

**Comparison of High vs. Standard Dose Flu Vaccine in Pediatric Stem Cell Transplant Recipients**

**DMID Protocol Number 16-0117**

**Protocol Version 8.0**

**Date: 9/12/2019**

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**Sep. 12, 2019**

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**Statement of Compliance**

This clinical trial will be conducted in accordance with the protocol and Good Clinical Practices (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR 46; 21 CFR Parts 50 and 56; 21 CFR Part 312).
- ICH E6; 62 Federal Register 25691 (1997)
- NIH Clinical Terms of Award

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

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**SIGNATURE PAGE 1**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

*The Lead Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.*

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*Name/Title*

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**Signature Page 2**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

The Investigator(s) of record (signature(s) on 1572) from each participating clinical site should sign the Signature Page 2 as appropriate. The Signature Page 2 should be maintained at each site.

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Institution: \_\_\_\_\_

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## A. Specific Aims and Hypothesis:

- 1. Hypothesis 1:** *We hypothesize that the high-dose trivalent inactivated influenza vaccine (HD-TIV) group will have a greater frequency of  $\geq 4$ -fold rise, HAI titer  $\geq 1:40$ , and higher geometric mean titer (GMT) to influenza A antigens compared to the standard dose quadrivalent inactivated influenza vaccine (QIV) group in pediatric hematopoietic stem cell transplant (HSCT) recipients.*

**Specific aim 1:** To determine whether HD-TIV compared with standard dose QIV will increase the probability of achieving either a  $\geq 4$ -fold rise in HAI titer, a HAI titer  $\geq 1:40$ , or higher GMT HAI to influenza A antigens in pediatric HSCT recipients.

- 2. Hypothesis 2:** *The administration of HD-TIV in pediatric HSCT recipients will be well tolerated and the safety profile will be similar to standard dose QIV.*

**Specific aim 2:** To determine the frequency and severity of solicited local injection site adverse events and solicited systemic adverse events related to HD-TIV compared with standard dose QIV in pediatric HSCT recipients.

- 3. Hypothesis 3:** *HD TIV vaccination will induce higher protective HAI titers and higher frequencies of circulating activated T-follicular (Tfh) cells and circulating B cell plasmablasts, it will also induce higher levels of influenza-specific B and T cell responses compared to standard dose QIV.*

**Specific aim 3:** To define the relationship between HAI titers, ex-vivo T and B cell phenotype, and ex-vivo influenza-specific T and B cell response in pediatric HSCT recipients receiving either HD-TIV or standard dose QIV.

## B. Background and Significance:

### 1. Burden of Influenza:

Over 13,000 hematopoietic stem cell transplants (HSCT) are performed each year in the United States, according to the Center for International Blood and Marrow Transplant Research.<sup>1</sup> Mortality due to infections is seen in 8-17% of HSCT patients who died within 100 days post-transplant.<sup>1</sup> Influenza A and B are important causes of morbidity and mortality in high-risk individuals, including HSCT recipients;<sup>2</sup> however, the majority of disease is due to circulating influenza A/H3N2 or influenza A/H1N1,<sup>3</sup> including in hospitalized children.<sup>4</sup> In a prospective viral surveillance study involving 37 European transplant centers, 3.5% of the patients had a documented respiratory virus, 16 subjects with influenza virus A, and of those 23%, of confirmed influenza patients died.<sup>5</sup> Reported mortality rates in HSCT associated to influenza range around 15-17%,<sup>5,6</sup> however, the rates are even higher in patients with influenza-associated pneumonia, where the case fatality rate in HSCT recipients varied from 9.5 to 75%.<sup>2,5-8</sup> In the general population, an influenza epidemic can be associated with attack rates of 10–20%; however, attack rates are higher in individuals with cancer and HSCT recipients.<sup>9-12</sup>

Moreover, significant morbidity and mortality were noted in HSCT recipients during the recent influenza A/H1N1 pandemic, with several reports of pneumonia, lower respiratory tract infections, rhabdomyolysis, and even death.<sup>13-19</sup> Since immunosuppressed individuals can shed influenza virus for prolonged periods after infection, they pose significant risk for promoting nosocomial influenza outbreaks,<sup>20-22</sup> and the development of antiviral resistance.<sup>23</sup> HSCT recipients infected with pandemic influenza A/H1N1 and treated with oseltamivir had high rates of development of antiviral resistance while on antiviral therapy.<sup>18,24-26</sup> The risks for severe influenza or fatal outcome in HSCT recipients include lymphopenia, older age in adults and younger age in children (<5 years), neutropenia, influenza soon after transplantation or chemotherapy, steroid treatment, and

lack of early antiviral therapy.<sup>8,11,27,28</sup> Thus, influenza infection in HSCT recipients poses both a significant individual and community risk.

Machado *et al.* retrospectively reviewed vaccination records of 177 HSCT recipients to evaluate risk factors for acquiring influenza and the efficacy of influenza vaccination 6 months post-HSCT.<sup>2</sup> Nasal washes from adult subjects and nasal aspirates from children were assessed for influenza by a direct immunofluorescence assay (DFA) during a single influenza season. Of the 43 subjects were eligible to receive the influenza vaccine, only 19 (44%) subjects were immunized. Of the 19 subjects who did receive influenza vaccine, only two (10.5%) of them had nasal samples positive for influenza. Among the remaining 24 unvaccinated individuals, 12 (50%) were diagnosed with influenza infection. These data suggest a potential influenza vaccine efficacy of 80%.<sup>2</sup> A limitation of this study, however, is that the investigators did not use PCR for diagnosis, a more sensitive method than DFA for detecting influenza virus. However, it is unclear whether this limitation may have led to an overestimation or underestimation of influenza vaccination efficacy in this population.<sup>29</sup>

## 2. Prior Influenza Vaccine Trials in HSCT Recipients:

Influenza vaccination is the primary mode for prevention of influenza infection. Protection is primarily mediated by virus-specific antibodies that depend on an intact humoral response. Both B cell and T cells responses are impaired in HSCT recipients, functional recovery of B and T lymphocytes can take up to 2 years or even longer.<sup>30</sup> Limited data are available regarding influenza vaccine responses in pediatric HSCT recipients because the majority of influenza vaccine trials have been conducted in adult HSCT recipients.<sup>31-45</sup> Only 5 of these trials included children, and only one exclusively included children, with total enrollment of 5 subjects.<sup>33</sup> Therefore, dedicated influenza vaccine trials in pediatric HSCT patients are needed.

Despite limited clinical data for influenza vaccine efficacy in this population, yearly vaccination is recommended, beginning 3-6 months after HSCT.<sup>46</sup> However, the optimal post-transplantation vaccine schedule has not been established. Existing data for influenza vaccination in HSCT recipients are primarily from subjects who received influenza vaccination between 6 months and 3 years after HSCT.<sup>46</sup> Thus, little data exist to support vaccinating pediatric HSCT recipients earlier than 6 months or later than 3 years post-transplant.<sup>46</sup> The percentage of HSCT recipients that achieve seroprotective hemagglutinin inhibition (HAI) titers (defined as  $\geq 1:40$ ) one month after standard influenza vaccination is very low when compared to healthy controls. While this impaired vaccine-induced immune response is likely due to incomplete immune reconstitution or immunosuppressive therapies, the exact immune mechanisms of HSCT recipients' poor response to influenza vaccination are not well described. Notably, graft versus host disease (GVHD), low number of CD19<sup>+</sup> B cells, and earlier timing of vaccination post-transplant have been implicated as factors associated with lower titers after influenza vaccine.<sup>8</sup>

The authors in the 2013 publication, *European Guidelines for the Prevention and Management of Influenza in HSCT Patients*, recommends yearly inactivated influenza vaccine (IIV) each influenza season to HSCT recipients; vaccine is preferably given prior to the influenza season, usually at least 3 months after HSCT and a second dose of vaccine after 3-4 weeks is advised, although the second dose may only have marginal benefit.<sup>8</sup> Results from trials comparing two doses of influenza vaccine are conflicting: some suggest no benefit with 2 doses, while others demonstrate an increase in influenza titers after the second dose in HSCT recipients.<sup>18,31,41,44,47</sup> The trials that used ASO3-adjuvanted H1N1 vaccine, which is not available in the United States, suggest higher titers are induced with a 2-dose schedule.<sup>18,44,47</sup>

In contrast, the 2013 *IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host* recommends yearly vaccine with IIV and it can be administered 6 months after HSCT or as early as 4 months after HSCT during an influenza outbreak.<sup>48</sup> Thus, both the optimal timing of influenza vaccination and the ideal number of doses needed remain unclear. A better understanding of immune responses to influenza vaccination (e.g. B and T cell responses to influenza antigens) is also necessary. A promising strategy and

only immediate practical alternative to overcome the poor immunogenicity of influenza vaccine may be to increase the antigen dose in the vaccine.<sup>49</sup> This strategy has been successful in individuals  $\geq 65$  years, a group with a historically poor response to influenza vaccines compared to healthy young adults.<sup>50-52</sup>

### 3. Prior Experience with HD-TIV in the Elderly:

**a. Phase 1 Trial:** Since the elderly population responds poorly to standard dose influenza vaccine compared to younger adults, a higher dose influenza vaccine was hypothesized to be more immunogenic in this population.<sup>50</sup> The first trial enrolled 202 adults  $\geq 65$  years who were randomly assigned to 15, 30, or 60  $\mu$ g of hemagglutinin per strain or placebo.<sup>52</sup> Mean serum HAI antibody titers one month after immunization in groups given 0, 15, 30 and 60  $\mu$ g dosages were 23, 37, 50, and 61 against influenza A/H1N1; 43, 86, 91, and 125 against influenza A/H3N2; and 10, 14, 18, and 24 against influenza B, respectively.<sup>52</sup> Mean serum HAI and neutralizing antibody levels against the three vaccine antigens in participants given the 60 $\mu$ g dosage were 44% to 71% and 54% to 79%, respectively, higher than those in participants given the standard 15  $\mu$ g dosage. Among recipients with low pre-immunization antibody titers, the rate of seroconversion was nearly double for those who received 60  $\mu$ g, as compared to 15  $\mu$ g, dosage level.<sup>52</sup> Dose-related increases in the occurrence of injection site reactions were observed, but all dosages were well tolerated.

**b. Phase 2 Trial:** A multicenter, phase II, randomized, double-blind, stratified study enrolled individuals  $\geq 65$  years of age to receive either 15  $\mu$ g versus 60  $\mu$ g of TIV.<sup>51</sup> Oral temperature, injection site, and systemic symptoms and signs were recorded in a diary daily for one week after immunization. Sera were obtained before immunization and one month after immunization. A total of 414 subjects were enrolled, 206 received HD-TIV and 208 received standard dose TIV. Subjects given the HD-TIV reported more local and systemic reactions but only local pain and myalgia were significantly increased. The HD-TIV vaccine induced a higher frequency of  $\geq 4$ -fold serum antibody increases in both HAI (16.8-27.9%) and neutralization tests (11.9-24.5%) for all three vaccine viruses in the total group as well as in subjects vaccinated and not vaccinated the previous year.<sup>51</sup> Mean titers of antibody attained, the magnitude of antibody increases, and the frequencies of persons with final HAI antibody titers  $\geq 1:32$ ,  $\geq 1:64$ , and  $\geq 1:128$  were all greater for the HD-TIV group in both serologic tests (e.g., HAI and neutralization assays), for all titer groups  $\geq 1:32$ ,  $\geq 1:64$ , and  $\geq 1:128$ , and for all vaccine viral strains compared to the standard dose TIV.<sup>51</sup>

**c. Phase 3 and 3b Trials, HD-TIV has Increased Immunogenicity and Efficacy in the Elderly:** A phase III, multicenter, randomized, double-blind study enrolled individuals  $\geq 65$  years of age to compare HD-TIV to standard dose TIV.<sup>53</sup> HD-TIV was administered to 2575 subjects and standard dose TIV was administered to 1262 subjects. Individuals who received HD-TIV had higher mean post-vaccination GMT (**Table 1**). The HD-TIV vaccine met

Table 1.	HD-TIV	Standard Dose	GMT ratio
H1N1	116	67	<b>1.7</b>
H3N2	609	333	<b>1.8</b>
B	69	52	1.3

superiority criteria for both influenza A strains ( $>1.5$  GMT ratio), and the responses for influenza B met non-inferiority criteria. For all strains, seroprotection rates were higher in those individuals who received HD-TIV than in those who received standard dose TIV. Local reactions were more frequent in individuals who received HD-TIV, but the reactions were mild to moderate. The superiority of immune responses to influenza A antigens in the HD-TIV, compared to the standard-dose group, in this phase III trial led to the licensure of HD-TIV in individuals  $\geq 65$  years.<sup>50</sup> In addition, not only does the HD-TIV induced significantly higher antibody responses in this population, it provided better protection (relative efficacy, 24.2%) against laboratory-confirmed influenza illness compared to standard dose TIV.<sup>54</sup>

### 4. Prior Experience with HD-TIV in the Immunocompromised Subjects:

**a. Adult HSCT Recipients.** This single-center, randomized, double-blind, phase I safety and immunogenicity trial, conducted at Vanderbilt University, compared HD to standard dose TIV in adult allogeneic HSCT

recipients, not on immunosuppressive therapy for treatment of active GVHD, and at least 6 months post-transplant. Subjects were randomized in a 2:1 fashion to receive 2010-11 or 2011-12 TIV HD-TIV or standard dose TIV. Forty-four subjects were enrolled (19 in year 1 and 25 in year 2) at a median of 7.9 months after allogeneic HSCT, median age of 50.1 years, 61% male, and 100% white, and 29 HD and 15 SD subjects. HD group had higher median IgG level (676 vs. 469, p=0.025). The HD group reported more local symptoms compared to standard dose. No serious adverse events (SAEs) were attributed to the vaccine, and no differences in systemic reactions were noted. The HD group had a higher percentage of individuals with a HAI titer  $\geq 1:40$  to H3N2 after HD-TIV, (81% versus 36%, p=0.004) and higher GMT [207.9 versus 30.3, 177.6 95% CI difference, (63.5 - 401.8)], with GMT ratio 6.9. These results are published in *Biology of Blood and Marrow Transplant*.<sup>55</sup>

**b. Pediatric Solid Organ Transplant (SOT) Recipients.** This multi-center, randomized, double-blind, phase I safety and immunogenicity trial, conducted at Vanderbilt and the Children's Hospital of Pittsburgh during the 2011-12 influenza season, compared HD to standard dose TIV in pediatric SOT patients. Enrollees were 3-17 years of age and at least 6 months post-transplant. The mean age was 11.25 years, 68% were male, transplanted organs were 45% renal, 26% heart, 21% liver, 5% lung, and 5% intestinal, with median of 2.2 years since transplant. Twenty-three subjects were given HD and 15 were given standard dose TIV. No individuals had rejection associated with vaccination. Fatigue and body ache were greater in the HD group compared to the standard dose group, but no differences in local reactions were noted. Subjects in the HD group had a higher percentage of a 4-fold rise to H3N2 compared to the standard dose group (56% versus 13%, p=0.08). These results were published in *Pediatric Transplantation*.<sup>49</sup>

**c. Pediatric Acute Lymphoblastic Leukemia (ALL) Subjects.** This single-center, randomized, double-blind, phase I safety and immunogenicity trial was conducted at Vanderbilt University, comparing HD to standard dose TIV in children 3-17 years of age with ALL. Fifty subjects were enrolled (20 in year 1 and 30 in year 2), with a mean age of 8.25 years, 62% were male, and 78% were receiving maintenance therapy. Thirty-four subjects were given HD and 16 were given standard dose. Safety data revealed no differences between the groups for total solicited systemic and local reactions; however, the standard dose group reported more fatigue and headache. No SAEs were attributed to vaccination. The immune response, measured by a  $\geq 4$ -fold rise in HAI titer, was similar for each vaccine antigen in both groups; however, descriptive data in ALL recipients comparing specific B-cell immune response to each antigen suggest better responses with HD-TIV (unpublished data, Dr. Jon McCuller's laboratory, St. Jude, Memphis, TN). The main results are published in *Pediatric Blood Cancer*.<sup>56</sup>

**5. Inclusion of Quadrivalent Inactivated Influenza Vaccine (QIV).** Although two influenza B lineages have been co-circulating since the 1980s, TIV contains only one B strain, which provides little-to-no protection against the alternate B-lineage strain; however, about 70% of recent B viruses have been antigenically related to the B virus component of the trivalent flu vaccines.<sup>3</sup> A standard-dose QIV is currently available and provides additional protection against the second B strain while retaining non-inferior immunogenicity to the other 3 TIV strains.<sup>57,58</sup> High dose QIV will not be available for the upcoming influenza season (*personal communication with Sanofi Pasteur*). This study will be the first to evaluate standard dose QIV and HD-TIV in this population.

**6. Rationale.** Patients who have undergone HSCTs have a higher burden of disease from influenza infection compared with healthy controls, with significant morbidity and mortality due to influenza disease. They are also at high risk of influenza-associated complications, particularly pneumonia. Thus, strategies to reduce influenza disease in this highly susceptible population are critical, especially since these individuals respond poorly to standard dose IIV. HD-TIV has increased immunogenicity and efficacy in adults  $\geq 65$  years compared with standard dose.<sup>54</sup> Therefore, the use of HD-TIV appears to be a promising and practical alternative intervention to improve vaccine-induced immune responses in pediatric HSCT recipients. ***We hypothesize that HD-TIV will be more immunogenic compared with standard dose QIV and will remain well-tolerated in this vulnerable population.*** Thus, for this protocol we propose to compare the immunogenicity and safety of HD-TIV to standard-dose QIV.

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Since the majority of influenza illness is due to influenza A and HD-TIV licensure was based on influenza A antigen responses, the results of these studies could be generalizable to HD-QIV, should it become commercially available in the future. In addition, influenza B antigens have lower HAI titers compared to influenza A antigens, especially in children, including those without co-morbidities.<sup>59</sup> Therefore, if the results from this trial reveal superior HAI titers to influenza A antigens, a HD-QIV vs. standard-dose QIV trial will not be necessary. Moreover, this study has significant potential to impact clinical practice in pediatric HSCT patients. Demonstration of safety and greater immunogenicity of HD-TIV versus standard dose QIV in this population could alter current influenza vaccine recommendations. Additionally, successful use of HD-TIV to enhance influenza-specific immune responses in pediatric HSCT patients could reduce influenza disease burden, morbidity, and mortality in these high-risk patients.

### C. Research Design and Methods:

**1. Study Design:** The proposed study is a multi-center, phase II immunogenicity and safety trial comparing HD-TIV to standard dose QIV in pediatric HSCT recipients. Subjects will be randomized in a 1:1 fashion to receive either 2 doses of 0.5 mL HD-TIV (60 $\mu$ g of each influenza antigen) or 2 doses of standard dose QIV (15 $\mu$ g of each influenza antigen) of the season-specific vaccine 28-42 days apart. HAI and microneutralization (MN) titers to influenza virus antigens, phenotypic B and T cell responses, B and T cell specific influenza responses, complete blood count with differential and platelets (CBC d/p), quantitative CD4 $^{+}$ /CD8 $^{+}$ /CD19 $^{+}$  levels, and quantitative serum IgM and IgG concentrations will be measured prior to the first and second vaccine dose, 28-42 days after the second vaccine dose, and 180 days ( $\pm$ 42 days) after second vaccine. If children are receiving intravenous (IV)/subcutaneous (SC) immunoglobulin (IG) during any visit, additional sera will be collected to measure HAI and MN titers following IVIG/SCIG dose administration. A subset of children will have cellular immune responses measured 5-10 days after each vaccination. Approximately 20-40 mL\* of venous blood will be obtained at each of these visits. Parents/subjects will record solicited events for 7 days after each vaccination (Day 0-7). On days 1-3 and 8-10, an attempt of telephone and/or electronic communication will be made to assess for solicited AEs following each vaccination. Each female of childbearing age will be given a pregnancy test before each vaccination. If she is pregnant, she will not be eligible for the study.

\*Note, for all blood draws, if blood is being drawn and discarded for clinical reasons, blood volumes can exceed 40 mls.

Individuals enrolled in the study during one season will be asked if they would like to participate in the study during a second year, i.e. the following season. Subjects who participate a second year will not be asked to participate a third time. For the 2019-2020 season, subjects who were enrolled and participated in the study for the first time during the 2018-2019 season will be approached and asked to participate a second year.

**Influenza Surveillance:** Active surveillance for influenza-like symptoms will begin when influenza season starts in each site's community. Influenza season begins in the specific community, defined as in previous trials by identification of at least 2 positive respiratory tests for influenza, with at least 10% of diagnostic tests positive during 2 consecutive weeks in the local clinical or research laboratory.<sup>60,61</sup> Enrollment will continue during influenza season with nasal swabs obtained at all main visits during the influenza season to document the occurrence of influenza virus detection both prior to and after vaccination.

During the influenza season, the study staff will attempt to do a weekly telephone and/or electronic communication with the participants to detect and document any influenza like illness (ILI).

**If subjects meet ILI criteria (see below),** a nasal swab will be collected.

**ILI criteria: One of following criteria met:**

- **Fever:**  $\geq 38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ); or
- **Two or more of any of the following:** respiratory symptoms (rhinorrhea, sinus congestion, post-nasal drip, shortness of breath, cough, wheezing, sputum production, sore throat, sneezing, watery eyes, ear pain, hoarseness); or systemic symptoms (myalgias and headache)

**2. Primary and Secondary Study Objectives:****a. Primary Objectives:**

- To determine whether HD-TIV compared with standard dose IV will increase the probability of achieving a  $\geq 4$ -fold rise in HAI titers,  $\geq 1:40$  HAI titer, or higher GMT titers to influenza A antigens in pediatric HSCT recipients.

**b. Secondary Objectives:**

- To determine whether HD-TIV compared with standard dose QIV will increase the probability of achieving a  $\geq 4$ -fold rise in HAI titers,  $\geq 1:40$  HAI titer, or higher GMT titers to influenza B antigens in pediatric HSCT recipients.
- To determine the frequency and severity of solicited local injection site adverse events (e.g. pain/ tenderness, redness, and swelling/Induration at injection site) with HD-TIV compared to standard QIV in pediatric HSCT recipients.
- To determine the frequency and severity of solicited systemic adverse events (e.g. fevers, headache, fatigue/malaise, nausea, body ache/myalgia, general activity level, and vomiting) with HD-TIV compared to standard dose QIV in pediatric HSCT recipients.
- To define the relationship between HAI titers, ex-vivo T and B cell phenotype, and ex-vivo influenza-specific T and B cell response in pediatric HSCT recipients receiving either HD-TIV or standard dose QIV.
- To correlate HAI responses to MN responses.
- To compare the persistence of HAI and MN titers for all four antigen seven months after the last vaccine dose.
- To compare influenza detection by PCR during influenza season in pediatric HSCT recipients receiving either HD-TIV or standard dose QIV.
- To assess HAI and MN response in children undergoing two consecutive years of vaccination using the same antigen dose.
- To evaluate neuraminidase inhibition titers (NAI) responses in children undergoing two consecutive years of vaccination and correlate them to HAI responses.

**3. Study Area:** The study will be conducted in the Outpatient Pediatric Oncology/HSCT Clinics or Clinical Trial Centers at the following sites: Table 2 includes yearly average number of HSCT transplants per site (**Table 2**).**Table 2. Sites and Average Number of Yearly Allogeneic Transplants**

Site	Average Number of Yearly transplants	Potential During Study Period
Children's Mercy Hospital	25	56
Columbus Nationwide Children's Hospital	25	56
Vanderbilt University	30	68
Children's Hospital of Philadelphia (CHOP)	35	79
Seattle Children's Hospital	50	113
St. Jude Children's Research Hospital	50	113

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<b>UCSF (University of California San Francisco)</b>	50	113
<b>Benioff Children's Hospital</b>		
<b>Cincinnati Children's Hospital</b>	90	203
<b>Texas Children's Hospital</b>	100	225
<b>TOTAL</b>	<b>455</b>	<b>1026</b>

**4. Study Population:**

**A. A target of at least 200 pediatric patients who received an allogeneic HSCT over three enrollment years (2016-2017, 2017-2018, 2018-2019) and met the inclusion/exclusion criteria outlined below:**

**1. Inclusion criteria**

- a. Allogeneic HSCT recipients who are 3-35 months post-transplant;
- b. 3-17 years of age, inclusive;
- c. Available for duration of study;
- d. Patients with stable GVHD for at least 4 weeks will be eligible (stable is defined as having no major increases in systemic immunosuppressive therapy for GVHD; adjustments of established medications to obtain a stable target level are acceptable and do not impact eligibility). Parent/legal guardian willing and capable of signing written informed consent;
- e. Parent/legal guardian expected to be available for entire study;
- f. Parent/legal guardian can be reached by telephone and/or electronic communication.
- g. Subjects must have a platelet count of  $\geq 30,000$  to receive the immunizations. Patients requiring platelet transfusions are eligible to enroll and must have a platelet count  $\geq 30,000$  within 72 hours prior to their immunization, or platelet count  $\geq 75,000$  without transfusion documented within 30 days for subjects <12 months post-transplant and within 90 days for subjects 12-35 months post-transplant.

**2. Exclusion criteria**

- a. History of hypersensitivity to previous influenza vaccination or severe hypersensitivity to eggs/egg protein;
- b. History of Guillain-Barre syndrome;
- c. Evidence of hematologic malignancy or disease relapse post-transplant (stable mixed chimerism is permitted);
- d. History of receiving current year seasonal influenza vaccine post-transplant;
- e. Pregnant female;
- f. History of proven influenza disease after September 1, 2018 prior to enrollment
- g. Non-allogeneic (e.g. autologous) or syngeneic hematopoietic SCT recipients;
- h. History of known active infection with HIV, Hepatitis B or Hepatitis C;
- i. History of known severe latex hypersensitivity;
- j. Subjects who have received stem cell boost or delayed donor lymphocyte infusion within 90 days prior to enrollment, including day of enrollment;
- k. Receipt of IVIG/SCIG <27 days prior to calendar day of vaccination;
- l. Subjects who have participated in year 1 and/or 2 of the study, and received study vaccine

**Criteria for temporarily delaying vaccine administration:** The following conditions are temporary or self-limiting, and a subject may be included in the study once the condition has resolved, provided that the subject is otherwise eligible: 1). Fever  $\geq 100.4^{\circ}\text{F}/38.0^{\circ}\text{C}$  (oral measurement), or an acute illness within 48 hours of

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enrollment 2). Receipt of any live vaccines within four weeks or any inactivated vaccines within two weeks prior to potential study vaccination.

Note: if patients were eligible for vaccine 1, they will be eligible to receive vaccine 2 regardless of any changes on their GVHD status, unless it is deemed not medically safe to receive influenza vaccine.

For subjects who were enrolled and vaccinated in 2016-17, 2017-18, or 2018-19, the goal is to enroll individuals who participated in the previous influenza season year and administer the same vaccination as the previous year. These subjects are referred to as repeaters. For example, subjects enrolled in 2016-17 could re-enroll in 2017-18, subjects enrolled in 2017-18 could re-enroll in 2018-19, and subjects in 2018-19 are deemed eligible to re-enroll in 2019-20 as repeaters. Subjects may only enroll as a repeater one time and must enroll the year after their original enrollment. Subjects must receive at least one vaccine to be eligible as a repeater in the subsequent year.

## **B. Enrollment Criteria for Subjects who Participated in the previous influenza season**

- Repeaters will retain their original study ID and their randomization number
- Previous screen failures will not be enrolled.
- If visit 4 from the previous influenza season and visit 1 from the current influenza season year occur on the same day, lab results from visit 4 (prior to consent) can be part of visit 1.

### **1. Inclusion criteria**

- a. Available for duration of study;
- b. Patients with stable GVHD for at least 4 weeks will be eligible (stable is defined as no major change in systemic immunosuppressive therapy for worsening GVHD; adjustment of actual dose to obtain a stable target level is acceptable).
- c. Subjects must have a platelet count of  $\geq 30,000$  to receive the immunizations. Patients requiring platelet transfusions are eligible to enroll and must have a platelet count  $\geq 30,000$  within 72 hours prior to their immunization, or platelet count  $\geq 75,000$  without transfusion documented within 30 days for subjects <12 months post-transplant and within 90 days for subjects 12-35 months post-transplant.
- d. Parent/legal guardian willing and capable of signing written informed consent;
- e. Parent/legal guardian expected to be available for entire study;
- f. Parent/legal guardian can be reached by telephone and/or electronic communication.

### **2. Exclusion criteria**

- a. History of hypersensitivity to previous influenza vaccination or severe hypersensitivity to eggs/egg protein;
- b. History of Guillain-Barre syndrome;
- c. Evidence of hematologic malignancy or disease relapse post-transplant (stable mixed chimerism is permitted);
- d. History of receiving current year seasonal influenza vaccine post-transplant;
- e. Pregnant female;
- f. History of proven influenza disease after September 1, 2019 but prior to enrollment
- g. History of known active infection with HIV, Hepatitis B or Hepatitis C;
  - h. Subjects who have received stem cell boost or delayed donor lymphocyte infusion within 90 days of enrollment, including day of enrollment
  - i. Receipt of IVIG/SCIG <27 days prior to calendar day of vaccination
  - j. Non-allogeneic (e.g. autologous) or syngeneic hematopoietic SCT recipients;
  - k. Subjects who have participated in year 1 and/or 2 of the study and received study vaccine.

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**Criteria for temporarily delaying vaccine administration:** The following conditions are temporary or self-limiting, and a subject may be included in the study once the condition has resolved, provided that the subject is otherwise eligible: 1). Fever  $\geq 100.4^{\circ}\text{F}/38.0^{\circ}\text{C}$  (oral measurement), or an acute illness within 48 hours of enrollment 2). Receipt of any live vaccines within four weeks or any inactivated vaccines within two weeks prior to potential study vaccination.

Note: if patients were eligible for vaccine 1, they will be eligible to receive vaccine 2 regardless of any changes on their GVHD status, unless it is deemed not medically safe to receive influenza vaccine.

Note: Previous Screen failures who were not vaccinated can be enrolled and will be assigned the same study ID number.

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An overview of the study schedule and procedures are described in **Table 3**.

Table 3.	Screening period	Visit 1	Phone / email	Optional Visit	Visit 2	Phone/Email	Optional Visit	Visit 3	Influenza Season	Visit 4 ^	June 30th
Days		0	1-3 and 8-10* days	5-10 days after visit 1	28-42 days	1-3 and 8-10* days after visit 2	5-10 days after visit 2	28-42 days after visit 2		180 ±42 days after visit 2	Day 0 until June 30th
Consent	X	X									
Inclusion/exclusion		X			X						
Physical examination#, oral temperature		X			X						
Peripheral venipuncture or via central line		X		X	X		X	X		X	
HAI, NAI, and microneutralization assay		X**			X**			X**		X	
B/T cell responses		X		X	X		X	X		X	
CBC d/p#		X			X			X		X	
Quantitative CD4, and CD8, CD19#		X			X			X		X	
Quantitative serum IgG, IgM#		X			X			X		X	
Study vaccine administration (HD-TIV or standard dose)		X			X						
Memory aid review			X			X					
Adverse event assessment		X	X	X	X	X	X				
Concomitant medication collection		X	X	X	X	X	X	X			
Immunizations reviewed		X			X			X		X	
Telephone and/or Electronic communication			X			X			Weekly		
Pregnancy Test (if applicable)		X			X						
Collection of Nasal Swab for PCR testing for Influenza***		X^			X^			X^	If symptomatic	X^	X
Proven clinical influenza illness #review		X	X	X	X	X	X	X	X	X	X

\*8-10 day telephone and/or electronic communication are not required if the subject is seen at the optional visit within this window period;

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# If these tests/procedures are performed as standard of care prior to enrollment, but on same calendar day of vaccination, they will not need to be repeated and these data can be collected as part of study information.

\*\*a second blood draw will be obtained post-IVIG/SCIG if IVIG/SCIG is administered at this visit.

^a swab will be collected during influenza season.

\*\*\* Nasal swabs will be collected from symptomatic patients throughout the study period.

## Proven clinical influenza illness is any breakthrough influenza illness confirmed by laboratory testing (i.e. Rapid antigen assay, PCR, virus culture, ,etc.

^^ Optional for repeaters in the 2019-20 season

**5. Treatment Groups:** There will be two groups – HD-TIV versus standard dose QIV. The children will be randomized in a 1:1 HD-TIV (100 subjects) versus standard dose QIV (100 subjects) for current enrollment season.

Treatment Group	Target # (all study years)
<u>Group 1</u> 0.5 mL HD-TIV	100
<u>Group 2</u> 0.5 mL standard dose QIV	100

**a. Randomization:** Subjects will be randomized 1:1 to either HD-TIV or standard dose QIV. Randomization will be frequency-matched within each site to ensure balance between the groups and will be implemented using the Randomization Module within Vanderbilt's REDCap database. The investigational pharmacy at each of the 9 institutions will distribute the assigned study vaccine. Because we are evaluating the immunogenicity of early timing of influenza vaccine post-transplant, we will limit enrollment to 60 (30%) subjects to  $\geq 12$  months post-transplant.

**For block randomization:**

1. For subjects 12-35 months since transplant, we will do block randomization on the following question: "Is the subject currently being treated for GVHD with systemic steroids?" (yes/no); if yes, they will be evenly distributed for randomization.
2. For subjects 3-11 months since transplant, block randomization will be on the following question: "Is the subject currently being treated for GVHD with systemic steroids or does the subject fall into one or more the following criteria: history of campath (alemtuzumab); history of anti-thymocyte globulin (ATG); cord transplant; haploidentical transplant; or post-transplant cytoxan (cyclophosphamide)?"
3. Repeaters will retain their randomization number given from their initial enrollment and will not be re-randomized

**b. Enrollment:** Subjects will be enrolled from the Outpatient Pediatric Oncology/HSCT units, clinics, or clinical research centers at each institution. The healthcare team will help identify individuals who are eligible and will ask permission to be approached about the study. The research team will inform the subjects and their parents/guardians of the study and its procedures. Consent will be given to them to review. Ample time will be given to explain the study and answer any questions prior to signing the consent.

**6. Data Collection:**

The following information will be collected from each subject but not limited to:

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- a. Type of transplant: (Bone marrow, peripheral blood, both bone marrow and peripheral blood, cord blood or cord blood and peripheral blood; type of HSCT (HLA-identical sibling, HLA-mismatched relative, unrelated)
- b. Underlying disease name and underlying disease risk
- c. Transplant cell dose
- d. Transplant conditioning regimen and post-transplant immunosuppressive medications
- e. History of acute or chronic GVHD
- f. GVHD status
- g. HLA match
- h. History of IVIG/SCIG administration
- i. Chimerism status
- j. Gender (patient/donor gender)
- k. Race/ethnicity
- l. Age
- m. Social History (school, daycare, etc.)
- n. Household members (# of children)
- o. History of influenza vaccination (pre and post-transplant)
- p. Past medical history
- q. CMV status (donor/recipient) and CMV viral load information
- r. Medications

**7. Reporting Adverse Events:**

The investigator is responsible for reporting:

- Any Grade 3 Adverse event that is not attributable to underlying disease for which the transplant was undertaken, **or** not attributable to GVHD, **or** not attributable to complications of immunosuppressive medications that are observed or reported through 7 days following vaccination (Day 0 through Day 7), regardless of their relationship to study product.
- Any other AE will not be reported unless it meets the SAE criteria (see Section 16.f).

Initial vaccine reactions will be assessed for at least 15 minutes after vaccination. Subjects will be asked to record both solicited vaccine reactions and any unsolicited AEs on a memory aid for 7+ days after each vaccination (Day 0 through Day 7). Study personnel will attempt contacting the subjects by telephone and/or electronic communication at 1-3 days and 8-10 days after vaccination to review any AEs and SAEs. Adverse events and serious adverse events will be collected through 7 days following vaccination.

Solicited **systemic AEs** will be collected for 7+ days post each vaccination and will include the following: fevers, headache, fatigue/malaise, nausea, body ache/myalgia, general activity level, and vomiting. Solicited **injection site AEs** will include the following: pain, tenderness, redness/erythema, and swelling/induration at injection site.

**Reporting of Deviations:** All deviations will be reported to the IRB at the time of annual continuing review. Note: if the deviation affects patient safety and/or risk, the event will be reported immediately.

**8. Study Withdrawal / Discontinuation:**

**a. Reasons for Withdrawal or Discontinuation of Study Product**

- 1. Subjects will be able to withdraw from the study at any time point.
- 2. A study subject will be discontinued from participation in the study if the following occur:

- a. Any clinical adverse event (AE), laboratory abnormality, intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject. However, the subject may continue to be followed for safety purposes.
- b. Development of any exclusion criteria may be cause for discontinuation from the study, except for individuals who were 17 at enrollment and turned 18 year old during the study.
- c. Subjects may be removed from the study for failure to make follow-up visits.
- d. Subjects may be removed from the study if new information becomes available that makes further participation unsafe.

**b. Handling of Withdrawals**

Every attempt should be made to collect all data specified by the protocol relative to study vaccine received, including post-immunization blood samples. All AEs will be followed to adequate resolution or until considered stable.

**9. Follow-up Record Retention:**

No follow-up visits are needed once the study is completed. A copy of the paper records will be retained for at least 7 years after completion of the study. The information stored in the ONCORE and/or REDCap database will be kept indefinitely. The samples (blood) collected will be labeled with the same numeral ID and stored in the respective laboratories: HAI and MN to Sanofi laboratory and nasal specimens and PBMCs to Vanderbilt. With the permission of the subjects any leftover samples will be kept and used for future research and will be stored at Vanderbilt. A separate IRB approval will be sought prior to the use of these samples.

**10. Investigational Product and Risk Information:**

Fluzone Quadrivalent® a Federal Drug Administration (FDA)-approved vaccine and is recommended for all pediatric patients  $\geq 6$  months.<sup>62</sup>

Fluzone® HD-TIV has not yet been approved for individuals  $< 65$  years of age. The current seasonal influenza vaccine will be used for each study year (e.g. 2016-2017 or 2017-2018 or 2018-2019 or 2019-2020).

**a. Acquisition:** Fluzone Quadrivalent® and Fluzone® HD-TIV, preservative free, licensed product formulated for the 2016-2017 and/or 2017-2018 and/or 2018-2019 and/or 2019/2020 influenza season will be donated by Sanofi Pasteur and distributed to each site of the 9 institutions.

**b. Formulation, Packaging, and Labeling:** Fluzone Quadrivalent® and Fluzone® HD-TIV, preservative free, licensed product, Sanofi Pasteur, Swiftwater, PA. The 2016-2017 recommendations are the following: an A/California/7/2009 (H1N1)-like virus; an A/Hong Kong/4801/2014 (H3N2)-like virus; and a B/Brisbane/60/2008-like virus (this is a B/ Victoria lineage virus) in both products except in Fluzone Quadrivalent®, there is an additional B/Phuket/3073/2013-like virus (this is a B/ Yamagata lineage virus). The Fluzone package inserts for the 2016-2017 influenza season for both vaccines will be available in the Protocol Library.

Fluzone Quadrivalent® and Fluzone® HD, preservative free, licensed product formulated for the 2017-2018 influenza season, Sanofi Pasteur, Swiftwater, PA will be obtained. Formulation, Packaging, and Labeling: Fluzone Quadrivalent® and Fluzone® HD, preservative free, licensed product, Sanofi Pasteur, Swiftwater, PA. The 2017-2018 recommendations are the following: A/Michigan/45/2015 (H1N1)pdm09-like virus; an A/Hong Kong/4801/2014 (H3N2)-like virus; and a B/Brisbane/60/2008-like virus (this is a B/ Victoria lineage virus); and in Fluzone Quadrivalent®, additional B virus, B/Phuket/3073/2013-like virus, (this is a B/ Yamagata lineage virus). The Fluzone package inserts for the 2017-2018 influenza season for both vaccines will be available in the Protocol Library.

Fluzone Quadrivalent® and Fluzone® HD, preservative free, licensed product formulated for the 2018-2019 influenza season, Sanofi Pasteur, Swiftwater, PA will be obtained. Formulation, Packaging, and Labeling: Fluzone Quadrivalent® and Fluzone® HD, preservative free, licensed product, Sanofi

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Pasteur, Swiftwater, PA. The 2018-2019 recommendations are the following: A/Michigan/45/2015 (H1N1)pdm09-like virus; an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus; and a B/Colorado/06/2017-like virus (this is a B/ Victoria lineage virus); and in Fluzone Quadrivalent®, additional B virus, B/Phuket/3073/2013-like virus, (this is a B/ Yamagata lineage virus). The Fluzone package inserts for the 2018-2019 influenza season for both vaccines will be available in the Protocol Library.

The 2019-2020 influenza strain recommendations are the following: A/Brisbane/02/2018 (H1N1)pdm09-like virus; A/Kansas/14/2017 (H3N2)-like virus; and B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) for both HD-TIV and SD-QIV; and in Fluzone Quadrivalent®, additional B virus, B/Phuket/3073/2013-like virus (B/Yamagata lineage). The Fluzone package inserts for the 2019-2020 influenza season for both vaccines will be available in the Protocol Library.

**c. Product Storage and Stability:** The vaccine will be stored in the original package to protect from light. The vaccine will be stored in secure, limited-access, temperature-monitored refrigerator environments at 2°C to 8°C (35.6°F to 46.4°F) until needed. The temperature of the storage unit will be monitored for the duration of the trial, and documentation of proper dedicated storage will be maintained. It will not be frozen. In the event of accidental deep-freezing or disruption of the cold chain, vaccines will not be administered.

**d. Dosage, Preparation and Administration of Study Intervention/ Investigational Product**

Either dose (0.5 ml) of TIV or QIV (Fluzone® HD-TIV, Sanofi Pasteur) or (Fluzone Quadrivalent®, Sanofi Pasteur) will be administered intramuscularly in either the right or left arm. In preparing either vaccine, the pre-filled syringe will be gently shaken and visually inspected for particulate matter and/or discoloration prior to administration (the TIV/QIV may normally be clear to slightly opalescent). If either condition exists, the pre-filled syringe will not be used.

Subjects will be randomized in a 1:1 fashion to receive either 2 doses of 0.5 mL HD-TIV (60µg of each influenza antigen) or 2 doses of standard dose QIV (15µg of each influenza antigen) of the current seasonal influenza vaccine (e.g. 2016-2017 or 2017-2018 or 2018/2019 or 2019/2020) 28-42 days apart. The repeaters retain their randomization code.

Each of these study products will be labeled according to manufacturer specifications and include the statement "Caution: New Drug – Limited by Federal Law to Investigational Use."

**e. Modification of Study Intervention/Investigational Product for a Participant**

No dose modifications will be allowed.

**11. Side Effects with Influenza Vaccination.** The side effects listed in the package insert include:

**a. Local Reactions:** In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%–64% of subjects) that lasts ≤ 2 days. These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities.

**b. Systemic Reactions:** Fever, malaise, myalgia, and other systemic symptoms can occur following vaccination and most often affect persons who have had no exposure to the influenza virus antigens in the vaccine (e.g., young children). These reactions begin 6 to 12 hours after vaccination and can persist for 1–2 days. Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus vaccine is not associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections. Immediate, presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions likely are caused by residual egg protein. Although current influenza vaccines contain

only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have experienced hives, have had swelling of the lips or tongue, or have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had allergic responses to egg protein—also might be at increased risk for allergic reactions to influenza vaccine, persons with known allergies to eggs or who developed an allergic reaction to previous influenza vaccines will not be enrolled in this study. The tip caps of the prefilled syringes may contain natural rubber latex, which may cause allergic reactions in latex sensitive individuals. (Therefore, individuals with history of hypersensitivity to previous influenza vaccination or severe hypersensitivity to eggs/egg protein are excluded).

The adverse event profile of TIV administration in pediatric immunocompromised recipients has been comparable to that reported in healthy individuals receiving TIV.<sup>63</sup> With the exception of soreness at the injection site, adverse reactions to TIV are uncommon.<sup>64</sup> Minor reported side effects include: low grade fever, chills, local redness, bruising, pain, swelling at injection site, headache, malaise, and/or joint or muscle pain. Very rare side effects include severe weakness or unusual feeling in the arms or legs, high fever, and/or unusual bleeding. In some years, Guillain-Barre syndrome has been reported but rarely in children.<sup>64-66</sup>

## 12. Risk Information:

- a. **Influenza vaccine:** The adverse event profile of TIV administration in hematopoietic SCT recipients has been comparable to that reported in healthy individuals receiving TIV.<sup>34,35,46</sup> With the exception of soreness at the injection site, adverse reactions to TIV or QIV are uncommon.<sup>64</sup> Minor reported side effects include: low grade fever, chills, local redness, bruising, pain, swelling at injection site, headache, malaise, and/or joint or muscle pain. Very rare side effects include severe weakness or unusual feeling in the arms or legs, high fever, and/or unusual bleeding. In some years, Guillain-Barre syndrome has been reported, but rare in children.<sup>65,66</sup>
- b. **Blood draw risk:** Pain, redness, soreness, bruising, or very rarely infection may occur at the needle stick site. Rarely some people faint. If subjects have central venous catheters, blood will be obtained through their catheter.
- c. **Nasal swab:** minor discomfort from nasal swabs, and a rare event of bleeding from a nasal swab. If this occurs, pressure will be applied to the nares to stop the bleeding.

## 13. Study Visit Schedule: (see Table 3 for details)

- a. **Screening:** Subjects will be screened by history and physical exam to make sure that all eligibility criteria are met. No baseline laboratory screening will be performed prior to enrollment. However, if CBC d/p, quantitative CD4, CD8, CD19, IgM and IgG are obtained as part of standard of care prior to enrollment and on the same calendar day as vaccination, these data will be collected and will not need to be repeated after consent is signed. In addition, consent may be obtained prior to visit 1.
- b. **Enrollment/Baseline:** Prior to each vaccination, inclusion and exclusion criteria, as well as any reason to delay vaccination will be reviewed.
- c. **Follow up:** Follow-up telephone and/or electronic communication will be completed both 1-3 and 8-10 days after each vaccination visit. If the subject is seen as part of the optional visit and this visit is within

the 8-10 days communication window period, this would replace the 8-10 day telephone and/or electronic communication.

**d. Final Study Visit:** The final visit will be  $180 \pm 42$  days after visit 2.

**e. Unscheduled Visits:**

**May occur for further evaluations of AEs/SAEs.**

- Review current health status since the last visit.
- Memory aid will be reviewed if the unscheduled visit occurs within 7 days of vaccination.
- All concomitant medications will be recorded if the early termination occurs within 28 days of vaccination.
- A targeted physical examination and vital signs may be performed, as indicated.

**Early Termination Visit:** Subject Withdrawal Criteria: Subjects have the right to withdraw from the study at any time.

**Events Which Warrant Withdrawal:** The investigator may drop/withdraw a subject from the study if deemed appropriate. Criteria for termination of a subject include: lost to follow-up, non-compliance with the protocol, and/or clinically significant adverse events (e.g., immediate allergic reaction to vaccine, severe or anaphylactic in type), which constitute contraindications to further vaccine administration.

**Data Collection for Withdrawn Subjects:** Every attempt should be made to collect all data specified by the protocol relative to study vaccine received, including post-immunization blood samples.

## **14. Study Procedures/Evaluation:**

### **Screening Periods/Supplemental Visit, prior to Visit 1, Day 0.**

- Subject and/or Parents/legal guardians are able to sign written informed consent prior to Visit 1. Also, if individuals sign a consent and are later deemed not eligible for vaccination, then this will also be listed as a supplemental visit with screen failure. If the subject was temporarily unable to receive vaccine and later becomes eligible (as in the case of recent prior other vaccine receipt), they can proceed with the following study procedures.

### **Days 0 to 90 :**

Patients requiring platelet transfusions are eligible to enroll and must have a platelet count  $\geq 30,000$  within 72 hours prior to their immunization. For subjects <12 months post-transplant, if a platelet count of  $\geq 75,000$  is documented without transfusion support within 30 days of the immunization or 12-35 months post-transplant within 90 days, then an additional platelet count does not need to be repeated prior to immunization.

### **Visit 1: Day 0:**

- Subject and/or Parents/legal guardians will sign written Informed Consent if not already signed prior to Visit 1.
- Medical history
  - Inclusion/exclusion criteria will be checked
  - Prior/concomitant medications will be recorded
  - Written documentation of prior influenza immunizations will be collected
- Targeted physical examination will be conducted including measurement of oral temperature (must be  $\leq 100.4^{\circ}\text{F}/38^{\circ}\text{C}$ ). Except for oral temperature, if a physical exam is completed as a part of standard of care, another physical exam does not need to be completed. For females of childbearing age a pregnancy test will be performed.
- Approximately 20-40 mL of blood will be collected by venipuncture or from a central line prior to vaccination for HAI and MN assays to influenza virus antigens, phenotypic B, and T cell responses, B and T cell specific influenza responses, CBC d/p, quantitative CD4 $^{+}$ /CD8 $^{+}$ /CD19 $^{+}$  levels, and quantitative serum IgM and IgG concentrations (if CBC d/p, quantitative CD4, CD8, CD19, IgM, and IgG are obtained as part of standard of care prior to enrollment and on the same calendar day as vaccination, these data will be collected and will not need to be repeated)

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- Study vaccine will be administered.
- Study staff or clinical research center staff will observe the subjects closely for at least 15 minutes post-vaccination, with appropriate medical treatment readily available in case of rare anaphylactic reaction following the administration of vaccines.
- If IVIG/SCIG is given the same day, it may be given before or after the vaccination, and a second blood draw will be obtained post-IVIG/SCIG if administered on same calendar day.
- A memory aid form with reaction measurements, a measurement gauge, thermometer and instructions will be provided for the subject to record oral temperatures and any general or local reactions occurring during the vaccination day (day 0) and the next 7 days. Information on the memory aid form will be collected from the subject through telephone calls and/or electronic communication in the week following vaccination or received by mail. If memory aid data were not received by any of the methods mentioned, subjects may return it on the day of their next visit.
- The subject will be given contact information for study personnel. The subject will be educated about any potential reactions following vaccination. They will be instructed to contact study personnel for reactions that are Grade 3, as well as any other medical event that is concerning to subject.
- Only during influenza season, a nasal swab will be obtained regardless of symptoms.

**Days 0-7:**

After the vaccination:

- The following data will be recorded on the memory aid form by the subjects each day:
  - Oral temperature
  - Local reactions
  - General reactions
  - Concomitant medications given

**Days 1-3 and Days 8-10: Telephone and/or electronic communication:**

- An attempt of telephone and/or electronic communication will be made/sent between Days 1-3 and again on Days 8-10 to:
  - Appropriate data will be collected and they will ensure the memory aid forms are being completed correctly
  - Any adverse events that have occurred will be collected
  - Questions the subject may have will be answered
  - Any concomitant medication will be recorded
  - If the subject is seen as part of the optional visit and this visit is within the 8-10 days communication window period, this would replace the 8-10 day telephone and/or electronic communication.

**Visit 2: Days 28-42**

- Medical history
  - Inclusion/exclusion criteria will be checked- patients will be eligible to receive vaccine 2 if they received vaccine 1, regardless of GVHD status changes- but changes must be documented.
  - Concomitant medications will be recorded
- Targeted physical examination will be conducted including measurement of oral temperature (must be  $\leq 100.4^{\circ}\text{F}/38^{\circ}\text{C}$ ). If a physical exam is completed as a part of standard of care, another physical exam does not need to be completed. For females of childbearing age a pregnancy test will be performed.
- Approximately 20-40 mL of blood will be collected by venipuncture or from a central line prior to vaccination for HAI and MN assays to influenza virus antigens, phenotypic B, and T cell responses, B and T cell specific influenza responses, CBC d/p, quantitative CD4 $^{+}$ /CD8 $^{+}$ /CD19 $^{+}$  levels, and quantitative serum IgM and IgG concentrations.
- Study vaccine will be administered.

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- The subjects will be observed closely for at least 15 minutes post-vaccination, with appropriate medical treatment readily available in case of rare anaphylactic reaction following the administration of vaccines.
- If IVIG/SCIG is given the same day, it may be given before or after the vaccination, and a second blood draw will be obtained post-IVIG/SCIG if administered on same calendar day.
- A memory aid form with reaction measurements, a measurement gauge, thermometer and instructions will be provided for the subject to record oral temperatures and any general or local reactions occurring during the vaccination day (day 0) and the next 7 days. Information on the memory aid form will be collected from the subject through telephone calls and/or electronic communication in the week following vaccination or received by mail. If memory aid data were not received by any of the methods mentioned, subjects may return it on the day of their next visit.
- The subject will be given contact information for study personnel. The subject will be educated about any potential reactions following vaccination. They will be instructed to contact study personnel for reactions that are Grade 3, as well as any other medical event that is concerning to the subject.
- Only during influenza season, a nasal swab will be obtained, regardless of symptoms.

**Days 0-7: After the second vaccination:**

- The following data will be recorded on the memory aid form by the subjects each evening:
  - Oral temperature
  - Local reactions
  - General reactions
  - Concomitant medications given

**Days 1-3 and Days 8-10 after second vaccination:** Telephone and/or electronic communication

- An attempt of telephone and/or electronic communication will be made/sent between Days 1-3 and again on Days 8-10:
  - Appropriate data will be collected, and they will ensure the memory aid forms are being completed correctly
  - Any adverse events that have occurred will be collected
  - Questions the subject may have will be answered
  - Any concomitant medication will be recorded

**Visit 3: 28-42 Days after Visit 2**

- Solicited AEs/unsolicited AEs will be reviewed and recorded in through 7 days following vaccination #2
- Targeted physical examination will be conducted if indicated.
- Any concomitant medication will be recorded.
- Any new immunizations since last visit will be reviewed and recorded.
- Approximately 20-40 mL of blood will be collected for HAI and MN assays to influenza virus antigens, phenotypic B, and T cell responses, B and T cell specific influenza responses, CBC d/p, quantitative CD4<sup>+</sup>/CD8<sup>+</sup>/CD19<sup>+</sup> levels, and quantitative serum IgM and IgG concentrations.
- A second blood draw will be obtained post-IVIG/SCIG if administered.
- Only during influenza season, a nasal swab will be obtained, regardless of symptoms.
- For the 2019/2020 enrollment season, subjects who are not able to return for visit 3 will have an arrangement for a blood draw to be done locally and shipped to the research team. Subjects will also be called and asked about their health and medication changes. Also, they will be asked to collect a nose swab and mail it to the research team.

### **Influenza Surveillance:**

Active surveillance for influenza-like symptoms will begin when influenza season starts at each site's community. Influenza season begins in the specific community, defined as in previous trials by identification of at least 2 positive respiratory tests for influenza, with at least 10% of diagnostic tests positive during 2 consecutive weeks in the local clinical or research laboratory.<sup>60,61</sup> Enrollment will continue during influenza season with nasal swabs obtained at all main visits to document the occurrence of influenza virus detection both prior to and after vaccination.

Study staff will attempt to collect nasal swabs from patients who meet the ILI criteria during the entire study period.

When the flu season starts, the study staff will attempt to do a weekly telephone and/or electronic communication with the participants to detect and document any influenza like illness (ILI). Patients who meet the ILI criteria will be asked to collect a nasal swab and mail it back to the study site.

#### **ILI criteria: One of following criteria met:**

- **Fever:**  $\geq 38.3^{\circ}\text{C}$  ( $101^{\circ}\text{F}$ ); or
- **Two or more of any of the following:** respiratory symptoms (rhinorrhea, sinus congestion, post-nasal drip, shortness of breath, cough, wheezing, sputum production, sore throat, sneezing, watery eyes, ear pain, hoarseness); or systemic symptoms (myalgias and headache).

A nasal swab will be collected. If distance is an issue or if symptoms start on a weekend, subjects will be given PrimeStore MTM to take to their local pediatrician's office, or with proper instructions, home collection can be done, and arrangements will be made for specimens to be sent either to the local academic center or directly to Vanderbilt in Nashville, TN. Specimens should be collected within 7 days of onset of symptoms, ideally within 48 hours.

Note: For subjects who finish their visit 4 before the end of the flu season, influenza surveillance will continue until the end of the flu season at their site's community.

### **Visit 4: 180 Days $\pm$ 42 after Visit 2**

- Approximately 20-40mL of blood will be collected for HAI and MN assays to influenza virus antigens, phenotypic B, and T cell responses, B and T cell specific influenza responses, CBC d/p, quantitative CD4 $^{+}$ /CD8 $^{+}$ /CD19 $^{+}$  levels, and quantitative serum IgM and IgG concentrations.
- A second blood draw will be obtained post-IVIG/SCIG if administered.
- Only during influenza season, a nasal swab will be obtained, regardless of symptoms.
- For the 2019/2020 enrollment season, visit 4 will be optional and subjects who volunteer to participate will have the procedures outlined above.

### **Optional visits: 5-10 days after each vaccination**

- Only those subjects who volunteer, will return for a blood draw only.
- Approximately 20-40 mL of blood will be collected for B and T cells responses.
- If within the 8-10 days phone call window, this would replace the 8-10 day telephone and/or electronic communication.

Note: Data for proven clinical influenza infection will be collected during the study period and through June 30<sup>th</sup>.

### **15. Laboratory Procedures:**

- a. **Specimen Preparation, Handling, and Shipping:** Blood will be collected from a vein or from a central line from subjects. Study personnel or clinical research staff will collect the blood samples, label without personal identifiers, and deliver to the laboratory for preparation of serum and freezing of the sera until further testing and/or shipment to Sanofi laboratory for HAI and MN testing and B and T cell influenza-specific testing at Vanderbilt. Other clinical labs will be sent the local lab.
- b. **Hemagglutination Inhibition Assays (HAI):** Sera will be shipped to **Sanofi** laboratory for HAI testing. Sera will be initially diluted 1:10 per protocol.<sup>67</sup> Pre-vaccination and post-vaccination sera will be analyzed simultaneously to minimize variability in the HAI assay. HAI titers will be determined for each influenza antigen included in QIV 2016-2017 or 2017-2018 or 2018-2019.
- c. **Neuraminidase Inhibition Assays (NAI):** Sera will be shipped to Vanderbilt for NAI testing and results will be compared to HAI. NAI testing will be done at Dr. Florian Krammer's lab in Mt. Sinai.
- d. **Microneutralization assays:** Sera will be shipped to **Sanofi** laboratory for MN testing and results will be compared to HAI.<sup>68</sup>
- e. **Influenza-specific B and T cell Responses and Immunophenotyping of B and T cells:** Samples will be collected at baseline, 5-10 days (optional) and 28-42 days after each vaccination and 180 days ( $\pm$ 42 days) after second vaccination. After ficoll separation, peripheral blood mononuclear cells (PBMC) will be cryopreserved for future analysis. Each site will do this locally and the off-sites will ship to **Dr. Sypros Kalams** laboratory at Vanderbilt in Nashville, TN. This will ensure all time points from each individual can be evaluated simultaneously. We propose to study B and T cell responses to vaccination with mass cytometry technology (CyTOF), and functional assays such as *in-vitro* IL-21 production in response to vaccine antigen.
- f. **Nasal swabs:** a nasal swab will be collected by either using viral transport media or using PrimeStore MTM, which can be stored at room temperature until ready for shipment to Vanderbilt in Nashville, TN for PCR testing for influenza.

## 16. Specification of Safety Parameters:

Safety will be assessed by frequency, incidence and severity of AEs and SAEs solicited in-clinic and via memory aids, telephone and/or electronic communication conversations, concomitant medications, and periodic physical evaluations.

**Safety monitoring plan post 15 minute vaccination:** Either a nurse, NP, or LPN will administer the vaccine. The subject will wait at least 15 minutes to be observed by the research staff or clinical research staff. These individuals will be in a location that will have access to individuals with advanced cardiac life support skills.

## Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

### a. Adverse Events, Reactogenicity, Serious Adverse Events

The investigator is responsible for reporting:

- Any Grade 3 Adverse event that is not attributable to underlying disease for which the transplant was undertaken, **or** not attributable to GVHD, **or** not attributable to complications of immunosuppressive medications **and** are observed or reported through 7 days following vaccination, regardless of their relationship to study product.
- Any other AE will not be reported unless it meets the SAE criteria (see Section 16.f).

A physician, nurse, nurse practitioner, and/or physician's assistant will assess initial vaccine reactions for at least 15 minutes after vaccination. Subjects will be asked to record both solicited vaccine reactions

(reactogenicity) and any unsolicited AEs on a memory aid for 7+ days after each vaccination (Day 0 through Day 7). Study personnel will attempt to contact the subjects by telephone and/or electronic communication at 1 to 3 days and again 8-10 days after each vaccination to review any AEs and SAEs.

AEs and SAEs will be collected through 7 days following each vaccination. Adverse events will be followed until resolution or until considered stable. **Solicited injection site AEs** will include the following: pain, tenderness, erythema/redness, and swelling/induration (**Table 4**). **Solicited systemic AEs** will be collected for 7+ days post each vaccination and will include the following: fevers, fatigue/malaise, headache, nausea, body ache/myalgia, generally activity, and vomiting (**Table 5**).

**b. Definition of Adverse Event:**

**Adverse Event:** The International Conference on Harmonization (ICH) guideline E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally related to the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews or by a vaccine recipient presenting for medical care.

AEs must be graded for severity and relationship to study product (see below). Severity can be assessed by a licensed clinician (i.e., physician, nurse, nurse practitioner, physician's assistant). Relationship to study product can only be assessed by a clinician licensed to make medical diagnoses (i.e. physician, nurse practitioner, physician's assistant) listed on the Form FDA 1572.

Adverse events characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the data collection forms and eCRF.

**c. Severity of Event:** AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, the following guidelines will be used to quantify severity:

- **Grade 1 -Mild:** events require minimal or no treatment and do not interfere with the patient's daily activities.
- **Grade 2 -Moderate:** events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 -Severe:** events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating **or Life-threatening**, i.e. any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that had it occurred in a more severe form, might have caused death.

**d. Relationship to study products/vaccines:**

The investigator's assessment of the relationship of an AE to the study drug/vaccine is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. AEs must have their possible relationship to study vaccine assessed using the following terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related –** The event is temporally related to the administration of the study product and no other etiology explains the event.
- **Not Related –** The event is temporally independent of study product and/or the event appears to be explained by another etiology.

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**e. Reactogenicity:**

Reactogenicity events are AEs that are known to occur with this type of vaccine. The following Toxicity Grading Scales will be used to grade local and systemic (both quantitative and subjective) reactions:

**Table 4. Local Solicited Adverse Events**

<b>Local Reaction</b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>
Pain	Subject is aware of pain but it does not interfere with daily activity and no pain medication is taken	Subject is aware of pain; there is interference with daily activity or it requires therapeutic measures	Subject is aware of pain and it prevents daily activity or requires a healthcare visit
Tenderness	The area immediately surrounding the injection site hurts only when touched and it does not interfere with daily activity	The area immediately surrounding the injection site hurts only when touched and it interferes with daily activity	The area immediately surrounding the injection site hurts when touched and it prevents daily activity
Swelling/Induration	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema/Redness	0.5 to 2.5 cm	>2.5 cm to <5 cm	≥5 cm
Induration/Swelling	0.5 to 2.5 cm	>2.5 cm to <5 cm	≥5 cm

**Table 5. Systemic Solicited Adverse Events**

<b>Systemic (Subjective)</b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>
Fatigue/Malaise	No interference with activity	Some interference with activity	Incapacitating, prevents daily activity, may necessitate medical care or absenteeism
Headache	No interference with activity	Some interference with activity	Incapacitating, prevents daily activity, may necessitate medical care or absenteeism
Nausea	No interference with activity	Some interference with activity	Incapacitating, prevents daily activity, may necessitate medical care or absenteeism
Body ache/myalgia (not at injection site)	Less active than normal without interference with	Less active than normal with interference with	Incapacitating, prevents daily activity, may necessitate medical care or absenteeism

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	essential daily tasks (e.g. eating, sleeping)	essential daily tasks (e.g. eating, sleeping)	
General activity level	Less active than normal without interference with essential daily tasks (e.g. eating, sleeping)	Less active than normal with interference with essential daily tasks (e.g. eating, sleeping)	Incapacitating, prevents daily activity, may necessitate medical care or absenteeism
Vomiting	1-2 times a day	3-4 times a day	>4 times a day
<b>Systemic (Quantitative)</b>	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>
<b>Fever (°C) – ORAL</b>	$\geq 38.0 - < 38.3$ $\geq 100.4 < 101^{\circ} F$	$\geq 38.3 - < 39$ $\geq 101 - < 102^{\circ} F$	$\geq 39$ $\geq 102^{\circ} F$

**f. Serious Adverse Event:**

An SAE is defined as an AE meeting one of the following conditions:

- Results in death during the period of protocol defined surveillance except deaths that are the result of trauma or accident.
- Is life-threatening (defined as a subject at immediate risk of death at the time of the event).
- Requires inpatient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance.
- Results in a persistent or significant disability/incapacity.
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Note\***

The SAEs should not be attributable to underlying disease for which the transplant was undertaken, or not attributable to GVHD, or not attributable to complications of immunosuppressive medications.

**g. Reporting Procedures:**

Adverse events including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected for unsolicited adverse events includes event description, date of onset, investigator assessment of severity, investigator assessment of relationship to study product, date of resolution of the event, seriousness, and outcome. The severity of non-serious AEs will be assessed by a licensed clinician (i.e., medical doctor, nurse, nurse practitioner, physician's assistant). The relationship of non-serious AEs will be assessed by a licensed clinician (i.e., medical doctor, nurse practitioner, physician assistant) listed on the Form FDA 1572. All AEs occurring during the AE reporting period of the study will be documented appropriately regardless of relationship. AEs will be followed to adequate resolution or until considered stable.

Any medical condition that is present at screening will be considered a baseline condition and will not be reported as an AE. If the severity of any pre-existing medical condition increases during the study period, then it will be recorded as an AE.

## **h. Serious Adverse Event Detection and Reporting**

SAEs as defined in Section 16.f will be:

- Notified to the IND Sponsor/Lead PI (Dr. Natasha Halasa), local site PI and/or Sub-Is and DMID Pharmacovigilance Group (PVG) within 24 hours of knowledge of the SAE.
- Assessed for severity and relationship by a licensed clinician listed on the FDA Form 1572 as the PI or a Sub-Investigator.
- Recorded on the appropriate SAE report form.
- Followed through resolution by a study physician.
- Reviewed by an Independent Safety Monitor (ISM), Data and Safety Monitoring Board (DSMB) (periodic review unless related), DMID, and IRB.
- SAEs related to the study vaccine that are unexpected and fatal or life-threatening will be reported to the FDA no later than 7 calendar days after SAE awareness.
- SAEs related to the study vaccine that are unexpected and serious (not fatal or life-threatening) are to be reported to the FDA no later than 15 calendar days after SAE awareness.
- All other SAEs will be submitted with the FDA Annual Report in summary form.
- All SAEs unexpected and deemed related to the study vaccine will be reported to Sanofi within 7-15 calendar days after SAE awareness.

SAEs occurring through 7 days following vaccination will also be reported to the local IRB within 1-2 calendar days as the team becomes aware of the SAE or per local IRB protocol/procedures.

Any AE that meets a protocol-defined serious criterion as defined in Section 16.f will be submitted immediately (within 24 hours of site awareness) on a SAE form to the DMID Pharmacovigilance Group, to the following address:

**DMID Pharmacovigilance Group**

**Clinical Research Operations and Management Support (CROMS)**

**6500 Rock Spring Dr. Suite 650**

**Bethesda, MD 20817, USA**

**SAE Hot Line: 1-800-537-9979 (US)**

**SAE FAX Phone Number: 1-800-275-7619**

**SAE Email Address: [PVG@dmidcroms.com](mailto:PVG@dmidcroms.com)**

In addition to the SAE form, selected SAE data fields must also be entered into the database. Refer to the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the ISM when they are provided to the DMID Pharmacovigilance Group. The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of this study, if the site Principal Investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to study product, the site Principal Investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

MedWatch reports will also be submitted to the DMID Pharmacovigilance Group.

### **i. Independent Safety Monitor (ISM) and the Data Safety Monitoring Board (DSMB):**

An Independent Safety Monitor (ISM) is a physician at the enrollment site with relevant expertise whose primary responsibility is to provide independent medical assessment in a timely fashion at each site. Each site will have an ISM and back-up ISM. Participation is for the duration of the study.

The ISM should be able to readily access participant records in real time, have the privileges to examine the subject, and provide an independent medical assessment and recommendation to the IND sponsor and DMID. The primary focus of the ISM is to independently review all SAEs with follow-up through resolution and thoroughly investigate those events considered unexpected. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. The ISM may be a faculty member at the clinical site but will not be under the direct supervision of the PI. It is the responsibility of the PI to ensure that the ISM is apprised of all new safety information relevant to the study product and the study.

Safety oversight will be conducted by a Data Safety and Monitoring Board (DSMB) that is an independent group with expertise to interpret data from this study and will monitor subject safety and advise DMID and the IND sponsor. The DSMB members will be separate and independent of study personnel participating in this study and should not have scientific, financial, or other conflict of interest related to this study. The committee will consist of a minimum of 3 members. A simple majority will be considered a quorum for meeting purposes.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB and defines the data elements to be assessed and the procedures for data reviews. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews/meetings will be defined in the charter. The DSMB will review applicable data to include, but not limited to, overall study progress and participant, clinical, safety, reactogenicity, and immunogenicity data. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the IND sponsor and DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during this study as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation to the IND sponsor and DMID as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

DMID or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of this trial. The DMID Medical Monitor is empowered to stop enrollment and study vaccinations if adverse events that meet the halting criteria are reported. The DMID Medical Monitor and the ISM will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during this study.

The DSMB will review study progress and participant, clinical, safety, reactogenicity, and immunogenicity data at the following times:

- Data review for safety and reactogenicity at specified times during the course of this trial – every 6 months, starting after the first patient is enrolled until the end of the study.
- Final review – 6 to 8 months after clinical database lock to review the cumulative unblinded safety, reactogenicity, and immunogenicity data for this study. The data will be provided in a standard

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summary format. The DSMB may be asked to provide recommendations in response to questions posed by the IND sponsor and DMID.

- Ad hoc when a halting rule is met, for immediate concerns regarding observations during this study, or as needed – for a specific safety concern, such as SAE deemed related to the study vaccine.

### j. Halting Rules:

The ISM of each site, DMID, and DSMB will be provided safety data in order to advise on matters of safety, including halting the trial. The safety data will consist of immediate reactogenicity events (in the 15 minutes after vaccination), reactogenicity events recorded on the memory aid (each day for the week after vaccination), AEs, and SAEs. The data will be entered into ONCORE and/or REDCap and provided to the ISM, DMID, and DSMB for review. The presentation of the data will include whether any events contributing towards a halting rule have been met. The frequency of DSMB review will be defined in the charter.

The study will be halted (for further DSMB review/recommendation) if any of the following occur and it was not the result of trauma or accident, scheduled hospitalization or surgery, and is not attributable to disease relapse, GVHD, or and infection due to the immunosuppressed state of the patient. No new subjects will be enrolled if:

1. If one subject has an SAE and the adverse event is deemed severe within 7 days of vaccine that is determined to be related to the study vaccine by the site PI in consultation with the site ISM and the study PI, no new subjects will be enrolled. The SAEs will be reviewed by the DSMB for the relationship with the study vaccine and further discussed with DMID to determine continuation of the study.
2. If four or more subjects have the same Grade 3 event in any reactogenicity category (excluding grade 3 redness/ induration size or grade 3 fever) that is determined to be study vaccine-related, no new subjects will be enrolled. The AEs will be reviewed by the DSMB for the relationship with the study vaccine. For 2019-20, based on safety data from the previous years, the number of subjects will be increased to eight prior to halting.
3. 3 or more subjects have urticaria considered to be study vaccine-related.
4. 1 or more subjects have intramuscular injection-site ulceration, abscess, or necrosis.
5. 1 or more subjects have laryngospasm, bronchospasm or systemic anaphylaxis within 24 hours of administration of study vaccine.
6. 1 or more subjects have acute weakness of limbs or cranial nerve innervated muscles.
7. Any death occurring within the first 7 days following administration of study vaccine.

If any of the halting rules are met, the study will not proceed with the remaining enrollment or vaccinations without a review by and recommendation from the DSMB to proceed. CBER will be notified if a stopping rule has been met at any time during the study. DMID retains the authority to suspend additional enrollment and study interventions/administration of study product during the entire trial, as applicable.

### k. Safety Oversight:

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

## I. Data and Safety Monitoring Committee/Quality Assurance:

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for clinical trials through the Data and Safety Monitoring Committee (DSMC). The committee will convene on a quarterly basis and *ad-hoc* as necessary. The DSMC provides oversight of the internal audit function. During audits the

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Quality Assurance (QA) auditor will review selected case histories. In addition they will conduct a regulatory and pharmacy audit as needed. The data presented to the DSMC will be blinded unless the committee requests un-blinded data. The DSMC will determine if the findings in the audit report require a response from the Principal Investigator. After reviewing submitted corrective action plans, the committee has the authority to approve the continuation of the study, increase the frequency of auditing, suspend accrual, or terminate a protocol; however, this will be in discussion with the DSMB.

This trial will be monitored continuously by the study's principal investigator and on a weekly and monthly basis by the Research Team. Quarterly safety and monitoring reports are available to the DSMC. The DSMC reviews all serious adverse events reported during the previous quarter for all clinical trials active at the VICC and makes recommendations to address concerns of patient safety. Since data from REDCap will be transferred to Oncore, the DSMC will be able review all safety data from all nine sites.

A Quality Assurance auditor under the direction of the DSMC will audit this clinical trial quarterly for compliance with adverse event reporting, regulatory and studies requirements, and data accuracy and completion. Audit reports detailing the findings are provided to the DSMC.

Any DSMC communications regarding safety evaluations will be shared with the Chair of DSMB and the DSMB. This information will also be shared with FDA-CBER and NIH.

### **m. Blinding:**

All study staff, subjects, and their parent/guardians will be blinded to which vaccine the subject will receive, except for an un-blinded vaccinator. This individual will not inform the study team, subjects, and/or their parent/guardians which vaccine they administered to the subject. The un-blinded vaccinator will not participate in any other study activities. If the study vaccine is provided in a blinded manner, then research staff will be able to administer the vaccine, and an un-blinded vaccinator will not be necessary. The pharmacy will be un-blinded and will have a record of which vaccine was given to each subject.

### **n. Vaccine Labeling Plan:**

The following statement will be used: "Caution: New Drug – Limited by Federal (or United States) law to investigational use" and subjects and parents/guardians will be informed of this during the consent process.

## **17. Statistical Considerations:**

- a. **Sample Size Calculations:** A total of 200 children will be targeted, with 100 in each group. This is based on the assumption, with 80% power, that 20% of the children in the standard dose group will achieve a protective titer compared to 40% of the HD-TIV group for at least one influenza antigen. Accounting for a 20% drop out rate, 100 children in each group will be needed.

Strain	Expected Seroprotection HD-TIV	Expected Seroprotection standard dose	N (HD)	N (SD)	Power	Total N with 20% drop out
<b>Expected HD-TIV seroprotection is twice as of standard dose</b>						
A	40%	20%	80	80	80%	200
A	50%	25%	55	55	80%	138
A	60%	30%	40	40	80%	100
A	70%	35%	28	28	80%	70

- b. **Immunogenicity analysis:** The probability of achieving a 4-fold (or greater) rise in post-vaccination HAI titers relative to baseline, as well as the probability of a HAI titer greater than

1:40, will be estimated using a binomial model. We will calculate the Bayesian posterior distribution of the probabilities under all 4 combinations of standard and HD-TIV crossed with a single dose and two doses. From these probabilities, odds ratios will be calculated along with 95% credible intervals. These quantities will be modeled as a logit-linear function of several covariates, including CD4<sup>+</sup>/CD8<sup>+</sup>/CD19<sup>+</sup> and IgG levels, absolute neutrophil and lymphocyte count (or their ratio), time from post-transplant to enrollment, type of preparative regimen, donor status, and stem cell source. In addition, the distributions of geometric mean HAI titers for high and standard dose recipients will be estimated via log-normal models and expressed as ratios in order to evaluate the evidence for higher GMT in the HD-TIV sample, after one and two vaccines. In addition, we will compare each group to document if they meet serological criteria by WHO biological standards for influenza vaccines (>40% for seroconversion, GMT >2.5-fold increase, and >70% with  $\geq 1:40$ ).<sup>69</sup>

- c. **Safety analysis:** For the primary analysis of the safety data, the proportion of subjects in each group experiencing at least one solicited AE will be calculated along with 95% posterior credible intervals. The difference between the rates of solicited AEs between the groups will be estimated by calculating the posterior 95% credible interval of the difference in proportions. For each group and each event, solicited and unsolicited AEs will be descriptively summarized. Severities of solicited and unsolicited AEs will also be descriptively summarized for each group and each type of event. Descriptive statistics will include number experiencing event, mean and 95% posterior credible interval. Maximum size of redness and swelling may be descriptively summarized for each group and event; proportion of events lasting longer beyond Day 3 may also be descriptively summarized.
- d. **Specific B and T cells responses:** We will estimate the association between HAI titers and expression of ICOS and CD40L on CD4+CXCR5+ T cells. We anticipate that the frequency of circulating T<sub>FH</sub> cells with expression of ICOS and CD40L will directly correlate with higher influenza titers. We will also estimate the association between HAI titers and the distribution of circulating plasmablasts (CD19+CD27+CD38+), using either parametric linear models or Gaussian processes if the relationship cannot adequately be modeled linearly. In addition to the phenotypic analysis, we will perform in vitro stimulation of PBMC with influenza antigen. We will measure the degree of ICOS and CD40L expression of CD4+CXCR5+ T cells in the presence or absence of antigen, and model the relationship between response and HAI titer, where we predict responders to have higher HAI titers. Comparisons between marker expression on CD4+CXCR5+ T cells in the presence or absence of antigen and correlations between HAI titer and Marker expression on CD4+CXCR5+ T cells will be evaluated by building models that regresses T cell counts on HAI titers. We will compare both linear and non-linear fits to the data, and choose the optimal model as determined by a model selection criterion, such as AIC. Should the parametric models not adequately fit the data, we will use a semi-parametric regression via Gaussian processes as a robust alternative.
- e. **Influenza-Like-Illness assessment.** The percentage of individuals in each group that test positive for influenza by PCR and the number of ILIs in each group during the influenza season will be compared.

## 18. Ethics/Protection of Human Subjects:

### a. Ethical Standard:

The investigator(s) will ensure that this study is conducted in full conformity with the principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National

Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 312, 21 CFR 50, 56, and, if applicable, ICH E6; 62 Federal Regulations 25691 (1997).

**b. Institutional Review Board:**

1. The protocol, informed consent documents, and all types of volunteer educational information must be submitted to the IRB for review and must be approved before the study is initiated.
2. The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial.
3. Should amendments to the protocol be required, the amendments will be written by the study team and submitted to the FDA and IRB.
4. The investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but at least once a year. The investigator must also keep the IRB informed of any significant adverse events.
5. The study may be discontinued for administrative reasons or if new data about the investigational product/regimen resulting from this or any other studies become available, and/or on advice of the DSMB, DSMC, Investigator, and/or IRB. If a study is prematurely terminated or suspended, the Investigator shall promptly inform the IRB of the reason for termination or suspension.
6. If for any reason the study is prematurely terminated, the Investigator will promptly inform the subject's parent or legal guardian and ensure appropriate therapy and follow-up for volunteers.
7. All key study staff regularly undergo training in human subjects issues conducted by the participating site or their IRBs.

**c. Informed Consent Process:**

1. In obtaining and documenting informed consent, investigators and the research team will comply with the applicable regulatory requirements, Good Clinical Practice, and ethical principles. The written Informed Consent (IC) Form will be approved by the Institutional Review Board/Ethics Committee (IRB/EC) prior to starting the study.
2. Potential subjects will be informed about the scope of the study, expected benefits, and possible risks. They will also be informed that participation is voluntary and can be terminated at any time without reason.
3. The extent of confidentiality of subject records is defined in the IC and applicable data protection legislation will be provided to the parent/legal guardian. Subjects will be informed that the sponsor or sponsor's designee, monitor, auditor, IRB/EC, and the regulatory authority (ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating laws and regulations. By signing a written IC form, the subject's legally acceptable representative is authorizing such access.
4. The IC will be explained thoroughly to the subject. Ample time will be given to answer all questions. A signature will be obtained prior to any study procedures. A signed and dated copy of the IC will be given to the subject's parents/guardians and subject.
5. Subjects may also receive IRB approved information about the vaccines to be used in the study.
6. Assents will be used for children in this study (verbal assents for children 3-6 years, if applicable, and signed assents for children 7-17 years of age).

**d. Exclusion of Women, Minorities, and Children (Special Populations):**

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This study will be inclusive of children 3-17 years of age HSCT recipients who meet the inclusion/exclusion criteria, regardless of religion, sex, or ethnic background.

**e. Subject Confidentiality:**

1. All information will be in the research record that will be handled by the research personnel. The results of the research study may be published, but volunteers' names or identities will not be revealed. Records will remain confidential.
2. In order to maintain subject confidentiality, records will be kept locked and results of tests will be coded to prevent association with volunteers' names. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. Volunteers' records will be available to the FDA, NIH, external monitors, and the IRB.
3. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.
4. The following confidential information will be collected into folders and stored in a safe, locked location, identified only by code number: age, gender, race, family history, social history, full address, phone number (home, cell, and work), and date of birth, fax number, secondary name, birth history, and contact number, and email address of the subject's parent/legal guardian.
5. The records will be sent to storage after study completion and data analysis.
6. Serum samples will be collected during this study and stored with their subject ID as the only identifiers. Laboratory assays containing data from the study will be labeled only with volunteer code numbers.
7. The information in the REDCap or ON-Core database will only include non-identifiable information.

**f. Study Discontinuation:**

If the study is discontinued, enrolled subjects will continue to be followed for safety assessments. No further doses of vaccine will be administered. Samples will be stored at Vanderbilt.

**g. Future Use of Stored Specimens:**

Subjects will be asked for permission to keep any remaining specimen for possible use in future research studies, such as testing for antibodies against other viruses or bacteria. By the end of the study, all samples will be stored at Vanderbilt. The samples may be shared with other investigators. The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on samples prior to obtaining new, written permission (consent) from the subject. Each sample will be labeled with a unique number to protect the subject's confidentiality. There is a small risk of loss of confidentiality. The samples will be stored indefinitely.

There are no benefits to subjects in the collection, storage, and subsequent research use of specimens. Reports about future research done with subject's samples will NOT be kept in their health records, but subject's samples may be kept with the study records or in other secure areas. Subjects can decide if they want their samples to be used for future research or have their samples destroyed at the end of the study. A subject's decision can be changed at any time prior to the end of the study by notifying the study doctors or nurses in writing. However, if a subject consents to future use and some of their blood has already been used for research purposes, the information from that research may still be used.

**19. Data Handling and Record Keeping:**

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a

change or correction, cross out the original entry with a single line and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

**a. Data Capture Methods:**

For all the sites, the data will be entered into a standardized, secured database: **REDCap** (Research Electronic Data Capture) system. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.<sup>70</sup> The research team at each site will be given a user name and pass codes to be able to enter data from their sites locally.

At Vanderbilt, safety data from REDCap maybe transferred to **On-line Clinical Oncology Research Environment = ONCORE (OnCore)** is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with National Cancer Institute (NCI) designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Also the system is capable in storing basic protocol information (e.g., IRB approval dates, dates for annual renewals, etc.) and clinical trials research data. Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all Vanderbilt Ingram Cancer Center (VICC) clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource. A copy of the paper records will be retained for at least 7 years after completion of the study. The information stored in the ONCORE and REDCap database will be kept indefinitely.

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**20. Publication Policy:**

The intention of this study is to publish the data from this trial. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

**21. Certificate of Confidentiality:**

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

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The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The Certificate of Confidentiality applies *only* under US law.

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