Title: Immune response to influenza vaccination and effect on reproductive hormone

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JHSPH IRB Research Plan for New Data Collection

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Study Title: **Immune response to influenza vaccination and effect on reproductive hormone**

IRB No.: **00005392**

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I. Aims of the Study: Describe the aims/objectives of the research and/or the project's research questions or hypotheses.

Pregnant women are a priority group for the receipt of the seasonal inactivated influenza vaccine because of: i) the increased risk of adverse outcomes to themselves and their fetuses should they become ill with influenza, and ii) the need to protect infants during a period when they are too young to receive the vaccine themselves. Although the seasonal inactivated influenza vaccine has been shown to be safe and well tolerated in the second and third trimesters of pregnancy, little data exist on the outcomes of vaccination during the first weeks of pregnancy. If adverse outcomes occur, then this may be tied to hormonal changes that are secondary to inflammatory cytokine responses following vaccination. During a healthy pregnancy, steroid hormones, including estradiol, progesterone, and cortisol increase substantially and contribute to reductions in inflammatory cytokine concentrations that are necessary to support a successful pregnancy [1-3]. Through the mechanisms of bidirectional communication between endocrine and immune cells, questions arise as to whether activation of immune cells by infection or vaccination and the subsequent production of inflammatory cytokines, including TNF-□, could change steroid hormone concentrations and the outcome of pregnancy [4]. This open label prospective trial expands our pilot study conducted during the 2013-2014 influenza season in which we examined the effect of seasonal inactivated influenza vaccine (IIV) on inflammatory cytokines and hormonal responses in healthy women of reproductive age. Our initial findings showed a non-significant 20% decrease in serum progesterone vaccination as compared to the same menstrual cycle time point (day 17) in the non-vaccinated month[5]. Initial findings also showed increases in some cytokine levels after vaccination [5]. With the additional participants provided by this amendment, we would like to repeat our initial pilot study during 1 or 2 additional influenza seasons with some modifications, in order to better understand the early responses to influenza vaccine and the effects on hormones. The women will be recruited at the Center for Immunization Research, Johns Hopkins Bloomberg School of Public Health, followed for one menstrual cycle to measure estradiol, progesterone, and cytokines and then vaccinated with the seasonal inactivated influenza vaccine prior to ovulation during a second month. At the investigator's discretion, or if there is active circulation of influenza virus in Baltimore, we will vaccinate during the first menstrual cycle (prior to ovulation) and then follow for a second menstrual cycle for comparison. After vaccination, they will be followed for cytokine and chemokine responses as well as changes in the concentrations of estradiol and progesterone hormones.

Primary Objectives:

1. To explore whether receipt of IIV during the second week of the menstrual cycle (i.e., the week prior to ovulation) is associated with changes in steroid hormone levels, particularly decreases in progesterone, following ovulation.
2. To assess the feasibility of conducting further research in this area.

Primary Endpoints:

1. Changes in levels of estradiol and progesterone one week after receipt of influenza vaccination.

Exploratory Objectives:

1. To explore whether inflammatory cytokine responses to IIV receipt are associated with changes in reproductive hormone levels.

2. Identify optimal biomarkers of the inflammatory response after vaccination.

3. To collect peripheral blood mononuclear cells (PBMC) for future studies of cellular immune response.

Exploratory Endpoints:

1. Assess the inflammatory cytokine responses (including C-reactive protein [CRP]) to IIV.
2. To record adverse events in the 7 days after vaccination, including fever, myalgia, malaise, and hypersensitivity reactions.

II. Background and Rationale: Explain why this study is being done. Summarize briefly what is already known about the issue and reference previously published research, if relevant.

Pregnant women are at risk for complications with influenza infection resulting in greater morbidity and mortality than non-pregnant women during seasonal epidemics, but especially during pandemics. Influenza vaccination decreases maternal respiratory illness, reduces fetal and neonatal death [6], and improves neonatal health by improving birth weight and by preventing early neonatal infection. Since 2004, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention has recommended that all pregnant women receive the inactivated influenza vaccine (IIV), regardless of trimester [7]. Inactivated influenza vaccines are safe in pregnant women, although limited data are available for women vaccinated in the first trimester; much of these data have been summarized in a recent review [8]. Studies have looked at spontaneous abortions (SAB) and fetal loss in relation to both seasonal and adjuvanted pandemic vaccines [6, 9, 10] and found either no increase or a decrease in fetal loss associated with influenza vaccination. It is, however, difficult to determine whether vaccination in the earliest weeks of pregnancy is related to SABs. One retrospective study utilizing sites in the Vaccine Safety Datalink found a statistically non-significant increase in SABs in women who received the influenza vaccine the week before ovulation (and conception)[10]. The study we are proposing is in part designed to understand the cytokine and hormonal responses to IIV in menstruating women, in order to better understand the effects of vaccination on the earliest days of pregnancy.

During a normal pregnancy, concentrations of estrogens and progesterone increase over the three trimesters to maintain the pregnancy and decrease pro-inflammatory responses. Women with high baseline inflammation (e.g., high CRP) have lower levels of progesterone at all states of the menstrual cycle [11], and pro-inflammatory responses are linked to pregnancy loss [4]. Recent studies are starting to look at early cytokine responses to influenza vaccine in pregnant women, and have shown increases in inflammatory markers, especially CRP and TNFα [12, 13].

Cytokines are essential immune mediators which orchestrate the immune response to natural infection and vaccination [14]. Changes in serum cytokine profiles have proven to be useful as biomarkers to define stages of pathogenesis for numerous infectious and autoimmune diseases and cancers [15-17]. The predictive value of cytokines is likely due to the central role that cytokines play in orchestrating protective immunity to pathogens, including influenza viruses [14]. These cytokine responses must be balanced to prevent pathologies. Host responses to some influenza A strains (e.g., H5N1) can trigger uncontrolled cytokine production (i.e. “cytokine storm”) leading to severe immunopathology and even death [18]. Some studies, however, demonstrated that vaccine-induced changes in serum cytokines correlate strongly with activation of both innate and adaptive immune defenses [19-21]. These data suggest that changes in global cytokine profiles after vaccination may provide useful insight into vaccine

efficacy and could potentially serve as correlates of protection [20-22]. Despite this, there are remarkably few studies that have examined the host cytokine response to seasonal influenza vaccines.

We have been interested in whether serum cytokines could be used as a tool to better understand the immune response to seasonal influenza vaccines. We have examined the kinetics of cytokine responses in healthy, adult men and women after vaccination with the IIV. In our small study (n=20) we found that there were detectable cytokine responses by 3 hours after vaccination, and statistically significant changes within the first 7 hours. In looking at 15 cytokines and chemokines, we found that IP-10 and IFN-γ were significantly increased from baseline 7-24 hours after vaccination. (Manuscript in preparation). In a recently published study, we determined the effects of TIV and live attenuated influenza vaccine (LAIV) on serum cytokines in healthy adult men and women over two influenza vaccine seasons [23]. Our data indicated that TIV, but not LAIV, was associated with significant decreases in serum IL-8 and TNF-□□ levels at 14 and 28 days post-vaccination. This is consistent with research done by Christian, et al, who found a decrease in IL-8 levels in non-pregnant women (but not pregnant women) after vaccination [13], and with our unpublished work which shows that IL-8 is decreased at 44 hours and remains decreased to 14 days after IIV.

Despite the decreases seen in IL-8 in non-pregnant adult men and women, two recent studies looking at inflammatory responses in pregnant women after influenza vaccination showed an increase in concentrations of IL-8, CRP, IL-6, TNFα, and MIF 48 hours after influenza vaccination [12, 13]. Discrepancies among studies might be caused by whether studies recruited women only [12, 13] or combined outcome data from both women and men [23]. No group has looked to see if these inflammatory responses after vaccination affect steroid hormone levels or if they have any effect on the earliest stages of pregnancy. This study is designed to explore these questions.

During our initial pilot study conducted during the 2013-2014 influenza season we examined the earliest immune responses to influenza vaccine and the potential impact on reproductive and stress hormones on women of reproductive age. Our initial findings showed no significant changes in serum hormone levels of estrogen, progesterone and cortisol after vaccination, compared with similar time points in a baseline menstrual cycle without vaccination. However, a non-significant 20% decrease in serum progesterone was observed after vaccination as compared to the non-vaccinated month[5]. Initial findings also showed increases in some cytokine levels after vaccination, compared with levels before vaccination during the vaccination menstrual cycle; cytokine levels were not assessed during the baseline menstrual cycle without vaccination[5]. Studying a larger number of women over 1 or 2 additional influenza seasons would help us better understand the effects of IIV on early immune responses and hormone levels.

III. Study Design:

A.

This is an open label study looking at the effect of influenza vaccine on cytokines and reproductive hormones. We will recruit women of reproductive age who are not on hormonal birth control, measure their cytokines and reproductive hormones for 1 month to establish a baseline, and then vaccinate them with the seasonal inactivated influenza vaccine just prior to ovulation, and follow the cytokines and reproductive hormones for the remainder of their cycle. We will use commercially available urine Luteinizing hormone (LH) strips to measure ovulation.

B. Provide a sample size and a justification as to how you arrived at that number. If you use screening procedures to arrive at a final sample a table may be helpful.

The power calculations are based on specific aim 1, with regards to changes in progesterone.

SA1: To determine if vaccination with IIV prior to ovulation (day 11 of menstruation) is associated with changes in post-ovulation serum reproductive (progesterone and estradiol) hormone concentrations.
-H 1: Post-vaccination serum progesterone concentrations will be lower in the month after vaccination than measured prior to vaccination.

We are planning to study 30 adult non-pregnant women each year. Based on the results from the first 30 student enrollees, we estimate the log (base 10) mean (SD) serum concentration of progesterone during the luteal phase of menstruation prior to vaccination is 0.71 (0.51), and 0.58 (0.54) post vaccination. This difference of -0.13 on the log (base 10) scale corresponds to a median ratio of 0.74 in other words, a 26% decrease in median progesterone levels after vaccination. The observed correlation in these log concentration values was 0.60. For a total sample size of 90 women (base task order and 2 option years), assuming similar standard deviation in log (base 10) pre- and post- vaccination values as observed in the initial sample of 30, the following table shows to the power to detect a given median post-vaccination to pre-vaccination concentration ratio for several pre- and post- concentration correlation values. These results are based on a type-1 error level of .05.

	Correlation		
Median Ratio	0.55	0.60	0.65
0.75	*0.63**	*0.69*	*0.74*
0.70	*0.82*	*0.86*	*0.90*
0.65	*0.93*	*0.95*	*0.97*

* values in italics give estimated power to detect the specified median ratio

for a specified correlation between the pre- and post-vaccination progesterone values

IV. Participants:

Describe the study participants and the population from which they will be drawn. Specify the inclusion and exclusion criteria. If you plan to include children, note their ages and whether you will include children in foster care. Note if the participants are particularly vulnerable in terms of cognitive limitations, education, legal migration status, incarceration, poverty, or some combination of factors.

Women aged 18-39 years will be recruited from Johns Hopkins University Campuses as well as from the surrounding community in East Baltimore. We will aim to include approximately equal numbers of women who have and have not previously received an H1N1-containing influenza vaccine.

A. Inclusion Criteria:

1. Women 18-39 years of age who are in good health.

2. Good general health as a result of review of medical history and/or clinical testing at the time of screening.
3. Available for the duration of the trial.
4. Willingness to participate in the study as evidenced by signing the informed consent document.
5. Willing to be abstinent or to use non-hormonal methods of contraception for the duration of the study.
6. History of normal menstrual cycles (26 to <35 days in length) for ≥3 months prior to enrollment.
7. Willingness to refrain from routine vaccination (except as administered during study) for the duration of the study.

B. **Exclusion Criteria:**

1. Use of contraceptive pills, patch, injection or other hormonal therapies in the preceding 3 months. Or 6 months for Depo-Provera.
2. A history of hypersensitivity, including anaphylaxis to any of the components of IIV or to eggs.
3. Previous receipt of the same-season influenza vaccine.
4. Pregnancy as determined by a positive urine or serum human choriogonadotropin (β-hCG) test at any point during the study or in the preceding 3 months.
5. Currently is lactating or breast-feeding.
6. Fewer than 3 normal menstrual cycles since conclusion of last pregnancy or last use of hormonal birth control.
7. A history of autoimmune disease, or any other chronic medical condition considered clinically significant by the investigator.
8. History of HIV, Hepatitis C or active Hepatitis B.
9. Known immunodeficiency syndrome.
10. History of Guillain-Barré syndrome.
11. Use of chronic oral or intravenous administration (≥14 days) of immunosuppressive doses of steroids, i.e., prednisone >10 mg per day, immunosuppressants or other immune-modifying drugs within 30 days of starting this study. (Use of topical, nasal or inhaled steroids is permitted)
12. Receipt of a live vaccine within 4 weeks or a killed vaccine within 2 weeks prior to study start or during study.
13. Receipt of blood or blood-derived products (including immunoglobulin) within 6 months prior to study vaccination.
14. Receipt of another investigational vaccine or drug within 30 days prior to study start, or during study.
15. Ongoing, daily use of analgesics or anti-inflammatory medications, including nonsteroidal anti-inflammatories. Occasional use, and use associated with menstrual periods is acceptable.

a. Provide sample size and a clear justification as to how you arrived at your projected sample size.
We will evaluate the effect of vaccine on 90 women (see below; this includes the 30 women enrolled in the pilot study). Women who drop out before completing data collection for two menstrual cycles will be replaced. We may need to enroll up to 120 women in order to ensure a complete data set.

V. <u>Study Procedures</u>:

In this section, provide details of your procedures, particularly as they relate to human subjects. If this is a multi-center study, make the role of JHSPH clear. If the JHSPH will serve as **data coordinating center**, indicate in the sections below which procedures JHSPH will not be performing. Additional information regarding data coordinating centers is requested in a later section. If your study will develop in phases, address each item below by phase.

A. **Recruitment Process:**

1. Describe how you will identify, approach, and inform potential participants about your study. Include details about who will perform these activities and what their qualifications are.

   IRB-approved recruitment information will be posted and distributed throughout the campuses of the Johns Hopkins University, Including the Schools of Public Health, Medicine and Nursing as well as other locations as allowed in the greater Baltimore area. In addition, the CIR has ongoing recruitment using IRB-approved advertising (electronic and/or other media publications and advertising), social media, an IRB-approved screening protocol (H.22.02.04.19. A2), and a large data base of former CIR clinical trial participants and initial contacts that we can query for potential recruits.

   Subjects may be initially evaluated through a JHSPH IRB-approved general screening protocol (IRB# H22040219A2). This protocol is used at the CIR to screen all potential adult volunteers for vaccine trials. After an initial phone screen (using IRB approved Phone Screen/Initial Contact form) by clinic staff focused on providing background information of the trial and a review of basic inclusion and exclusion criteria, a screening visit may be scheduled. After signing a screening consent, subjects may be asked to provide a medical history and/or laboratory specimens, and to undergo a physical examination. This general screening protocol is used to verify that the subject is healthy and potentially eligible for a vaccine trial. Subjects will be screened up to 30 days prior to enrollment in the study, depending on the timing of menstrual cycles.

   To assure that adequate time is given for the subject to consider study participation, a read-only copy of the IRB approved ICF may be sent via postal service, email, and/or fax prior to the screening visit.

   Retention of Study Subjects
   We will employ several strategies aimed at retaining participants through study completion. During screening, we will obtain detailed primary locator information, as well as secondary contact information. Subjects will also provide information for people who may be contacted if primary and secondary means of contact fail. Locator information will be reviewed with subjects at each visit (i.e., addresses, phone numbers, email addresses). In addition, birthday cards/holiday cards may be mailed to check addresses, and reminders may be sent using various methods (including but not limited to phone, email, text messaging, and postal mail). All data will be maintained and updated in a password protected locator database.

2. Address any privacy issues associated with recruitment. If recruitment itself may put potential participants at risk (if study topic is sensitive, or study population may be stigmatized), explain how you will minimize these risks.

   No special privacy concern exists with the study or the recruitment process.

   Recruitment and participation in the study will not put the subject at any additional risk to privacy.

B. **Consent Process**:

1. Describe the following details about obtaining informed consent from study participants. If a screening process precedes study enrollment, also describe the consent for screening.

   a. **Who will obtain informed consent, and their qualifications:**

The PI and/or the study coordinator or other designated individuals will obtain informed consent. Anyone who obtains informed consent from participants will have received human subjects training and will be trained on the study and consent. He/she will be so designated on a designation and log, and the process will be overseen by the PI and study coordinator.

b. **How, where, and when the consent discussion(s) will occur:**

During the screening visit, each subject will be given a IRB-approved informed consent form and allowed ample time to read the consent, allowed to ask questions about the study, have his/her questions answered, and given time to decide if he/she would like to participate in the study.

c. **The process you will use to determine whether a potential participant meets eligibility criteria:**

Healthy subjects will be recruited for this study. Potential subjects will respond to posted flyers, website postings, and newspaper advertisements by telephone call or email to the clinical trial site. Study staff will respond to inquiries by phone. Study staff will provide a brief, scripted synopsis of the research study that includes basic inclusion and exclusion criteria in compliance with the CIR IRB approved screening protocol. Subjects who express interest in participating in the study will be asked to complete a telephone pre-screen to assess general health status and basic eligibility. Potential volunteers determined to be generally healthy and meeting basic eligibility requirements are scheduled for an in-person screening

After the initial screening process has been completed, eligible and willing subjects will be asked to return to the CIR for study specific consenting. These subjects will read the study consent form, be encouraged to ask questions, and then answer a multiple-choice questionnaire to evaluate comprehension of study procedures, requirements, and risks. Study staff trained to obtain informed consent and delegated to do so will conduct the consenting process. Study staff will review the completed comprehension assessment questionnaire with the subject. The questionnaire helps the study staff to identify gaps in the subjects' understanding of participating in the research study. If a subject answers any questions incorrectly, study staff will review the pertinent study information with the subject until the subject verbalizes understanding. The subject will then be given a 2nd, and 3rd attempt to answer 70% or more of the questions correctly. The subject and staff member obtaining consent will both sign the comprehension assessment. Both subject and staff member obtaining consent will sign, date, and time the Informed Consent Form and a signed copy of the consent will be given to the subject.

d. Whether you will obtain a signature from the participant or will use an oral consent process:

Written informed consent will be used for this study. All subjects must sign the Informed Consent to participate. Both subject and staff member obtaining consent will sign, date, and time the Informed Consent Form and a signed copy of the consent will be given to the subject.

e. Whether you will obtain a legally authorized representative's signature for adults lacking capacity:

N/A

f. If children are included in the study, if and how you will obtain assent from them:

N/A

g. If children are included in the study, how you will obtain permission for them to participate from their parent, legal guardian, or other legal authority (if child is in foster care or under government supervision) :

N/A

h. If you are seeking a waiver of informed consent or assent, the justification for this request:

N/a

i. Whether you will include a witness to the consent process and why:

N/A

j. If the language is unwritten, explain how you will communicate accurate information to potential participants and whether you will use props or audio materials:

N/a

2. Identify the countries where the research will take place, and the languages that will be used for the consent process.

Country	**Consent Document(s) (Adult Consent, Parental Permission, Youth Assent, etc.)**	**Languages**
USA	Adult Informed Consent Form	English

Study Implementation:

1. Describe the procedures that participants will undergo. If complex, insert a table below to help the reviewer navigate.

		Month	screening	1						2						
Procedure	Blood volume	Day	-30 to -0	0	11	12	13	17	21	28	39	40	41	45	49	56
Complete History/ Physical			X													
Obtain Informed Consent			X													
Interim Clinical Evaluation				X	X			X	X	X	X	X	X	X	X	X
Urine pregnancy test			X	X							X					X
VACCINATION											**X**					
Progesterone/ estradiol	5			X	X			X	X	X	X			X	X	X
Cytokines (serum)	5				X	X	X				X	X	X			
HAI	5										X					X
PBMC	30				X				X		X				X	
Daily blood volume			0	5	40	5	5	5	35	5	45	5	5	5	35	10
Cumulative Total blood volume			0	5	45	50	55	65	95	100	145	150	155	160	195	205

2. Describe the number and type of study visits and/or contacts between the study team and the participant, how long they will last, and where/how they will take place.

Each subject will be expected to come to approximately 14 visits
Each participant will spend about 3-4 months in the study, from screening to completion

NOTE: At the investigator's discretion or if influenza is circulating in the community at the time of enrollment, the procedures of days 39-56 will be flipped with Day 11-28. In addition the two months of the study may not be continuous, for scheduling reasons, there may be 1-2 months in between.

Day 0 +/- 4 days (1st day of menstrual cycle)

1. Verify that study-specific Informed Consent was obtained.
2. Ensure that all inclusion/exclusion criteria are met.
3. Collect brief history of any new illnesses or problems since last visit
4. Review pregnancy prevention counseling.
5. Obtain blood for measurement of progesterone, and estradiol.
6. Train subjects on the REDCap survey website, or on memory card.
7. Instruct on LH strip use at home.

Day 10-17

1. Participant to utilize LH strip at home, and call study staff when positive.
2. Participant to record on memory card results of LH strip.

Day 11 +/-2 days (prior to ovulation),

1. Collect brief history of any new illnesses or problems since last visit
2. Review pregnancy prevention counseling.
3. Obtain blood for measurement of progesterone and estradiol and measurement of cytokines
4. Collect approximately 30 cc of blood for Peripheral Blood Mononuclear Cell (PBMC) processing.

Day 12, Day 13

1. Obtain blood for measurement of cytokines.

Day 17 +/-2 days (after ovulation), Day 21 +/- 2 days
Day 28 +/- 5 days (1st day of menstrual cycle)

1. Collect brief history of any new illnesses or problems since last visit
2. Review pregnancy prevention counseling.
3. Obtain blood for measurement of progesterone, and estradiol.

Day 21 +/- 2 days:

1. Collect approximately 30 cc of blood for PBMC processing.

Day 38-45

1. Participant to utilize LH strip at home, and call study staff when positive.
2. Participant to record on memory card results of LH strip.

Day 39 +/- 3 days (~ 11 days after menstruation; prior to ovulation)

1. Collect brief history of any new illnesses or problems since last visit
2. Review pregnancy prevention counseling.
3. Obtain blood for measurement of progesterone, estradiol, baseline cytokines and Hemagglutination Inhibition Assay (HAI).
4. Obtain approximately 30 cc of blood for PBMC processing.
5. Check urine pregnancy test.
6. Vaccinate subject with IIV.

Day 40 +/-1 day (1 day after vaccination), Day 41 +/-1 day (2 days after vaccination)

1. Collect brief history of any new illnesses or problems since last visit, ask about adverse events after vaccination.
2. Review pregnancy prevention counseling.
3. Obtain blood for measurement of cytokines.
   Days 41-43 (2-4 days after vaccination).

   Subject to answer questions reactogenicity in the REDCap database or on the memory card.

Day 45 +/-1 day (6-8 days after vaccination), Day 49 +/- 1 day (10-12 days after vaccination)

1. Collect brief history of any new illnesses or problems since last visit; ask about adverse events after vaccination.
2. Review pregnancy prevention counseling.
3. Obtain blood for measurement of progesterone, and estradiol.

Day 49 +/- 1 day (10-12 days after vaccination)

1. Obtain approximately 30 cc for PBMC processing.

Day 56 +/-4 days (1st day of menstruation)

1. Get brief history of any new illnesses or problems since last visit.
2. Check urine pregnancy test.
3. Obtain blood for measurement of progesterone, estradiol and for HAI.

3. Describe the expected duration of the study from the perspective of the individual participant and duration overall.

Each participant will spend about 3-4 months in the study, from screening to completion.
Each subject will be expected to come to approximately 14 visits

4. Provide a brief data analysis plan and a description of variables to be derived.

The data will be analyzed using the computer software STATA (version 13, Stata Corp, College Station, TX). Each participant will serve as her own control. Summary data of the baseline characteristics of participants will be described using mean (SD) and median for continuous variables or frequencies and proportions for categorical data, as appropriate. Vaccine HAI titers will measured prior to vaccination (day 39) and at 17 days following vaccination (day 56)

PA1: To determine if vaccination with IIV prior to ovulation (day 11 of menstruation) is associated with changes in post-ovulation serum reproductive (progesterone and estradiol) hormones concentrations.
-H 1: Post-vaccination serum reproductive hormone concentrations will be lower in the post-vaccination cycle than measured prior to vaccination.

The skewness of the hormone concentration distributions will be checked using Kolmogorov-Smirnov test or Shapiro-Wilks test. Transformation of the non-normal data to achieve normality will be attempted using natural logarithms or other mathematical functions. In the event that power transformations fail to normalize the data then non-parametric tests will be used. The mean difference (SD) between pre-vaccination serum hormone (progesterone and estradiol) concentrations and post-vaccination serum hormone concentrations measured during the luteal phase (days 17, 21, 28) of menstruation for each participant will be estimated using paired t-test for parametric data or by the Wilcoxon matched-pairs signed rank sum test for non-parametric data. A p-value < 0.05 will be considered statistically significant in all analyses. Stratified analyses will be conducted to determine if host characteristics modify the effects of vaccination on hormonal responses.

EA1: To determine if serum inflammatory biomarker (cytokines, chemokines, and C-reactive protein) concentrations differ following vaccination with IIV.

-H2: Serum pro-inflammatory biomarker concentrations at 24- and 48-hours post vaccination will be increased relative to baseline concentrations.

The skewness of the cytokine concentration distributions will be checked using Kolmogorov-Smirnov test of normality. Transformation of the non-normal data to achieve normality will be attempted using natural logarithms. In the event that natural logarithm transformation fails to normalize the data then non-parametric tests will be used. Relationships between the different inflammatory biomarkers interest will be analyzed using Pearson's correlation or with Spearman's rank test, as needed. The mean difference (SD) in cytokine concentrations between baseline and at 24 hours post-vaccination, and between baseline and 48 hours post-vaccination within individuals will be evaluated by paired t-test for parametric data or by the Wilcoxon matched-pairs signed rank sum test for non-parametric data. Stratified analyses will be used to determine if host characteristics

modify the effects of vaccination on hormonal responses. Our study design will also allow us to look at differences in cytokines at various points in the nonvaccination menstrual cycle.

EA2: To determine if post-vaccination inflammatory biomarker responses to IIV receipt (days 40 and 41) are associated with changes in reproductive hormone levels during the second menstrual cycle.

-H3: Changes in serum pro-inflammatory responses between baseline and 24(and/or 48)-hours post-vaccination, will be inversely correlated with serum reproductive hormone concentrations during the second menstrual cycle.

Correlations between changes in post-vaccination serum pro-inflammatory biomarkers (days 39 to 40, 39 to 41) and changes in serum hormone responses during the second menstrual cycle (days 45 to 49, 45 to 56), will be calculated using Pearson's correlation coefficient and evaluated using the paired t-test for parametric data or Spearman's rank correlation test and the Wilcoxon matched-pairs signed rank sum test for non-parametric data. In addition, we will correlate changes in the hormone levels observed in the second cycle to the first cycle (days 17 to 21, 17 to 28) using the same analytical techniques.

EA4: To describe the frequency of adverse events in the 7 days after vaccination, including fever, myalgia, malaise, and hypersensitivity reactions, and to determine if these adverse events are associated with cytokines responses.

-H4: Adverse events, specifically fever, myalgia and malaise after vaccination, are associated with a greater inflammatory cytokine response than seen in people who do not experience these events.

The frequency and proportion of participants who experience vaccine-associated adverse symptoms will be reported. In addition, differences in mean (SD) serum inflammatory biomarker concentrations at 24 and 48 post-vaccination and mean (SD) changes in serum concentrations following vaccination by adverse symptom status will be explored using t-tests.

5. Answer the following **if they are relevant to your study design**:

A. If the study has different arms, explain the process for assigning participants (intervention/control, case/control), including the sequence and timing of the assignment.

Subjects will be screened for eligibility based on their age, medical, vaccination and menstrual history, and birth control methods used. All participants will receive the same influenza vaccine. We will aim to enroll equal numbers of women who have received an H1N1 containing vaccine with influenza vaccine naïve women. This will allow us to compare responses of women with previous vaccination with those without prior history of vaccine.

B. If human biospecimens (blood, urine, saliva, etc.) will be collected, provide details about who will collect the specimen, the volume (ml) and frequency of collection, how the specimen will be used, stored, identified, and disposed of when the study is over. If specimens will be collected for use in future research (beyond this study), complete the "Biospecimen Repository" section below.

Specimens will be collected by the PI, nurses and staff trained in the proper collection of samples and blood draws. Serum specimens will be collected during this study. Any remaining specimens at the conclusion of the study will be retained under the CIR biorepository protocol (CIR 213 IRB Number R.22.05.04.29.A2.)

C. If genetic/genomic analyses are planned, address whether the data will be contributed to a GWAS or other large dataset. Address returning unanticipated incidental genetic findings to study participants.

N/A

D. If clinical or laboratory work will be performed at JHU/JHH, provide the JH Biosafety Registration Number.

N/A

E. If you will perform investigational or standard diagnostic laboratory tests using human samples or data, clarify whether the tests are validated and/or the lab is certified (for example is CLIA certified in the U.S.). Explain the failure rate and under what circumstances you will repeat a test. For all human testing (biomedical, psychological, educational, etc.), clarify your plans for reporting test results to participants and/or to their families or clinicians. Address returning unanticipated incidental findings to study participants.

Diagnostic tests will not be performed. All of our assays are for research purposes, with the exception of urine pregnancy tests

We will report results of urine pregnancy to the subjects. Urine □-HCG testing will be performed at the clinical trial site using an FDA-approved urine pregnancy test kit under a CLIA waiver.

FDA-approved LH strips will also be used, but not as a basis for any clinical intervention.

Other assays performed will be done for research purposes:

Antibody responses to vaccine: Serum HAI testing to look at antibody responses to the IIV will be done on serum collected before and after vaccination. These assays will be performed by the CIR laboratory, which has a >25 year history in performing these assays for a variety of influenza strains as part of a number of NIH funded influenza vaccine research studies. The laboratory uses CDC reagents and methods[25-28].

Assessment of serum progesterone and estradiol: Serum samples will be sent to the Ligand Assay and Analysis Core of the Center for Research in Reproduction at the University of Virginia School of Medicine. The Ligand Assay and Analysis Core conducts hormone assays for National Institute of Child Health and Development (NICHD)-supported investigators across the country. This facility provides services on a fee for service basis for NICHD-supported as well as external investigators. The price structure for assays are different for NICHD-supported projects and external users. Details about the Ligand Assay and Analysis Core can be found at: http://www.medicine.virginia.edu/research/institutes-and-programs/crr/lab-facilities.

Soluble markers of inflammation: Serum cytokines and chemokines and CRP will be measured using the Meso Scale Discovery (MSD) platform (MSD, Gaithersburg, MD), and will be performed in Dr. Bream's laboratory. The soluble markers of inflammation to be measured include but are not

limited to: CRP, IL-2, IL-6, IL-8, IL-10, IL-12p70, IFN-□, TNF-□, GM-CSF, IP-10, TARC, MCP-1, MCP-4, Eotaxin, and Mip-1□.

F. If your study involves medical, pharmaceutical or other therapeutic intervention, provide the following information:

a. Will the study staff be blind to participant intervention status?

No

b. Will participants receive standard care or have current therapy stopped?

Standard of care

c. Will you use a placebo or non-treatment group, and is that justifiable?

No placebo group. Everyone will get the seasonal influenza vaccine.

d. Explain when you may remove a participant from the study.

Noncompliance with study protocol

e. What happens to participants on study intervention when the study ends?

They return to their normal schedule.

f. Describe the process for referring participants to care outside the study, if needed.

There should not be a reason to refer participants for care because of the study. Should a medical problem be identified that needs further care, participants will be referred to their primary care provider or one will be identified if they are need of one.

VI. Data Security and Confidentiality Protections:

A. Personally Identifiable Information (PII):

Please identify the Personally Identifiable Information (PII) that you may be collecting and using at any of the following stages of your study: ***Recruitment***, ***Consent,*** *and* ***Study Implementation***.

Name, signature, initials, or other identifiable code	X
Geographic identifier: address, GPS location, etc.	X
Dates: birth, death, clinical service, discharge, etc.	X
Contact information: phone numbers, email address, etc.	X
ID: Social Security Number, driver's license number, etc.	X
Health record identifiers: medical record, insurance plan number, etc.	☐
Account numbers	☐
Device identifiers: e.g., implants	☐
Internet identifiers: IP address, social media accounts	☐
Biometric identifiers, including finger and voice prints	☐
Audio recordings	☐
Video or full face photographic images	☐

Genomic/genetic data	☐
Any other unique identifying number, characteristic, or code (note: this does not mean the unique code assigned by the investigator to code the data)	☐
Other: Click here to enter text.	☐

B. **Recruitment:**

Will you collect identifiers for the purpose of contacting potential participants? Yes ☒ X No ☐

If **yes**, will you retain the identifiers after the recruitment contact has been made? Yes ☒ X No ☐

C. **Data Collection:**

In what form will you collect and store PII? When you respond, think of PII collected for recruitment, consent, and other study purposes.

1. **Hard Copy/Paper:** Yes ☒ X No ☐

If yes, please answer the following:

a. How will the data be kept secure during transfer from study collection site to storage site?

Identifiers will be collected from subjects including name, date of birth, address, phone number. These will be kept in source documents and databases as described below. Source documents with personal identifiers will be stored in locked rooms with limited access. Databases with personal identifiers are secure, password protected.

All data forms, evaluation forms, reports, and other records that leave the site will be identified only by a coded number in order to maintain participant confidentiality. Hard copies of data collection materials that have identifiers will be kept locked in a secure cabinet or room with limited access by specified individuals. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB the OHRP or the sponsor's designee.

When possible, redacted (de-identified) versions of the data collection sheets will be used for coding and analysis.

b. Will the data be secured in a locked cabinet or room? Yes ☐X No ☐

c. Are the data collection forms and study data stored without personal identifiers and separate from the study IDs/code? Yes ☐ No ☐X

d. How long after study completion will you keep the hard copy/paper forms? We keep paper forms for at least 5 years and until the sponsor notifies us they can be destroyed.

2. **Electronic:** Yes ☒ No ☐

If yes, please answer the following:

a. Will the data be collected/stored on a portable device (laptop, mobile phone, tablet, PDA)

protected by encryption? Yes X No ☐

b. Will the data be stored on a secure server or in the Cloud/Web?

Secure Server X Cloud/ Web ☐

c. Will it be encrypted? Yes ☐X No ☐

d. Will you be backing up your data? Yes X No ☐

3. **Audiotape:** Yes ☐ No ☒

If yes, please answer the following:

a. Will you store the audiotape securely in a locked cabinet/room until transcription is complete? Yes ☐ No ☐

b. Will the audiotape be destroyed after transcription? Yes ☐ No ☐

If no, why not?

4. **Photograph/Video:** Yes ☐ No ☐

If yes, please answer the following:

a. Will the photographs/videos be stored securely in a locked cabinet or room? Yes ☐ No ☐

b. Will the photograph/video be destroyed? Yes ☐ No ☐

If yes, when?

D. **PII De-Identification of Data Used for this Study:**

When will you destroy the PII and/or the code linking the PII with the study ID?
After 5 years at the request of the sponsor.

E. **Data Storage and Analysis:**

One of the keys to protecting PII is the proper use of tools to share and conduct your analysis. JH and JHSPH offers several options for you to consider. Please select the system that you plan to use to protect your study data by clicking the box. Consult JHSPH IT for assistance if needed.

☐ **JH Virtual Desktop**: IT@JH provides (for a monthly fee) a virtual Windows desktop.

☒ **JHSPH SharePoint and File Shares**: These systems provide a managed and secure platform for your research project. They also provide a built-in encrypted backup solution.

□ X **JHSPH RedCAP or HPCC**: These are departmentally managed applications.

☒ **JHBox**: Johns Hopkins Box (JHBox) is a secure cloud-based file sharing and file storage service.

□ **Independent Departmental Servers and Systems**: These servers are typically managed by departmental or research team IT staff.

□ **Other**: Please provide details regarding any other systems being utilized.

F. **Other Data Security Measures:**

In addition to the details regarding data collection, please review the following questions. This additional information will be utilized to assist in the development of a comprehensive Data Security plan. This would include the systems used to analyze the data, data security contacts and additional requirements.

1. Do you have a designated person on your research team other than the PI who is the technical contact for a Data Security plan? Yes ☐ No X
   If yes, please provide a contact name:

2. Does your sponsor have other specific data security requirements for the study data? Yes ☐ No X
   If possible, please explain:

3. Please add any other information that you believe is relevant to data security. N/A

G. **Certificate of Confidentiality:**

Will the study data stored in the **United States** be protected by a Certificate of Confidentiality?

If yes, explain who will apply for and maintain the Certificate. N/A
(http://grants.nih.gov/grants/policy/coc/appl_extramural.htm)

H. Will you use clinical data of 500 records or more from Johns Hopkins Hospital and its affiliates?
Yes ☐ No X

If yes, please complete the JHM Data Security Checklist available on the JHSPH IRB website: www.jhsph.edu/irb and upload a copy of the checklist to the "Miscellaneous" section.

VII. Risks of the Study:

A. Describe the risks, discomforts, and inconveniences associated with the study and its procedures, including physical, psychological, emotional, social, legal, or economic risks, and the risk of a breach of confidentiality. These risks should be described in the consent documents.

Risks to the participants are associated with the small risk that their personal information may be accidentally released. This is unlikely, as all reasonable effort will be made to restrict confidential information to those authorized to see it.

The inactivated influenza vaccine is routinely recommended by the ACIP for persons aged >=6 months. The vaccine is generally well tolerated. The most common adverse events are fever, rash, injection site reactions, myalgia's and malaise. Rarely, there is a risk of allergic reaction, and in extremely rare circumstances, Guillain-Barré syndrome (1-2 additional cases per million people vaccinated). The risks of receiving the influenza vaccine while on study should not be any greater than the risk of receiving vaccine through routine preventative care, and are outlined in the CDC's Vaccine Information Sheet: http://www.cdc.gov/vaccines/hcp/vis/index.htm.

Phlebotomy: the main risk of phlebotomy is a bruise at the site of the needle insertion.

B. Describe the anticipated frequency and severity of the harms associated with the risks identified above; for example, if you are performing "x" test/assessment, or dispensing "y" drug, how often do you expect an "anticipated" adverse reaction to occur in a study participant, and how severe do you expect that reaction to be?

We will be using the licensed inactivated influenza vaccine at the recommended dose. This vaccine has been used in millions of people each year, with well described adverse reactions. The most frequent adverse event related to influenza vaccination is pain at the injection site which can occur in up to 64% of people who receive the vaccine, and is usually mild and resolves within 2 days. Approximately 2% of subjects experience a myalgia/malaise syndrome that is also self-limited.

C. Describe steps to be taken to minimize risks. Include a description of your efforts to arrange for care or referral for participants who may need it.

The PI and trained nurses will be used to administer the influenza vaccine.

D. Describe the research burden for participants, including time, inconvenience, out of pocket costs, etc.

Subjects will have to make 12 visits to the CIR clinic, and scheduling of these visits will be based on their menstrual cycles. The initial screening and consenting visit and the vaccination visit are likely to be the longest visits, taking up to 2 hours each. The remainder of the visits will be approximately 30 minutes or less. In addition to the study visits, subjects are asked to check for LH surge using LH test strips, and to report adverse events or concomitant medication. There will be no out of pocket expense, subjects will be reimbursed for parking or bus fare.

E. Describe how participant privacy will be protected during data collection if sensitive questions are included in interviews.

Interviews will occur in private rooms with closed doors in order to protect subject privacy.

VIII. Direct Personal and Social Benefits:

A. Describe any potential direct benefits the study offers to participants ("payment" for participation is not a direct personal benefit).

The subjects will receive the seasonal influenza vaccine at no cost to themselves, and so may benefit from being protected from illness due to influenza

B. Describe potential societal benefits likely to derive from the research, including value of knowledge learned.

This study will allow us to better understand the effect of influenza vaccine on inflammatory cytokine responses, and to better describe the effects of these inflammatory cytokines on reproductive hormones. With time, and larger samples, this and studies like it may allow us to better describe the effects of the influenza vaccine on the initiation and maintenance of a pregnancy.

IX. Payment:

A. Describe the form, amount, and schedule of payment to participants. Reimbursement for travel or other expenses is not "payment," and if the study will reimburse, explain.

Participants will receive $75 per visit as compensation for their participation in this study; if they complete each visit per the protocol, they will receive an additional $100 bonus, for a total compensation of $1150. They will also be provided with bus tokens or parking vouchers.

B. Include the possible total remuneration and any consequences for not completing all phases of the research.

Subjects will not be compensated for any study visits that they miss. In addition, the bonus will be withheld if they miss more than 1 study visit.

X. Study Management:

A. Oversight Plan:

1. Describe how the study will be managed.

   Vaccine will be obtained from the Johns Hopkins Hospital Pharmacy.

   Dr. Talaat will be responsible for drug management and dispensing, aided and advised by Beulah Sabundayo, PharmD, MPH.

2. What are the qualifications of study personnel managing the project?

   Kawsar Talaat, MD is a licensed physician, Assistant Scientist/faculty member of JHSPH, trained in CITI Human subjects protection, and Good Clinical Practice for clinical research studies. She is the Principal Investigator for several clinical research studies approved by the JHSPH-IRB and the WIRB.

   Beulah Sabundayo is a licensed pharmacist and is trained in CITI Human subjects protections, and Good Clinical Practice for clinical research studies.

3. How will personnel involved with the data collection and analysis be trained in human subjects research protections? (Use the JHSPH Ethics Field Training Guide available on the JHSPH IRB website: www.jhsph.edu/irb.)

   All staff participating in the data collection and analysis are trained in CITI Human subjects protections, and Good Clinical Practice for clinical research studies.

4. If the PI will not personally be on-site throughout the data collection process, provide details about PI site visits, the supervision over consent and data collection, and the communication plan between the PI and study team.

   The PI will be onsite regularly during the data collection process. I will oversee the study staff, review study documents. I speak with the study team at least weekly, and often daily.

B. Recordkeeping:

Describe how you plan to ensure that the study team follows the protocol and properly records and stores study data collection forms, IRB regulatory correspondence, and other study documentation. For assistance, contact housecall@jhu.edu.

The PI will ensure that all study staff are trained in CITI Human Subjects Protection, Good Clinical Practices, and the Sponsor Protocol/Research Plan to execute the duties outlined in the study. Study information, data and reports will be documented and stored in the subject's binder. Regulatory files and relevant correspondence will be keep in a secure location in the CIR Regulatory Office

Safety Monitoring:

1. Describe how participant safety will be monitored as the study progresses, by whom, and how often. Will there be a medical monitor on site? If yes, who will serve in that role?

We will be using a licensed vaccine whose safety is well established by decades of use. At the CIR, we have established procedures to ensure that the safety of study participants is closely monitored throughout the study period. A clinician (physician, PA or NP or RN) is present for all inoculations. Procedures to be followed in the event of anaphylaxis are posted in each examination room, and emergency kits containing medications for immediate hypersensitivity reactions and anaphylaxis are readily available. Clinical information obtained during the course of each trial is reviewed promptly by the PI. Certain local and systemic reactogenicity events are expected after vaccination, and at each visit, volunteers are queried about possible adverse reactions. If detected, the reactogenicity event will be recorded in the case report form. Included will be date(s) of occurrence, duration, degree of severity, and probable relationship to vaccine. The PI will monitor study data as they become available and will make determinations regarding the presence and grading of adverse events. The events will be evaluated with regard to the known complications associated with influenza vaccines and their relationship to the vaccine will be evaluated as possibly, probably, or definitely related, or unlikely or not related. All AEs will be assessed for relationship to the vaccine using the recently published CISA causality algorithm developed for adverse events following immunization [29].

2. If a Data Safety Monitoring Board (DSMB), or equivalent will be established, describe the following:
No Data safety monitoring board meeting today.

4. Describe plans for interim analysis and stopping rules, if any.

As this is not an IND study, no stopping rules will be in place

D. **Reporting Unanticipated Problems/Adverse Events (AE's) to the IRB (*all studies must complete this section*)**:

Describe your plan for reporting to the IRB and (if applicable) to the sponsor. Include your plan for government-mandated reporting of abuse or illegal activity.

Any serious adverse event will be reported to the IRB and the Sponsor within 1 business day of the Principal Investigator becoming aware of the event. Serious events will be reported to VAERS

E. **Other IRBs/Ethics Review Boards:**

If other IRBs will review the research, provide the name and contact information for each IRB/ethics review board and its Federal Wide Assurance, if it has one (available on OHRP's website at http://www.hhs.gov/ohrp/assurances).

This protocol will be reviewed by the CDC as the Sponsoring agency. CDC will request to rely on the JHSPH IRB.

F. Collaborations with non-JHSPH Institutions:
No collaborating institutions.

For studies that involve collaboration with non-JHSPH institutions, complete the chart below by describing the collaboration and the roles and responsibilities of each partner, including the JHSPH investigator. This information helps us determine what IRB oversight is required for each party. Complete the chart for all multi-collaborator studies.

Insert Name of Institutions in Partner column(s); add additional columns if necessary.

	JHSPH	Partner 1	Partner 2
Primary Grant Recipient			
Collaborator			

For the following, indicate "P" for "Primary", "S" for "Secondary" (as appropriate to role and level of responsibility.) Add additional items if useful.

1.	Human subjects research ethics training for data collectors			
2.	Day to day management and supervision of data collection			
3.	Reporting unanticipated problems to the JHSPH IRB/Sponsor			
4.	Hiring/supervising people obtaining informed consent and/or collecting data			
5.	Execution of plan for data security/protection of participant data confidentiality, as described in the Data Security and Confidentiality Protections section above .			
6.	Biospecimen processing, storage, management, access, and/or making decisions about future use			

COMPLETE THE FOLLOWING SECTIONS WHEN RELEVANT TO YOUR STUDY:

XIII. Creation of a Biospecimen Repository:

Explain the source of the biospecimens, if not described above, what kinds of specimens will be retained over time. Clarify whether the specimens will be obtained specifically for repository purposes, or will be obtained as part of the core study and then retained in a repository.

Once the study has been completed, any left over serum samples and PBMCs will be transferred to the CIR's repository samples.

A. Describe where the biospecimens will be stored and who will be responsible for them.

Specimens will be stored in freezers in the CIR laboratory at the Johns Hopkins Bloomberg School of Public Health building. Access to these freezers is restricted, and the freezers are locked.

B. Describe how long the biospecimens will be stored, and what will happen at the end of that period.

Specimens will be stored indefinitely. Once the protocol is completed, they will be transferred to the repository protocol.

C. Explain whether the biospecimens will be shared with other investigators, inside and outside of JHU, how the decision to share will be made, and by whom. Include your plans, if any, for commercial use. Also explain how downstream use of the specimen will be managed, and what will happen to left-over specimens.

Specimens may be stored with investigators inside and outside of JHU, based on decisions made by the investigators and the sponsor. Any samples shared will be coded without personal identifiers and the person or institution with whom they are shared will not have access to any codes to link samples to the subjects. Samples cannot be used for commercial use, nor can recipients of the samples share them with other entities without the express permission of the investigators or sponsor.

D. Describe whether future research using the biospecimens will include specimen derivation and processing (cell lines, DNA/RNA, etc.), genomic analyses, or any other work which could increase risk to participants. Explain what additional protections will be provided to participants.

No. Future research will not include derivation, processing, genomic analysis, or other work that increases risk

E. If future research could yield unanticipated incidental findings (e.g., an unexpected finding with potential health importance that is not one of the aims of the study) for a participant, do you intend to disclose those findings to the study participant? Please explain your position.

Yes, we will disclose any findings of potential health importance to the participants

F. Explain whether the specimens will be identifiable, and if so, how they will be coded, who will have access to the code, and whether the biospecimens will be shared in linked (identifiable) form.

Specimens will be coded with the subject study number, and will have no personal identifiers on them. The code that links specimens will be kept by the study team. Should biospecimens be shared, that code will not be shared, and so any investigator receiving specimens in the future will not be able to link samples to individuals.

G. Explain whether the repository will have Certificate of Confidentiality protections.

Yes, we're covered by a 308d CDC Assurance of Confidentiality

H. Explain whether a participant will be able to withdraw consent to use a biospecimen, and how the repository will handle a consent withdrawal request.

Yes, a participant may in the future withdraw consent to use a biospecimen. In that case, the repository will pull the specimen and destroy it. Should a specimen be completely anonymized, we will not be able to remove it from the repository

I. Describe data and/or specimen use agreements that will be required of users. Provide a copy of any usage agreement that you plan to execute with investigators who obtain biospecimens from you.

We currently have no plans to share samples with other investigators. If that changes, we will notify and obtain approval from the IRB.

XV. Drug Products, Vitamins, Food and Dietary Supplements:

Complete this section if your study involves a drug, botanical, food, dietary supplement or other product that will be applied, inhaled, ingested or otherwise absorbed by the study participants. If you will be administering drugs, please upload the product information.

A. List the name(s) of the study product(s), and the manufacturer/source of each product.

Name of Study Product	Manufacturer/Source
(Fluzone Quadrivalent	Sanofi Pasteur

B. List each study product by name and indicate its approved/not approved status.

Approved by the FDA and Commercially Available	Approved by Another Gov't Entity (provide name)	Cleared for Use at Local Study Site
(Fluzone Quadrivalent		

C. If your study product has an Investigational New Drug (IND) application through the U.S. Food and Drug Administration, provide the IND number, the Investigators Brochure and complete and upload into PHIRST the Drug Data Sheet available on the JHSPH IRB website www.jhsph.edu/irb.

N/A

D. If your study product is a marketed drug, provide the package inserts or other product information. If the study product WILL NOT be used for its approved indication, dose, population, and route of administration, provide a detailed rationale justifying the off label use of the study product.

We will be using the seasonal, licensed inactivated quadrivalent Influenza vaccine at the recommended dose. We will use the standard, FDA approved and CDC recommended dose.

See attached.

E. If the study product is not an FDA approved drug, and is being used without an IND (e.g., dietary supplements, botanicals, etc.), provide safety information (as applicable) and a certificate of analysis.

N/A

G. Explain who will be responsible for drug management and supply, labeling, dispensing, documentation and recordkeeping.

Dr. Kawsar Talaat will be responsible for drug management and dispensing, aided and advised by Beulah Sabundayo, PharD, MPH

H. What drug monitoring and/or regulatory oversight will be provided as part of the study?

N/A