# EIRB Protocol Template (Version 1.30)

## 1.0 General Information

***Please enter the full title of your study:**

IDCRP-120 A Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED)

***Please enter the Protocol Number you would like to use to reference the protocol:**

IDCRP-120 (v13.0, eIRB 1.30, 13DEC2022)
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

**Is this a multi-site study (i.e. Each site has their own Principal Investigator)?**

Yes

**Does this protocol involve the use of animals?**

○ Yes ◉ No

## 2.0 Add Site(s)

**2.1 List sites associated with this study:**

| Primary Dept? | Department Name |
|---|---|
| ◉ | **R and E** - Uniformed Services University of the Health Sciences (USUHS) |

## 3.0 Assign project personnel access to the project

**3.1 *Please add a Principal Investigator for the study:**

BURGESS, TIMOTHY H, MD, MPH

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

**3.2 If applicable, please select the Research Staff personnel:**

A) Additional Investigators

AGAN, BRIAN K, MD
Associate Investigator
Collins, Limone C
Associate Investigator

Pollett, Simon David
Associate Investigator
Simons, Mark Paul, PhD, MSPH CDR
Associate Investigator
Williams, Alan LEWIS, MD
Associate Investigator

B) Research Support Staff

Becher, Dorothy Ann
Research Coordinator
Chapo, Elisa Wago
Research Coordinator
Fritschlanski, Mark Robert
Research Coordinator
Kosh, Lakeesha Jenielle
Research Coordinator
Nevo, Lev N/A, M.D.
Research Coordinator
Shaikh, Saira Yousaf
Research Coordinator
Spevak, Marianne V, BSHS
Team Member

**3.3 *Please add a Protocol Contact:**

BURGESS, TIMOTHY H, MD, MPH
Becher, Dorothy Ann
Chapo, Elisa Wago
Collins, Limone C
Fritschlanski, Mark Robert
Kosh, Lakeesha Jenielle
Nevo, Lev N/A, M.D.
Shaikh, Saira Yousaf

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

**3.4 If applicable, please select the Designated Site Approval(s):**

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

## 4.0 Project Information

**4.1 Is this a research study?**

(•) Yes ( ) No

**4.2 What type of research is this?**

- [x] Biomedical Research
- [ ] Clinical trial (FDA regulated)
- [ ] Behavioral Research
- [ ] Educational Research
- [ ] Psychosocial Research
- [ ] Oral History
- [x] Other

Describe other:

Randomized open-label trial of FDA-licensed influenza vaccines.

**4.3 Are you conducting this project in pursuit of a personal degree?**

- ○ Yes
- ◉ No

**4.5 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?**

- ◉ Yes
- ○ No

**4.6 Do you believe this human subjects research is exempt from IRB review?**

- ○ Yes
- ◉ No

## 5.0 Personnel Details

**5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:**

| Name: (Last, First, M.I.) | Phone Number: | Email Address: | Associated Institution: |
|---|---|---|---|
| Fries, Anthony<br>Role on Protocol: Associate Investigator | 937-938-2847 | anthony.fries.ctr@us.af.mil | USAFSAM |
| Name: (Last, First, M.I.)<br>Macias, Elizabeth<br>Role on Protocol: Associate Investigator | Phone Number:<br>937-938-3175 | Email Address:<br>elizabeth.macias@us.af.mil | Associated Institution:<br>USAFSAM |
| Name: (Last, First, M.I.) | | | |

| | | | |
|---|---|---|---|
| Seshadri, Srihari<br>Role on Protocol:<br>Associate Investigator | Phone Number:<br>703-681-5709 | Email Address:<br>srihari.seshadri.civ@mail.mil | Associated Institution:<br>IHB |
| Name:<br>(Last, First, M.I.)<br>Sheeler, Cindee<br>Role on Protocol:<br>Administrator | Phone Number:<br>301-816-8436 | Email Address:<br>csheeler@idcrp.org | Associated Institution:<br>IDCRP |
| Name:<br>(Last, First, M.I.)<br>Bowers , Renee<br>Role on Protocol:<br>Administrator | Phone Number:<br>301-816-8458 | Email Address:<br>rbowers@idcrp.org | Associated Institution:<br>IDCRP |
| Name:<br>(Last, First, M.I.)<br>Richard, Stephanie<br>Role on Protocol:<br>Epidemiologist | Phone Number:<br>301-816-8429 | Email Address:<br>srichard@idcrp.org | Associated Institution:<br>IDCRP |
| Name:<br>(Last, First, M.I.)<br>Waickman, Adam<br>Role on Protocol:<br>Associate Investigator | Phone Number:<br>315-464-7653 | Email Address:<br>waickmaa@upstate.edu | Associated Institution:<br>SUNY Upstate Medical University |
| Name:<br>(Last, First, M.I.)<br>Williams, Maya<br>Role on Protocol:<br>Infectious Disease Directorate | Phone Number:<br>301-319-7446 | Email Address:<br>maya.williams1.mil@mail. | Associated Institution:<br>NMRC |
| Name:<br>(Last, First, M.I.)<br>Memoli, Matthew<br>Role on Protocol: | Phone Number:<br>301-443-5971 | Email Address:<br>memolim@niaid.nih.gov | Associated Institution:<br>NIAID |

| | | | |
|---|---|---|---|
| Site Investigator | | | |
| Name:<br>(Last, First, M.I.)<br>Sundaram, Appuv<br>Role on Protocol:<br>Senior Scientist | Phone Number:<br>301-319-7199 | Email Address:<br>appavu.k.sundaram.ctr@mail.mil | Associated Institution:<br>NMRC |
| Name:<br>(Last, First, M.I.)<br>Ewing, Daniel<br>Role on Protocol:<br>Lead Investigator | Phone Number:<br>301-319-9017 | Email Address:<br>Daniel.f.ewing.civ@mail.mil | Associated Institution:<br>Lead Investigator |
| Name:<br>(Last, First, M.I.)<br>Currier, Jeffrey<br>Role on Protocol:<br>Collaborator | Phone Number:<br>240-994-3911 | Email Address:<br>jeffrey.r.currier.civ@health.mil | Associated Institution:<br>Walter Reed Army Institute of Research (WRAIR) |
| Name:<br>(Last, First, M.I.)<br>Friberg-Robertson, Heather<br>Role on Protocol:<br>Collaborator | Phone Number:<br>301-319-9224 | Email Address:<br>heather.l.friberg-robertson.civ@health.mil | Associated Institution:<br>Walter Reed Army Institute of Research (WRAIR) |

**5.2** **Will you have a Research Monitor for this study?**

- ○ Yes
- ◉ No
- ○ N/A

Research Monitor Role:

If applicable, you may nominate an individual to serve as the Research Monitor:

No Users have been selected.

## 6.0 Data/Specimens

**6.1 Does the study involve the use of existing data or specimens only (no interaction with human**

**subjects)?**

○ Yes ◉ No

## 7.0 Funding and Disclosures

**7.1 Source of Funding:**

| Funding Source | Funding Type | Amount |
|---|---|---|
| DHP | : Operations and Maintenance (O&M)<br>HU00012020082 | 2722000 |

Total amount of funding:

2722000

**7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?**

○ Yes ◉ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

## 8.0 Study Locations

**8.1 Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study?**

○ Yes ◉ No

| IRB Name | Review Date | Determination |
|---|---|---|
| No records have been added | | |

**8.2 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)**

◉ Yes ○ No

**8.3 Study Facilities and Locations:**

| Institution | Site Name | Site Role | FWA or DoD Assurance Number | Assurance Expiration Date | Is there an agreement? | IRB Reviewing for Site |
|---|---|---|---|---|---|---|
| Navy | Naval Health Research Center | Laboratory analyses | FWA00013516 | 11/16/2025 | : IAIR | : USUHS IRB #1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Air Force | USAFSAM | Laboratory analyses | FWA00000609 | 08/29/2023 | : IAIR | : USUHS IRB #1 |
| Navy | Navy Medical Research Center | Laboratory analyses | FWA00000152 | 06/05/2024 | : IAIR | : USUHS IRB #1 |
| Army | Walter Reed Army of Institure Research | Laboratory analyses | FWA00000015 | 11/20/2023 | : Other | : USUHS IRB #1 |
| | Johns Hopkins University | Laboratory analyses | FWA00005752 | 10/01/2023 | : Other | : USUHS IRB #1 |
| | | | | | | |

Other:

| Other Institution Site | Site Role | FWA or DoD Assurance Number | FWA or DoD Expiration Date | Is there an agreement? | IRB Reviewing for Site |
|---|---|---|---|---|---|
| No records have been added | | | | | |

**8.4 Are there international sites?**

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

**8.5 Is this an OCONUS (Outside Continental United States) study?**

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

## 9.0 Study Details

**9.1 Abstract/ Summary:**

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

This four-year, pragmatic, prospective study will compare the effectiveness of the licensed egg-based inactivated influenza vaccine to the effectiveness of two other types of licensed vaccines, the cell-

culture based inactivated influenza vaccine and the recombinant influenza vaccine, in the prevention of laboratory-confirmed influenza infection in active duty members, military retirees, and other DoD beneficiaries.

Enrollment will be restricted to adults 18 years of age and older who are preparing to receive seasonal influenza vaccination at participating DoD sites. Subjects will receive one of the three licensed influenza vaccines types for evaluation of effectiveness. There is no exclusion for pregnancy, as none of these licensed products are contraindicated in pregnant women.

A total of 18,000 eligible subjects will be block randomized in 1:1:1 (cell-culture-based vaccine, the recombinant vaccine, or the egg-based vaccine) over four influenza seasons (2018-2019, 2019-2020, 2020-2021, 2021-2022).

During the enrollment period subjects may opt-in or opt-out of a buccal swab and a same-day and post-vaccination self-collected blood sample.

Subjects who experience acute influenza-like illness symptoms during surveillance will be asked to complete a brief (5 min) online FLUPRO symptom severity questionnaire daily for 7 days. Additionally, subjects will complete an acute and a convalescent visit; these visits may be completed in person or virtually.

Those who choose to have an in-person acute visit will have either a self-collected Mitra kit or an intravenous blood draw (subject's choice), and two nasal swabs (one self-collected, one collected by study staff). The convalescent in-person visit procedures will consist of either a self-collected Mitra kit or an intravenous blood draw (subject's choice- preferably, consistent with the first visit).

Those who choose virtual visits will self-collect a nasal swab and a Mitra kit blood sample and send then to the appropriate location. At the convalescent visit, subjects will self-collect and send in a Mitra kit blood sample.

At the first ILI visit study coordinators will record ILI history, hospitalizations status, and work days lost. At the second ILI visit during the convalescent phase of llness, coordinators will collect updated information on hospitalization status and work absences. This information will be collected at both the in-person and virtual visits.

All subjects will also be asked for permission to review their recorded medical encounters in order to ascertain whether they sought care for influenza-like illness. The test results will be for research purposes and will not be used to guide case management.

Immunogenicity substudy: Up to 1200 subjects (approximately 400/arm) from the main study will be enrolled in a vaccine immunogenicity substudy. Substudy participants will have blood drawn up to 30 days prior to vaccination and then approximately one month post-vaccination in order to compare the effect of the vaccines on humoral and cellular immune responses.

End of study self-collected Mitra kit: Approximately 1,000 subjects who develop an ILI will be asked to collect and send in a self-collected Mitra blood kit. These individuals will be selected from the groups who completed the substudy or the same-day/post-vaccination blood sampling.

Study Period: Oct 2018 – Sep 2023
• Enrollment: Oct 2018 –Dec 2018, Sep 2019- Jan 2020, Sep 2020-Jan 2021, Sep 2021- Jan 2022
• Influenza-like illness (ILI) surveillance: Oct 2018 – May 2019, Sep 2019 – May 2020, Sep 2020-May 2021, Sep 2021-May 2022
• Analysis/Interpretation: May 2019 - Sep 2023

**9.2 Key Words:**

Provide up to 5 key words that identify the broad topic(s) of your study

influenza, vaccine, effectiveness, immunogenicity, antibody

**9.3 Background and Significance:**

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

**9.3.1 Influenza Vaccine Effectiveness**

Globally, seasonal influenza epidemics cause three to five million severe cases and 300,000 to 500,000 deaths annually according to the World Health Organization (1). A century after the 1918 pandemic, influenza remains a leading cause of morbidity and a major threat to operational readiness in the United States Armed Forces. More than 90% of active duty personnel in the US receive influenza vaccinations annually (2)(Midterm vaccine effectiveness VRBPAC report - appendix #1). Despite high coverage, influenza-like illness frequently leads to clinical visits, missed duty days and hospitalizations. Findings from a recent study conducted by the Armed Forces Health Surveillance Branch(AFHSB) show that the number of incident hospitalizations for pneumonia and influenza averaged 1000 cases per year for active duty personnel between 2000 and 2012 (3). Influenza alone accounted for nearly 14,000 days in hospital and 95,000 lost-duty days between 2011 and 2013 (4). The current 2017-2018 influenza season, with A(H3N2) as the predominate subtype, appears to be the worst in a decade. Infection rates for rivaled those of the 2009 H1N1 influenza pandemic (5). The overall percentage of influenza-positive respiratory specimens from active duty members and military beneficiaries is 17.4% and 25.6%, figures that highlight the significant burden of influenza in this population (6).

Seasonal strain-specific vaccination remains the foundation of influenza prevention and control. The effectiveness of seasonal influenza vaccines varies considerably by season and has generally been higher against influenza A(H1N1) pdm09 and B viruses than against A (H3N2) viruses, even when well-matched with circulating strains (7). The overall vaccine efficacy (VE) is estimated to be 19% in armed forces personnel, despite 90% vaccination coverage, while the overall VE is 51% in military beneficiaries assuming vaccine coverage of approximately 40% (2). In contrast, mid-season estimates of overall adjusted VE against influenza associated with medically attended acute respiratory infections the general United States population is 36% (8). The reasons for the disparities in VE are not yet known.

There are multiple factors that may contribute to suboptimal influenza vaccine effectiveness. These include prior influenza exposure and vaccination history could influence subsequent responses to seasonal influenza vaccines. Furthermore, host factors such as age and coexisting conditions affect vaccine effectiveness (1, 7). It may also be due the timing of vaccination, vaccine failure, or some other undetermined factors related to transmission or virulence of influenza in this population. Another factor that may alter the effectiveness of influenza vaccines is the substrate used to produce them. In the United States, most influenza-vaccine viruses are propagated in eggs, although some are produced either in cell culture or by a recombinant protein expression system. Residue changes in the vaccine virus hemagglutinin protein, the antigen responsible for virus attachment and a target of neutralizing antibodies that arise during passage in eggs have been suggested to confer antigenic differences that may result in decreased vaccine effectiveness in specific circumstances (9, 10). Additional studies are needed to assess whether VE against circulating influenza viruses vary by vaccine formulation, including comparisons between egg-based and non-egg-based vaccines.

**9.3.2 Immune Responses to Seasonal Influenza Vaccines**

Antigenic relatedness (match) between vaccine and circulating virus strains greatly affects influenza vaccine effectiveness. Determining which strains to include in new vaccines requires global coordination among organizations that provide i) surveillance of circulating influenza strains, ii) antigenic analyses of emerging strains in comparison to vaccine viruses, and iii) evaluation of human post-vaccination antibody responses to determine whether antibodies are reactive with recent virus isolates. The latter analysis requires panels of sera drawn from subjects up to 30 days before and 21-35 days after influenza vaccination.

Egg-adaptive mutations in vaccine strains used to formulate past influenza vaccines may have reduced VE by altering antigenicity (3) and immunogenicity (4). Influenza viruses that are isolated in cells and used for vaccine manufacture have the potential to overcome this problem. Until the current 2017-2018 influenza season, the Madin-Darby canine kidney (MDCK)-cell-culture based inactivated influenza vaccine, Flucelvax, used egg-based viruses as seeds. This year, Flucelvax used a wild type, cell-culture based virus as its H3N2 vaccine seed and did not contain egg-adaptive mutations. The effect of this change on vaccine immunogenicity and antibody reactivity is currently unknown. Similarly, the recombinant HA influenza vaccine, FluBlok, does not use egg-adapted viruses. Therefore, we are now in a good position to compare how these egg-adaptive mutations affect antibody responses and HI and neutralization titers to matched- and mismatched-vaccine strains. Sera collected from individuals vaccinated with egg-based and cell-culture-based influenza vaccines provide the opportunity to compare the potential effectiveness of these vaccines against circulating viruses.

Due to a lack of appropriate sera panels, there is currently insufficient information on whether the cell-culture-based influenza vaccines that lack egg-adaptive mutations induce antibodies that react more broadly with circulating strains than egg-based influenza vaccines. Therefore, sera panels from individuals vaccinated with different influenza vaccine formulations are needed to aid antigenic analyses of all vaccine formulations. As a secondary objective, we propose to collect pre- and post-immunization sera from subjects at DoD clinics who have received either egg- or cell-culture -based influenza vaccines to investigate potential differences in antibody responses to these vaccines types.

**9.3.3 Scientific Merit**

We propose to conduct a prospective study to compare immune responses and effectiveness of immunization to prevent influenza acquisition in DEERS-eligible adults (≥18 years and older) receiving egg-based, cell-culture-based, or recombinant inactivated influenza vaccines. This study will be conducted at selected military treatment facilities in a well-described military population comprised of individuals with both high (active duty personnel) and moderate (military retirees/beneficiaries) vaccination coverage. The study results would provide new and important information on the immune responses and vaccine effectiveness by vaccine formulation. Publication in a high impact journal is likely as this information may have important influenza vaccination policy implications for both the military and the US population at large. The immunogenicity data may inform the development of effective universal influenza vaccines.

## 9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions /hypotheses

***Primary Aim:***

*Specific Aim #1: Comparison of the relative effectiveness (prevention of laboratory-confirmed influenza illness) of three types of licensed seasonal influenza vaccines.*

*Research Question*: Is either the cell-culture based vaccine or the recombinant vaccine more effective than egg-based vaccine?
There are two hypotheses of interest based on influenza attack rates (AR):

Assuming relative VE of 30% => $1 - AR_1/AR_{egg} = 0.3$

Therefore $1 - 0.3 = AR_1/AR_{egg} = RR$ therefore $0.7 = AR_1/AR_{egg} = RR$ ($AR_1$=attack rate in either cell-culture based or recombinant vaccine)

*Ho: RR=1 vs HA: RR< 1; p=0.025;*
*The RR to be tested is defined as: 1) RR1=ARcell / ARegg and 2) RR2=ARrecombinant / ARegg*

***Endpoint:***

Influenza attack rates in the egg-based, cell-culture-based, and recombinant protein influenza vaccines arms of the study in the 2018-2019, 2019-2020, 2020-2021, and 2021-2022 seasons.

**Secondary Aim**

*Specific Aim #2: (Immunogenicity substudy) Determine whether cell-culture-based, egg-based and recombinant influenza vaccines give comparable HI and PVN titers to egg- and cell-matched vaccine antigens. An outcome of this objective is the potential to determine whether cell-*culture*-based vaccine antigens can provide broader coverage of circulating viruses than egg-based vaccine antigens.*
Research Question: Is the proportion of subjects who seroconvert in either the cell-culture based or recombinant vaccine arm of the study greater in the either that in the egg-based vaccine arm of the study?
*There are two hypotheses of interest for Specific Aim 2, based on the seroconversion rates (SCR)*
*$H_0$: RR=1 vs $H_A$: RR>1; p=0.025;*
*The RR to be tested is defined as: 1) RR1=SCRcell / SCRegg and 2) RR2=SCRrecombinant / SCRegg*

**Endpoints:**

- Humoral responses: HAI titer, anti-NA titer, virus-neutralizing titer
- Cellular responses (exploratory): frequency of antigen-specific CD4 and CD8 cells, B cells

SA 2.1: To obtain post-vaccination sera panels to determine breadth of reactivity to circulating strains.

SA 2.2: To identify individuals who responded to H1N1, H3N2, B/Victoria and B/Yamagata vaccine components.

SA 2.3: To evaluate differences in serum reactivity between egg-, cell-culture-based and recombinant antigens.

SA 2.4: Compare the breadth of the antibody response elicited by egg, cell-culture-based and recombinant vaccines to circulating strains.

SA 2.5: To examine the breadth of reactivity against past strains

**Exploratory Aims**

*Specific Aim #3: To determine if the impact of the influenza vaccine on disease burden and the attributable healthcare costs differs by product type.*
Influenza-like Illness (ILI) case definition: ILI will be defined as:

- Cough or sore throat AND
- Feverish/chills OR Muscle/body aches or fatigue

***Endpoints***

- Incidence of PCR-confirmed influenza cases
- Frequency of influenza-confirmed hospitalization
- Frequency of influenza-like illness
- Work days lost due to influenza
- Work days lost due to influenza-like illness
- Healthcare costs/utilization attributable to influenza
- Healthcare cost/utilization attributable to influenza-like illness

*Specific Aim #4: To evaluate the association host single nucleotide polymorphisms (SNPs) and immune responses to the influenza vaccine, influenza acquisition and influenza severity*

- Frequency of SNPs by influenza status and by influenza severity
- Frequency of SNPs by geometric mean titer (GMT) cutoff
- Frequency of SNPs by mean fold rise (MFR) cutoff
- Frequency of SNPs by influenza status
- Frequency of SNPs by influenza severity classification

**Tertiary Aim**
Specific Aim #5 Assess the burden of COVID-19 and explore the inter-relationship between influenza and COVID-19
Research questions: What is the burden of COVID-19 in the PAIVED cohort? What is the burden of co-infection with influenza and COVID-19 and how does it impact the severity of infection when compared with influenza-only or COVID-19-only infection? Which symptoms differentiate COVID-19 from influenza?
Endpoints:

- Incidence of COVID-19, incidence of co-infection with influenza
- Severity of COVID-19, symptoms associated with COVID-19 infection (compared with influenza, other respiratory viruses)

**9.5 Study Design:**

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled,

cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This pragmatic, prospective study will assess the relative effectiveness of the licensed egg-based inactivated influenza vaccine to the effectiveness of two other licensed vaccines, the cell-culture-based inactivated influenza vaccine and the recombinant influenza vaccine, in the prevention of laboratory-confirmed influenza infection in active duty members, military retirees and beneficiaries over four consecutive influenza seasons. Subject recruitment will take place at military treatment facilities (MTFs). Subjects will be adults ≥ 18 years old who are DEERS-eligible for care in the MHS. At enrollment, following the provision of informed consent, study staff will collect data on subject demographics and medical history (co-morbidities, history of influenza, and history of influenza vaccination). In contrast to standard practice, where vaccine selection is guided by individual preference or vaccine availability, study subjects will be randomly allocated by study investigative team to receive one of the three types of vaccine.

All subjects will be give the option to participate in a buccal swab collection for host genomic studies during the enrollment period. Subjects participating in the immunogenicity substudy will have their blood drawn up to 30 days prior to influenza vaccination and again at day 21-35 post-vaccination to assess changes in immune responses to the vaccines. Those not participating in the substudy may opt in to have blood collected on the day of vaccination and post-vaccination using a Mitra device.

Subjects will undergo surveillance for influenza-like illness (ILI) during the influenza season, beginning 4 weeks post-vaccination and ending when nationwide influezna activity has returned to baseline (typically at the end of May). During this period, automated weekly email or text messages will be sent to subjects asking them if they have experienced ILI symptoms in the past 7 days. Subjects who meet the ILI case definition will be asked to complete an online 7-day symptom severity questionnaire and to schedule an ILI acute and convalescent virtual visit with a study coordinator, ascertain a self-collected nasal swab and self-collected blood samples. At the acute ILI virtual visit study coordinators will record subjects ILI history, hospitalization status, and work absences. The convalescent virtual ILI visit will take place approximately 28 days after answering "yes" to the surveillance survey (trigger"). Information on hospitalization status, and work absences will be updated at this visit.

Subjects will be monitored through as many ILI episodes as they experience, though subjects will only be compensated for the first 3 episodes. ILI episodes must be separated by at least 30 days. Information on ILI health care utilization and cost for data will be abstracted from the Military Health System Data Repository (MDR) database by IDCRP study staff at the end of each influenza season.

Up to 18,000 eligible subjects (or 6,000 subjects distributed evenly between the 3 study arms) will be block randomized in 1:1:1 (cell-culture-based vaccine, the recombinant vaccine, or the egg-based vaccine).

**The study will compare the effectiveness of three types of FDA-licensed influenza vaccines used in DoD populations to prevent influenza acquisition. The vaccines are listed below:**

- Licensed cell culture-based influenza vaccine:
  - Flucelvax Quadrivalent (Seqirus) (15µg HA/strain)
- Licensed recombinant vaccines:
  - Flublok Quadrivalent (Protein Sciences) (45µg HA/strain)
- Licensed egg-culture based influenza vaccines:
  - Fluarix Quadrivalent (GlaxoSmithKline) 15µg HA/strain
    *OR*
  - FluLaval Quadrivalent (ID Biomedical Corp. of Quebec) 15µg HA/strain
    *OR*
  - Afluria Quadrivalent (Seqirus) 15µg HA/strain

*Randomization Process:*
Eligible subjects at each site will be randomized to receive a single dose of cell culture-based vaccine versus recombinant vaccine versus one of three standard dose egg-based vaccines.

Subjects will be randomized in a 1:1:1 ratio to one of 3 vaccine formulations offered. Block randomization will be used in order to reduce bias and achieve balance in the allocation of subjects to treatment arms. An IDCRP biostatistician not involved in the study will generate a series of randomization vaccine codes. The roster for each site will be sent to the study staff, who, after enrolling the subject, will use the list to determine which vaccine each subject will receive. The vaccine allocations will be made sequentially using the roster.

### 9.6 Target Population:

Describe the population to whom the study findings will be generalized

U.S. military active duty members, midshipman, recruits, retirees, students, and their adult beneficiaries, along with U.S. adult population.

### 9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

If there are significant differences in either the immunogenicity or effectiveness between vaccines, influenza vaccination policy in the U.S. military may change to provide better protection against influenza. Conversely, if the differences in immunogenicity or vaccine effectiveness are minimal, the current immunization recommendations should not change. This study has the potential to provide high visibility to military infectious disease research, given the importance and global relevance of the research question being addressed

## 10.0 Study Procedures, Data Management, and Privacy

### 10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Receipt of egg-based, cell-culture-based, or recombinant influenza vaccination is a requirement for study participation. All study assessments will be performed by members of the investigative team who are specifically designated to perform such activities in a clinical setting (according to site practices, local law, and as designated on the appropriate study documents). Study procedures will be performed in a clinical setting at participating MTFs (e.g., immunization clinic) or other clinical setting where vaccines are being administered in accordance with each site's vaccination policy.

**Detailed Description of Assessments**

**Study Timeline**

| Study Day/Follow-up Interval | ***Pre-Vax*** | **Baseline** | **Post-Vax** | **Surveillance** | **ILI** | |
|---|---|---|---|---|---|---|
| | *Day -30 to 0* | Day 0 | Day 21-35 | Weekly (throughout the flu season) | ILI Visit 1 | ILI-Day 28±7 from trigger date |
| Eligibility assessment | ***Research*** | Research | | | | |
| Informed Consent & HIPAA Authorization | ***Research*** | Research | | | | |
| Randomization | | Research | | | | |
| Vaccination | | Standard of Care | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Demographics, enrollee interview, medical history (comorbidity/chronic diseases, influenza vaccination history, influenza history) | ***Research*** | Research | | | |
| Blood sample | ***Research*** (Substudy Only) | Research (Optional same-day Mitra) | ***Research*** (Only for substudy and optional post-vax Mitra) | Research | Research |
| Cheek cell (Buccal) swab (opt in) | | Research-optional | | | |
| Acute ILI Surveillance | | | | Research | |
| FLU-PRO 7-day Symptom Severity Survey via email | | | | Research | |
| Nasal specimen (self collection ) | | | | Research | |
| ILI history (IH) | | | | Research | |
| Hospitalization (status, duration) and other AEs | | | | Research | Research |
| Duty/work days lost related to ILI episode (RW) | | | | Research | Research |

Medical history/demographic interview may occur prior to or following randomization/vaccination

**Enrollment: Virtual or in-person**
Sites will follow their MTF specific guidelines for consenting. Subjects may enroll in the study through e-consent or paper consent ICDs. E-consent links will be sent out to previous enrolled subjects and the use of through the use of QR codes for those enrolling electronically. Anyone e-enrolling will first complete a e-screening tool that will only allow those who meet the enrollment criteria to be enrolled. Potential subjects will review and sign the ICD with the clinical research coordinator(s) (CRCs) or may email/call study staff with questions, prior to signing an e-consent. Prior to any subject procedure being completed, study staff will confirm the subject signed the e-consent in real-time in REDCap. If REDCap is not available (due to connectivity issues, etc.), the subject will sign a paper copy of the consent with the study staff prior to any subject procedure being completed.

*The following procedures will take place:*

- Administration of informed consent
    - Subject informed consent, and HIPAA authorization, and California Subject's Bill of Rights (if applicable).
    - The clinical research coordinator(s) will review the informed consent document with the subject. The Principal Investigator will review and document compliance of the informed consent document within 30 days of consent.
    - Potential subjects may be given an electronic copy of the informed consent document, educational items, and electronic briefs for review prior to study day 0.
- Contact information (source: patient-completed questionnaire)
- Demographics (source: patient-completed quiestionnaire)
    - age
    - sex
    - weight

    - height
    - ethnicity
    - race
    - DEERS status (active duty, retiree, beneficiary)
    - Military rank (active duty only)
- Subject may opt-in for a same-day and post vaccination self-collected blood sample using a Mitra Device. If they opt-in, their first sample will be taken the same day as their vaccination and their second sample will be taken 14-30 days later. Subjects may be asked to provide an end of study mitra kit.

***Immunogenicity substudy subjects only***
Study Day -30-0

- Venipuncture blood draw (approximately 40 mL)

Study Day 21-35

- Venipuncture blood draw (approximately 40 mL)

***Acute Influenza-like Illness Surveillance***
The main study will rely on the identification/ascertainment of individuals with acute ILI. During the ILI surveillance period, subjects will receive an automated email or text message (via REDCap platform) at 1 week intervals asking them if they have experienced ILI in the preceding 7 days. Subjects will get a reminder email or text 72 hours later and again 24 hours later if they have not responded to the weekly ILI surveillance. Influenza-like Illness (ILI) will be defined as:

- Cough OR sore throat AND
- Feverish/Chills OR Body aches/fatigue

The email or text messages (sent on a weekly basis) will also remind subjects to contact their medical provider should they experience any of the emergency signs described on the CDC's influenza website (**https://www.cdc.gov/h1n1flu/homecare/warningsigns.htm**, (Kellerman AL et al. Web-based self-triage of influenza-like illness during the 2009 H1N1 influenza pandemic. Ann Emerg Med. 2010 Sep;56(3):288-294). They are:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen
- Sudden dizziness
- Confusion
- Severe or persistent vomiting (vomiting that goes on)
- Flu-like symptoms that improve but then return with fever and worse cough

*Collection of ILI symptom presence and severity data for a sequential 7-day period using the FLUPRO questionnaire*

Email or text messages responses from subjects who report symptoms meeting the ILI case definition will trigger an email or text message to a study coordinator, who will then contact the subject to schedule a virtual acute ILI visit. Subjects who respond to the email/text message stating that they are experiencing ILI symptoms will be sent a web link to a 7-day ILI severity questionnaire that will record the severity of ILI symptoms that they experienced in the past 24-72 hours in the online questionnaire. They will also receive daily email/text reminders to enter the symptom severity information for the past 24 hours for each of the remaining six days.

*ILI surveillance in military trainees/recruits*

Internet/email/text message access is not available to military recruits/trainees, and therefore they will not complete the FLUPRO questionnaire should they develop ILI symptoms. As such, at enrollment they will be guided to report to sick call should they develop acute ILI symptoms during the study follow-up period. Study coordinators will be on hand at the appropriate medical clinic to obtain acute ILI Visit Day 1 data and specimen collection. A convalescent ILI visit is not required for military recruits /trainees. **ILI Visits have the option of taking place virtually or in-person**

**VIRTUAL ILI VISIT PROCEDURES**

Acute ILI Visit #1 : visit during an acute phase of ILI episode

S*ubjects who develop ILI symptoms will undergo the following procedures*:

- Self-collected nasal swab specimen.
- Self-collected blood sample (40 µL)
- ILI History
- If hospitalized:
    - ILI hospitalization status
    - Number of days hospitalized (if hospitalized for care)
- Number of work/duty days absent related to ILI episode

**Visit #2- Convalescent Visit (21-35 post trigger): visit during convalescent phase of ILI episode**
*Subjects who develop ILI symptoms will undergo the following procedures:*

- Self- collected blood sample (40 µL)
- If hospitalized
    - ILI  hospitalization status
    - Number of days hospitalized (if hospitalized for care)
- Total number of work/duty days absent related to ILI episode

**IN-PERSON VISIT PROCEDURES**

**Visit #1- Acute ILI Visit**
S*ubjects who develop ILI symptoms will undergo the following procedures*:

- Self-collected nasal swab specimen.
- CRC collected nasal swab specimen
- In-clinic self-collected blood sample (40 µL) or intravenous blood draw (16 mL) (subject's choice)
- ILI History
- If hospitalized
    - ILI hospitalization status
    - Number of days hospitalized (if hospitalized for care)
- Number of work/duty days absent related to ILI episode

**Visit #2- Convalescent Visit (21-35 post trigger)**

In-clinic self-collected blood sample (40 µL) or intravenous blood draw (16 mL) (subject's choice, consistent with the first visit, if possible)

- If hospitalized
    - ILI  hospitalization status
    - Number of days hospitalized (if hospitalized for care)
- Total number of work/duty days absent related to ILI episode

**ILI Healthcare utilization and costs**
Data on health care utilization and costs attributed to ILI episode will be abstracted from the MDR at the end of each influenza season.

**Deviations:**
Missed nasal specimens (in-person and/or self-collected) and self-collected blood samples (in-person and/or self-collected) will be considered protocol deviations

**Collection of the Human Biological Specimens/Specimen processing:**
***Blood:***

- All subjects who develop ILI during the current influenza season will provide specimens as part of the acute ILI visit and convalescent ILI visit  . Recruits/trainees with an ILI will not be required to provide convalescent blood samples. Blood may be collected via venipuncture in clinic (16 mL per timepoint) or with a Mitra kit (40 µL per timepoint).  Up to 16 mL will be collected at each of these visits; up to 96 mL total over the course of follow up.
- Subjects may opt-in for a day of vaccination and post vaccination self-collected blood sample (40 µL per timepoint).
- *Immunogenicity substudy subjects only*: Subjects in the substudy will undergo phlebotomy up to 30 days prior to vaccination and again 21-35 days post-vaccination to assess changes in humoral and cell-mediated immunity in response to influenza vaccination. Approximately 40

mL will be collected at each of these two visits and the end of study self-collected blood sample; approximately 80 mL over the course of the study. A sample of the stored serum samples will be shipped to the FDA CBER, or other partner, laboratories for analysis. Subjects who participate in the substudy will not be selected to provide the optional same-day/post-vax blood samples.

- Approximately 1,000 subjects who report at least one ILI during the surveillance period AND are participating in either the substudy or the day of vaccination/post vaccination blood samples may be asked to complete an end of study mitra kit (40 µL). This is being conducted in order to estimate the influenza seroconversion rate in this population and to evaluate whether we can determine if influenza cases are missed during surveillance.

***Nasal Swabs:***

For virtual appointments, there will be one self-collected nasal swab collected for each ILI case. For in-person visits there will be one self-collected nasal swab and one in-clinic nasal swab for each ILI case. Self-collected nasal (mid-turbinate) swabs are collected once ILI symptoms are identified, through the ILI Surveillance Survey. An additional a in-clinic swab (mid-turbinate) will be taken for subjects who have in-person visits. Labelled specimens will be shipped to Naval Health Research Center (NHRC) or U.S. Air Force School of Aerospace Medicine (USAFSAM). Specimens received at laboratories will be logged into a project database and labeled according to the lab's standard procedures. A link to the Study ID will be maintained. Specimens will be assessed using sensitive molecular detection methods for detection of influenza, as well as other respiratory viruses and bacteria of interest.

***Buccal Swabs:***

Host-Genetic Analysis: One buccal cheek swab will be collected on the day of vaccination from those subjects that opt-in to assess the association between host genetic polymorphisms on respiratory infection acquisition and on immune responses to vaccination.

***Salivary Antibody Evaluation:***

At the US Naval Academy, saliva collected by oral swabs will be evaluated for antibodies to SARS-CoV-2 and other respiratory viruses (e.g. influenza A/B) using multiplex microbead immunology assays. Differences between antibody types and magnitudes between serum and saliva will be evaluated over the duration of study participation. See USNA Site-Specific Protocol for further details.

**10.2 Data Collection:**

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

Data Collection
Study data will be derived from source documents and then transcribed onto electronic CRFs (eCRFs). Study data may also be entered directly on the eCRFs as original observations and thus have the dual function of source document and data capture form at the study site. In the case where a source documentation is not completed on the CRF directly, the transcriptions will occur on an ongoing basis during the study in accordance with Good Clinical Practice (GCP) guidelines by study staff delegated this task on the Delegation/Responsibilities Log. Study staff should maintain in the regulatory files a list of CRFs that serve the dual purpose of source documentation and CRF.

DCC programmers will pull MDR records on enrolled subjects at the end of the influenza season (or end of study, as applicable) in an attempt to confirm relevant health information, such as comorbidities, prescription medications, history of influenza and other vaccination history of influenza and other respiratory infections (i.e., influenza, SARS-CoV-2, and other respiratory pathogen test results), healthcare utilizations and costs associated with ILI. Evaluations mandated by this research protocol will have no impact on standard of care assessment and treatment.

Names and email will be collected prior to enrollment using the MHS Portal J6 email list. This will allow access to send recruitment materials along with e-consents to potential study participants.

Demographics: Following administration of informed consent, collected demographic data will include but not be limited to age, sex, DEERS status, and military rank.

Past Medical History: Information on subjects' past medical history will be captured at or after enro llment. The information collected will focus on comorbidities, history of influenza and other respiratory infections (e.g., SARS CoV-2), and history of influenza and other vaccinations. Medical history information will be collected via electronic or paper questionnaires, or through an MDR pull. Coordinators will review the subjects' questionnaire responses for completeness. Health information from up to five years prior to a subject's study enrollment may contribute to the MDR record data pull.

FluPRO daily symptom questionnaire information will be entered into a REDCap web form on a URL provided by the DCC. Subjects will be provided a direct link to access the website and enter their study data.

FLUPRO Questionnaire: Subjects who report ILI symptoms which meet the study case definition for ILI will be sent a link to a web-based version of the 7-day FLUPRO Questionnaire. FLUPRO is a tool designed to evaluate patient-reported ILI symptoms and their severity. Subjects will be responsible for entering the symptoms for 7 consecutive days beginning with the day they reported meeting the ILI case definition. Subjects who experience ILI symptoms may be compensated for up to three new ILI episodes per season. ILI episodes must be separated by at least 30 days.

ILI history: ILI history will be captured at the ILI Visit 1. Information recorded includes date of ILI onset, duration of illness, number of reduced/limited activity due to illness, and number of school/work days missed.

Concomitant Medications: If any over the counter fever reducers and pain reducing medications are being taken at the time of enrollment it will be noted by the subject on the enrollment form. Any prescribed medications taken throughout the subject's participation in the study, to include: antibiotic, influenza antiviral, antiemetic, antihistamine, antipyretic, bronchodilator, decongestant, systemic steroid, or other immunomodulator will be gathered through an MDR pull.

Hospitalization status: At the ILI Visit 1, subjects will be asked if ILI episode resulted in hospitalization (in-patient). If the episode resulted in hospitalization, information on duration of hospitalization and severity (e.g. ICU status and oxygen administration as proxies for severity). This information will be updated at the ILI Visit 2 Day 28 visit.

Return to Work: Information on the total number of days from illness onset that subjects were not able to perform their normal activities is recorded at the ILI Vist 1 and updated at the ILI visit 2.

Data Management Plan
Procedures and policies related to data collection, completion of forms/logs, and the management and use of data after collection are outlined in the current version of the Data Management Plan (DMP).

Study Records Retention
The PI at each site is responsible for retaining all essential documents listed in the International Conference on Harmonization (ICH)/ Good Clinical Practice (GCP) Guidelines. All essential documentation for all study subjects are to be maintained by the investigator in a secure storage facility according to each military treatment facility's requirement. These records are also to be maintained in compliance with IRB, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law.

DCC
Access to study files at DCC (eCRFs) is restricted to staff members given specific study related tasks to perform. The files are maintained on controlled-access servers in accordance with DCC standard procedures.

**10.3 At any point in the study, will you request, use, or access data from a DoD Database or the Military Health System (MHS)?**

(•) Yes ( ) No

**10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance. The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the**

**management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force *MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS. *MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.**

**Are you an MHS workforce member?**

- (•) Yes, I am an MHS workforce member
- ( ) No, I am not an MHS workforce member

**Are you an MHS business associate?**

- ( ) Yes, I am an MHS business associate
- (•) No, I am not an MHS business associate

**10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?**

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**dha.ncr.pcl.mbx.privacyboard@mail.mil**)

- (•) Yes, then complete the questions below according to the data consult
- ( ) No, then complete the questions below according to the best of your knowledge

**10.6 Indicate how you will request data from the MHS. Select all that apply.**

- [ ] Talking with MHS health care providers or MHS health plans about specific research participants
- [ ] Obtaining MHS hard copy records specific to research participants
- [x] Obtaining data from an MHS information system(s)

**10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.**

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

- [x] Data Extract
- [x] Access

**10.8 Do you intend to use only de-identified data from the MHS in your research study?**

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

( ) Yes (•) No

**10.9 Indicate the MHS information system(s) from which you will seek to obtain data**

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
**PHI Systems:**

| MHS Information System | Requesting Data |
|---|---|
| : AHLTA | : Yes |
| : CHCS | : Yes |
| : ESSENTRIS | : Yes |
| : MDR | : Yes |

**PII-Only Systems:**

| MHS Information System | Requesting Data |
|---|---|
| MHS Genesis | : Yes |

| Information System | Requesting Data |
|---|---|
| No records have been added | |

**10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?**

- (•) Yes, will merge data
- ( ) No, will not merge data

**10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems. If you answered "yes" to question 10.9 above, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.**

| Data Element(s) | MHS | Non-MHS Systems | MHS Hard Copies |
|---|---|---|---|
| 1. Names | ☐ | ☑ | ☐ |
| 2. Postal address with only town, city, state and zip code | ☐ | ☑ | ☐ |
| 3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, | | | |

| | | | |
|---|---|---|---|
| zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000 | ☐ | ☐ | ☐ |
| 4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death | ☑ | ☑ | ☐ |
| 5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older" | ☐ | ☐ | ☐ |
| 6. Telephone numbers | ☐ | ☑ | ☐ |
| 7. Fax numbers | ☐ | ☑ | ☐ |
| 8. Electronic mail addresses | ☐ | ☑ | ☐ |
| 9. Social Security numbers (SSNs) | ☐ | ☑ | ☐ |
| 10. Medical record numbers | ☐ | ☐ | ☐ |

| | | | |
|---|---|---|---|
| 11. Health plan beneficiary numbers | ☐ | ☐ | ☐ |
| 12. Account numbers | ☐ | ☐ | ☐ |
| 13. Certificate /license numbers | ☐ | ☐ | ☐ |
| 14. Vehicle identifiers and serial numbers, including license plate numbers | ☐ | ☐ | ☐ |
| 15. Device identifiers and serial numbers | ☐ | ☐ | ☐ |
| 16. Web Universal Resource Locators (URLs) | ☐ | ☐ | ☐ |
| 17. Internet Protocol (IP) address numbers | ☐ | ☐ | ☐ |
| 18. Biometric identifiers, including finger and voice prints | ☐ | ☐ | ☐ |
| 19. Full-face photographic images and any comparable images | ☐ | ☐ | ☐ |
| 20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank) | ☑ | ☑ | ☐ |

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

Participants receiving >$600 in compensation in one calendar year must fill out a W9 in order to receive a 1099 at the end of the year for IRS tax reporting purposes. Social security numbers are collected for this reason alone.

**10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?**

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

**10.13 HIPAA Privacy Rule and Use of Protected Health Information in Research:**

- ○ N/A – will not use or disclose protected health information (PHI)
- ○ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ◉ Waiver/alteration of HIPAA Authorization is being requested

**10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:**

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

The only electronic links between the subject's name, DoD ID, SSN, and Study ID number will be on tracking spreadsheets at the clinical sites used for collecting information on ILI cases, as needed, from electronic medical records and will only be accessed by authorized study staff. During the study, source documents will be held in a secure cabinet with restricted access. Team members with access to the documents are counseled on the importance of maintaining the confidentiality of subjects' medical records and trained on human subjects' protection and HIPAA. All staff involved in this study have completed the required human subjects' protection and ethics training. In all electronic records used for data analysis, the subjects are not referenced by name, but only Study ID number. This method is designed to protect study subjects' medical information. All measures are put in place to protect the privacy of all subjects. The study will utilize passwords and firewalls to maintain confidentiality of data accessed via computer. The summary report generated from the interviews and completed questionnaires will not contain any subject identifying information.

To determine whether an individual has been enrolled previously at another study site, study staff at all sites will have the ability to query IDCRP data management systems to locate an individual. The data management systems are secure and can only be accessed by authorized individuals using a unique user ID/password combination.

The REDCap data entry system includes a server accessible by standard web browsers and device-based applications. The server is hosted, maintained, and kept secure by the Henry M Jackson Foundation IT department. REDCap data is encrypted using 64-bit DES technology, and the REDCap server is configured to accept HTTPS connections only.

Tablets will be configured as follows:

- The internal hard drive or folders containing study data will be encrypted
- Username/password will be required to log on to the tablet

- Study data transmission will employ a secure transmission protocol, (i.e SSL)

Email and cell phone number collection:

- Subject e-mails and cell phone numbers will be collected in REDCap accessed on a tablet using a secure wireless connection or on a computer using a secure landline connection, to the Infectious Disease Clinical Research Program Data Coordination Center. Emails and cell phone numbers may also collected on paper source documents and transcribed into tablets.
- Study data will be stored on the tablet hard drive only when the tablet is in offline mode; both the hard drive and the data folders are encrypted
- The tablet will periodically be uplinked via a secure connection at which time the study data will be transferred securely to the central study database

FluPRO daily symptom questionnaire:

- No personally identifying information will be collected in the questionnaire
- FluPRO daily symptom questionnaire information will be entered into a REDCap form via a URL provided by the DCC directly to the subject; the URL will be unique to the specific subject and questionnaire.

Salivary Sample Analysis will be performed at Johns Hopkins University (JHU). JHU will receive only coded samples and data, labeled by study ID.

### 10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

Research use of data collected through this protocol will be coded and will not contain identifiers. Any DHA-derived PHI will be de-identified. Access to these data will be highly limited. Much of the subsequent research using the materials collected under the auspices of this study will be accomplishable through approved exempt or non-human use sub-studies. All research using the materials collected under this protocol will be conducted in accordance with an IRB-reviewed protocol. Data and tissue samples released for research use will be labeled by Subject ID only; data will be shared without any identifiers or links to individuals. The DCC will not share identifying information with investigators without explicit IRB approval.

## 11.0 Statistical/Data Analysis Plan

### 11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

The statistical plans discussed below are not final or definitive. They will need to evolve as the flu seasons develop and we communicate with other ILI study centers and the sponsors. In case of

a severe epidemic, they may have to change substantially. Detailed statistical protocols will need to be created for the specific studies that will fulfill secondary objectives. The statistical considerations below for the secondary objectives will serve as starting points for the more detailed statistical plan .

**Primary Aim**

*Specific Aim #1: Comparison of the effectiveness (prevention of laboratory-confirmed influenza illness) of three types of licensed seasonal influenza vaccines.*

*Research question*: Is either the cell-culture based vaccine or the recombinant vaccine more effective than egg-based vaccine? There are two hypotheses of interest based on influenza attack rates (AR):
Vaccine Effectiveness (VE)= $\frac{AR_0 - AR_1}{AR_0}$ x100% = (1-$AR_1/AR_0$)x 100%=(1-RR) x100%

when $AR_0$ is placebo, VE~= vaccine efficacy or via Nauta ("absolute vaccine efficacy") when $AR_0$ is the egg-based vaccine then the VE~= *relative* vaccine efficacy.
We want relative VE of 33% => 1 – $AR_1/AR_{egg}$ = 0.33 , therefore 1- 0.33 = $AR_1/AR_{egg}$ = RR
therefore 0.67 =RR (AR1 = attack rate in either cell-culture based or recombinant vaccine)

We have simplified the primary hypotheses for the study and have opted for two pairwise comparisons rather a single three-way comparison. There are two hypotheses of interest based on influenza attack rates (AR):
$H_0$: RR=1 vs $H_A$: RR < 1; alpha=0.025;
The RR to be tested is defined as: 1) RR1=$AR_{cell}$ / $AR_{egg}$ and 2) RR2=$AR_{recombinant}$ / $AR_{egg}$
Text: Statistics in Clinical Vaccine Trials by Jozef Nauta.

1. Endpoint:

   Influenza attack rates in the egg-based, cell-culture-based, and recombinant protein influenza vaccines arms of the study in the 2018-2019, 2019-2020, 2020-2021, and 2021-2022 seasons.

2. Ascertainment of primary outcome:
   Laboratory-confirmed influenza as ascertained by a sensitive and specific assay is needed to assess effectiveness. The best assay is RT-PCR from nasopharyngeal swab specimens (various assay platforms); one particular antigen detection assay has similar sensitivity and performance characteristics, but numerous available rapid antigen detection tests for influenza are poorly sensitive and have poor negative predictive value, thus risking false-negative results if relied upon for outcome. There is heterogeneity across MHS clinical laboratories with respect to the type of test that is employed. A key factor is that individuals must present for care to have outcome ascertainment. Thus, follow-up methodology will involve strategies to increase likelihood of presentation for evaluation of incident ILI following vaccination.

3. Statistical analysis:
   Incidence rates: To determine incidence, we will use the number of enrolled laboratory-confirmed influenza cases by vaccine formulation as the numerator. For the denominator, we will use the number of enrolled subjects by vaccine formulation. We estimate that approximately 30- 40 percent of the subjects and will develop ILI symptoms. Of this group, perhaps 30 percent will seek care, with symptom severity the leading predictor for seeking care. We realize that there is no effective way in a large study to avoid the potential for bias in case ascertainment due to differences in symptom severity. As a pragmatic study, our goal is not to eliminate bias but to minimize the impact of bias , by using a broad but standardized case definition and by providing incentives for symptomatic individuals to be assessed. We can also use symptom severity data from the FLUPRO questionnaire to explore the extent to which symptom severity scores differs by region.

   The ability of the study to detect a difference in effect is proportionate to the incidence of the outcome. A total of 172 influenza cases were reported among the 10,771 subjects enrolled in first three years of the study (2018-2021). The influenza attack rate has ranged from 0% in third season (COVID-19 pandemic), to 2.5% in the second season, with an overall attack rate 1.6% The observed attack rates are lower than baseline attack rates of 5% and 3% that formed the basis of sample size calculations for the first three years of the study. Consequently, the power to detect significant differences in VE between vaccine arms has been too low to due to the low attack rates. For the fourth year of the study is to increase the enrollment target from 15,000 to 18,00 to enhance power to detect significant differences in VE between attack rates are lower.

***Secondary Aims:***

*Specific Aim #2:*
*Determine whether cell-culture-based and egg-based influenza vaccines give comparable HI and PVN titers to egg- and cell-matched vaccine antigens. An outcome of this objective is the potential to determine whether cell-culture-based vaccine antigens can provide broader coverage of circulating viruses than egg-based vaccine antigens.*

Research Question:Is the proportion of subjects who seroconvert in either the cell-culture based or recombinant vaccine arm of the study greater than in the egg-based vaccine arm of the study.

There are two hypotheses of interest for Specific Aim 2, based on the seroconversion rates (SCR)

$H_0$: RR=1 vs $H_A$: RR < 1; p=0.025; The RR to be tested is defined as: 1) RR1=SCRcell / SCRegg and 2) RR2=SCRrecombinant / SCRegg

1. Endpoints:

- Humoral responses: HAI titer, anti-NA titer, virus-neutralizing titer
- Cellular responses (exploratory): frequency of antigen-specific CD4 and CD8 cells, B cells

SA 2.1: To obtain post-vaccination sera panels to determine breadth of reactivity to circulating strains.
This will be accomplished by recruiting consenting adults to an IRB-approved study conducted during a routine influenza vaccination campaign, collecting sera up to 30 days before and 21-35 days after vaccination with egg- or cell-culture-based or recombinant influenza vaccines. The samples will be de-identified and shipped to partner laboratories for aliquoting, storage, and antigenic analyses. We intend the study to be conducted during early vaccination campaigns performed at DoD facilities.

SA 2.2: To identify individuals who responded to H1N1, H3N2, B/Victoria and B/Yamagata vaccine components. This will be accomplished by testing pre- and post-vaccination sera for HA inhibition (HI) and pseudovirus microneutralization (PVN) antibody titers. Individuals who had a 4-fold or greater response against each matched antigen in the vaccine will be considered responders (i.e. if egg-based vaccine, the test will be conducted against egg-based antigen). The study will be designed to identify responders to egg- and cell-culture-based vaccines for each vaccine antigen (H1N1, H3N2, B/Yamagata and B/Victoria). For H3N2 strains that do not hemagglutinate, only PVN titers will be determined. The sera collected post-vaccination from responders will be aliquoted and distributed to laboratories performing assays to evaluate the breadth of antibody reactivity.

SA 2.3: To evaluate differences in serum reactivity between egg- , cell-culture-based and recombinant antigens.
We will test pre- and post-vaccination sera against antigens with sequences corresponding to the “other” platform. We will compare PVN antibody titers against egg- and cell-culture-based antigens for all strains included in the vaccine, and calculate the response rate (i.e. percent of individuals in each arm with a 4-fold or greater titer response) of each arm of the study against egg and cell antigens. The results from this test will indicate whether antibodies elicited in response to egg- and cell-culture-based vaccines are specific for the immunogen.

SA 2.4: Compare the breadth of the antibody response elicited by egg, cell-culture-based and recombinant vaccines to circulating strains.
To determine the breadth of antibody reactivity, post-vaccination serum PVN titers will be measured against cell-culture-based vaccine and emerging circulating virus antigens representing most clades from each subtype. Only cell-based sequences will be used in this analysis because these are representative of the original human isolate sequences. We

propose to include the HAs of at least 6-10 recent virus isolates per subtype/lineage. PVN titers against recent virus isolates that are >4 fold different from the homologous vaccine antigen will be considered low reactors (LRs). The breadth of reactivity will be scored by calculating the number of LRs identified for each study subject, e.g., sera that react to all antigens will be given a score of 100%, sera that react to no antigens will be given a score of 0% and sera that react to 4 of 10 antigens will be given a score of 40%. The overall breadth of reactivity for each study Arm will be calculated as the average breadth of reactivity for all persons in the Arm. If the difference between the groups is not significant, additional antigens within the subtype/lineage but that are known to be antigenically-distinct, may be tested.

SA 2.5: To examine the breadth of reactivity against past strains.
Recent studies demonstrate a back-boost effect following vaccination, i.e. increased antibody titers against influenza antigens from past vaccines or infections. The human immune responses are therefore impacted by prior vaccination history or infection. To retain the possibility of performing additional tests that examine the back-boost effect, left over sera will be stored for future additional investigations of how pre-existing breadth of antibody reactivity to past influenza strains influences responses to current influenza vaccines.

**Exploratory Aims**:
Specific Aim #3: To determine if the impact of the influenza vaccine on disease burden and the attributable healthcare costs differs by product type.
An analysis of the impact of ILI and SARI on health care utilization will allow a more detailed estimation of the burden of infections caused by these pathogens in military populations. The collection and analysis of health care utilization information will be useful for informing priorities for ARI control and will serve as a basis for the comparison of the effectiveness of different ILI control measures to enhance Force Health Protection.

Endpoints:

- Incidence of PCR-confirmed influenza cases
- Frequency of influenza-confirmed hospitalization
- Frequency of influenza-like illness
- Work days lost due to influenza
- Work days lost due to influenza-like illness
- Healthcare costs/utilization attributable to influenza
- Healthcare cost/utilization attributable to influenza-like illness

Specific Aim #4: To evaluate the association host single nucleotide polymorphisms (SNPs) on the immune responses to the influenza vaccine and on influenza severity

Endpoints:

- Frequency of SNPs by seroconversion status
- Frequency of SNPs by geometric mean titer (GMT) cutoff
- Frequency of SNPs by mean fold rise (MFR) cutoff
- Frequency of SNPs by influenza status
- Frequency of SNPs by influenza severity classification

**11.2 Sample Size:**

18000

**11.3 Total number of subjects requested (including records and specimens):**

18000

**11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm**

Arm 1: cell-culture based, 6,000.
Arm 2: recombinant influenza vaccine, 6,000.

Arm 3: egg-based influenza vaccine, 6,000.

Sub-study: Approximately 1,200 subjects total recruited from the main study population.

**11.5 Please provide a justification for your sample size**

**Main Study**

Based on an alpha of 0.025 (1-sided) and a power of 0.80, a sample size of 18,000 (6,000 per arm) subjects has the power to detect a 33% difference in effectiveness between egg-based vaccine and two other vaccine preparations, assuming an influenza incidence of 2.3% in the egg-based arm and 1.54% in the cell-culture-based and recombinant arms. It assumes that 15% of subjects will be lost to follow-up.

**Substudy**

Based on an alpha of 0.025 (1-sided) and a power of 0.80, a sample size of 1,200 subjects (400/arm) has the power to detect a 22% relative difference in seroconversion rate if there is a 50% seroconversion at day 28 among the egg-based vaccine recipients. It assumes that 15-20% of subjects will be lost to follow-up.

**11.6 Data Analysis Plan:**

See section 11.1

## 12.0 Participant Information

**12.1 Subject Population:**

The study is comprised of DEERS-eligible adults (active duty, retirees and beneficiaries) vaccinated (at an MTF) (will be vaccinated) with one of the licensed egg-based, cell-culture-based or recombinant influenza vaccines during the 2018-2019, 2019-2020, 2020-2021, 2021-2022 influenza seasons in the United States. Subjects enrolled in the study during 2018-2019, 2019-2020, and/or 2020-2021 may also be enrolled in the 2021-2022 season.

**12.2 Age Range:**

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [x] 65-74
- [x] 75+

**12.3 Gender:**

- [x] Male
- [x] Female
- [ ] Other

**12.4 Special categories, check all that apply**

- [ ] Minors /Children
- [x] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [x] Resident/trainee
- [x] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [ ] Wounded Warriors
- [ ] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

**12.5 Inclusion Criteria:**

| Order Number | Criteria |
|---|---|
| 1 | Eligible for care in DoD facilities (DEERS eligible) |
| 2 | Greater than or equal to 18 years of age |
| 3 | At a participating MTF site for the purpose of receiving a seasonal influenza vaccination. |
| 4 | Able to speak English and able to provide informed consent |
| 5 | Able to receive and respond to texts and/or emails, or a military recruit |

**12.6 Exclusion Criteria:**

| Order Number | Criteria |
|---|---|
| 1 | Adults intending to receive or who have received the current season's FluMist vaccine (LAIV). |
| 2 | Adults who have already received a Flu Vaccine within the current season |
| 3 | Individual who cannot receive a flu vaccine or standard dosing due to another medical condition |
| 4 | Allergic to gentamicin, polymyxin, and/or neomycin |
| | Individuals who fail to meet the inclusion criteria |

| | |
|---|---|
| 5 | |

## 13.0 Recruitment and Consent

**13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.**

**Identification and Selection of Subjects:**

Potential subjects may be encouraged using recruitment flyers that may be posted at the sites in areas such as acute care clinics, ward workrooms, the emergency room, the commissary, the post exchange and/or base exchange and outside MTFs (e.g. shipyard, military bases, branch clinics etc.) as appropriate (if accessible at the MTF (i.e., MAMC). Print advertisements may be placed in the command newspaper at each participating MTF. Sites may choose to disseminate the flyer via email to targeted audiences (e.g. house staff/attending physicians) or via the web using social media networks (i.e. Facebook). In addition, a recruitment poster/flyer may be provided to patients during intake by clinic staff to inform potential enrollees about the study. All advertisements will include information summarizing the study enrollment criteria, dates and locations for enrollment, and indicate that participation in research is voluntary.

All recruitment material will be reviewed and approved by the IRB prior to use.

**Eligibility Assessment Process:**

Any person eligible to receive care at one of the participating DoD inpatient facilities or outpatient clinics, and who meets all inclusion criteria and exclusion criteria is eligible for participation in the study. Eligibility for care is determined by the Defense Enrollment Eligibility Reporting System (DEERS). This will include individual active duty service members, retired military, and their eligible dependents. Attempts will be made to enroll subjects of all genders and racial and ethnic origins. Coordinators will confirm DEERS eligibility based on CAC, military identification and military health care documents.

**Recruitment Process:**

### *Electronic Enrollment:*

Potential subjects can be sent consents, educational and recruitment material via email 30 days prior to vaccination day up to two times prior to vaccination day.

E-consent links and QR codes will be given via email or in-person for potential subjects to sign up for the study. Subjects will receive a screening questionnaire and instruction sheet to ensure they understand the procedures, are eligible for the study, and have contact information for the staff if they have questions.

### *In-person recruitment:*

Recruitment and consent in the MTFs may take place up to 30 days prior to randomization and vaccination. Research protocol briefs may be given on a regular basis by the site PIs or a member of the study team to training programs and to the inpatient/outpatient health care staff in their primary care clinics as well as the emergency room staff. Following the medical briefing, a study investigator will give a 10-minute briefing that outlines the proposed research study. No officers in the chain of command will be present during the briefing or the consent process. It will be made clear during the briefing that enrollment is completely voluntary and that enrolling, or failing to enroll, will in no way affect their standing. Any healthcare worker who was not present at the briefing, will be given the opportunity to participate once they have received study information and are given the opportunity to ask questions.

After the investigator's briefing, there will be a 10-minute period (more time will be allowed if needed) for any questions potential subjects may wish to ask publicly. They will also be given the opportunity to ask additional questions in private. Questions on the nature of the study, the means by which it is to be accomplished, and the risks to the subjects will be addressed. Any questions that cannot be answered will be referred to the site PI. No study procedures will occur prior to the subject giving informed consent.

*Active duty members*
Recruitment and enrollment of active duty members in groups, may take place outside MTFs (e. g. military units, shipyard, etc.), or at command briefings for recruits. Following the medical briefing, a study investigator will give a 10-minute briefing that outlines the proposed research study. No officers in the chain of command will be present during the briefing or the consent process. It will be made clear during the briefing that enrollment is completely voluntary and that enrolling, or failing to enroll, will in no way affect their standing.

*Beneficiaries*
Prior (via electronically) or when beneficiaries arrive at the MTF (in person) to receive their influenza vaccination, the immunization or study staff are able to make beneficiaries aware of the study and may provide them with recruitment materials describing the study. Individuals who are interested learning more about the study will be directed to speak with a study staff team member. Beneficiaries will be given the opportunity to ask questions in private. Questions on the nature of the study, the means by which it is to be accomplished, and the risks to the subject will be addressed. Any questions that cannot be answered will be referred to the site PI. No study procedures will occur prior to the subject giving informed consent.

*Immunogenicity Substudy:* Substudy participants are recruited from subjects enrolled in the main study. Participation in the main study is a requirement for substudy enrollment. The study team will focus on recruitment and enrollment into the immunogenicity sub-study in the weeks preceding the start of vaccination. The recruitment strategy for the sub-study will be similar to the main study utilizing a combination of flyers, outreach in MTF clinics to target beneficiaries, group briefings for MTF health care works and offsite military units (e.g. sailors assigned to ships in dry dock, trainees at the Medical Education and Training Campus (METC), etc). Using a similar recruitment and enrollment strategy to the main (VE) study will allow for a similar composition of subjects between the sub-study and overall cohort. Subjects recruited during the 'pre-vaccination window' will be enrolled and complete the pre-vaccination blood draw, and then return for randomization and vaccination at the 'vaccination or Day 0' visit. Once the sites start vaccination visits, recruitment and enrollment efforts will prioritize the main (VE) study, although sites can continue enrollment in the immunogenicity sub-study in order to meet enrollment targets. Enrollments into the immunogenicity sub-study will be stratified by site but not by any other parameters (e.g. day of week, every 3rd enrollment etc). Of note, individuals must be enrolled in the main study (VE) in order to participate in the sub-study. Individuals who agree to participate in the sub-study will be required to complete the main study consent document (PAIVED ICD) in addition to the sub-study consent document (PAIVED Sub-Study ICD).

**13.2 Compensation for Participation:**

**FLUPRO Questionnaire:**
Subjects who develop ILI symptoms will receive $10 for their best effort in completing the 7 day entries, at the ILI Visit 1.

**Blood Collection:**

- $10 per self-collected blood sample
- $50 per venipuncture

Under 24 USC 30, payment to Federal Employees and Active Duty military personnel for participation in research while on duty is limited to blood donation and may not exceed $50 per blood draw. They may not receive any other payment or non-monetary compensation for participation in a research study unless they are off duty or on leave during the time they are participating in the protocol.

**Nasal swab**:
Individuals will be compensated $10 per each of the nasal specimens.

Participants may be compensated for up to three new ILI episodes per season. ILI episodes must be separated by at least 30 days. Recruits/trainees may be compensated if permitted per

military policy.In the event that a mitra kit or self-collected nasal swab is collected by a subject but the study staff does not receive it a subject may be compensated and can be compensated for a replacement.

**13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor**

For potential subjects who a e-consenting, there will be a pre-screen eligibility questionnaire.

**13.4 Consent Process:**

Are you requesting a waiver or alteration of informed consent?

(•) Yes ( ) No

What type?

☐ Waiver of documentation of informed consent
☑ Waiver or alteration of informed consent

Please explain why your study is eligible for the requested waiver

We are requesting an alteration of informed consent to a short form consent. Since we are looking to enroll a very large sample during a very short time, use of a short form consent will make the consent process more efficient, thereby giving staff members more time to answer any questions that the subjects may have. The short informed consent has all of the required elements.

Please explain the consent process:

**ICD and Assent Regulatory Requirements:**

The Informed Consent Document (ICD) will be reviewed and approved by the IRB prior to initiation of the study. The ICD Form contains a full explanation of the possible advantages, risks, and alternatives to participation, and availability of treatment in the case of injury.

An ICD, in compliance with applicable DoD regulations, 32 CFR 219, the Belmont Principles, the Health Insurance Portability and Accountability Act (HIPAA) Authorization, and California Subject' s Bill of Rights (if applicable) will be signed by the subject or representative before any study-related procedures are initiated for each subject. The investigator will retain the ICD and authorization form as part of the study records. Only PIs, research physicians, clinical coordinators, research assistants, and site managers listed in Personnel and Collaborators Protocol Attachment will present the protocol in lay terms to the subjects. As part of the informed consent process, study staff will describe study procedures, risks of the study, and alternative to participation to the potential subject either in person or electronically. All subjects will be given the opportunity to ask questions. Any question that cannot be answered by the study staff will be referred to the principal investigator (PI) and/or research physicians. Study staff will make all effort to answer questions to the subjects to satisfaction prior to granting consent. Informed consent includes the principle that it is critical the subject be informed about the potential risks and benefits. This information will allow the subject to make a personal risk versus benefit decision and understand the following general principles:

a. Participation is entirely voluntary,
b. Subjects may withdraw from participation at any time,
c. Refusal to participate involves no penalty, and
d. The individual is free to ask any questions that will allow him/her to understand the nature of the protocol.

Study staff will clearly state that enrollment in the study is completely voluntary. At the end of the discussion, all subjects will be provided an electronic copy or the paper consent form, the HIPAA authorization form, and the California Subject's Bill of Rights (if applicable) to carefully read and review before considering whether or not to participate.

Should the protocol be modified, the subjects consent document will be revised, as needed, to reflect the changes to the protocol. If the subject is directly affected by the change, and it is directed by the IRB, each subject will be re-consented per the previously defined process and

subjects will be offered a copy of the newly signed and dated ICD. The approved revision will be read, signed, and dated by the subject subjects.

**Informed Consent Process - Enrollment**

In response to a flyer or other print advertisement, a potential subject may call the study coordinator for more information regarding the study. The study coordinator will explain the study and/or ask the individual or group to come to the MTF for further discussion and possible enrollment. Following the recruitment procedures, those interested subjects will be offered the consent form and authorization forms to sign or paper or electronically. In accordance with DoD regulations, if a military member is interested in volunteering, their informed consent process will not take place in the presence of uniformed personnel in their chain of command or in the presence of a superior officer. At the time of consent, HIPAA authorization will also be obtained.

Study staff will be available to answer any questions an individual may have before deciding whether or not to participate in the study. When each individual has determined that they are interested in participating, they will sign the appropriate consent form in front of the designated study staff (listed in the Personnel and Collaborators Attachment). Each subject will have the ability to opt-in for a buccal swab and for same-day/post-vaccination self-collected blood samples. Subjects will elect to opt into this procedure in a designated area of the consent form and will do so without penalty or loss of entitlements. A copy of the signed ICD will be offered to the subject and the original document will be retained by the investigative team.

A subject is considered to be enrolled when they have signed a consent form and HIPAA authorization form (and California Bill of Rights, if applicable).

**Substudy enrollment:**
Study staff listed in the Personnel and Collaborators Attachment will ensure that each potential enrollee of the substudy is presented with the Substudy ICD . This ICD will be explained by the consenting study staff member and the potential participant will be able to ask any questions they may have. If a subject chooses to participate, the substudy ICD will be signed after the main ICD is completed and before any substudy procedures are done. Substudy participants will be offered a copy of their signed substudy ICD.

*Participation Log*
If individuals agree to participate, identifiers and the study ID, will be recorded in the participation log on a secure computer. Completed study procedures will be documented in the electronic participation log.

**13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.**

- (•) N/A
- ( ) Propose ombudsman

**13.6 Withdrawal from Study Participation:**

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

A subject may voluntarily end participation in the study at any time. If a subject withdraws, the investigator will make a reasonable effort to determine the reason for the subject's withdrawal from the study. Telephone calls, registered letters, and/or e-mail correspondence will be considered reasonable effort for subjects whom are deemed lost to follow up. "Lost to follow-up" is defined as a subject who enrolled in the study and received a randomly allocated vaccine but did not respond to any ILI surveillance, or a subject who reported ILI symptoms but then did not complete any ILI visit or ILI-related procedure**s.**

Subjects who withdraw because of study-related AEs will be followed to resolution of AE or as long as reasonably possible. In the event of a continuing study-related AE, the information will be provided to the Institutional Review Board (IRB).

For the immunogenicity sub-study, "lost to follow-up" is a sub-study subject who did not complete the two blood draws and will be reported to the IRB during continuing review. All data and specimens collected up to the time of withdrawal will be reported and retained.

## 14.0 Risks and Benefits

### 14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

FDA-approved influenza vaccines are made by a number of manufacturers and are classified as either "live attenuated" or "inactivated" influenza vaccines. This study will compare the relative effectiveness of three inactivated influenza vaccine formulations, an egg-based, a cell-culture-based, and a recombinant. The live attenuated vaccine (i.e. Flumist) will not be evaluated in this study. There are 3 separate egg-based vaccines being studied. To date, there is no published data to suggest that there are "clinically significant" differences in the rate of adverse events following immunization (AEFI). The CDC/ACIP's current guidance to providers is to administer any licensed, age-appropriate influenza vaccine with no preference expressed for one vaccine over another. Active duty members are required to receive an annual influenza vaccination and voluntary for retirees and beneficiaries. Approximately 90% of active duty members and healthcare workers and 40% of beneficiaries are vaccinated each season.

We contend that the PAIVED study meets the standard for a minimal risk study for the following reasons: the Centers for Disease Control and Prevention (CDC) and its Advisory Committee on Immunization Practices (ACIP) recommend that all patients 6 months of age and older be vaccinated annually against influenza. Moreover, the ACIP's current guidance to providers is to administer any licensed, age-appropriate influenza vaccine (Inactivated influenza vaccines (IIV), Recombinant influenza vaccine (RIV), or live attenuated influenza vaccine (LAIV4) with no preference expressed for one vaccine over another (Appendices 2-4). A summary of the common adverse effects following immunization (AEFI) associated with influenza vaccines to be used the study is presented in Appendix 5. To date, there no published data to suggest that there are "clinically significant" differences in the rate of adverse events following immunization (AEFI) with the various products and no nationally authoritative body has seen a need to preferentially avoid one vaccine's side effects for another product. Thus, it is well within the standard of care to give any patient any of the FDA-approved vaccines. It should be noted that among the products to be administered have different excipients (Fluarix contains gentamicin and Afluria contains neomycin and polymyxin) so participants with who are allergic to these medications would have an increased risk of an adverse event, consequently, allergies to gentamicin, neomycin and polymyxin has been added to the study exclusion criteria.

This **comparative effectiveness study** is designed to follow individuals who have allocated to receive one of three FDA licensed types influenza vaccine formulations in order to evaluate their relative impact of on risk of influenza acquisition and immune responses. Given that all the vaccines represent the standard of care and will be administered in accordance with ACIP recommendations, to those who are not allergic to vaccine components, the only increased risk to subjects in the study would be related to the risk of a blood draw (syncope, bruise, etc.) as well as any remote risk of PII compromise.

1. Rare (Event rate < 1%)

- Secondary infection and syncope from vasovagal reactions occur from blood collection in rare cases. Nasal swabs could trigger symptomatic nose bleeds in rare cases.

2. Less Likely (1% greater or equal Event Rate 5%)

- Nasal swabs may abrade or irritate mucosal surfaces already inflamed due to respiratory infections, leading to discomfort and minimal local bleeding.

3. Likely (5% greater or Equal Event Rate < 5%)

- Bruising and bleeding may occur as a result of blood collection procedure. Nasal swabbing for viral diagnostics
  and cheek swabbing for obtaining shed buccal cells (for future study of genetic polymorphisms) may cause local discomfort.

4. More likely (Event rate less or equal to 10%)

- No known risks

1. ***Risk of Phlebotomy***

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and rarely hematoma, infection, or fainting.
At the time of enrollment and at Day 21-35, each subject in the immunogenicity substudy will be asked about participation in other research studies to ensure that blood draws do not exceed the following amounts for all research protocols combined: 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period for adults. Subjects will also be asked to collect a minimal amount of blood for both ILI visits along with an opt-in pre and post vaccination using a small finger prick.

For assessment of risk in this class of subjects we look to the DHHS IRB Guidebook Chapter VI – Special Classes of Subjects. Section B of that chapter speaks to the risk of phlebotomy in pregnant women:
Obtaining this modest phlebotomy and nasal specimens from pregnant women should conform to the specific requirements of 45 CFR 46, section 207.

2. ***Risk of Nasal and Buccal Specimen Collection***

Nasal swabbing for pathogen diagnostics may cause brief, local discomfort. While less likely, obtaining a nasal swab may trigger sneezing, coughing, or a gag reflex, which is slightly more likely in subjects who are already suffering from these symptoms. Rarely, nasal swabs could trigger a symptomatic nosebleed.
Cheek swabbing for obtaining shed buccal cells (for future study of genetic polymorphisms) may cause local discomfort.

Any adverse event resulting from blood collection procedures will be managed according to standard clinical procedures.

3. ***Confidentiality Breach***

Another risk of participation in this study is that someone may accidently release information from the subject's medical records without the subject's permission. However, the investigators make every effort to protect subject's confidentiality and privacy by careful handling of records and data. Furthermore, the data base is secured by only using codes (subject's identification number and PIN), and not names or other individual. Extensive security measures have been taken to protect this information.

4. ***Risk Associated with Each Vaccine***

See Appendix 5 - comparison of vaccine side effects.

**14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):**

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

*Blood/Nasal swab collection*
Any adverse events resulting from blood collections and/or nasal swab procedures will be managed according to standard clinical procedures. Expected adverse events that are not serious, but are directly related, are reported at continuing review. Steps to minimize and

mitigate risks of participation are described in the appropriate, and respective, sections of the protocol.

*Data Management*
Data will be handled in accordance to the protocol and all applicable SOPs. The Flu Pro questionnaire will be used electronically. Subject's information will only be recorded using the subject's study number and their PIN number. The subject's study number and a PIN number are used by participants to access the electronic Flu Pro Diary. The subject study number is given to the participant by the clinical research coordinator. The PIN is a four digit number that is auto-generated in RedCAP and recorded by the subject so they may return at a later time to complete the Flu Pro Diary. Both are unique and non-identifying numbers.

Once the subject received instructions they will respond to each question. They will be able to review and modify his/her answers before completion/closure of the questionnaire. Upon completion/closure of the questionnaire, a notification message will be presented confirming this and the subject will no longer have access to that day's questionnaire. Study personnel at the site will be able to access the electronic FluPRO questionnaire data; only DCC personnel will be able to access and manage the questionnaire data.

Specimens label study identification codes will be sent to participating labs. No PHI will be transferred. Transmittal logs will be sent via secure file transfer.Details are outlined in the Data Management section of the protocol.

**14.3**
**Confidentiality Protections (for research records, data and/or specimens):**

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e. g., child or spouse abuse

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All data collected in this study will be strictly confidential in accordance with local, state, and federal law.

The only electronic links established between the subject name, DOD ID#, and the Study ID number will be on tracking spreadsheets at the clinical sites used for collecting information on ILI cases as applicable from the electronic medical record and will only be accessed by authorized study staff. During the study, source documents will be held in a secured cabinet with restricted access. Team members with access to the documents are counseled on the importance of confidentiality of subject medical records, and trained on human subjects' protection and HIPAA. All staff involved in this study have completed the required human subjects protection and ethics training. In all electronic records for data analysis, the subject is not referenced by name, but only Study ID number. This method is designed to protect the privacy of study subject medical information. All source documents will be held at the study site in the research spaces in secured cabinets with restricted access. All measures are in place to protect the privacy of all subjects. The study will utilize passwords and firewalls to maintain confidentiality of data accessed via computer. The summary report generated from the interviews and completed questionnaires will not contain any subject identifying information.

**14.4**
**Potential Benefits:**

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

*1. Benefits of participation in the study*

This no greater than minimum risk study provides no direct benefit to the subject. If the study results show that there are significant differences in the either the immunogenicity or effectiveness between vaccines then they would have important implication for influenza vaccination policy in the US military. Conversely, if the findings showed that the differences in immunogenicity or vaccine effectiveness were minimal, they would provide evidence in support of current immunization recommendations. This study has the potential to provide high visibility to military infectious disease research given the importance and global relevance of the research question being addressed.

**14.5 Privacy for Subjects:**

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Following group study briefings, potential subjects will have the opportunity to have their questions and concerns addressed by study staff member and to complete the consent form in a private setting. Please see Section 14.3 for additional details about maintaining a subject's privacy throughout the study.

**14.6 Incidental or Unexpected Findings:**

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

*Vaccine Effectiveness Study:* Achieving this objective involves the collection self-reported data (e.g. demographics, chronic/co-morbid conditions, etc.) and data abstracted from medical records (history of influenza, history of influenza vaccination, etc.), recording respiratory illness symptoms, and the analysis of nasal specimens for diagnosing influenza. Of these, only the diagnosis of influenza has the potential to impact case management. However, the results of the laboratory will not be known until the data collection phase of the study has been completed, and therefore, will not have the potential to improve the management of influenza cases.

*Immunogenicity substudy:* Laboratory analyses conducted for the substudy are specifically focused on HAI testing and immune responses to influenza vaccination. As such, the results may identify an influenza vaccine failure but have little scope to reveal an otherwise unknown life-threatening condition. However, in the event that a life-threatening immune abnormalities are detected in a study subject, the test results will be reported to the study team and the site PI, who would notify the subject's provider. The site PI would also follow-up with the subject.

De-identified study results will be reported in the aggregate and submitted for publication in a peer reviewed journal.

## 15.0 Study Monitoring

**15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).**

- ○ DSMP
- ○ DSMB
- ◉ Both
- ○ Not Applicable

A DSMP should describe the plan to monitor the data to verify that the data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored, and the frequency of monitoring. It should also include the plan to ensure the safety of subjects

This study is a comparison of the effectiveness of licensed influenza vaccines. These reviews will occur annually, dururing periods of low influenza activity when no enrollment is occurring.

Quality Assurance (QA) will be conducted at least once per site per year by a QA Reviewer(s)by someone who is not involved in the day-to-day collection of data or study procedures. QA will occur, as durings off season times. Only subjects that have not been previously checked in a prior QA review will be included in each annual QA review. The reviewer(s) will document any and all of their site-specific QA findings using the QA Checklist and Summary Cover Sheet. The findings should be posted on the PAIVED study portal on the IDCRP Intranet prior to the roll-out of the new Flu vaccine administration dates/ILI season. Any protocol deviations arising from QA review/visits will be reported to the ID IRB according to the protocol.

An independent Data Monitoring Committee appointed by the PI will conduct an interim review after one year to assess whether an early signal or trend exists that could affect equipoise. The DMC will be comprised of subject matter experts in influenza, epidemiology and statistics. The DMC will receive and review study reports from the PI at the one year point and at other times as deemed appropriate.

Describe the composition of your DSMB and how frequently it meets. Explain who will be responsible for ensuring data accuracy and integrity, how often interim data be reviewed - and by whom - and who will perform aggregate analysis of data and adverse events.

The **Data Monitoring Committee (DMC)** includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests. They will review the study prior to initiation and yearly thereafter, unless otherwise recommended by the Committee. The DMC may convene additional reviews as necessary. The DMC will review the study data to evaluate efficacy, study progress, and conduct of the study. The DMC will be responsible for conducting an interim analysis of the results comparing the vaccines for the primary endpoint using data from the first year of the trial (2018-2019). The results of the interim will be used to assess whether there is substantive evidence showing clinically meaningful differences in effectiveness exist between cell-culture-based, the recombinant licensed influenza and egg-based vaccines to warrant early termination of the study. Such a level of evidence would also facilitate more precise comparison of effects in patient subgroups and for secondary endpoints. Although application of this guideline is focused on influenza acquisition, if a similar level of evidence is achieved first in comparing severity between randomized arms, then termination of the study might also be considered.

**Safety Monitoring Plan:**
The USU IDCRP is providing the funds for this research. The IDCRP is a DoD program based at the USU with funding through an interagency agreement with the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID). As part of the NIAID support of this program, Office of Clinical Research Policy and Regulatory Operations (OCRPRO), Division of Clinical Research, NIAID and Regulatory Compliance and Human Subjects Protection Program (RCHSPP), Leidos Biomedical Research, Inc. personnel typically provide study monitoring for IDCRP to assure that appropriate regulations, the approved protocol, and NIAID Intramural Clinical Monitoring Guidelines are followed.

The Principal Investigator and the Chief of Quality Management will perform internal safety monitoring as needed. The internal monitors, may inspect all documents and records maintained by the site, including but not limited to medical records (office, clinic, or hospital) and pharmacy records for the subject in this study. The PI will obtain, as part of the informed consent, permission for monitoring or regulatory authorities to review, in confidence, any records identifying individuals in this clinical study.

Additionally, the Quality Management processes will be utilized to ensure regulatory and protocol-specific responsibilities are met. This process is outlined below.

The Clinical Quality Management Plan (CQMP) establishes the quality management guidelines for tasks to PAIVED. Quality Control (QC) activities will be conducted for each subject's study visit

by an individual at the study site who did not complete the study visit, such as another Clinical Research Coordinator (CRC) or the Site Manager (SM). Quality Assurance (QA) activities will be conducted annually by a QA Reviewer who is not involved in the day-to-day collection of data or study procedures. Following each QA Annual Review Visit, the QA Reviewer will complete a QA Annual Summary Report that will be uploaded to the Intranet and an overall QM study status summary will be shared with IDCRP Leadership. Any protocol deviations or reportable events arising from QC and QA reviews and/or visits will be reported to the USUHS IRB according to the protocol.

Leidos reviewed this project and it was determined that this study does not require independent data and safety monitoring.

## 16.0 Reportable Events

### 16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

### Reportable Events

A unanticipated problem (UP) may only involve exposure of a subject or others to an unexpected risk or the risk may culminate in a subject or another individual actually experiencing a harm that is generally described as an adverse event in clinical research or an adverse outcome in behavioral or social science research. UP that are directly related to study procedures will be reported within 48 hours to the IRB.

An adverse event is defined as any complaint of illness or injury that occurs during the period of study participation. These are recorded and inspected by the supervising physician investigator to determine severity and relatedness to participation (definite, probable, possible, or unlikely). The physician investigator is responsible for directly managing or coordinating management of adverse events following routine clinical practice. Because this is proposed to be a minimal risk study, the reporting of adverse events is limited to an analysis at the time of annual reporting.

UPs involving risk to the subject or others, adverse events, and serious adverse events will be reported only if they are directly related to study procedures (e.g., phlebotomy, nasal swab collection, etc. ) or determined by the study site investigator to be an event requiring reporting to the IRB. Stable chronic conditions which are present prior to enrollment and do not worsen are not considered adverse events or serious adverse events even if they meet the standard definition, and will be accounted for in the subject's medical history. They will not be reported as adverse events or serious adverse events.

Expected adverse events which are not serious are reported on the Annual Progress Report (APR) during the continuing review of the protocol. APR is mostly due in a 12-month cycle, the anniversary month of the protocol's initial approval or due in lesser than 12-month cycle as determined by the IRB for continuing review and approval.

A serious adverse event is any illness or injury occurring during the period of study participation that:
1) requires the subject to be admitted to a hospital
2) Causes permanent injury to the subject
3) Causes the death of a study subject

Serious Adverse Events:

The PI, within 48 hours, will report serious adverse events (SAE) directly relating to study procedures occurring in subjects enrolled at their site. This is accomplished by submitting an adverse event report memorandum to the IRB.

Unexpected (but not serious) adverse events occurring in subjects enrolled at a study site which, in the opinion of the PI, are possibly related to study procedures will be reported by the PI within 10 working days to the IRB using the same procedure.

A summary of all serious or unexpected adverse events also will be included in the APR.
Reporting Protocol Deviations

The PI or designee will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the study protocol or study-specific procedure. Investigators will report protocol deviations to the USU ID IRB within 10 business days that:
1) Relate to subject safety
2) Relate to the informed consent process
3) Are any other protocol deviations which, in the opinion of the PI, should be promptly reported to the IRB

Subject non-compliance with collection of nasal swabs will be considered a deviation. A log of all deviations will be reported annually in the continuing review report to the IRB and in the Final Study Report.

## Adverse Events (AE)

Expected adverse events that are not serious, but are directly related, are reported at continuing review.
Expected adverse events that are not serious and not related will not be recorded or reported. A continuing review report is mostly due in a 12-month cycle, the anniversary month of the protocol's initial approval or due in lesser than 12-month cycle, as determined by the IRB for continuing review and approval. An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Expected non-serious adverse events related to study procedures (e.g. phlebotomy, nasal swab collection, etc.) conducted by a study staff member will be reported to the IRB at continuing review.

Please note: Known side effects of the FDA-licensed influenza vaccines (CDC. Flu Vaccine Safety Information. **https://www.cdc.gov/flu/protect/vaccine/general.htm**) will **not** be reported as Adverse Events. The risks of side effects of the flu vaccine are generally mild and go away on their own within a few days.

Common side effects from the influenza vaccine include:

Soreness, redness, and/or swelling from the shot
Headache
Fever
Nausea
Muscle aches
The influenza vaccine, like other injections, can occasionally cause fainting.

A few research studies have found a possible small association of injectable influenza vaccine with Guillain-Barré syndrome (GBS). Overall, these studies estimated the risk for GBS after vaccination as fewer than 1 or 2 cases of GBS per one million people vaccinated. Other studies have not found any association. GBS also, rarely, occurs after acute influenza infection. Even though GBS following flu illness is rare, GBS is more common following influenza infection than following influenza vaccination. GBS has not been associated with FluMist, the nasal spray vaccine. (CDC. Flu Vaccine Safety Information. https://www.cdc.gov/flu/protect/vaccine/general.htm)

Serious Adverse Event (SAE)
This is a no greater than minimum risk study. We will not be monitoring subjects' medical records for events following the standard of care vaccination.

Unexpected Adverse Event
An AE is unexpected if it is not listed in the Package Insert (for the influenza vaccine) or is not listed at the frequency or severity that has been observed. All serious adverse events or

reportable events will be reported to the IRB in 15 calendar days or sooner if mandated by local regulation.

### Unanticipated Problem that is not an Adverse Event (UPnonAE)

An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, or accidental destruction of study records.
Protocol Deviation

Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:
1. Those that occur because a member of the research team deviates from the protocol;
2. Those that are identified before they occur, but cannot be prevented;
3. Those that are discovered after they occur; Non- serious deviations will be reported at the time of continuing review.

Deviations that require prompt reporting are:

1. Those that relate to the informed consent process;
2. Those that relate to subject safety;
3. Any other deviation in which the PI feels should be promptly reported

Serious Protocol Deviation
A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

## Documenting, Recording, and Reporting Adverse Events

All AEs and all SAEs occurring from the time the informed consent is signed through Day 28 will be documented, recorded, and reported.

At each contact with the subject, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the subject's medical record/source document,
- recorded on the Adverse Event Case Report Form (AE CRF) and reported as outlined below

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms will be recorded as the AE.

## Assessment of Adverse Event

The Investigator will evaluate all AEs with respect to Seriousness (criteria listed above), Severity (grading), and Causality (relationship to study agent and relationship to research) according to the following guidelines.

### Severity

The Investigator will grade the severity of each AE according to the National Institutes of Health, "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" Version 2.1, March 2017, which can be found at: http://rsc.tech-res.com/docs/default-source/safety /daids-ae-grading-table-mar2017.pdf

### Causality

Causality (likelihood that the event is caused by the study agent(s)) or research study participation will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- evidence to suggest a causal relationship
- is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- No evidence of a more likely alternative etiology.

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship

OR

- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship

OR

- definitely due to an alternative etiology

Note: Other factors should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

## 17.0 Equipment/non-FDA Regulated Devices

**17.1 Does the study involve the use of any unique non-medical devices/equipment?**

○ Yes ◉ No

## 18.0 FDA-Regulated Products

**18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?**

☐ Drugs
☐ Dietary Supplements
☑ Biologics
☐ Devices
☐ N/A

**18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:**

☑ Are drug(s) in this research being used in accordance to the approved labeling?
☐ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

| View Details | Drug Name | FDA Approved | A new drug or a new use of approved drug: | IND Number |
|---|---|---|---|---|
| ⊟ | **Trade Drug Name:** Flucelvax Quadrivalent (Seqirus)<br>**Generic Drug Name:**<br>**Investigational Drug Name:** | Yes | No | |

| | |
|---|---|
| Trade Drug Name: | Flucelvax Quadrivalent (Seqirus) |
| Generic Drug Name: | |
| Investigational Drug Name: | |
| Identify the name of the manufacturer or source of investigational drug/biologic: | Seqirus |
| Is the drug supplied at no cost? | Yes |
| Is the Drug FDA Approved: | Yes |
| Is this a new drug or a new use of an already approved drug | No |
| Is an IND necessary | No |
| IND Number | |
| Who holds the IND: | N/A |
| IND details: | |
| If FDA Approved and an IND is not required, Please provide a rationale for exemption: | |
| Are you currently using this IND in another research project? | No |
| If yes, list the IRB Number(s): | |
| Dose Range: | |
| Frequency: | |
| Route of administration: | |
| Will the investigational pharmacy be dispensing? | No |
| If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic: | |
| Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared: | |
| | |

| | |
|---|---|
| Indication(s) under Investigation: | |
| Where will the drug be stored | |
| Drug Storage Restrictions (including temperature, etc.): | |
| Administration Instructions: | |
| Possible Untoward Effects, Their Symptoms & Treatment: | |
| Potential or Actual Antidotes for Excessive or Adverse Drug Effect: | |
| Contraindications and Interactions, If Known: | |
| Investigators Authorized to Prescribe: | |

| | | | | |
|---|---|---|---|---|
| ⊟ | **Trade Drug Name:** Flublok® QIV (45µg HA/strain)<br>**Generic Drug Name:**<br>**Investigational Drug Name:** | Yes | No | |

| | |
|---|---|
| Trade Drug Name: | Flublok® QIV (45µg HA/strain) |
| Generic Drug Name: | |
| Investigational Drug Name: | |
| Identify the name of the manufacturer or source of investigational drug/biologic: | Protein Sciences |
| Is the drug supplied at no cost? | Yes |
| Is the Drug FDA Approved: | Yes |
| Is this a new drug or a new use of an already approved drug | No |
| Is an IND necessary | No |
| IND Number | |
| Who holds the IND: | N/A |
| IND details: | |
| If FDA Approved and an IND is not required, Please provide a rationale for exemption: | |
| Are you currently using this IND in another research project? | No |
| If yes, list the IRB Number(s): | |
| Dose Range: | |
| Frequency: | |
| Route of administration: | |
| Will the investigational pharmacy be dispensing? | No |
| If the source is not a FDA licensed facility, provide details regarding the purity, quality, | |

| | |
|---|---|
| stability and sterility of the investigational drug/biologic: | |
| Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared: | |
| Indication(s) under Investigation: | |
| Where will the drug be stored | |
| Drug Storage Restrictions (including temperature, etc.): | |
| Administration Instructions: | |
| Possible Untoward Effects, Their Symptoms & Treatment: | |
| Potential or Actual Antidotes for Excessive or Adverse Drug Effect: | |
| Contraindications and Interactions, If Known: | |
| Investigators Authorized to Prescribe: | |

| | | | | |
|---|---|---|---|---|
| ⊟ | **Trade Drug Name:** Flulaval® QIV (15 µg HA/strain)<br>**Generic Drug Name:**<br>**Investigational Drug Name:** | Yes | No | |

| | |
|---|---|
| Trade Drug Name: | Flulaval® QIV (15 µg HA/strain) |
| Generic Drug Name: | |
| Investigational Drug Name: | |
| Identify the name of the manufacturer or source of investigational drug/biologic: | ID Biomedical Corp. of Quebec |
| Is the drug supplied at no cost? | Yes |
| Is the Drug FDA Approved: | Yes |
| Is this a new drug or a new use of an already approved drug | No |
| Is an IND necessary | No |
| IND Number | |
| Who holds the IND: | N/A |
| IND details: | |
| If FDA Approved and an IND is not required, Please provide a rationale for exemption: | |
| Are you currently using this IND in another research project? | No |
| If yes, list the IRB Number(s): | |
| Dose Range: | |

| | |
|---|---|
| Frequency: | |
| Route of administration: | |
| Will the investigational pharmacy be dispensing? | No |
| If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic: | |
| Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared: | |
| Indication(s) under Investigation: | |
| Where will the drug be stored | |
| Drug Storage Restrictions (including temperature, etc.): | |
| Administration Instructions: | |
| Possible Untoward Effects, Their Symptoms & Treatment: | |
| Potential or Actual Antidotes for Excessive or Adverse Drug Effect: | |
| Contraindications and Interactions, If Known: | |
| Investigators Authorized to Prescribe: | |

| | | | | |
|---|---|---|---|---|
| ⊟ | **Trade Drug Name:** Fluarix QIV (15 µg HA /strain)<br>**Generic Drug Name:**<br>**Investigational Drug Name:** | Yes | No | |

| | |
|---|---|
| Trade Drug Name: | Fluarix QIV (15 µg HA/strain) |
| Generic Drug Name: | |
| Investigational Drug Name: | |
| Identify the name of the manufacturer or source of investigational drug/biologic: | GlaxoSmithKline |
| Is the drug supplied at no cost? | Yes |
| Is the Drug FDA Approved: | Yes |
| Is this a new drug or a new use of an already approved drug | No |
| Is an IND necessary | No |
| IND Number | |
| Who holds the IND: | N/A |
| IND details: | |
| If FDA Approved and an IND is not required, Please provide a | |

| | |
|---|---|
| rationale for exemption: | |
| Are you currently using this IND in another research project? | No |
| If yes, list the IRB Number(s): | |
| Dose Range: | |
| Frequency: | |
| Route of administration: | |
| Will the investigational pharmacy be dispensing? | No |
| If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic: | |
| Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared: | |
| Indication(s) under Investigation: | |
| Where will the drug be stored | |
| Drug Storage Restrictions (including temperature, etc.): | |
| Administration Instructions: | |
| Possible Untoward Effects, Their Symptoms & Treatment: | |
| Potential or Actual Antidotes for Excessive or Adverse Drug Effect: | |
| Contraindications and Interactions, If Known: | |
| Investigators Authorized to Prescribe: | |

| | | | | |
|---|---|---|---|---|
| ⊟ | **Trade Drug Name:** Afluria QIV (15 µg HA /strain)<br>**Generic Drug Name:**<br>**Investigational Drug Name:** | Yes | No | |

| | |
|---|---|
| Trade Drug Name: | Afluria QIV (15 µg HA/strain) |
| Generic Drug Name: | |
| Investigational Drug Name: | |
| Identify the name of the manufacturer or source of investigational drug/biologic: | Seqirus |
| Is the drug supplied at no cost? | Yes |
| Is the Drug FDA Approved: | Yes |
| Is this a new drug or a new use of an already approved drug | No |

| | |
|---|---|
| Is an IND necessary | No |
| IND Number | |
| Who holds the IND: | N/A |
| IND details: | |
| If FDA Approved and an IND is not required, Please provide a rationale for exemption: | |
| Are you currently using this IND in another research project? | No |
| If yes, list the IRB Number(s): | |
| Dose Range: | |
| Frequency: | |
| Route of administration: | |
| Will the investigational pharmacy be dispensing? | No |
| If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic: | |
| Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared: | |
| Indication(s) under Investigation: | |
| Where will the drug be stored | |
| Drug Storage Restrictions (including temperature, etc.): | |
| Administration Instructions: | |
| Possible Untoward Effects, Their Symptoms & Treatment: | |
| Potential or Actual Antidotes for Excessive or Adverse Drug Effect: | |
| Contraindications and Interactions, If Known: | |
| Investigators Authorized to Prescribe: | |

**18.4 Reporting Requirements for FDA-regulated research under IND and IDE:**

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

**18.5 Sponsor (organization/institution/company):**

☑ N/A

If applicable, provide sponsor contact information:

## 19.0 Research Registration Requirements

### 19.1 ClinicalTrials.gov Registration:

- ○ Registration is not required
- ○ Registration pending
- ◉ Registration complete

"NCT" number:

NCT03734237

### 19.2 Defense Technical Information Center Registration (Optional):

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

## 20.0 References and Glossary

### 20.1 References:

References:


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### 20.2 Abbreviations and Acronyms:

| | |
|---|---|
| AE | Adverse Event |
| AFHSB | Armed Forces Health Surveillance Branch |
| AHLTA | Armed Forces Health Longitudinal Technology Application |
| ARD | Acute Respiratory Disease |
| ARI | Acute Respiratory Infection |
| BAMC | Brooke Army Medical Center |
| BMI | Body Mass Index |
| CBC | Complete Blood Count |
| CDC | Centers for Disease Control and Prevention |
| CRC | Clinical Research Coordinator |
| CRF | Case Report Form |
| DCC | Data Coordination Center |
| DHHS | Department of Health and Human Services |
| DNBI | Disease and Non-Battle Injury |
| DoD | Department of Defense |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme Linked Immunosorbent Assay |
| FHP | Force Health Protection |
| FSH | Fort Sam Houston |
| GC-MS | Gas chromatography-mass spectrometry |
| GCP | Good Clinical Practice |
| GEIS | Global Emerging Infections Surveillance and Response System |
| HIPAA | Health Insurance Portability and Accountability Act |
| IHB | Immunization Healthcare Branch |
| ICD | Informed Consent Document |
| ICU | Intensive Care Unit |
| IDCRP | Infectious Disease Clinical Research Program |
| IDSA | Infectious Diseases Society of America |
| IFN | Interferon |
| IL | Interleukin |
| ILI | Influenza-like Illness |
| IRB | Institutional Review Board |
| LAIV | Live attenuated influenza vaccine |
| MCP | Macrophage Chemo-attractant Protein |
| MIP | Macrophage Inflammatory Protein |
| MAMC | Madigan Army Medical Center |
| MDR | Military Health System Data Repository |
| MTF | Military Treatment Facility |
| NHRC | Naval Health Research Center |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| NMCP | Naval Medical Center Portsmouth |
| NMCSD | Naval Medical Center San Diego |
| NMRC | Naval Medical Research Center |
| OCRPRO | Office of Clinical Research Policy and Regulatory Operations (formerly RCHSPB) |
| OHRP | Office for Human Research Protections |
| PCC | Program Coordination Center |

| | |
|---|---|
| PCR | Polymerase Chain Reaction |
| PI | Principal Investigator |
| PPM | Personal Protective Measures |
| RA | Research Assistant |
| RCHSPP | Regulatory Compliance and Human Subjects Protection Program |
| RCT | Randomized Controlled Trial |
| RR | Relative Risk (measured as a risk ratio, odds ratio, hazards ratio, etc.) |
| rRT-PCR | Real-time reverse transcriptase polymerase chain reaction |
| SAE | Serious Adverse Event |
| SARI | Severe Acute Respiratory Illness |
| SIQ | Sick in Quarters |
| SOIV | Swine-Origin Influenza Virus |
| SOP | Standard Operating Procedure |
| SPL | Specimen Processing Laboratory |
| SSN | Social Security Number |
| Study ID | Study Identification Number |
| US | United States |
| USU | Uniformed Services University of the Health Sciences |
| VE | Vaccine efficacy |
| WAMC | Womack Army Medical Center |
| WRAIR | Walter Reed Army Institute of Research |
| WRNMMC | Walter Reed National Military Medical Center |