8.1.1 for details pertaining to PCR assessment, and Section 5.1.1 for details pertaining to the assessment of rVE.

# 9 Reporting of Serious Adverse Events

## 9.1 Initial Reporting by the Investigator

Serious or unexpected adverse events (see 21 CFR 314.80) that may be related to Flublok, including any follow-up information, will be reported promptly to Sanofi Pasteur, national regulatory authorities (e.g., to the Vaccine Adverse Event Reporting System [VAERS]), and the KPNC Institutional Review Board, in accord with any applicable requirements.

KPVSC will perform the study in compliance with all applicable local and international pharmacovigilance laws and regulations. Although the conduct of the study is entirely the responsibility of KPVSC, Sanofi Pasteur/Protein Sciences as the manufacturer of Flublok Quadrivalent vaccine has legal obligations to report safety information to various regulatory authorities. Accordingly, in the event that individual charts are reviewed and there is written notation in the medical record indicating that a health care provider attributed a SAE, SUSAR, or AESI to any product manufactured by Sanofi Pasteur/Protein Sciences used in the conduct of the research, KPVSC agrees to report all SAEs, SUSAR, and AESIs possibly related to Flublok Quadrivalent vaccine. Pharmacovigilance reports to Sanofi Pasteur will be provided at the address provided below within 3 working days of KPVSC's awareness that a reportable SAE, SUSAR, or AESI has occurred to one of the two following addresses.

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: CL-CPV-Receipt@sanofi.com

- By express mail, to the following address:

  Global Pharmacovigilance and Epidemiology, Sanofi Pasteur Inc.,

  1 Discovery Drive, Swiftwater, PA, 18370-0187, USA

The reporting obligations as defined in the Study Agreement are the following:

- Adverse events of special interest (AESI): anaphylactic reactions/hypersensitivity, pericarditis, Guillain-Barre Syndrome, neuritis, convulsion, encephalomyelitis/transverse myelitis, thrombocytopenia, syncope, vasculitis
- Suspected Unexpected Serious Adverse Events (SUSAR): an adverse event, the nature or severity of which is not consistent with the applicable product information, such as a fatal outcome
- New Safety Findings

### 9.2 Follow-up Reporting by the Investigator

Any follow-up information received by the investigator regarding an SAE or AESI must be reported in the same procedure as explained in Section 9.1 (within 3 working days of KPVSC's awareness).

### 9.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE / AESI that occurs after a subject has completed the study but that is likely to be related to Flublok Quadrivalent vaccine must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 9.1.

### 9.4 Assessment of Causality

Not applicable for this EMR-based study.

### 9.5 Reporting SAEs to Health Authorities and IECs / IRBs

Please refer to Section 9.1. KPVSC will perform the reporting of SAEs to Health Authorities and IECs / IRBs in compliance with all applicable local and international pharmacovigilance laws and regulations.

## 10 Data Collection and Management

### 10.1 Data Collection

Pertinent data will be extracted from the KPNC databases to create study datasets in the required file format for analysis (e.g., Excel spreadsheets, SAS datasets). Databases from which data will be extracted include various encounters (inpatient, outpatient, hospitalizations, emergency department, etc.), laboratory tests, documentation of immunizations (e.g., influenza vaccination history), and clinical outcomes and diagnoses, as well as demographic and membership data.

### 10.2 Data Management

The data analyst will perform validation of the study data throughout the data management process by utilizing the following types of checks as applicable:

- Internal consistency checks (e.g. data undergo range checks, including consistency of dates of birth with vaccination dates, checks for completeness and missing values, etc.)
- External data checks (e.g. data from one database may be compared with data from other databases)
- Error checks written for specific databases.

### 10.3 Data Review

Please refer to Section 10.2.

## 11 Statistical Methods and Determination of Sample Size

### 11.1 Statistical Methods

Since we are not randomizing at the individual patient level, there is no vaccine being assigned to any patient. The intent is to balance Flublok versus SD-IIV comparisons by balancing the shipments and delivery of the vaccines by clinic and calendar week.

The preliminary analyses will compare the incidence of each of the outcomes in Flublok Quadrivalent vaccinees versus SD-IIV vaccinees. We plan to test the null hypothesis that Flublok is not any more effective than the comparator (i.e., a superiority test), using a 2-sided test, $p<0.05$. The primary analyses will use Cox regression to obtain an adjusted estimate of the relative hazard ratio (rHR) for each outcome, adjusted for age, sex, race/ethnicity, facility, and time-since-vaccination. The rHR at any point in the follow-up period is the instantaneous relative risk (RR) at that time (i.e., we are estimating rVE by (1–rHR), and testing the null hypothesis that rHR=0). In addition, we may adjust for an available comorbidity score and/or a measure of prior exposure to influenza vaccines (e.g., exposure to flu vaccine in the prior year, or number of flu shots in the past three years).

Risk sets will be conditioned (i.e., stratified) on calendar day, using a calendar timeline for the Cox regression. We expect many people to be vaccinated both years, and some might get "breakthrough" influenza both years. Getting Flublok in one year should be entirely unrelated to getting Flublok in another year, so robust standard errors are not needed. We will check our assumption that the vaccine received in one year is not related to vaccine received the next year. For each type of outcome, follow-up would end at the first outcome event in a season but could restart the next year when the individual is vaccinated again.

We do not know whether prior vaccination (i.e., booster or priming effect) affects VE of either Flublok Quadrivalent vaccine or SD-IIV, but we hypothesize that prior vaccination might be an effect modifier but not a potential confounder because what patients are vaccinated with in prior years should not be associated with what vaccine they receive in any of the 3 study seasons. We

will test to ascertain if, as expected, there is (1) no correlation between prior vaccination (before the study period) and vaccination during the 3 study seasons, and (2) no correlation between the type of vaccine received in one season and the type of vaccine received in any other study season(s). If we find that there is a relationship in either of these scenarios, we can treat prior vaccination ("prior" meaning before the study commenced, or "prior" as in vaccination in the first study season relative to the second study season) as a potential confounder. We would add variables that adjust for whether a patient was vaccinated during the past year(s), as well as which vaccine type they received. Further, if prior vaccination does modify VE, we may have adequate power to assess whether there is a boosting effect given our large sample size.

There is little possibility of confounding that may occur between patients tested versus those who are not tested. While not everyone with suspected influenza will be tested, the randomization process in vaccine supply (Flublok Quadrivalent vaccine versus SD-IIV) should result in an equal distribution of those who are and are not tested between the two vaccine groups throughout the season. We will attempt to mitigate possible bias and confounding as much as possible upfront by implementing our plans for supplying clinics with alternating shipments of vaccines. Because factors related to testing should be balanced, there is no reason to believe that the likelihood of being tested will be related to whether a person received Flublok Quadrivalent vaccine or SD-IIV.

We will also be monitoring the balance of potential confounders that may be related to influenza and to PCR testing in order to confirm that we are achieving the balance intended by our quasi-randomized shipment of vaccines to clinics. Once vaccinations begin, we will monitor on a weekly basis the balance of Flublok vaccinees versus SD-IIV vaccinees with respect to facility, sex, and age group (18–49 years and 50–64 years). Additional demographic variables such as race and ethnicity may also be monitored. We will also monitor balance with respect to comorbidities such as chronic obstructive pulmonary disease (COPD), asthma, and diabetes (to be specified further in the SAP). If we find that any facility is using Flublok or SD-IIV more (or less) than needed to achieve balance, we will work with the influenza program manager to adjust what is being administered. If despite our efforts, there is still imbalance, we can address these imbalances at the analysis stage, adjusting for, or stratifying by, the relevant covariates.

We plan to assess the outcomes that occur ≥14 days after vaccination up through April 30 of each influenza season. It is possible that patients enter, exit, and re-enter the KPNC population during the study period. At the analysis stage, we will make the most appropriate determination for how to handle such cases.

For outcomes not based on PCR-confirmed influenza (e.g., hospitalized pneumonia and cardio-respiratory events), we will develop an algorithm (to be described in the Statistical Analysis Plan) to measure the intensity of influenza circulation to guide when to start and stop following for such events (e.g., as determined by the algorithm, hospitalized pneumonia during June when influenza is not circulating would not be included).

## 11.2 Sample Size and Power Calculations

We calculated the least rVE that is detectable with 80% power in a 3-year study for several aims. As described in Section 11.1, we plan to test the null hypothesis that Flublok is not any more effective than the comparator (i.e., a superiority test), using a 2-sided test, $p<0.05$. Our allocation

ratio of 1:1 implies that each year, KPNC would give Flublok Quadrivalent vaccine to 400,000 members aged 18–64 years, and SD-IIV to another 400,000 similar KPNC members.

Each row of the tables in the Appendices (**Section 15**) shows power for a possible scenario for a given outcome and a specific age range. The expected incidence of the outcome in vaccinees who received SD-IIV (based on incidence observed in the 2016–2017 influenza season) is in column 4; the relative risk (estimated by the relative hazard ratio) associated with getting Flublok Quadrivalent vaccine versus a comparator is in column 5; the corresponding rVE in column 6; and the power in the last column. These power calculations estimate our power to test the null hypothesis that Flublok Quadrivalent vaccine VE does not differ from SD-IIV(s).

Because the comparison group will not be unvaccinated—they are getting SD-IIV—we will be estimating and testing rVE: i.e., the percent reduction in the incidence of "breakthrough cases" (e.g., influenza episodes in vaccinees) that results from the use of Flublok Quadrivalent vaccine rather than the SD-IIV vaccines.

As an example, for the outcome of PCR-confirmed flu diagnosis, the first row of the first table indicates that power is very high (>0.99) to detect a rVE of 0.30 (which amounts to a 30% rVE) in a 3-year study of vaccinees aged 18–64 years, assuming that influenza incidence in the comparator arm will be the same as it was in the 2016–2017 influenza season. Comparing rows 5 and 6 of the first table, our power to detect a rVE of 10% rather than 5% against test-positive influenza in those aged 18–64 years increases to 0.96 from 0.45.

Depending on priorities and data availability, we may potentially conduct subgroup analyses of rVE, including the subgroups defined by:

- influenza type A and B
- selected diagnoses or conditions (e.g., in 50–64 year olds, rVE of those with specified comorbid conditions, such as cardiac, pulmonary, and metabolic comorbidities)
- time periods and/or time-since-vaccination within a season
- specific comparator SD-IIV(s) (if more than one comparator is used)

# 12 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

## 12.1 Ethical Conduct of the Study / Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

## 12.2 Source Data and Source Documents

The source data are stored in the KPNC EMR.

## 12.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed agreement, including confidentiality, with Sanofi Pasteur. Sanofi Pasteur personnel (or designates) will not have any access to subject records for the present study. All data reported to Sanofi Pasteur by KPVSC will be deidentified and aggregated.

## 12.4 Monitoring, Auditing, and Archiving

### 12.4.1 Monitoring

Not applicable.

### 12.4.2 Audits and Inspections

The KPVSC has been using essentially the same system to manage data since 1985. Data management for data-only studies are performed by KPVSC almost entirely using the SAS system. Programs to manage data are used repeatedly, updating the SAS code as needed for protocol adherence.

Many utility macros have been created and maintained for use with the VSC data management programs. These stored compiled macros are available to KPVSC Data Analysts / Programmers for their use in constructing and testing programs.

Changes made to programs after the start of a study are documented as notes in the header/margin of the program or in the appropriate revision control system. Changes are applied only to copies of programs, and the original source is retained indefinitely. It is incumbent upon the Data Analyst / Programmer in charge of a particular task to document all programs and work performed; this includes code used as well as logs and listings produced.

Programming for vaccine studies at the KPVSC adheres to standards across all projects to ensure the preservation of code, logs, and listings, as well as good programming in data processing and transparency in methodology.

### 12.4.3 Archiving

KPNC databases created from KPNC EMRs are available for research purposes to KPVSC Data Analysts / Programmers for the duration that the project is open/approved by the KPNC IRB. Once the study is closed, the data are archived for future reference and regulatory compliance.

## 12.5 Financial Contract and Insurance Coverage

Not applicable.

## 12.6 Stipends for Participation

Not applicable.

## 12.7 Publication Policy

Each Party may publish and publicly present the final aggregated results of the Research Project, provided that KPVSC's investigator will lead all such publications and presentations. Sanofi Pasteur/Protein Sciences will not manipulate or reanalyze the results of the Research Project in any way. No less than thirty (30) days prior to submission to a publisher or any external forum, each Party shall provide the other party with a copy of any proposed publication or presentation for review and comment, which review shall be limited to determining whether the publication or presentation includes the disclosure of Confidential Information or patentable subject matter. Publications or presentations shall not include Protected Health Information" or "PHI," or the Confidential Information of the other Party (other than the final aggregated research results of the Research Project) without the written permission of such Party. If the reviewing Party believes that patentable subject matter is disclosed in the manuscript or presentation and so notifies the publishing Party in writing within the thirty (30) day review period, said publication will be withheld for a reasonable period of time (but not to exceed sixty (60) days) until all applicable patent filings are completed. With respect to public presentations, each Party shall use reasonable efforts to provide review and comments more promptly than the full period of review specified in this Section, if requested by the submitting Party.

Qualification for authorship and contributorship shall be determined in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," published by the International Committee of Medical Journal Editors (ICMJE). Publications shall carry appropriate acknowledgment of funding support from Sanofi Pasteur and a disclaimer that the contents are the responsibility of the authors and do not necessarily represent the official views of Institution.

# 13 Reference List

# 14 Signature Page

I have read this protocol, and I agree to conduct this trial according to the procedures outlined in the protocol, to comply with its requirements, related to ethical and safety considerations, and to comply with applicable regulations and Good Clinical Practice.

| | |
|---|---|
| **Nicola Klein, MD, PhD**<br>**Principal Investigator** | **Date** |

# 15 Appendices

**Power of 3-yr study comparing FluBlok v Comparators**
**Power to detect relative VE against 5 types of outcome events**
**By age group (or chronic disease status) and outcome**
**2-sided alpha=0.05 (likelihood ratio chi-sq test for superiority)**
**800,000 vaccinees expected per yr: 400K fluBlok v. 400K comparators**

**age=18-64 outcome=flu, test+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| 1 | 1,200,000 | 1,200,000 | 0.00218 | 0.70 | 0.30 | >.99 |
| 2 | 1,200,000 | 1,200,000 | 0.00218 | 0.75 | 0.25 | >.99 |
| 3 | 1,200,000 | 1,200,000 | 0.00218 | 0.80 | 0.20 | >.99 |
| 4 | 1,200,000 | 1,200,000 | 0.00218 | 0.85 | 0.15 | >.99 |
| 5 | 1,200,000 | 1,200,000 | 0.00218 | 0.90 | 0.10 | 0.96 |
| 6 | 1,200,000 | 1,200,000 | 0.00218 | 0.95 | 0.05 | 0.45 |

**age=18-64 outcome=hosp, flutest+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| 7 | 1,200,000 | 1,200,000 | 0.00089 | 0.70 | 0.30 | >.99 |
| 8 | 1,200,000 | 1,200,000 | 0.00089 | 0.75 | 0.25 | >.99 |
| 9 | 1,200,000 | 1,200,000 | 0.00089 | 0.80 | 0.20 | >.99 |
| 10 | 1,200,000 | 1,200,000 | 0.00089 | 0.85 | 0.15 | 0.95 |
| 11 | 1,200,000 | 1,200,000 | 0.00089 | 0.90 | 0.10 | 0.66 |
| 12 | 1,200,000 | 1,200,000 | 0.00089 | 0.95 | 0.05 | 0.22 |

**Power of 3-yr study comparing FluBlok v Comparators**
**Power to detect relative VE against 5 types of outcome events**
**By age group (or chronic disease status) and outcome**
**2-sided alpha=0.05 (likelihood ratio chi-sq test for superiority)**
**800,000 vaccinees expected per yr: 400K fluBlok v. 400K comparators**

**age=18-49 outcome=flu, test+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **13** | 680,301 | 680,301 | 0.00229 | 0.70 | 0.30 | >.99 |
| **14** | 680,301 | 680,301 | 0.00229 | 0.75 | 0.25 | >.99 |
| **15** | 680,301 | 680,301 | 0.00229 | 0.80 | 0.20 | >.99 |
| **16** | 680,301 | 680,301 | 0.00229 | 0.85 | 0.15 | >.99 |
| **17** | 680,301 | 680,301 | 0.00229 | 0.90 | 0.10 | 0.82 |
| **18** | 680,301 | 680,301 | 0.00229 | 0.95 | 0.05 | 0.29 |

**age=18-49 outcome=hosp, flutest+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **19** | 680,301 | 680,301 | 0.00065 | 0.70 | 0.30 | >.99 |
| **20** | 680,301 | 680,301 | 0.00065 | 0.75 | 0.25 | 0.98 |
| **21** | 680,301 | 680,301 | 0.00065 | 0.80 | 0.20 | 0.88 |
| **22** | 680,301 | 680,301 | 0.00065 | 0.85 | 0.15 | 0.64 |
| **23** | 680,301 | 680,301 | 0.00065 | 0.90 | 0.10 | 0.33 |
| **24** | 680,301 | 680,301 | 0.00065 | 0.95 | 0.05 | 0.12 |

**Power of 3-yr study comparing FluBlok v Comparators**
**Power to detect relative VE against 5 types of outcome events**
**By age group (or chronic disease status) and outcome**
**2-sided alpha=0.05 (likelihood ratio chi-sq test for superiority)**
**800,000 vaccinees expected per yr: 400K fluBlok v. 400K comparators**

**age=50-64 outcome=flu, test+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **25** | 519,699 | 519,699 | 0.00205 | 0.70 | 0.30 | >.99 |
| **26** | 519,699 | 519,699 | 0.00205 | 0.75 | 0.25 | >.99 |
| **27** | 519,699 | 519,699 | 0.00205 | 0.80 | 0.20 | >.99 |
| **28** | 519,699 | 519,699 | 0.00205 | 0.85 | 0.15 | 0.95 |
| **29** | 519,699 | 519,699 | 0.00205 | 0.90 | 0.10 | 0.66 |
| **30** | 519,699 | 519,699 | 0.00205 | 0.95 | 0.05 | 0.22 |

**age=50-64 outcome=hosp, flutest+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **31** | 519,699 | 519,699 | 0.00120 | 0.70 | 0.30 | >.99 |
| **32** | 519,699 | 519,699 | 0.00120 | 0.75 | 0.25 | >.99 |
| **33** | 519,699 | 519,699 | 0.00120 | 0.80 | 0.20 | 0.96 |
| **34** | 519,699 | 519,699 | 0.00120 | 0.85 | 0.15 | 0.79 |
| **35** | 519,699 | 519,699 | 0.00120 | 0.90 | 0.10 | 0.44 |
| **36** | 519,699 | 519,699 | 0.00120 | 0.95 | 0.05 | 0.15 |

**age=50-64 outcome=PneumoniaHosp,Dec-March**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **37** | 519,699 | 519,699 | 0.00248 | 0.70 | 0.30 | >.99 |
| **38** | 519,699 | 519,699 | 0.00248 | 0.75 | 0.25 | >.99 |
| **39** | 519,699 | 519,699 | 0.00248 | 0.80 | 0.20 | >.99 |
| **40** | 519,699 | 519,699 | 0.00248 | 0.85 | 0.15 | 0.98 |
| **41** | 519,699 | 519,699 | 0.00248 | 0.90 | 0.10 | 0.74 |
| **42** | 519,699 | 519,699 | 0.00248 | 0.95 | 0.05 | 0.25 |

**Power of 3-yr study comparing FluBlok v Comparators**
**Power to detect relative VE against 5 types of outcome events**
**By age group (or chronic disease status) and outcome**
**2-sided alpha=0.05 (likelihood ratio chi-sq test for superiority)**
**800,000 vaccinees expected per yr: 400K fluBlok v. 400K comparators**

**age=50-64 outcome=CVD hosp, Dec-March**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **43** | 519,699 | 519,699 | 0.00620 | 0.70 | 0.30 | >.99 |
| **44** | 519,699 | 519,699 | 0.00620 | 0.75 | 0.25 | >.99 |
| **45** | 519,699 | 519,699 | 0.00620 | 0.80 | 0.20 | >.99 |
| **46** | 519,699 | 519,699 | 0.00620 | 0.85 | 0.15 | >.99 |
| **47** | 519,699 | 519,699 | 0.00620 | 0.90 | 0.10 | 0.99 |
| **48** | 519,699 | 519,699 | 0.00620 | 0.95 | 0.05 | 0.53 |

**age=50-64 outcome=all hosp, Dec-March**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **49** | 519,699 | 519,699 | 0.05000 | 0.70 | 0.30 | >.99 |
| **50** | 519,699 | 519,699 | 0.05000 | 0.75 | 0.25 | >.99 |
| **51** | 519,699 | 519,699 | 0.05000 | 0.80 | 0.20 | >.99 |
| **52** | 519,699 | 519,699 | 0.05000 | 0.85 | 0.15 | >.99 |
| **53** | 519,699 | 519,699 | 0.05000 | 0.90 | 0.10 | >.99 |
| **54** | 519,699 | 519,699 | 0.05000 | 0.95 | 0.05 | >.99 |

**Power of 3-yr study comparing FluBlok v Comparators**
**Power to detect relative VE against 5 types of outcome events**
**By age group (or chronic disease status) and outcome**
**2-sided alpha=0.05 (likelihood ratio chi-sq test for superiority)**
**800,000 vaccinees expected per yr: 400K fluBlok v. 400K comparators**

**age=ChronicDis,50-64 outcome=flu, test+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **55** | 103,940 | 103,940 | 0.00286 | 0.70 | 0.30 | 0.98 |
| **56** | 103,940 | 103,940 | 0.00286 | 0.75 | 0.25 | 0.9 |
| **57** | 103,940 | 103,940 | 0.00286 | 0.80 | 0.20 | 0.73 |
| **58** | 103,940 | 103,940 | 0.00286 | 0.85 | 0.15 | 0.48 |
| **59** | 103,940 | 103,940 | 0.00286 | 0.90 | 0.10 | 0.24 |
| **60** | 103,940 | 103,940 | 0.00286 | 0.95 | 0.05 | 0.09 |

**age=ChronicDis,50-64 outcome=hosp, flutest+**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **61** | 103,940 | 103,940 | 0.00200 | 0.70 | 0.30 | 0.91 |
| **62** | 103,940 | 103,940 | 0.00200 | 0.75 | 0.25 | 0.78 |
| **63** | 103,940 | 103,940 | 0.00200 | 0.80 | 0.20 | 0.58 |
| **64** | 103,940 | 103,940 | 0.00200 | 0.85 | 0.15 | 0.36 |
| **65** | 103,940 | 103,940 | 0.00200 | 0.90 | 0.10 | 0.18 |
| **66** | 103,940 | 103,940 | 0.00200 | 0.95 | 0.05 | 0.08 |

**age=ChronicDis,50-64 outcome=PneumoniaHosp,Dec-March**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **67** | 103,940 | 103,940 | 0.00744 | 0.70 | 0.30 | >.99 |
| **68** | 103,940 | 103,940 | 0.00744 | 0.75 | 0.25 | >.99 |
| **69** | 103,940 | 103,940 | 0.00744 | 0.80 | 0.20 | 0.99 |
| **70** | 103,940 | 103,940 | 0.00744 | 0.85 | 0.15 | 0.87 |
| **71** | 103,940 | 103,940 | 0.00744 | 0.90 | 0.10 | 0.53 |
| **72** | 103,940 | 103,940 | 0.00744 | 0.95 | 0.05 | 0.17 |

## Power of 3-yr study comparing FluBlok v Comparators
## Power to detect relative VE against 5 types of outcome events
## By age group (or chronic disease status) and outcome
## 2-sided alpha=0.05 (likelihood ratio chi-sq test for superiority)
## 800,000 vaccinees expected per yr: 400K fluBlok v. 400K comparators

**age=ChronicDis,50-64 outcome=CVD hosp, Dec-March**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **73** | 103,940 | 103,940 | 0.01860 | 0.70 | 0.30 | >.99 |
| **74** | 103,940 | 103,940 | 0.01860 | 0.75 | 0.25 | >.99 |
| **75** | 103,940 | 103,940 | 0.01860 | 0.80 | 0.20 | >.99 |
| **76** | 103,940 | 103,940 | 0.01860 | 0.85 | 0.15 | >.99 |
| **77** | 103,940 | 103,940 | 0.01860 | 0.90 | 0.10 | 0.9 |
| **78** | 103,940 | 103,940 | 0.01860 | 0.95 | 0.05 | 0.36 |

**age=ChronicDis,50-64 outcome=all hosp, Dec-March**

| row | N expectd 3 yrs FluBlok | N expectd 3 yrs Comprtr | proportion of comparators who have the outcome | RR = 1 minus relative VE | Relative VE: % of breakthru cases prevented | Power (prob. of rejecting Ho if rel_VE is true) |
|---|---|---|---|---|---|---|
| **79** | 103,940 | 103,940 | 0.10000 | 0.70 | 0.30 | >.99 |
| **80** | 103,940 | 103,940 | 0.10000 | 0.75 | 0.25 | >.99 |
| **81** | 103,940 | 103,940 | 0.10000 | 0.80 | 0.20 | >.99 |
| **82** | 103,940 | 103,940 | 0.10000 | 0.85 | 0.15 | >.99 |
| **83** | 103,940 | 103,940 | 0.10000 | 0.90 | 0.10 | >.99 |
| **84** | 103,940 | 103,940 | 0.10000 | 0.95 | 0.05 | 0.97 |